Study Protocol and Statistical Analysis Plan Cover Page

TITLE	PV-10 Intralesional Injection vs Systemic Chemotherapy or Intralesional Oncolytic Viral Therapy for Treatment of Locally Advanced Cutaneous Melanoma
PROTOCOL NO	PV-10-MM-31
IND NO	70539
NCT NO	NCT02288897
EudraCT NO	2016-000317-78
INVESTIGATIONAL DRUG	PV-10 (10% w/v rose bengal disodium in 0.9% saline for injection)
DOSAGE FORM	Intralesional Injection
SPONSOR	Provectus Biopharmaceuticals, Inc. 10025 Investment Drive, Suite 250 Knoxville, TN 37932 USA
DATE	27 Mar 2018

Due to slow accrual during a period of rapidly changing trends in global drug development for cutaneous melanoma, the study was terminated early and no Statistical Analysis Plan was implemented. Please refer to protocol section 10 for statistical and analytical considerations.

TITLE	PV-10 Intralesional Injection vs Systemic Chemotherapy or Intralesional Oncolytic Viral Therapy for Treatment of Locally Advanced Cutaneous Melanoma
PROTOCOL NO	PV-10-MM-31
PHASE	3
IND NO	70539
EudraCT NO	2016-000317-78
INVESTIGATIONAL DRUG	PV-10 (10% w/v rose bengal disodium in 0.9% saline for injection)
DOSAGE FORM	Intralesional Injection
SPONSOR	Provectus Biopharmaceuticals, Inc. 10025 Investment Drive, Suite 250 Knoxville, TN 37932 USA
STUDY DIRECTORS	Eric Wachter, Ph.D. Provectus Biopharmaceuticals, Inc. Phone: +1 865-769-4011 x23 Mobile: [redacted] Fax: [redacted] David Sarson, Ph.D. Provectus Biopharmaceuticals Australia Pty Limited Phone: [redacted] Mobile: [redacted] Fax: [redacted]
DOCUMENT VERSION	1.5
REGION-SPECIFIC ADDENDA	Argentina, Russia
DOCUMENT HISTORY	Revised 27 Mar 2018 from ver. 1.4; 19 May 2017 from ver. 1.3; 25 Jun 2016 from ver. 1.2; 16 Feb 2016 from ver. 1.1; 06 Mar 2015 from ver. 1.0 (dated 03 Nov 2014)
DATE	27 March 2018

This protocol will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Conference on Harmonisation and all applicable federal and local regulations.

PROTOCOL SIGNATURE SHEET

The undersigned have reviewed the format and content of this protocol and have approved Protocol No. PV-10-MM-31, version 1.5 dated 27 March 2018, for issuance.

[redacted] 04 Apr 2018
Sponsor's Signature Date

Eric Wachter, Ph.D.
Chief Technology Officer
Provectus Biopharmaceuticals, Inc.

[redacted] 04 Apr 2018
Sponsor's Signature Date

David Sarson, Ph.D.
Director
Provectus Biopharmaceuticals Australia Pty Limited

INVESTIGATOR SIGNATURE SHEET

I have read the attached protocol PV-10-MM-31 version 1.5 dated 27 March 2018 and agree that it contains all the necessary details for performing the study.

I will provide copies of this protocol and the Investigator's Brochure information provided to me by the Sponsor to all members of the study team responsible to me who participate in the study. I will discuss this material with them to assure that they are fully informed regarding the test article and the conduct of the study.

I will assure that the protocol and informed consent documentation for this study, and all work conducted there under, will conform to institutional regulations and local and national laws and regulations.

I understand the protocol and will work according to it, the principles of Good Clinical Practice (current ICH guidelines) and the Declaration of Helsinki (1964), including all amendments up to and including the Fortaleza revision (2013).

_____ _____

Principal Investigator Date

_____

Printed Name

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REGION-SPECIFIC ADDENDA

ARGENTINA

Section 8.3 Pregnancy is replaced with the following:

Any pregnancy diagnosed during the study interval, or that occurs within 28 days after the last dose of study medication, must be reported immediately to the Principal Investigator. The Principal Investigator will notify the Sponsor or designee by following the procedures described in Section 8.2. The outcome of all such pregnancies (i.e., spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be documented and followed up on a form that will be provided by the Sponsor. The pregnancy will be followed to term and the outcome, including any premature termination, must be reported to the Sponsor. All live births must be followed for a minimum of 12 months. All reports of congenital abnormalities/birth defects and spontaneous abortions/miscarriages should be reported as an SAE. Elective abortion procedures, without complications, should not be considered as adverse events.

RUSSIA

KEY ITEMS	PROTOCOL POINTS IMPACTED	DESCRIPTION OF SIGNIFICANT CHANGES / EXPLANATIONS
Imlygic (talimogene laherparepvec)	**Section 1** Protocol Synopsis (**Subsections:** Primary Objectives, Study Design, Comparator Arm, Study Procedures and Evaluations, Study Schematic); **Section 3.1** Primary Objectives; **Section 4** Study Design; **Section 4.1** Study Subjects and Lesions; **Section 4.2.3** Comparator Arm; **Section 4.2.4** Toxicity Requiring Study Drug Discontinuation; **Section 4.3.1** Disease Progression; **Section 4.4.2** Safety; **Section 4.12** Study Schematic **Section 6** Study Medication; **Section 6.4** Talimogene Laherparepvec (**Sections 6.4.1-6.4.5**); **Section 7** Study Procedures and Evaluation; **Section 7.2.3. (Sections 7.2.3.1-7.2.3.9)** Comparator Arm (Talimogene Laherparepvec); **Section 7.3.1.** Extended Treatment (Talimogene Laherparepvec); **Section 7.3.1.4** Repetition of Extended Treatment (Talimogene Laherparepvec); **Section 7.3.2.2** Response Evaluations (every 12 weeks) (Talimogene Laherparepvec); **Section 7.3.3.2** Subjects in the Comparator Arm (Talimogene Laherparepvec); **Section 7.5** Treatment Discontinuation (Talimogene Laherparepvec); **Section 7.6** Subject Withdrawal and Final Follow-up (Termination Visit) (Talimogene Laherparepvec); **Section 8** Adverse events (Talimogene	Intralesional oncolytic viral therapy, also referred to as oncolytic virus, Imlygic, or talimogene laherparepvec, will not be used as a comparator in Russia as this drug is not approved and commercially available in the Russian Federation. Reference to this therapy is deleted from the enumerated sections of the study protocol with regard to study sites within the Russian Federation.

	Laherparepvec); **Section 10.1.** Determination of Sample Size; **Section 10.5.1.** Exposure to Study Drug; **Paragraph 12.** References (points 37, 87); **Appendix A** Schedule of Study Events – Comparator Arm (Talimogene Laherparepvec).	
Pregnancy follow-up	**Section 8.3** Pregnancy.	All live births must be followed for a minimum of 12 months.
Skindex-16 Questionnaire	The example copy of the Skindex-16 questionnaire provided in **Appendix H** is replaced with the Russian language version (shown below)	The validated Russian language version of the Skindex-16 questionnaire is provided. Copies of the questionnaire will be provided to all study sites within the Russian Federation.

Skindex16
©MMChren, 1997

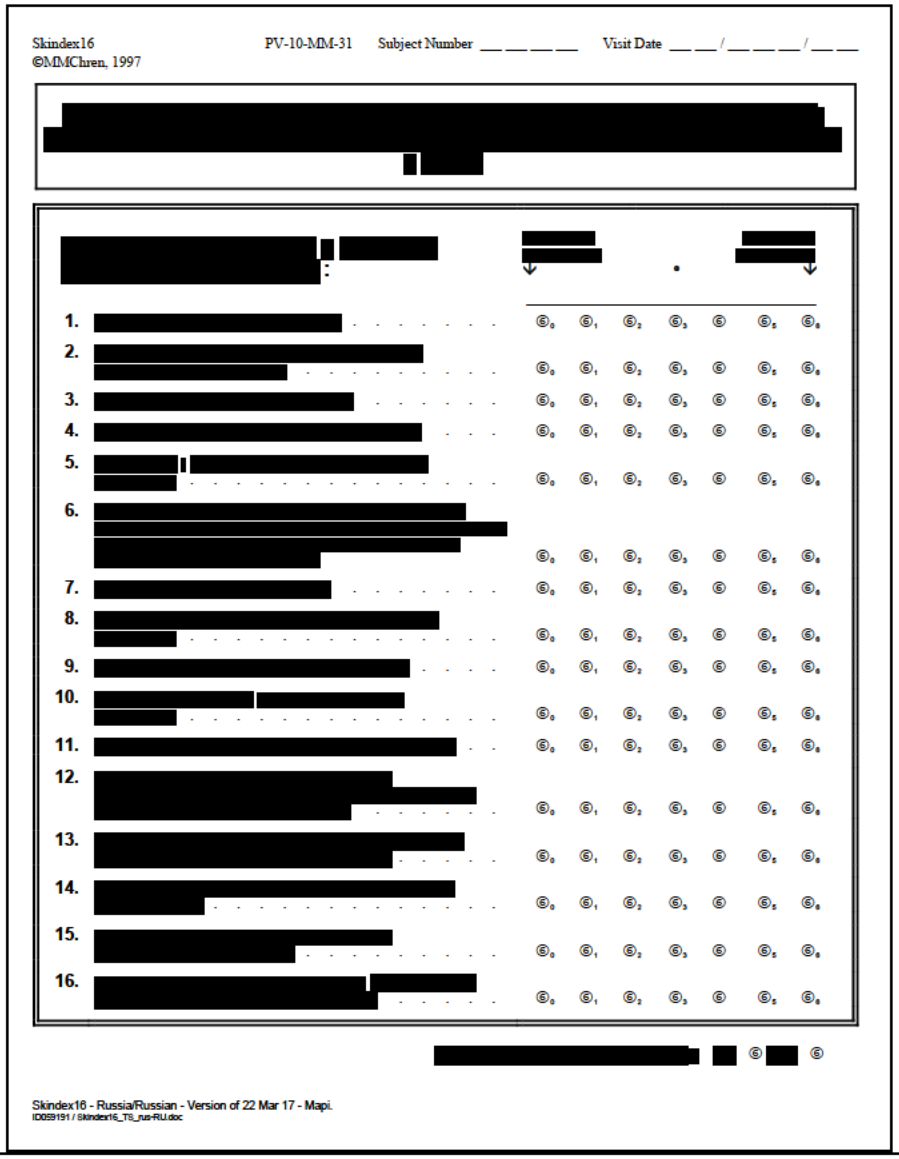
PV-10-MM-31 Subject Number ___ ___ ___ ___ Visit Date ___ ___ / ___ ___ ___ / ___ ___

[redacted]

(SKINDEX)

[redacted]

Skindex16 - Russia/Russian - Version of 22 Mar 17 - Mapi.
ID059191 / Skindex16_TS_rus-RU.doc



Skindex16
©MMChren, 1997

PV-10-MM-31 Subject Number ___ ___ ___ ___ Visit Date ___ ___ / ___ ___ ___ / ___ ___

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Skindex16 - Russia/Russian - Version of 22 Mar 17 - Mapi.
ID059191 / Skindex16_TS_rus-RU.doc

1 PROTOCOL SYNOPSIS

STUDY OVERVIEW

Study Rationale

Patients with locally advanced cutaneous melanoma present significant clinical challenges in the management of their disease. These patients are prone to frequent locoregional recurrence and eventual spread of their disease to other cutaneous, subcutaneous, soft tissue or nodal locations. Often there is a period of years prior to onset of life-threatening visceral metastasis, a time interval during which one or more locoregional interventions are appropriate. A well-tolerated locoregional therapy that elicits a durable response would provide significant clinical benefit to these patients because it represents both symptom control and delay of progression to more advanced locoregional disease while possibly forestalling eventual distant metastasis.

Assessment of clinical benefit in terms of progression-free survival (PFS) is a meaningful approach for these patients, with complete response rate (CRR) a logical secondary approach since it addresses both elimination of potentially symptomatic lesions and the avoidance of progression to a more symptomatic state. Assessment of change in disease symptoms provides a basis for supporting the clinical relevance of objective response parameters (i.e., PFS and CRR). Overall survival (OS) may have relevance for assessment of safety and efficacy in the context of a randomized controlled trial (RCT) with long term survival follow-up.

Investigational Drug

The drug product to be investigated in this clinical trial is PV-10 (10% w/v rose bengal disodium in 0.9% saline for injection). PV-10 is being studied for intralesional (IL) injection into solid tumors, where it may elicit both local oncolytic and systemic anti-tumor immune responses. Release of tumor antigens upon local oncolysis may stimulate an anti-tumor immune response that may augment local and systemic response, including tumor-specific reactivity in circulating T cells in treatment-refractory patients.

Indication

The indication under investigation is treatment of locally advanced cutaneous melanoma in patients who (1) are not candidates for targeted therapy and (2) are not candidates for an immune checkpoint inhibitor.

STUDY OBJECTIVES

Primary Objective

The primary objective of this randomized controlled trial (RCT) is to assess the effectiveness of intralesional (IL) PV-10 compared to the Investigator's choice of systemic chemotherapy or intralesional oncolytic viral therapy in treating locally advanced cutaneous melanoma. Effectiveness will be assessed by comparison of progression-free survival (PFS) between all intent-to-treat (ITT) subjects in the two study treatment arms.

Secondary Objectives

This study will also include assessment and comparison of the two study treatment arms with respect to:

- Complete response rate (CRR).
- Duration of complete response.
- Overall survival (OS).
- Safety and tolerability.

Exploratory Objectives

- Change from Baseline domain scores using the Skindex-16 instrument.
- Change in Investigator assessed lesion bleeding from Baseline.
- Change in Investigator assessed lesion ulceration from Baseline.
- Change in Investigator assessed lesion infection from Baseline.

STUDY DESIGN

This is a phase 3, international multicenter, open-label, RCT of single-agent IL PV-10 versus systemic chemotherapy or intralesional oncolytic viral therapy to assess treatment of locally advanced cutaneous melanoma in patients who (1) are not candidates for targeted therapy and (2) are not candidates for an immune checkpoint inhibitor. Subjects in the comparator arm will receive the Investigator's choice of dacarbazine (DTIC), temozolomide (TMZ) or talimogene laherparepvec as determined by Investigator preference and standard of care in the country or region.

Study Subjects and Lesions

Patients eligible for the study must have locally advanced cutaneous melanoma, consisting of recurrent, satellite or in-transit locally advanced cutaneous, subcutaneous, soft tissue, or superficial or palpable nodal melanoma metastases (i.e., AJCC 2009 Stage IIIB, Stage IIIC or Stage IV M1a). Eligible patients must have at least 1 measurable Target Lesion consisting of at least one cutaneous lesion (each lesion ≥ 10 mm in longest diameter or up to 5 lesions having a sum of longest diameters ≥ 10 mm), and / or at least one subcutaneous or soft tissue lesion (each lesion ≥ 10 mm in longest diameter by CT or MRI), and / or at least one superficial or palpable nodal lesion (each lesion ≥ 15 mm in short axis diameter by CT or MRI); no lesion > 50 mm in longest diameter; and no more than 50 total lesions at enrollment. Patients with pathological deep lymph nodes should not be enrolled due to potential risk of serious complications for oncolytic therapy to these nodes. Patients with existing or a history of visceral melanoma metastases are excluded from participation in the study. Patients must not be candidates for an immune checkpoint inhibitor and not be candidates for targeted therapy.

A minimum of 1 and no more than 5 measurable lesions, representative of the subject's disease, will be identified by the Investigator prior to treatment randomization as Target Lesions. All other lesions present at baseline regardless of their size will be designated as Non-Target Lesions and will also be measured and followed during the study interval.

The total tumor burden represented by all Study Lesions must allow for treatment of all Study Lesions with PV-10 during the initial treatment session (i.e., on study Day 1).

Subject Randomization and Treatment

A total of 225 eligible subjects will be randomized in a 2:1 ratio to the two treatment arms (i.e., PV-10 arm or comparator arm). Assignment of subjects to one of the two treatment arms will be made using a complete block randomization scheme stratified by prior immunotherapy treatment status (i.e., failure or naïve). Randomization will occur after designation of Target Lesions at Screening and within 14 days prior to study Day 1.

PV-10 Arm

Subjects will receive IL PV-10 to all Study Lesions on study Day 1. PV-10 should be re-administered at 28-day intervals until complete response, disease progression or study termination occurs.

Comparator Arm

Subjects will receive (a) intravenous dacarbazine or oral temozolomide, administered at consecutive 28-day intervals, or (b) intralesional talimogene laherparepvec administered on an initial 21-day interval followed by consecutive 14-day intervals, until complete response, disease progression or study termination occurs.

Crossover of Subjects in the Comparator Arm

Subjects in the comparator arm who have completed at least 1 cycle of study treatment and who meet the study protocol definition of disease progression but do not have evidence of visceral metastases or a decline in Eastern Cooperative Oncology Group (ECOG) status to ≥ 3 will be eligible to enter the crossover portion of the study and receive PV-10.

Subjects in the comparator arm who experience a toxicity requiring study drug discontinuation but do not have evidence of visceral metastases or a decline in ECOG status to ≥ 3 will be eligible to enter the crossover portion of the study.

Subjects crossing over must meet all study inclusion and exclusion criteria for clinical laboratories, thyroid function, concurrent or intercurrent illness and pregnancy at the time of crossover.

Clinical Trial Data Monitoring Committee

A Clinical Trial Data Monitoring Committee (CTDMC) will be implemented in compliance with FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees dated March 2006 for analysis of efficacy and safety.

Independent Review Committee

An Independent Review Committee (IRC) will determine disease progression status and tumor response by periodic blinded review of all study photographs, radiographic images and other relevant evidence documenting disease progression. These reviews will be reported to the CTDMC. Progression status will be reviewed periodically to confirm subject eligibility for crossover.

Interim Analysis

An interim assessment of efficacy and safety will be performed by the CTDMC when 50% of the events required for the primary endpoint (i.e., 81 disease progressions as defined in the study protocol) have occurred.

STUDY PROCEDURES AND EVALUATIONS

All subjects will be randomized within 14 days prior to study Day 1 and commence their assigned treatment on study Day 1. Designation of Target Lesions will be made prior to randomization.

Photodocumentation of Study Lesions will be performed at Screening; at study Day 1 prior to initiation of study treatment (i.e., baseline); at the end of each Treatment Cycle; and at all subsequent evaluations. Additional photographic documentation will be performed at intermediate times if disease progression is clinically identified or suspected.

Laboratory tests will be performed at Screening; at study Day 1 prior to initiation of study treatment (i.e., baseline); at the end of each Treatment Cycle; and at Final Follow-up. Subject self-assessment of symptoms (Skindex-16) will be performed at study Day 1 prior to initiation of study treatment (i.e., baseline); at the end of each subsequent Treatment Cycle; and at Final Follow-up.

Investigator assessment of study lesion bleeding, ulceration and infection will be performed at Day 1 prior to initiation of study treatment (i.e., baseline); at the end of each subsequent Treatment Cycle; at each Response Follow-up; and at Final Follow-up.

Comprehensive assessment of progression status (including assessment for the presence of visceral and nodal metastases) will be performed at Screening; at the end of the Initial Treatment Course; every 12 weeks thereafter; and at Final Follow-up. Clinical evaluation will be performed at 28-day intervals during the treatment phase of the study, commencing at the end of the first Treatment Cycle, and at any unscheduled visits during follow-up. Clinical evaluation of subjects undergoing long-term Response Follow-up will continue through Week 37 (for subjects receiving PV-10 or chemotherapy) or Week 38 (for subjects receiving talimogene laherparepvec). Assessment and documentation of adverse events and concomitant medications should be done at each study evaluation.

STUDY ENDPOINTS

Primary Endpoint

The primary study endpoint is progression-free survival (PFS) in the intent-to-treat (ITT) population. Assessment of progression will be performed by an Independent Review Committee (IRC) based on Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1 criteria. Events signaling progression include increase in size and/or number of Study Lesions, onset of visceral metastatic disease or death. Clinical evaluation will be performed at 28-day intervals during the treatment phase of the study, commencing at the end of the first Treatment Cycle, and at any unscheduled visits during follow-up. Comprehensive assessment of progression status will be performed at the end of the Initial Treatment Course and every 12 weeks thereafter until disease progression or study discontinuation occurs.

Secondary Endpoints

Efficacy

All secondary endpoints involving disease response and progression will be based on the IRC determination.

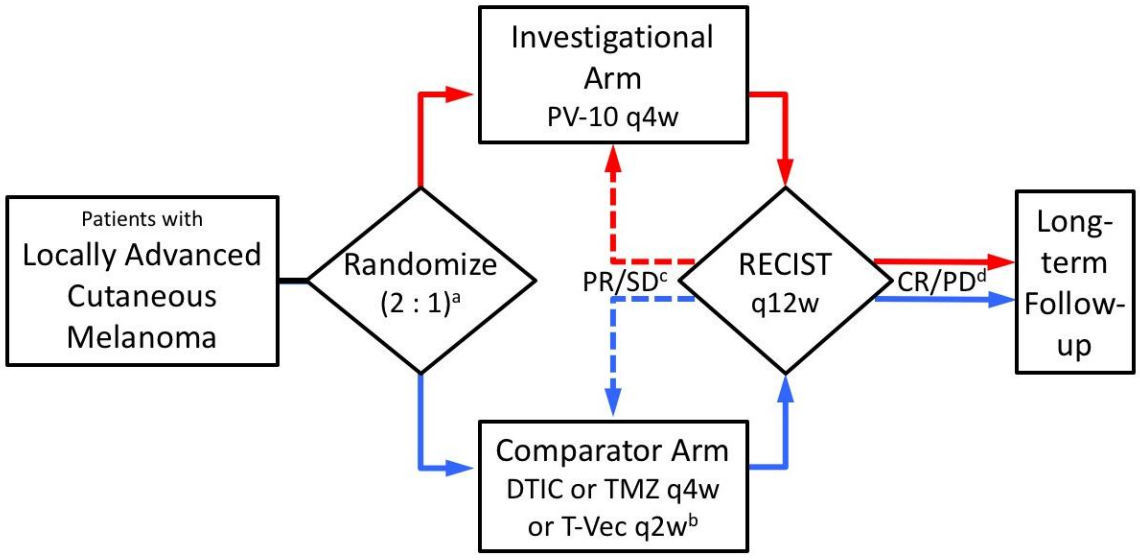
- Complete response rate (CRR) assessed according to RECIST ver. 1.1 criteria at the end of the Initial Treatment Course and every 12 weeks thereafter until disease progression or study discontinuation.
- Duration of complete response assessed based on the time from first documentation of complete response until disease progression.
- Overall survival (OS).

Safety

Safety and tolerability will be assessed by monitoring the frequency, duration, severity and attribution of adverse events and evaluating changes in laboratory values and vital signs.

STUDY SCHEMATIC

The study design schematic is presented below.



a. 225 patients randomized 2:1 (stratified for prior immune checkpoint inhibition)
b. T-Vec (talimogene laherparepvec) repeated after 3 weeks then q2w
c. Repeat treatment cycle if PR / SD
d. Cross-over allowed upon documented PD in comparator arm

ELIGIBILITY CRITERIA

Inclusion Criteria

1. Age 18 years or older, male or female.
2. Histologically or cytologically confirmed melanoma.
3. Recurrent, satellite or in-transit locally advanced cutaneous, subcutaneous, soft tissue, or superficial or palpable nodal melanoma metastases (i.e., AJCC 2009 Stage IIIB, Stage IIIC or Stage IV M1a).
4. At least 1 measurable Target Lesion that can be accurately measured by calipers, computed tomography (CT) or magnetic resonance imaging (MRI) consisting of at least one of the following:
   - at least one cutaneous lesion (each lesion ≥ 10 mm in longest diameter or up to 5 lesions having a sum of longest diameters ≥ 10 mm); and/or
   - at least one subcutaneous or soft tissue lesion (each lesion ≥ 10 mm in longest diameter by CT or MRI); and/or
   - at least one superficial or palpable nodal lesion (each lesion ≥ 15 mm in short axis diameter by CT or MRI).
5. No lesion > 50 mm in longest diameter; and no more than 50 lesions.
6. Estimated required PV-10 dose ≤ 15 mL (based on total tumor burden).
7. Performance Status: ECOG 0-2.
8. Not a candidate for treatment with an immune checkpoint inhibitor (e.g., failed or did not tolerate prior therapy, or due to co-morbidities, pre-existing autoimmune disease, drug unavailability or standard of care).
9. Not a candidate for targeted therapy with BRAF or combined BRAF/MEK inhibitors (e.g., failed or did not tolerate prior therapy, BRAF V600 wild-type or due to drug unavailability or standard of care).
10. Clinical Laboratories (per central laboratory results):
    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L and platelet count ≥100 x 10^9/L.
    - Creatinine ≤ 3 times the upper limit of normal (ULN).
    - Estimated creatinine clearance (CrCl) or estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2.
    - Total bilirubin ≤ 3 times the upper limit of normal (ULN).
    - Aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) ≤ 5 times the upper limit of normal (ULN).
    - LDH ≤ 2 times the upper limit of normal (ULN).
11. Thyroid function abnormality ≤ Common Toxicity Criteria for Adverse Effects (CTCAE) Grade 2.
12. Candidate for at least one comparator drug:
    - Subjects must be candidates for at least one of the designated comparator drugs.

Exclusion Criteria

1. Presence or history of visceral metastasis (including lung metastases) or presence of bone metastases.
2. Presence of more than 50 melanoma lesions.
3. Radiation therapy to any Study Lesion within 6 weeks of initial study treatment.
4. Chemotherapy or other systemic cancer therapy within 4 weeks of initial study treatment (6 weeks for nitrosoureas or mitomycin), or regional chemotherapy (limb infusion or perfusion) within 12 weeks of initial study treatment.
5. Immunotherapy for cancer within 4 weeks of initial study treatment.
6. Local treatment (e.g., surgery, cryotherapy, laser ablation, or intralesional oncolytic therapy) to any Study Lesion within 4 weeks of initial study treatment.
7. Anti-tumor vaccine therapy within 6 weeks of initial study treatment.
8. Investigational drug therapy within 4 weeks of initial study treatment.
9. Concurrent or Intercurrent Illness:
    - Impaired wound healing or other extremity complications due to diabetes mellitus in subjects whose Study Lesions are located in an extremity.
    - Severe peripheral vascular disease in subjects whose Study Lesions are located in an extremity.
    - Significant concurrent or intercurrent illness, psychiatric disorders, or alcohol or chemical dependence that would, in the opinion of the Investigator, compromise the subject's safety or compliance or interfere with interpretation of study results.
    - Uncontrolled thyroid disease or cystic fibrosis.
    - Clinically significant acute or unstable cardiovascular, cerebrovascular (stroke), renal, gastrointestinal, pulmonary, immunological, endocrine, or central nervous system disorders.
10. Pregnancy:
    - Female subjects who are pregnant or lactating.
    - Female subjects who have positive serum pregnancy test taken within 21 days prior to initiation of study treatment.
    - Female subjects of child-bearing potential who are unwilling to use highly effective contraception (e.g., combined (estrogen and progestogen containing) or progestogen-only hormonal contraceptives, intrauterine devices, bilateral tubal ligation, vasectomized partner, sexual abstinence or equivalent measures) for the duration of study treatment and for 6 months after cessation of study treatment.
    - Sexually active male subjects with female partners of childbearing potential, unless willing to take contraceptive measures for the duration of study treatment and for 6 months after cessation of study treatment.
11. Contraindication for all comparators:
    - Subjects with contraindications to all of the designated comparator drugs.

STUDY DURATION

Subjects will remain in the Treatment and Response Follow-up phases of the study until onset of disease progression, unmanageable toxicity or study termination by the Sponsor. Subjects will also be monitored for survival until death, loss to follow-up, withdrawal of consent or study termination by the Sponsor. The estimated study duration is approximately 60 months.

STUDY CENTERS

Subjects will be enrolled from approximately 60 total sites in North America, South America, Oceana, Asia and Europe. Sites in other geographical regions may be added at the Sponsor's discretion.

2 STUDY BACKGROUND

The incidence of cutaneous melanoma has steadily risen by 3%-8% annually over several decades and now represents a lifetime risk of 1 in 50 men in the United States and 1 in 25 men in Australia [1, 2]. In 2018 an estimated 91,270 new cases of melanoma will be diagnosed and about 9,320 patients will die of the disease in the United States [3]. It is estimated that 82-85% of melanoma patients present with localized Stage I and II disease, 10-13% with regional Stage III disease and 2-5% with Stage IV metastatic disease [4]. Five-year survival for Stage III patients ranges from approximately 24% (gross nodal disease) to 70% (microscopic nodal disease) dropping to approximately 10% for Stage IV M1c patients [4, 5].

Standard treatment of primary melanoma is wide local excision, while lymphadenectomy is employed for accurate staging and treatment of regional nodal metastases. Treatment of advanced melanoma involving visceral metastases with high-dose interleukin-2 [6-8] or with dacarbazine, temozolomide or paclitaxel with or without cisplatin or carboplatin chemotherapy has demonstrated response rates under 20% [9-12]. Biochemotherapy with dacarbazine or temozolomide chemotherapy in combination with interferon alpha-2b and IL-2 has produced slightly improved response rates and progression-free survival in advanced metastatic melanoma but is substantially more toxic than chemotherapy alone with no survival benefit [13-15]. The recently approved agents ipilimumab (IPI), a novel immune checkpoint inhibitor directed to the cytotoxic T lymphocyte antigen-4 (CTLA-4), and vemurafenib (VEM), an inhibitor of the protein kinase BRAF in patients with the BRAF V600E mutation, have shown modest survival benefit in patients with unresectable visceral metastatic disease [16-18]. Second-generation immune checkpoint inhibitors such as pembrolizumab have exhibited improved response with lower toxicity but may exhibit lower efficacy in Stage III patients (i.e., 27% objective response rate (ORR) for M0 patients vs 34% for the ITT population consisting mostly of M1a-M1c patients) [19].

Despite recent gains in the treatment of patients with visceral metastases, Stage IIIB, Stage IIIC and Stage IV M1a patients with regional recurrent, satellite or in-transit cutaneous, subcutaneous, soft tissue, or superficial or palpable nodal disease (i.e., locally advanced cutaneous melanoma) present a continuing clinical challenge in the management of their disease. Regional hyperthermic isolated limb perfusion (ILP) or infusion (ILI) of melphalan may be used to treat regional limb metastases [20, 21]. Intralesional injection with Bacillus Calmette-Guérin (BCG), interferon-alpha immunotherapy or laser ablation are sometimes used to achieve regional control of the cutaneous disease even though limited tumor responses are obtained [22, 23]. Topical imiquimod has also been used to manage superficial lesions in this patient population [24]. Radiation therapy as adjuvant treatment is an option, but it is relatively ineffective in controlling existing regional disease and has no demonstrated effect on overall survival [25, 26]. The observation that melanoma may be susceptible to immunologic response has led to efforts to develop autologous and allogeneic vaccines [27-29] as well as in situ treatment methods capable of stimulating an anti-tumor immune response [30-32]. Unfortunately, these methods generally have been less successful than desired. Dacarbazine, temozolomide or paclitaxel chemotherapy is widely used globally as

standard of care in these patients [33-35]. However, because these chemotherapy agents only provide infrequent, limited, short-term control of disease spread, their use is often recommended in context of a clinical trial [36]. Likewise, ipilimumab, pembrolizumab and agents directed toward the BRAF V600 mutation, such as vemurafenib, have demonstrated minimal rates of objective response or delay of progression [16-19]. Patients who (1) have failed or are not otherwise candidates for targeted therapy and (2) have failed or are not otherwise candidates for ipilimumab or another immune checkpoint inhibitor have extremely limited options. Recent approval of talimogene laherparepvec in the United States provides patients with an additional option (intralesional oncolytic viral therapy) [37], although its relevance is not universally endorsed.

The lack of definitive treatment options for such patients is highlighted by the recommendation of clinical trial participation by the National Comprehensive Cancer Network [36].

2.1 Study Rationale

Patients with locally advanced cutaneous melanoma continue to present significant clinical challenges in the management of their disease. These patients are prone to frequent locoregional recurrence and eventual spread of their disease to other cutaneous, subcutaneous, soft tissue or nodal locations. Often there is a period of years prior to onset of life-threatening visceral metastasis, a time interval during which one or more locoregional interventions are appropriate.

Current therapies for locally advanced cutaneous melanoma afford marginal benefit in patients with locoregional disease. All of these therapeutic options (e.g., hyperthermic perfusion/infusion with melphalan, intralesional injection with BCG or IFN, local ablation therapy, radiotherapy, oncolytic viral therapy or systemic therapy) have shown at best modest efficacy in control of either symptoms or progression of the disease.

A well-tolerated locoregional therapy that elicits a durable response would provide significant clinical benefit to these patients because it represents both symptom control and delay of progression to more advanced locoregional disease while possibly forestalling eventual distant or visceral metastasis.

Accordingly, assessment of clinical benefit in terms of progression-free survival (PFS) is a meaningful approach for these patients. Assessment of clinical benefit in terms of complete response rate (CRR) provides a logical secondary approach since it addresses both elimination of potentially symptomatic or otherwise bothersome lesions and the avoidance of progression to a more symptomatic state. Assessment of change in disease symptoms provides a basis for supporting the clinical relevance of objective response parameters (i.e., PFS and CRR). While an overall survival (OS) endpoint may be problematic for this subset of patients who may exhibit a lengthy duration between clinical presentation of their regional cutaneous disease and progression to disseminated systemic disease, this standard endpoint

may have relevance for assessment of safety and efficacy in the context of a randomized controlled trial (RCT) with long term survival follow-up.

2.2 Investigational Drug

The drug product to be investigated in this clinical trial is PV-10 (10% w/v rose bengal disodium in 0.9% saline for injection).

PV-10 is being studied for intralesional (IL) injection into solid tumors, where it may elicit both local oncolytic and systemic anti-tumor immune responses. PV-10 is preferentially retained in tumor cells while rapidly cleared from surrounding normal tissue, thereby having the potential to induce local tumor oncolysis while sparing normal tissue function and appearance. Release of tumor antigens upon local oncolysis may stimulate an anti-tumor immune response that may augment local and systemic response, including tumor-specific reactivity in circulating T cells in treatment-refractory patients [38, 39].

The indication under investigation in this study is treatment of locally advanced cutaneous melanoma in patients who (1) are not candidates for targeted therapy and (2) are not candidates for an immune checkpoint inhibitor.

2.3 Preclinical Experience

The preclinical rationale for efficacy is based primarily on IL PV-10-induced tumor oncolysis in murine models of melanoma, breast carcinoma, hepatocellular carcinoma, multi-drug resistant small cell lung carcinoma and prostate adenocarcinoma using human and murine cell line xenografts or homografts [38, 40-47]. These studies demonstrated that PV-10 can elicit selective tumor oncolysis when injected at a dose of approximately 0.5 mL/cm^3 (i.e., 50 mg RB/cm^3) lesion volume. Necrosis induced from IL PV-10 is largely confined to injected tumors, sparing normal perilesional tissue. Histological examination of tumor and perilesional tissue from mice obtained at terminal sacrifice is characterized by minimal perilesional inflammation and damage with negligible residual PV-10 noted in perilesional tissue compared to tumor undergoing necrosis.

Evidence using immunocompetent and immune-deficient mice with murine cell homografts indicates that IL PV-10 oncolysis of injected tumors can induce a potent host-mediated tumor-specific immune response against non-treated tumors (i.e., bystander effect) [38-39, 48-52]. This bystander effect appears to result from exposure of the treated host to antigenic tumor fragments released to the immune system upon oncolysis of treated tumors. For instance, oncolysis of subcutaneous Hepa1-6 hepatocellular carcinoma tumors with IL PV-10 led to complete eradication of injected tumors and partial or complete regression of uninjected synchronous tumors on the opposite flank, while control injections with saline had no effect on either tumor. Similarly, oncolysis of subcutaneous B16-F10 melanoma tumors led to dramatic reduction in the number of synchronous lung metastases vs control animals [38, 53]. Recruitment of dendritic cells to tumor-draining lymph nodes within 24 hours of

tumor oncolysis with PV-10 appears to be an intermediate step in eliciting anti-tumor T cell response [39, 54].

Following IL PV-10 injection in mice, rose bengal is preferentially retained in tumor tissue for more than 24 hours at levels 3-10-fold greater than in perilesional tissue, and persists in tumor tissue for over 72 hours while being rapidly cleared from surrounding normal tissue [55]. Approximately 50% of rose bengal is cleared from normal tissue within 6 hours with only approximately 4% of the initial dose present in normal issue after 72 hours. The clearance half-life ($t_{1/2}$) of rose bengal following subcutaneous administration to normal tissue has been estimated to be about 7 hours. The whole body clearance $t_{1/2}$ was 2 days with peak blood concentrations at about 30 minutes. The elimination $t_{1/2}$ was 1.2 days, which is similar in magnitude to the whole body clearance [56].

Rose bengal is not metabolized in humans and is excreted via the biliary system, primarily into the intestines; however, if there is marked impairment of liver function or saturation of the hepatic excretion process it is also excreted via the kidneys [57-61].

Non-clinical testing of CYP and UGT enzyme inhibition using cryopreserved human hepatocytes showed direct inhibitory effects of rose bengal at relatively high (50 – 78 µg/mL) and similar IC_{50} values for all enzyme systems assessed [62]. Because these IC_{50} values are approximately 10-fold higher than the anticipated maximum plasma concentrations that have been observed after the highest total intralesional dose of PV-10, Provectus believes that there is a low risk of clinically significant interaction upon co-administration of PV-10 with CYP / UGT modulating drugs.

Toxicity studies show that PV-10 administered subcutaneously in mice at 50-500 mg RB/kg is well tolerated with no histologic evidence of tissue necrosis [63]. Direct intrahepatic injection of PV-10 at 20 mg RB/kg in dogs resulted in focal necrosis that was limited to the injection site with no evidence of adverse effects to adjacent hepatic parenchyma and no evidence of systemic adverse effects [64]. PV-10, tested in the Bacterial Reverse Mutation Assay, was not mutagenic under normal laboratory conditions or when protected from incidental light exposure [65]. Genotoxicity assessment of RB in rats was negative at doses up to and including 150 mg/kg/day over three successive days [66]. Assessment of potential adverse effects on embryo and fetal development in rats was complicated by injection site toxicity upon daily intravenous administration to the tail vein on 12 consecutive days: a dosage level of 2 mg/kg/day was considered to be the no observed adverse effect level (NOAEL) for maternal toxicity while 8 mg/kg/day was considered to be the NOAEL for embryo/fetal development [67].

2.4 Melanoma Clinical Trial Experience

Provectus has an active Investigational New Drug Application (IND 70539) with the United States Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) Division of Oncology Products 2 (DOP2) covering IL study of PV-10 for oncolysis of cutaneous and hepatic solid tumors.

2.4.1 Phase 1

In an open-label, single-arm phase 1 study PV-10-MM-01, PV-10 was injected into 114 melanoma lesions in 20 subjects [68]. Additionally, 43 measurable untreated lesions (20 subjects) were monitored for assessment of bystander response. PV-10 was administered by single intralesional injection to uniformly infiltrate each lesion at a dose of 0.5 mL / cm^3 lesion volume (V_L), calculated according to V_L = (length • width • height) / 2. Doses ranged from 11 to 1500 mg RB (i.e., 0.11 to 15.0 mL PV-10). The mean and median doses per subject were 266 mg RB (2.66 mL PV-10) and 121 mg RB (1.21 mL PV-10) respectively. Subjects were followed for 12-24 weeks after PV-10 injection.

2.4.1.1 Safety

Most adverse events were mild-to-moderate grade, and there were no deaths or any treatment or study discontinuations for drug-related adverse events. The most common adverse events at least possibly related to study treatment were injection site pain (reported by 75% of subjects) followed by local inflammation or cellulitis (25%), injection site pruritus (15%) and injection site blistering, erythema and dryness at 10% incidence.

Two subjects experienced photosensitivity reactions. One subject experienced a mild photosensitivity reaction limited to the treated limb (lower extremity) upon exposure of the skin to direct sunlight while gardening within the first week following treatment. This reaction resolved spontaneously within three weeks without desquamation, blistering or other sequelae. The other subject experienced a severe generalized photosensitivity reaction in skin receiving prolonged exposure to bright sunlight during car travel home within 4 hours following treatment. This reaction resolved spontaneously within 2 weeks with mild desquamation but no blistering or other sequelae. This subject, a 73-year-old female, received PV-10 to two lesions (1300 mg and 200 mg RB) and was taking hydrochloro-thiazide (a potential photosensitizer) at the time of the adverse event, which may have contributed to the reaction [69]. The only other severe adverse event was transient severe injection site pain experienced by one subject following PV-10 injection.

An additional subject exhibited moderately elevated thyroid stimulating hormone (TSH) levels at screening (1.3 x Upper Limit of Normal [ULN]) which increased to 3.5 x ULN at day 14 post-treatment and then spontaneously returned to baseline by week 4 and remained stable through final follow-up. Free T3 and Free T4 levels were within normal limits at screening and remained stable throughout the study interval. The subject required no intervention and remained asymptomatic throughout the study interval. Contribution from an undiagnosed thyroid abnormality in this subject could not be ruled out based on elevated TSH levels at screening.

2.4.1.2 Efficacy

Forty percent of the study subjects achieved an objective response of their Target Lesions based on modified RECIST criteria (i.e., overall complete response [CR] or partial response [PR] of treated Target Lesions at the end of the study interval) and 75% achieved disease

control (i.e., overall CR, PR or stable disease [SD]). Fifteen percent of the subjects achieved an overall objective response and 55% achieved disease control of their monitored untreated Bystander Lesions.

Among those subjects exhibiting an objective response of their Target Lesions to PV-10, 25% also experienced an objective response of their Bystander Lesions, and 100% experienced disease control in these lesions. In contrast, among those subjects failing to achieve an objective response of their Target Lesions, only 8% experienced an objective response of their Bystander Lesions while 75% experienced disease progression in their Bystander Lesions. The difference in rate of disease control between these two groups was highly significant ($p = 0.001$). In summary, response of Bystander Lesions as a function of objective response of Target Lesions was significantly better in the positive response cohort relative to the negative response cohort.

2.4.2 Phase 2

Provectus has also completed an 80 subject, open-label, single-arm phase 2 study (protocol PV-10-MM-02) involving intralesional injection of PV-10 into 1-10 measurable cutaneous or subcutaneous melanoma Target Lesions and up to 10 additional cutaneous or subcutaneous melanoma Non-Target Lesions (up to 20 total injected lesions per subject) administered over 1-4 treatment cycles not less than 4 weeks apart [70, 71]. The protocol allowed an additional one to two measurable cutaneous or subcutaneous melanoma Bystander Lesions to be left untreated at the investigator's discretion and followed for assessment of bystander response. PV-10 was administered to uniformly infiltrate each lesion at a dose of 0.5 mL / cm^3 lesion volume, with a minimum dose of 0.1 mL per injection. Thirty nine subjects (572 lesions) underwent one PV-10 treatment cycle, 26 subjects (202 lesions) underwent two treatment cycles, 16 subjects (48 lesions) underwent three treatment cycles and 3 subjects (5 lesions) underwent four treatment cycles. In the first treatment cycle, 636 lesions were injected, while 245 lesions injected in the second cycle (week 8), 92 in the third cycle (week 12) and 167 in the fourth cycle (week 16). The median dose among the 80 subjects was 347 mg RB per subject, ranging from 30 to 2600 mg RB. Forty-five untreated Bystander Lesions among 42 subjects were monitored for bystander response. Study subjects were followed for up to 52 weeks after their initial PV-10 injection.

2.4.2.1 Safety

All subjects experienced one or more adverse events at some point during the study. Most events were mild-to-moderate grade, while 15% of subjects had at least one Grade 3 adverse event deemed to be at least possibly related to treatment. There were 3 treatment discontinuations and one study discontinuation reported for drug-related adverse events. The most common adverse events at least possibly related to study treatment were injection site pain (reported by 80% of subjects) followed by injection site edema (41%), vesicles (39%), skin discoloration (31%), and swelling (28%). Injection site pruritus (21%), erythema (14%), infection (8%), inflammation (8%) and photosensitivity reaction (8%), along with headache (16%), were the other most common adverse events.

Severe adverse events at least possibly related to study treatment involved 10 incidences (12% of subjects) of severe injection site pain following PV-10 administration, along with single incidences of injection site cellulitis, erythema, infection, necrosis, swelling, peripheral edema and vesicles, and single incidences of dysphagia due to neck or facial swelling proximate to injected lesions and of general photosensitivity reaction. There were 6 reports (8%) of mild (3) or moderate (3) photosensitivity at the injection site and one report (1%) of a severe generalized photosensitivity reaction following PV-10 administration. Six subjects (8%) experienced serious adverse events that required hospitalization. Two subjects were hospitalized for moderate or severe neck or facial swelling adjacent to injected lesions, leading to significant dysphagia in one of the subjects; one subject experienced severe skin flap necrosis adjacent to a treated subcutaneous melanoma lesion; one subject experienced moderate pyrexia and injection site pain followed by moderate injection site ulceration; one subject experienced severe locoregional blistering and possible infection of the injected limb; and one subject experienced a severe photosensitivity reaction upon exposure to direct and indirect sunlight following PV-10 administration to metastatic lesions on a lower extremity. All of these adverse events resolved without sequelae. In 5 of these 6 cases the adverse events accompanied larger than average exposure to PV-10 (i.e., 5-15 mL). No life threatening or fatal adverse events at least possibly related to the study treatment were reported, and there were no reports of iodide thyrotoxicity or iodide sensitivity.

2.4.2.2 Efficacy

Fifty-one percent of study subjects achieved an objective response of their Target Lesions (i.e., 26% CR and 25% PR) based on modified RECIST criteria and 69% achieved disease control (i.e., CR, PR or SD). Thirty-three percent of the subjects achieved an overall objective response (26% CR, 7% PR) and 50% achieved disease control of their monitored untreated Bystander Lesions. Response rates among Stage III subjects were significantly higher than those of Stage IV subjects, with 60% of Stage III subjects achieving an objective response in their Target Lesions vs 22% of Stage IV subjects; Bystander Lesion response showed similar trends, with 40% objective response observed in Bystander Lesions among Stage III subjects vs 17% among Stage IV subjects. A key difference between Stage III and Stage IV subjects was duration of time under study treatment: 11% of Stage III subjects failed to remain on study until the first planned disease assessment at 8 weeks whereas 39% of Stage IV subjects failed to reach this milestone, primarily due to early global deterioration.

Bystander Lesion response was highly correlated with successful oncolysis of a subject's Target Lesions. Among those subjects exhibiting an objective response of their Target Lesions to PV-10, 61% also experienced an objective response of their Bystander Lesions. In contrast, among those subjects failing to achieve an objective response of their Target Lesions, only 18% experienced an objective response of their Bystander Lesions. In summary, as observed in phase 1, response of Bystander Lesions was significantly higher in PV-10 responsive subjects relative to non-responsive subjects.

Exploratory analysis of PFS (by mRECIST) as a function of untreated disease burden yielded results consistent with those observed for objective response rate, with a mean of at least 9.8 months for Stage III subjects having all known tumor burden treated and at least 8.9 months for Stage III subjects with only their bystander lesion(s) untreated. When multiple lesions were untreated in Stage III subjects mean PFS dropped to 6.0 months, while for Stage IV subjects and those with extensive untreated disease burden, PFS fell to 2.6 months. PFS for the first two groups were significantly longer than that of the final group upon pairwise multiple comparison ($p < 0.05$ and $p = 0.04$, respectively). Early global deterioration of Stage IV subjects appears to play a major role in these differences in response [71].

The pattern of regression of cutaneous Bystander Lesions was replicated in visceral lesions in a number of Stage IV subjects. Twenty subjects in the phase 2 study presented evidence of nodal or visceral disease that was documented at screening. Overall, 9 of 20 subjects (45%) exhibited regression or stasis of these untreated visceral lesions. This rate is similar to the rate of response observed in cutaneous Bystander Lesions.

The correlation of regression of untreated cutaneous, subcutaneous and visceral lesions with oncolysis of PV-10 injected lesion supports nonclinical evidence of a beneficial immunologic response stimulated by PV-10 oncolysis [38]. It is possible that progression of micrometastases in locally advanced melanoma patients can be forestalled due to this reported bystander effect after local administration. This effect appears to be maximized when all existing disease is treated.

2.4.2.3 Extended PV-10 Treatment

Due to the limited dosing schedule allowed under protocol PV-10-MM-02, nine subjects withdrew early from that study to receive additional PV-10 treatment of new or recurrent locoregional disease under continuation protocol PV-10-MM-02X. This allowed potential extended use of PV-10 for locoregional management of melanoma to be evaluated at intervals of 4 weeks or greater.

An example of clinical benefit possible with extended use of PV-10 is provided by subject 0601 / AJD, male, age 79, with Stage IIIC (N2) recurrent scalp and periauricular metastases at enrollment (5 years after initial diagnosis). This subject had previously undergone multiple surgical excisions, completion lymph node dissection and 30 Gy adjuvant radiation therapy. He received IL PV-10 to 13 lesions at study Day 0 (two lesions were left untreated as Bystander Lesions); this was followed by injection of 15 lesions at study Week 8 and injection of 10 lesions at Week 16. Due to the presence of residual locoregional disease, he withdrew from protocol PV-10-MM-02 at Week 24 to receive three additional cycles of PV-10 at Week 32 (9 lesions injected), Week 43 (8 lesions injected) and Week 52 (4 lesions injected) under protocol PV-10-MM-02X. At Week 77 there was no evidence of melanoma; he expired at Week 164 from a cardiovascular co-morbidity without recurrence of his melanoma.

As of enrollment closure on June 30, 2016, 180 melanoma patients had been enrolled under expanded access protocol PV-10-EA-02 (Open Label Expanded Access for Investigational Use of PV-10 in Patients Who are not Eligible for an Existing PV-10 Clinical Trial, for Whom There is no Comparable or Satisfactory Alternative Therapy and Whom, in the Opinion of the Investigator, May Benefit from PV-10 Administration). This protocol allowed repeat administration of PV-10 at intervals of 2 weeks or greater (mean 1.8 treatment courses for the first 135 participants, range 1 – 8, with 49 patients receiving a single course, 27 receiving two courses, 14 receiving three courses, 1 receiving 4 courses and 2 receiving 8 courses). Based on reports of serious adverse events among these patients, the adverse event profile for these repeat administrations is similar to that observed in phase 2 study PV-10-MM-02.

2.4.2.4 Pharmacokinetics

Plasma specimens from 10 subjects participating in the phase 2 clinical study of PV-10 (10% RB) for treatment of metastatic melanoma (study PV-10-MM-02) were assayed for RB using a GLP-validated HPLC/fluorescence bioassay. An apparent bi-exponential pharmacokinetic profile was observed indicating a rapid initial distribution/absorption phase ($C_{initial}$ = 542 ng/mL; $t_{1/2,D/A}$ = 5.9 hr; $k_{D/A}$ = 0.0020 min^{-1}) and an extended elimination phase ($t_{1/2,E}$ = 100 hr; k_E = 0.00012 min^{-1}) following IL PV-10 injection [70, 72]. These results are consistent with prior literature and nonclinical toxicology data and indicate (a) PV-10 exhibits prolonged retention within injected tumors and (b) that cumulative toxicity is unlikely for repeat dosing at intervals of 7 days or greater due to rapid clearance from the bloodstream.

To provide context for the maximum systemic exposure upon intralesional injection of PV-10 relative to historic use of 100 mg rose bengal as an intravenous liver function diagnostic [57-61], Provectus conducted a clinical trial evaluating the pharmacokinetic profile and safety of rose bengal in 8 healthy volunteers receiving a single 100 mg intravenous dose of rose bengal (study PV-10-PK-01) [73]. The dose level and manner of administration were chosen to mimic historic human dosing as a liver function diagnostic and the results were compared to pharmacokinetic data obtained in patients receiving intralesional PV-10. Peak plasma concentrations of and rose bengal (mean of 33.8 µg/mL) were detected at the first sampling point (5 min) after intravenous administration and declined rapidly over the first hour, with approximately 93% of total area under the curve occurring within 3 hours of administration. The mean peak plasma concentration of rose bengal administered intralesionally to melanoma patients (study PV-10-MM-02) was 2.0 µg/mL, 17-fold lower than that of the healthy volunteers (study PV-10-PK-01). One melanoma patient received the maximum dose (1498 mg) and experienced a similar systemic exposure (2.6 µg/mL). The maximum exposure observed in melanoma patients (18.0 µg/mL) was almost 2-fold lower than that of the healthy volunteer study. The single 100 mg intravenous dose of rose bengal in study PV-10-PK-01 resulted in no evidence of treatment-emergent safety signals based on adverse events, clinical laboratory, vital signs, ECG and infusion site evaluations.

2.5 IL PV-10 Dose Rationale

The clinical dosing schema for PV-10 is unique to the intralesional route of administration. It was derived from *in vivo* nonclinical pharmacology studies and is based on a space filling model of uniform exposure of tumor tissue to rose bengal via intralesional injection while attempting to minimize the amount of available extravasate that is absorbed into systemic exposure. A rose bengal concentration of 10% was determined to be the minimum concentration that had consistent tumor necrotic effects in the murine pharmacology models. Thus, this concentration is constant and the dose is modified based on the volume of PV-10 (10% rose bengal) needed to fill approximately 50% of any given tumor volume. The total dose of PV-10 is determined by the size and number of lesions that are injected for a given patient (maximum allowed total dose of rose bengal is 1500 mg per treatment cycle) using this algorithm. Due to tumor necrosis and eschar formation, the injected tumor is not re-injected (if needed) until healing or regrowth of the tumor is evident at least 2-4 weeks after the prior injection. This dosing schema has been verified in 130 melanoma patients in phase 1 and 2 clinical testing and an additional 180 melanoma patients treated under expanded access [39, 68, 70, 71, 74-76].

The maximum human intralesional dose to be investigated in this clinical trial is 1500 mg RB (i.e., 15 mL PV-10, or 25 mg RB/kg at 60 kg body weight per treatment cycle).

Safety of rose bengal is well established from previous human experience with approved products given either parenterally as a diagnostic aid in determining liver function (Robengatope® sodium rose bengal ^{131}I injection USP administered intravenously, 112 mg RB/dose) or instilled into the eyes as a diagnostic for conjunctival epithelial abrasion (Minims™ rose bengal eye drops, 0.5 mg RB/dose). There are no known adverse events reported in the literature for the use of these rose bengal products.

The results of bridging rat toxicology studies conducted by Provectus are consistent with the published scientific literature indicating rose bengal does not have systemic toxicological effects, mutagenic potential, and female reproductive and development effects at relatively high exposures [66, 67]. This lack of toxicity was demonstrated at doses that represent exposures to rose bengal that are up to 20-fold greater than the maximum exposure attained in the treatment of the target patient population when given intralesionally (i.e., 500 mg/kg injected subcutaneously in female hairless mice [63] vs the 25 mg/kg maximum human intralesional dose in completed, current and proposed clinical studies of PV-10 based on 1500 mg rose bengal disodium administered to a 60 kg human; and an approximate 17-fold differential in mean peak plasma concentration for melanoma patients in Study PV-10-MM-02 vs healthy volunteers in pharmacokinetics Study PV-10-PK-01 [73]).

The maximal human intralesional dose of 1500 mg RB (i.e., 25 mg RB/kg at 60 kg body weight is about 13 times greater than the maximum Robengatope® intravenous dose (112 mg RB IV). This intralesional level has been shown to result in a peak systemic exposure comparable to that observed with the IV diagnostic, and has been successfully utilized in a number of clinical studies on several solid tumor types. Safety of the maximal IL dose of PV-

10 is supported by: (a) intravenous use at a dose of up to 400 mg RB in humans without adverse effect [61]; (b) safety of intravenous doses up to 40 mg RB/kg in rabbits [77]; (c) toxicology studies showing safety and tolerance of subcutaneous doses of ≥50 mg RB/kg in mice [63]; (d) human pharmacokinetic data demonstrating a bi-exponential pharmacokinetic profile with a rapid initial distribution/absorption phase ($t_{1/2,A}$ = 5.9 hr) and an extended elimination phase ($t_{1/2,E}$ = 100 hr) from metastatic melanoma lesions injected with PV-10 [72]; (e) safety data from completed phase 1 and phase 2 clinical trials involving 130 metastatic melanoma patients receiving intralesional PV-10 to 751 lesions at doses up to 1500 mg per treatment cycle [39, 68, 70, 71, 75]; and (f) safety data from another 180 melanoma patients receiving PV-10 under expanded access at doses up to 1500 mg per treatment cycle at intervals of 2 weeks of greater [74, 76].

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to assess the effectiveness of intralesional (IL) PV-10 compared to the Investigator's choice of systemic chemotherapy or intralesional oncolytic viral therapy in treating locally advanced cutaneous melanoma.

Effectiveness will be assessed by comparison of progression-free survival (PFS) between all intent-to-treat (ITT) subjects in the two study treatment arms.

3.2 Secondary Objectives

This study will also include assessment and comparison of all ITT subjects in the two study treatment arms with respect to:

- Complete response rate (CRR).
- Duration of complete response.
- Overall survival (OS).
- Safety and tolerability.

3.3 Exploratory Objectives

- Change from Baseline to each visit where the variable is assessed in each of the Skindex-16 self-assessment instrument domain scores.
- Change in Investigator assessed lesion bleeding from Baseline to each visit where clinical evaluation or assessment of progression status is performed.
- Change in Investigator assessed lesion ulceration from Baseline to each visit where clinical evaluation or assessment of progression status is performed.
- Change in Investigator assessed lesion infection from Baseline to each visit where clinical evaluation or assessment of progression status is performed.

4 STUDY DESIGN

This is a phase 3, international multicenter, open-label, randomized controlled trial of single-agent IL PV-10 versus Investigator's choice of systemic chemotherapy (dacarbazine [DTIC] or temozolomide [TMZ]) or intralesional oncolytic viral therapy (talimogene laherparepvec) to assess treatment of locally advanced cutaneous melanoma in patients who (1) are not candidates for targeted therapy and (2) are not candidates for an immune checkpoint inhibitor.

4.1 Study Subjects and Lesions

Patients eligible for the study must have locally advanced cutaneous melanoma, consisting of recurrent, satellite or in-transit locally advanced cutaneous, subcutaneous, soft tissue, or superficial or palpable nodal melanoma metastases (i.e., AJCC 2009 [4] Stage IIIB, Stage IIIC or Stage IV M1a). Eligible patients must have at least 1 measurable Target Lesion consisting of at least one cutaneous lesion (each lesion ≥ 10 mm in longest diameter or up to 5 lesions having a sum of longest diameters ≥ 10 mm), and / or at least one subcutaneous or soft tissue lesion (each lesion ≥ 10 mm in longest diameter by CT or MRI), and / or at least one superficial or palpable nodal lesion (each lesion ≥ 15 mm in short axis diameter by CT or MRI); no lesion > 50 mm in longest diameter; and no more than 50 total lesions at enrollment.

Patients with **pathological deep lymph nodes** should not be enrolled due to potential risk of serious complications for oncolytic therapy to these nodes (see protocol Section 6.1.3.1). If a patient with one or more pathological deep lymph node is enrolled in the study, review of eligibility by the Medical Monitor is required prior to randomization; patients deemed by the Medical Monitor not to be candidates for oncolytic therapy will be classified as screen failures.

Patients with existing or a history of visceral melanoma metastases are excluded.

Patients must (1) not be candidates for an immune checkpoint inhibitor and (2) not be candidates for treatment with targeted therapy.

Per RECIST ver. 1.1 criteria [78] a minimum of 1 and no more than 5 measurable lesions, representative of the subject's disease, will be identified by the Investigator ***prior to treatment randomization*** as **Target Lesions**. Target Lesions should be selected on the basis of their size (lesions with the longest diameter) and suitability for reproducible repeated measurement, study photography and/or radiologic assessment. Cutaneous lesions may be designated as Target Lesions if they are ≥ 10 mm in longest diameter or have a sum of longest diameters ≥ 10 mm. Subcutaneous or soft tissue lesions may be designated as Target Lesions if they are ≥ 10 mm in longest diameter as measured by CT or MRI. Superficial or palpable nodal lesions may be designated as Target Lesions if they are ≥ 15 mm in short axis diameter as measured by CT or MRI. If possible, Target Lesions should be at least 10 mm from any other lesion. If the largest lesion does not lend itself to reproducible measurement,

the next largest lesion that can be measured reproducibly should be selected as a Target Lesion. Each Target Lesion will be assigned a unique identifying number and will be tracked throughout the study (i.e., until subject withdrawal from the study or transition to Survival Follow-up).

All other lesions will be designated as **Non-Target Lesions** and will also be followed during the study interval. Although individual Non-Target Lesions will not be tracked, their individual measurements will be used for calculation of PV-10 or talimogene laherparepvec dose.

Target Lesions and **Non-Target Lesions** together will constitute **Study Lesions**.

The total tumor burden represented by all Study Lesions must allow for treatment of all Study Lesions with PV-10 during the initial treatment session (i.e., on study Day 1).

4.2 Subject Randomization and Treatment

A total of 225 eligible subjects will be randomized in a 2:1 ratio to the two treatment arms (i.e., PV-10 arm or comparator arm).

4.2.1 Randomization

Assignment of subjects to one of the two treatment arms will be made by an independent interactive web-based response system (IWRS) using a complete block randomization scheme stratified by prior immunotherapy treatment status (i.e., failure or naïve).

Randomization will occur **after** designation of Target Lesions at Screening and within 14 days prior to study Day 1.

4.2.2 PV-10 Arm

Subjects will receive IL PV-10 to all Study Lesions on study Day 1.

PV-10 should be re-administered at 28-day intervals until complete response, disease progression or study termination occurs.

4.2.3 Comparator Arm

Subjects will receive (a) intravenous dacarbazine or oral temozolomide, administered at consecutive 28-day intervals, or (b) intralesional talimogene laherparepvec administered on an initial 21-day interval followed by consecutive 14-day intervals, until complete response, disease progression or study termination occurs.

4.2.4 Toxicity Requiring Study Drug Discontinuation

Treatment with PV-10, systemic chemotherapy or intralesional talimogene laherparepvec will be permanently discontinued if toxicity requiring discontinuation of treatment occurs.

Toxicity requiring discontinuation of PV-10 is defined as: onset of Grade 3 or higher dysphagia, locoregional thrombus, iodide sensitivity or thyrotoxicity, or Grade 4 photosensitivity reaction, regardless of duration, occurring within 28 days after any dose of PV-10; or onset of any Grade 3 non-hematologic or Grade 4 hematologic toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) occurring within 28 days after any dose of PV-10 that is persistent for 14 days or longer.

Toxicity requiring discontinuation of dacarbazine or temozolomide is defined as: onset of a Grade 3 non-hematologic or a Grade 4 hematologic toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) occurring at any time from the first dose of dacarbazine or temozolomide and up to 28 days after the last dose that is persistent for 14 days or longer; or the requirement of more than 2 dose reductions.

Toxicity requiring discontinuation of talimogene laherparepvec is defined as: onset of a Grade 3 non-hematologic or a Grade 4 hematologic toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) occurring at any time from the first dose of talimogene laherparepvec and up to 28 days after the last dose that is persistent for 14 days or longer; or a delay of dosing by more than 4 weeks due to the occurrence of an adverse event that is considered related to talimogene laherparepvec. This includes delay due to immune-mediated events.

Any adverse event requiring a non-study therapy for melanoma will also constitute a toxicity requiring discontinuation of the study drug.

4.3 Primary Endpoint Assessment

The primary study endpoint is progression-free survival (PFS) in the intent-to-treat (ITT) population.

Assessment of progression will be performed by an Independent Review Committee (IRC) based on RECIST ver. 1.1 criteria [78] based on review of standardized study photographs, radiologic studies and pertinent clinical data. Events signaling progression include increase in size and/or number of Study Lesions, onset of visceral metastatic disease and death. Evaluation criteria are summarized in **Appendix G**.

4.3.1 Disease Progression

Disease progression is defined as one or more of the following:

- An increase of Target Lesion tumor burden of ≥ 20% over nadir (i.e., ≥ 20% increase in the sum of the longest diameters of Target Lesions at the assessment time *vs* smallest sum of longest diameters on study) and an absolute increase of at least 5 mm; Target Lesions 5 mm or less in diameter will be assigned a default diameter of 5 mm until they exceed this length by 1 mm or are no longer present [78].
- Unequivocal progression of existing Non-Target Lesions.
- The appearance of any Unequivocal New Lesions (defined below), including new nodal disease.[1]
- Any onset of visceral metastatic disease.[2]
- A disease-related deterioration of performance status to ECOG ≥ 3.
- Any Study Lesion requiring palliative surgery.

Deterioration of ECOG performance status due to non-melanoma related events will not be deemed progression.

Equivocal New Lesions are any small unconfirmed lesions that **present or are first observed after study Day 1** and **may indicate disease progression**. Continued study treatment (i.e., intralesional administration of PV-10 or talimogene laherparepvec or continuation of systemic chemotherapy) and follow-up evaluation are appropriate to clarify if such Equivocal New Lesions represent **unequivocal disease progression** (i.e., merit change of study therapy) (**Appendix G**). If any Equivocal New Lesion becomes unequivocal evidence of disease progression the date of progression will be deemed to have occurred at the date of the initial observation of the first of any such Equivocal New Lesions. Unequivocal New Lesions will be included with Non-Target Lesions for response classification.

Target Lesions exhibiting clinical manifestations of wound healing deemed by the Investigator to be at least possibly related to study treatment will be followed to resolution, provided any remaining disease does not qualify the subject for disease progression. If any Target Lesion cannot be accurately measured due to eschar, incomplete re-epithelialization or other similar condition of the lesion secondary to an apparent effect of study treatment that makes demarcation of lesion borders equivocal, the lesion will be deemed not evaluable (NE) at that visit. Patients thereby deemed NE may continue to receive study treatment while any lesions deemed NE are followed to resolution.

[1] Suspicious nodal disease in the absence of other unequivocal evidence of progression must be confirmed by histopathology or PET/CT prior to classification as disease progression and withdrawal of the subject from the study. If confirmed, the date of progression will be deemed to have occurred at the date of initial observation.

[2] Equivocal distant metastatic disease in the absence of other evidence of progression must be confirmed by histopathology or radiology, or by clinical assessment, at least 4 weeks after initial discovery, prior to withdrawal of the subject from the study. If confirmed, the date of progression will be deemed to have occurred at the date of initial observation. For suspected visceral disease, radiologic assessment at least 4 weeks after initial discovery is recommended.

Histological or cytological confirmation of complete response may be necessary in cases where it is difficult to distinguish residual disease from normal tissue. In such cases at least one representative residual lesion location should be investigated (e.g., by fine needle aspirate/biopsy, punch biopsy, excisional biopsy or incisional biopsy) before assigning a status of complete response. Assessment of tissue may be performed using histopathology or cytology.

4.3.2 Clinical Evaluation

Clinical evaluation will be performed at 28-day intervals during the treatment and response follow-up phases of the study, commencing at end of the first Treatment Cycle, and at any unscheduled visits during follow-up. This will include evaluation for all clinical changes in disease status indicative of progression (i.e., meriting change of study therapy). This evaluation is supplanted by **comprehensive assessment** of progression status at 12-week intervals (protocol Section 4.3.3).

4.3.3 Comprehensive Assessment of Progression Status

Comprehensive assessment of progression status will be performed at the end of the Initial Treatment Course and every 12 weeks thereafter until disease progression or study discontinuation occurs. This will include assessment for all changes in disease status meeting the study protocol definition of **disease progression** as defined in protocol Section 4.3.1.

4.3.4 Photodocumentation of Study Lesions

Standardized digital photography of Study Lesions will be performed at Screening, at study Day 1 prior to initiation of study treatment (i.e., baseline) and at all subsequent evaluations to accurately identify, track and confirm status of Study Lesions; additional photographic documentation will be performed at any unscheduled visits or visits where disease progression is clinically identified or suspected. Specifications for study photography are found in **Appendix E.**

4.3.5 Radiologic Documentation of Non-Cutaneous Study Lesions

Radiologic documentation of non-cutaneous Study Lesions (i.e., subcutaneous, soft tissue or nodal Study Lesions) will be performed at Screening and at all subsequent comprehensive assessments of progression status to accurately identify, track and confirm status of these Study Lesions. Computed tomography (CT) is recommended for non-cutaneous Study Lesions located in the chest, abdomen and pelvis. If non-cutaneous Study Lesions are located beyond the chest, abdomen and pelvis (e.g., in an extremity or the head or neck) scanning by CT (preferred) or by magnetic resonance imaging (MRI) must include all affected body regions. Consistent scanning methodology should be used throughout the study interval for each Study Lesion. Specifications for radiologic imaging are found in **Appendix D.**

4.4 Secondary Endpoint Assessments

4.4.1 Efficacy

All secondary endpoints involving disease response and progression will be based on the IRC determination.

- Complete response rate (CRR) of all ITT subjects will be assessed according to RECIST ver. 1.1 criteria [78] at the end of the Initial Treatment Course and every 12 weeks thereafter until disease progression or study discontinuation occurs.

- Duration of complete response, for all ITT subjects who achieve a complete response, will be assessed based on the time from first documentation of complete response until disease progression.

- Overall survival (OS) status of all ITT subjects will be assessed by telephone, personal contact (e.g., clinic visit) or other unequivocal documentation of subject status at 12-week intervals commencing at the time of subject transition to Survival Follow-up.

4.4.2 Safety

Safety and tolerability will be assessed by monitoring the frequency, duration, severity and attribution of adverse events and evaluating changes in laboratory values and vital signs.

Clinical assessment of the incidence and severity of systemic and locoregional adverse events (AEs) and suspected adverse drug reactions (ADRs) of all ITT subjects receiving PV-10 will be performed following each treatment with IL PV-10, at follow-up 7 days following each treatment, and at the completion of each Treatment Cycle.

For all ITT subjects receiving systemic chemotherapy, clinical assessment for AEs will be performed at the initiation of each Treatment Cycle and at the completion of each Treatment Cycle.

For all ITT subjects receiving talimogene laherparepvec, clinical assessment for AEs will be performed at the initiation of each Treatment Cycle and at the completion of each Treatment Cycle.

Adverse events, including laboratory abnormalities, will be graded by the Common Terminology Criteria for Adverse Events (CTCAE) and coded according to MedDRA 17.1 or higher terminology.

The subset of adverse events that are considered by the Investigator to have a possible, probable or certain relationship to study drug will be considered to be treatment-related adverse events. If the Investigator does not specify the relationship of the adverse event to

study drug, the adverse event will be considered to be treatment-related.

The following locoregional injection site reactions will be documented in the case report forms (CRFs) to assist in differentiating administration site conditions from locoregional or systemic events:

- Injection Site Edema
- Injection Site Erythema
- Injection Site Infection
- Injection Site Inflammation
- Injection Site Pain
- Injection Site Pruritus
- Injection Site Swelling
- Injection Site Vesicles

Laboratory tests (complete blood count, comprehensive metabolic panel and thyroid function) and vital signs (temperature, heart rate and blood pressure) will be performed at Screening, study Day 1, at the end of each Treatment Cycle, and at Final Follow-up.

Vital sign results will be reviewed for clinically notable abnormalities according to the criteria shown below.

Parameter	Low Threshold	High Threshold
Systolic blood pressure	< 85 mm Hg	≥ 160 mm Hg
Diastolic blood pressure	< 50 mm Hg	≥ 100 mm Hg
Heart rate	< 45 bpm	> 100 bpm

mm Hg: millimeters of mercury; bpm: beats per minute

4.5 Exploratory Endpoint Assessments

Exploratory analyses will be conducted based on patient reported outcome or Investigator determination.

- Change from Baseline to each visit where the variable is assessed in each of the patient reported Skindex-16 instrument domain scores.

- Change in Investigator assessed lesion bleeding, using the CTCAE grading schema for “skin and subcutaneous tissue disorders – other, bleeding.” Change will be assessed from Baseline to each visit where clinical evaluation or assessment of progression status is performed.

- Change in Investigator assessed lesion ulceration, using the CTCAE grading schema for “skin and subcutaneous tissue disorders – skin ulceration.” Change will be

assessed from Baseline to each visit where clinical evaluation or assessment of progression status is performed.

- Change in Investigator assessed lesion infection, using the CTCAE grading schema for "infections and infestations – skin infection." Change will be assessed from Baseline to each visit where clinical evaluation or assessment of progression status is performed.

4.6 Crossover of Subjects in the Comparator Arm

Subjects in the comparator arm who have completed at least 1 cycle of study treatment and who meet the study protocol definition of disease progression (protocol Section 4.3.1) but do not have evidence of visceral metastases or a decline in ECOG status to ≥ 3 will be eligible to enter the crossover portion of the study and receive PV-10 (protocol Section 7.4).

Subjects in the comparator arm who experience a toxicity requiring study drug discontinuation (protocol Sections 6.2.3, 6.3.3 or 6.4.4) but do not have evidence of visceral metastases or a decline in ECOG status to ≥ 3 will be eligible to enter the crossover portion of the study.

Candidates for crossover must meet all study inclusion and exclusion criteria for clinical laboratories, thyroid function, concurrent or intercurrent illness and pregnancy at the time of crossover.

The Investigator will submit a request for crossover, current clinical photographs and the most recent radiology data to initiate review by the Sponsor. Upon submission of progression status and study inclusion and exclusion criteria data to the Sponsor the Investigator will be notified within 7 days on the eligibility of the subject for crossover; progression status of these subjects will be reviewed periodically by the Independent Review Committee to confirm eligibility for crossover.

4.7 Clinical Trial Data Monitoring Committee

A Clinical Trial Data Monitoring Committee (CTDMC) will be implemented in compliance with FDA *Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees* dated March 2006 for analysis of efficacy and safety. It will consist of qualified individuals not involved with the conduct of the study. The establishment, composition, role, duty and responsibilities of the CTDMC will be addressed in the approved CTDMC charter. The Sponsor will not have voting membership on the CTDMC nor participate in closed session reviews of study data by committee members, but the rationale for any proposed change to the study or study conduct will be reviewed with the Sponsor. Responsibility for the study will continue to reside with the Sponsor.

4.8 Independent Review Committee

An Independent Review Committee (IRC) will determine disease progression status and tumor response by periodic blinded review of all study photographs, radiographic images (e.g., CT and MRI) and other relevant evidence documenting disease progression. These reviews will be reported to the CTDMC. The IRC will consist of qualified individuals not involved with the conduct of the study. The establishment, composition, role, duty and responsibilities of the IRC will be addressed in the approved IRC charter. The Sponsor will not have a representative on the IRC.

4.9 Interim Analysis

An interim assessment of efficacy and safety will be performed by the CTDMC when 50% of the events required for the primary endpoint (i.e., 81 disease progressions as defined in the study protocol) have occurred.

In order to control the overall type one error rate at the 5% level, with no adjustment to the alpha level at the final analysis, an alpha level of 0.00001 will be used for the interim analysis.

The CTDMC may recommend early stopping of the study at the interim analysis (based on efficacy) if the stratified log rank test comparing the PFS in the two treatment arms results in a two-sided p-value <0.00001.

4.10 Study Duration

Subjects will remain in the Treatment and Response Follow-up phases of the study until onset of disease progression, subject request to discontinue, unmanageable toxicity or study termination by the Sponsor.

Subjects will also be monitored for survival until death, loss to follow-up, withdrawal of consent or study termination by the Sponsor.

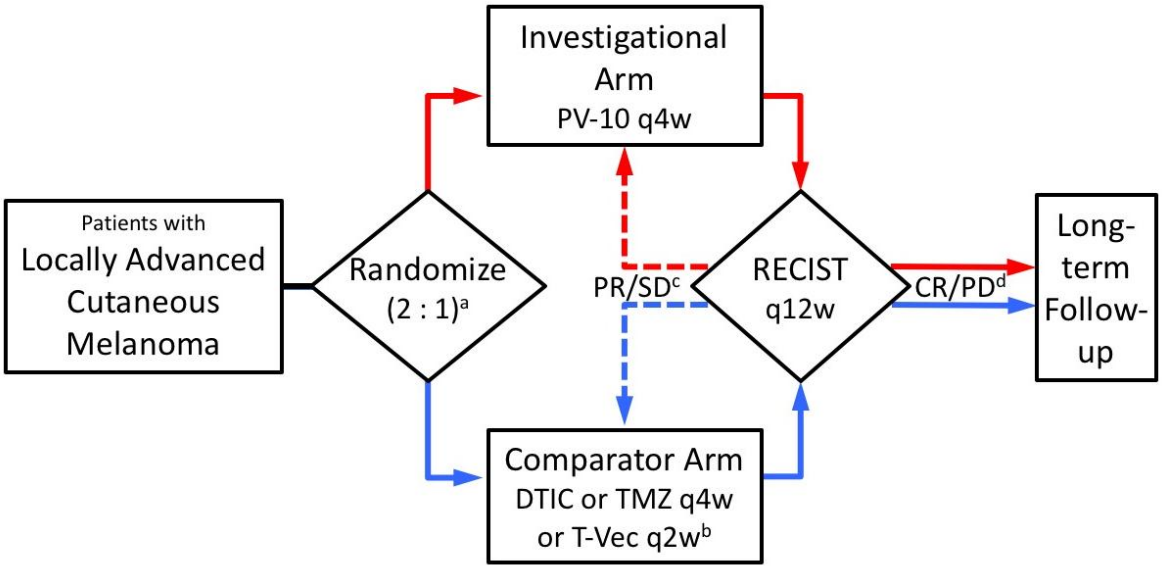
The estimated study duration is approximately 60 months.

4.11 Study Centers

A total of approximately 225 patients (approximately 150 in the PV-10 arm and 75 in the comparator arm) will be enrolled from approximately 60 total sites in North America, South America, Oceana, Asia and Europe. Sites in other geographical regions may be added at the Sponsor's discretion. It is estimated that the accrual rate will be approximately 5-10 subjects per month over an 48-month enrollment period. It is estimated that the primary study endpoint will be achieved within one year after enrollment is completed.

4.12 Study Schematic

The study design schematic is presented below.



a. 225 patients randomized 2:1 (stratified for prior immune checkpoint inhibition)
b. T-Vec (talimogene laherparepvec) repeated after 3 weeks then q2w
c. Repeat treatment cycle if PR / SD
d. Cross-over allowed upon documented PD in comparator arm

5 ELIGIBILITY CRITERIA

5.1 Study Population

Two hundred twenty five (225) subjects with locally advanced cutaneous melanoma, consisting of recurrent, satellite or in-transit locally advanced cutaneous, subcutaneous, soft tissue, or superficial or palpable nodal melanoma metastases (i.e., AJCC 2009 [4] Stage IIIB, Stage IIIC or Stage IV M1a), and with at least 1 and no more than 50 melanoma lesions, will be enrolled in this study.

5.2 Inclusion Criteria

1. Age 18 years or older, male or female.

2. Histologically or cytologically confirmed melanoma. This can be based on the original diagnostic biopsy. No new biopsies are required.

3. Recurrent, satellite or in-transit locally advanced cutaneous, subcutaneous, soft tissue, or superficial or palpable nodal melanoma metastases (i.e., AJCC 2009 [4] Stage IIIB, Stage IIIC or Stage IV M1a).

4. At least 1 measurable Target Lesion that can be accurately measured by calipers, computed tomography (CT) or magnetic resonance imaging (MRI) consisting of at least one of the following:
   - at least one cutaneous lesion (each lesion ≥ 10 mm in longest diameter or up to 5 lesions having a sum of longest diameters ≥ 10 mm); and/or
   - at least one subcutaneous or soft tissue lesion (each lesion ≥ 10 mm in longest diameter by CT or MRI); and/or
   - at least one superficial or palpable nodal lesion (each lesion ≥ 15 mm in short axis diameter by CT or MRI).

5. No lesion > 50 mm in longest diameter; and no more than 50 lesions.

6. Estimated required PV-10 dose ≤ 15 mL (based on total tumor burden).

7. Performance Status: ECOG 0-2.

8. Not a candidate for treatment with an immune checkpoint inhibitor (e.g., failed or did not tolerate prior therapy, or due to co-morbidities, pre-existing autoimmune disease, drug unavailability or standard of care).

9. Not a candidate for targeted therapy with BRAF or combined BRAF/MEK inhibitors (e.g., failed or did not tolerate prior therapy, BRAF V600 wild-type or due to drug unavailability or standard of care).

10. Clinical Laboratories (per central laboratory results):
    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L and platelet count ≥100 x 10^9/L.
    - Creatinine ≤ 3 times the upper limit of normal (ULN).
    - Estimated creatinine clearance (CrCl) or estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2.
    - Total bilirubin ≤ 3 times the upper limit of normal (ULN).
    - Aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) ≤ 5 times the upper limit of normal (ULN).
    - LDH ≤ 2 times the upper limit of normal (ULN).

11. Thyroid Function:
    - Thyroid function abnormality ≤ CTCAE Grade 2.

12. Candidate for at least one comparator drug:
    - Subjects must be candidates for at least one of the designated comparator drugs.

5.3 Exclusion Criteria

1. Presence or history of visceral melanoma metastasis (including lung metastases) or presence of bone metastases.

2. Presence of more than 50 melanoma lesions.

3. Radiation Therapy:
    - Subjects who have received radiation therapy to any Study Lesion within 6 weeks of initial study treatment.

4. Chemotherapy:
    - Subjects who have received chemotherapy or other systemic cancer therapy within 4 weeks of initial study treatment (6 weeks for nitrosoureas or mitomycin).
    - Subjects who have received regional chemotherapy (limb infusion or perfusion) within 12 weeks of initial study treatment.

5. Immunotherapy:
    - Subjects who have received immunotherapy for cancer within 4 weeks of initial study treatment.

6. Local Treatment:
    - Subjects who have received local treatment (e.g., surgery, cryotherapy, laser ablation, or intralesional oncolytic therapy) to any Study Lesion within 4 weeks of initial study treatment.

7. Anti-Tumor Vaccine:
   - Subjects who have received anti-tumor vaccine therapy within 6 weeks of initial study treatment.

8. Investigational Drug Therapy:
   - Subjects who have received an investigational drug within 4 weeks of initial study treatment.

9. Concurrent or Intercurrent Illness:
   - Subjects with impaired wound healing or other extremity complications due to diabetes mellitus whose Study Lesions are located in an extremity.
   - Subjects with severe peripheral vascular disease (e.g., severe claudication [pain occurring after less than 200 meters of walking], rest pain, ischemic ulceration or gangrene) whose Study Lesions are located in an extremity.
   - Subjects with significant concurrent or intercurrent 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.
   - Subjects with uncontrolled thyroid disease or cystic fibrosis.
   - Subjects with clinically significant acute or unstable cardiovascular, cerebrovascular (stroke), renal, gastrointestinal, pulmonary, immunological, endocrine, or central nervous system disorders.

10. Pregnancy:
    - Female subjects who are pregnant or lactating.
    - Female subjects who have positive serum ßHCG pregnancy test taken within 21 days prior to initiation of study treatment.
    - Female subjects of child-bearing potential who are unwilling to use highly effective contraception (e.g., combined (estrogen and progestogen containing) or progestogen-only hormonal contraceptives, intrauterine devices, bilateral tubal ligation, vasectomized partner, sexual abstinence or equivalent measures) for the duration of study treatment and for 6 months after cessation of study treatment.
    - Sexually active male subjects with female partners of childbearing potential, unless willing to take contraceptive measures for the duration of study treatment and for 6 months after cessation of study treatment.

11. Contraindication for all comparators:
    - Subjects with contraindications to all of the designated comparator drugs.

6 STUDY MEDICATIONS

Subjects will be randomly assigned on a 2:1 basis to receive either PV-10 or comparator. Subjects in the comparator arm will receive the Investigator's choice of dacarbazine, temozolomide or talimogene laherparepvec as determined by Investigator preference and standard of care in the country or region.

PV-10 will be provided by the Sponsor.

Where dacarbazine, temozolomide or talimogene laherparepvec are commercially available and approved standard of care, they will not be provided by the Sponsor nor their use reimbursed unless required by local regulations. Where reimbursement is required, standard reimbursement schedules (such as those established by CMS in the United States) will be used. In regions where dacarbazine, temozolomide or talimogene laherparepvec are standard care but supply may not be assured, they will be provided by the Sponsor.

6.1 PV-10

PV-10 (10% w/v rose bengal disodium in 0.9% saline for injection) will be supplied in single-use glass vials containing 5.0 mL (to deliver).

PV-10 must be stored protected from light at 15-30°C (59-86°F). PV-10 should be protected from unnecessary light exposure prior to use.

6.1.1 Supply of PV-10

Receipt and disposition of all PV-10 used for this study will be documented in the Investigational Product Accountability Record (IPAR) or equivalent for review by study monitors.

6.1.2 PV-10 Administration

6.1.2.1 Initial Treatment Considerations

Up to 50 cutaneous, subcutaneous, soft tissue, or superficial or palpable nodal lesions will be designated as Study Lesions and treated with PV-10 according to the following criteria:

- 1-5 measurable lesions consisting of at least one cutaneous lesion (each lesion ≥ 10 mm or up to 5 cutaneous lesions having a sum of longest diameters ≥ 10 mm), and / or at least one subcutaneous or soft tissue lesion (each lesion ≥ 10 mm in longest diameter by CT or MRI), and / or at least one superficial or palpable nodal lesion (each lesion ≥ 15 mm in short axis diameter by CT or MRI), none > 50 mm in longest diameter, will be designated as Target Lesions (lesion designation will be made prior to randomization).

- All remaining lesions will be designated as Non-Target Lesions (up to a total of 50 Study Lesions, i.e., Target + Non-Target Lesions).
- All Study Lesions should be treated on study Day 1.

6.1.2.2 PV-10 Dosing

A. Due to risk of hemorrhage, PV-10 should not be administered to lesions contiguous with, encompassing or infiltrating major blood vessels (see protocol Section 6.1.3.1).

B. Each lesion should be uniformly infiltrated with PV-10 via intralesional injection. Use of a "fanning" technique is recommended, starting at the far margin and slowly withdrawing the needle during each fractionated injection. Multiple injection tracks should be applied, using a single puncture when possible and while re-injecting at multiple angles into the treated lesion to minimize tearing and leakage until the entire lesion is uniformly infiltrated. To reduce outflow of injected PV-10 via the needle track, a fine gauge needle (e.g., 24-32 g) should be used for injection.

C. Because PV-10 is a viscous liquid, only syringes with a secured (e.g., Luer-Lok™) or permanently attached needle should be used for injection.

D. Each Study Lesion should be injected based on estimated lesion volume (V_L) using the longest lesion diameter, where V_L is estimated using a spherical model according to:

$$V_L\ (cm^3) = [\pi/6000] \bullet [\text{diameter (mm)}]^3.$$

To assure complete infiltration of each injected lesion, the injected dose should be calculated as 0.5 mL PV-10 per cm^3 lesion volume (i.e., PV-10 volume is 50% of estimated lesion volume); an additional volume of 0.10 mL per lesion is added to this amount to minimize potential under-dosing:

$$V_{PV\text{-}10}\ (mL) = [V_L \bullet 0.5\ mL/cm^3] + 0.10\ mL.$$

A **dosing table** is provided in **Appendix B** based on this model. This table should be used for determining the recommended dose of PV-10 to be injected into each lesion according to longest lesion diameter.

- The recommended dose for lesions up to 38 mm longest diameter is calculated using the above equations to arrive at the doses shown in **Appendix B**; a constant recommended dose is used for lesions 39 to 50 mm.

- Note that **irregularly shaped lesions** (i.e., lesions that are flat, elongated or otherwise irregular in shape) may require less than the volume recommended in **Appendix B** for complete infiltration.

- PV-10 is a **dark red liquid**, the majority of which should be retained in the injected lesion; however, tissue surrounding the injected lesion is likely to **rapidly turn bright pink**.

- If the recommended volume of PV-10 cannot be injected into a lesion, the actual injected amount should be recorded.

- Ultrasound may be used for measurement of subcutaneous, soft tissue, or superficial or palpable nodal lesions for determining dose of PV-10 and to guide injection of these lesions.

E. A maximum total volume of 15 mL PV-10 can be administered at each treatment session.

6.1.2.3 Treatment of Persistent Lesions and Equivocal New Lesions

Study Lesions that are persistent may be retreated according to the treatment plan described under Sections 6.1.2.1 and 6.1.2.2 every 28 days. Lesions that exhibit eschar, incomplete re-epithelialization or other similar condition secondary to an apparent effect of study treatment should not be retreated until resolution of this secondary condition unless there is clear evidence of residual tumor tissue.

Equivocal New Lesions that do not meet the study definition of disease progression (see protocol Section 4.3.1) should be treated according to the treatment plan described under protocol Sections 6.1.2.1 and 6.1.2.2.

6.1.3 Warnings and Precautions

6.1.3.1 Warnings

PV-10 should not be administered to lesions (including pathological deep lymph nodes) contiguous with, encompassing or infiltrating major blood vessels. The Investigator is advised of the possibility of hemorrhage from lesions involving major blood vessels or otherwise highly vascular lesions following PV-10 oncolysis of such lesions. Necrosis of tumor tissue supporting or infiltrating vasculature may result in catastrophic failure of such vasculature. The consequences of such failure involving a major blood vessel could be acutely life threatening or fatal.

6.1.3.2 Precautions

Subjects administered greater than 5 mL of PV-10 shall be observed for onset of post-treatment acute adverse effects every 15 minutes for the first hour and then hourly until 4 hours following dosing. Otherwise, subjects shall be observed every 15 minutes for the first hour following dosing.

Specific precautions are as follows:

Lesion Bleeding. Necrosis of tumor tissue in highly vascular lesions may result in bleeding up to a few days or weeks after PV-10 administration. This bleeding could potentially be severe or life threatening. The possibility of such bleeding may be exacerbated in subjects taking anticoagulants or having clotting abnormalities.

Discomfort and Irritation. Mild to moderate pain at the injection site has been noted by the majority of subjects in phase 1 and 2 clinical testing during, and for up to several hours or more following, PV-10 administration, with severe pain reported in approximately 10% of subjects. Subjects should be advised that they may experience discomfort, tenderness or irritation of the injected lesions for a day or more, and should be offered analgesics if discomfort is severe or persistent. Use of local anesthesia or sedation may be appropriate during administration of PV-10 to minimize discomfort. Because PV-10 is excreted through the liver, anesthetics or sedatives that are cleared through the liver should be avoided to preclude potential toxicity due to possible competition from PV-10 excretion.

PV-10 Outflow. PV-10 is dark red in color and a portion of the drug may escape from the injection site for several hours or more following administration. Following injection, the lesions should be covered with a protective bandage to capture any such outflow. Subjects should be advised to expect some pink or red discoloration of these bandages and to leave bandages in place for at least 24 hours post-administration. While PV-10 is not toxic, it may permanently stain clothing and other fabrics; subjects should be advised to avoid contact of treatment sites with stainable materials for at least 24 hours after PV-10 administration.

Discoloration of Skin. Subjects should be advised to expect some pink or red discoloration of the injected lesions and surrounding skin for several days as PV-10 is cleared from the vicinity of injected lesions.

Discoloration of Stool or Urine. Since PV-10 is excreted unmetabolized by the liver via bile (and secondarily by the kidneys via urine), subjects should be advised to expect pink or red discoloration of stool and urine for up to several days after PV-10 administration.

Photosensitivity Reaction. PV-10 may enter the circulatory system from the tumor vasculature or surrounding blood vessels following IL injection causing cutaneous accumulation of RB, which can be photoactivated by ambient light exposure and lead to photosensitivity reaction. Approximately 10% of subjects in prior clinical studies of PV-10 have experienced photosensitivity reactions, ranging from mild to severe, and either locoregional to the injection site or generalized. To minimize risk of photosensitivity reaction, exposure of skin and eyes to bright light (especially direct or indirect sunlight) should be avoided for 48 hours following PV-10 administration.

To reduce the risk of photosensitivity reaction it is recommended that subjects remain indoors, away from outside windows, until sunset on the day of PV-10 administration. Additional precautions recommended on discharge following PV-10 administration

include donning of slacks and long-sleeved shirts, hats, closed shoes, gloves and sunglasses during daylight hours. Skin of the face and neck may be particularly susceptible during this period and exposure of these areas may lead to periorbital edema or dysphagia.

If possible, subjects should remain indoors, away from windows, during daylight hours for 48 hours after PV-10 administration.

Skin should be protected from prolonged exposure to direct sunlight (covered if exposed to sunlight for more than a few minutes) for two weeks after PV-10 administration or until pink or red skin discoloration in the treated area due to presence of PV-10 has resolved, whichever is longer, to minimize risk of possible photosensitivity reaction.

Because PV-10 absorbs both visible and ultraviolet light, sunscreen does not provide adequate protection against photosensitivity reaction.

Concomitant medications posing a clinically significant risk of photosensitivity may increase risk of photosensitivity reaction.

- Subjects should avoid unnecessary use of medications posing a clinically significant risk of photosensitivity, such as thiazide diuretics (refer to **Appendix C** for a list of medications) within 5 half-lives prior to PV-10 administration. These medications should also be avoided for 48 hours following PV-10 administration.

- Subjects receiving a large dose of PV-10 (i.e., 5 mL or greater) must avoid unnecessary use of medications posing a clinically significant risk of photosensitivity within 5 half-lives before PV-10 administration and for 1 week following PV-10 administration; subjects using such medications should be considered to be at elevated risk of photosensitivity reaction.

Subjects exhibiting gross pink or red discoloration of the skin remote from the injection site, or pink or red discoloration of urine, within 48 hours following PV-10 administration, should be considered to be at elevated risk of photosensitivity reaction due to the likely presence of high levels of PV-10 in the skin and should avoid going outdoors during daylight hours until these symptoms abate.

Incidences of severe photosensitivity reaction should be addressed by keeping the affected subject indoors, under subdued light with adequate support for 48-72 hours or until treatment-emergent abnormalities (e.g., periorbital or facial edema, potential dysphagia) normalize to less than Grade 3. Systemic corticosteroids and/or antihistamine (e.g., diphenhydramine) have been used in the management of severe cases [61].

Local Inflammation, Swelling, Blistering or Infection. Localized inflammation, swelling, blistering or infection lasting up to several weeks has been observed following PV-10 administration, possibly related to the occurrence of necrotic tumor tissue at the

injection site in subjects having compromised local circulation or immune system function. To preclude onset of cellulitis or other infection it may be appropriate to prescribe prophylactic antibiotics prior to or at the time of PV-10 administration.

Dysphagia. Localized swelling of the neck may occur following injection of head or neck lesions, and may lead to temporary dysphagia.

Locoregional Thrombus. Thrombus formation near the injection site has been noted in at least one subject with a history of severe peripheral vascular disease. Subjects with a history of peripheral vascular disease or superficial or deep vein thrombosis should be advised to contact study personnel immediately if thrombosis symptoms present during the week following PV-10 administration. Since locoregional erythema and edema are frequently associated with PV-10 administration, high-risk subjects may require diagnostic imaging or other detailed assessment to differentiate such response from possible thrombosis. It may be appropriate to prescribe prophylactic anticoagulant to high-risk subjects prior to, at the time of, or following PV-10 administration.

Iodide Sensitivity. About 1-2% of individuals experience sensitivity to high doses of iodinated materials, including apparent acute allergic reactions. Such reactions have generally been associated with intravenous administration of iodinated contrast media (e.g., at doses on the order 5,000 mg iodine per bolus) or high dose prophylaxis using potassium iodide. PV-10 contains approximately 50 mg I/mL. While the maximum dose of PV-10 represents a total dose of only 750 mg iodide, and while this is delivered as a cutaneous depot (thereby limiting potential maximum serum levels of iodide), there exists a chance for occurrence of iodide sensitivity reactions. Accordingly, subjects should be advised of the potential for such sensitivity and monitored for onset of any severe allergic response following PV-10 administration, particularly during the first hour following administration. Symptoms can include fever, gastrointestinal distress, erythema, hives, pruritus, sinusitis, joint inflammation, swelling of salivary glands, bronchial spasm, thyroid abnormalities (such as goiter) and shock. Individuals at particular risk include those with a history of adverse reaction to iodinated agents, such as contrast media or prophylactic iodide, or allergy to shellfish or other seafood.

Iodide Thyrotoxicity. While the maximum dose of PV-10 represents a total dose of 750 mg iodide this is well below the iodide exposure common with the use of iodinated contrast media (e.g., ca. 5,000-6,000 mg iodide for a typical iohexol dose), and while thyroid effects are uncommon at such doses of contrast media [79-82], adverse effects of the thyroid are possible whenever large doses of iodide are administered. Particularly susceptible subjects are those with defective or absent thyroid autoregulation, such as that associated with Hashimoto's thyroiditis, radioiodine- or surgically-treated Graves' hyperthyroidism, and cystic fibrosis [83]. Potential effects from excess iodide include iodide goiter, hypothyroidism and thyrotoxicosis (Jod-Basedow disease). These effects often resolve when excess iodide dissipates [83]. Nonetheless, subjects with uncontrolled thyroid disease or cystic fibrosis should not receive PV-10. Assessment of thyroid

function (T3, T4 and TSH) is included in all scheduled lab tests to monitor for potential adverse effects on thyroid function.

Intravenous Risk. Because the effects of a large intravenous bolus dose of PV-10 are unknown, direct injection of PV-10 into major tumor vasculature must be avoided.

Myelosuppression. Intralesional administration of PV-10 is not believed to result in myelosuppression and should not adversely impact subsequent tolerance of chemotherapy.

Reproductive Risks. There are no safety data on PV-10 in pregnant women. In preclinical studies in rats at doses similar to those of this study, there were no effects on embryo/fetal development or morphology [67]. Additionally, literature referencing previous human use of rose bengal disodium as a liver function diagnostic includes multiple reports of use in infants and pregnant women. Nevertheless, as an appropriate precaution in compliance with current Heads of Medicines Agencies Clinical Trials Facilitation Group (HMA CTFG) guidelines for highly effective contraception, female subjects of childbearing potential must use highly effective contraception to avoid pregnancy while they are receiving PV-10 and for 6 months after cessation of PV-10 treatment, and pregnancy testing should be performed monthly during PV-10 treatment and for 6 months after cessation of treatment. Male subjects should be advised to take contraceptive measures during and for 6 months after cessation of PV-10 treatment.

6.1.4 Dose Modification

If the indicated volume of PV-10 cannot be injected into a lesion, the actual injected amount should be recorded. Amounts greater than those indicated in the dosing table (**Appendix B**) must not be used. Dose modification is likely to be necessary when lesions are irregularly shaped (i.e., lesions that are flat, elongated or otherwise irregular in shape may require less than the volume recommended in **Appendix B** for complete infiltration).

6.1.5 Toxicity Requiring Study Drug Discontinuation

Onset of Grade 3 or higher dysphagia, locoregional thrombus, iodide sensitivity or thyrotoxicity, or Grade 4 photosensitivity reaction, regardless of duration, occurring within 28 days after any dose of PV-10, or onset of any Grade 3 non-hematologic or Grade 4 hematologic toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) occurring within 28 days after any dose of PV-10 that is persistent for 14 days or longer, will constitute a toxicity requiring study drug discontinuation.

Subjects experiencing a toxicity requiring study drug discontinuation will permanently discontinue study treatment. Those subjects without objective evidence of disease progression at the time of treatment discontinuation may continue Response Follow-up at the discretion of the Investigator (protocol Section 7.3.2); all other subjects discontinuing study

treatment due to toxicity will enter the Survival Follow-up phase of the study (protocol Section 7.7).

6.1.6 Concomitant Medications

Unnecessary use of medications posing a clinically significant risk of photosensitivity, such as thiazide diuretics, should be avoided for 5 half-lives before and 1 week following PV-10 administration (see **Appendix C** for a list of these medications). Subjects receiving a dose of PV-10 $\geq$ 5 mL must avoid unnecessary use of these medications for one week after PV-10 treatment.

6.2 Dacarbazine

Dacarbazine for injection is an antineoplastic alkylating agent.

Dacarbazine has been shown to be mutagenic, teratogenic and carcinogenic in animals, and may pose increased risk for teratogenic effects exists in humans. Therefore, dacarbazine must not be used during pregnancy or breastfeeding. Female subjects of childbearing potential must use highly effective contraception to avoid pregnancy during dacarbazine treatment and for 6 months after cessation of dacarbazine treatment, and pregnancy testing should be performed monthly during dacarbazine treatment and for 6 months after cessation of treatment. Male subjects should be advised to take contraceptive measures during and for 6 months after cessation of dacarbazine treatment.

Dacarbazine is a moderate immunosuppressive agent. Administration of live vaccines to patients who are immunocompromised as a result of treatment with chemotherapeutics such as dacarbazine can cause serious and potentially fatal infections. Immunization with live vaccines should therefore be avoided during dacarbazine therapy. It is generally advised to use live virus vaccines with caution after stopping chemotherapy and to take the patient's immune status into account, depending also on the disease and other therapies. Vaccination with live vaccines should be administrated no sooner than 3 months after the completion of chemotherapy.

6.2.1 Dacarbazine Dose and Schedule

Dacarbazine will be administered at an initial dose of 850 mg/m^2 IV every 28 days in a manner consistent with prescribing information or approved summary of product characteristics (SmPC) and standard procedures of the local institution. Treatment will be continued until the occurrence of disease progression as defined in the study protocol, intolerable toxicity or for 2 cycles after complete response.

Body surface area (BSA) in m^2 may be calculated using the Du Bois formula,

$$BSA = 0.007184 \times W^{0.425} \times H^{0.725}$$

or the Mosteller formula,

$$BSA = (W \times H / 3600)^{0.5}$$

where weight (W) is in kg and height (H) is in cm.

6.2.2 Repeat Dosing and Dose Modification

Repeat dosing and dose modifications will be made according to the following criteria [35]:

- Repeat dosing is allowed 28 days or more after each prior dose provided that absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L.
- A dose reduction by 25% will be made if a CTCAE Grade 3 or 4 hematologic toxicity occurs.
- A dose reduction by 50% will be made if a CTCAE Grade 3 or 4 non-hematologic toxicity occurs.
- A dose reduction by 25% will be made if a delay in repeat dosing of 14 days or more is necessary.
- In the event of a dose reduction, re-escalation is not permitted.

Subjects with CTCAE Grade 3 or 4 laboratory abnormalities will have weekly laboratory testing until values have returned to ≤ CTCAE Grade 2.

In the event of a dosing delay, all subsequent study events should be delayed commensurately.

6.2.3 Toxicity Requiring Study Drug Discontinuation

Any CTCAE Grade 3 non-hematologic or CTCAE Grade 4 hematologic toxicity having an onset at any time from the first dose of dacarbazine and up to 28 days after the last dose and that is persistent for 14 days or longer will constitute a toxicity requiring study drug discontinuation.

The requirement of more than 2 dose reductions also constitutes a toxicity requiring study drug discontinuation.

Subjects experiencing a toxicity requiring study drug discontinuation will permanently discontinue study treatment with dacarbazine. Those subjects without objective evidence of disease progression at the time of treatment discontinuation may continue Response Follow-up at the discretion of the Investigator (protocol Section 7.3.2) and may be eligible to enter the crossover portion of the study (protocol Section 7.4); all other subjects discontinuing

study treatment due to toxicity will enter the Survival Follow-up phase of the study (protocol Section 7.7).

6.2.4 Concomitant Medications

Appropriate medications for prophylaxis or treatment of side effects of dacarbazine may be used at the discretion of the Investigator.

6.3 Temozolomide

Temozolomide, an alkylating agent, is available as capsules for oral administration and as a powder for injection. Only the capsule form for oral administration may be used in this study.

There are no safety data on temozolomide in pregnant women. In preclinical studies in rats and rabbits receiving 150 mg/m2 temozolomide, teratogenicity and/or fetal toxicity were demonstrated. It is not known whether temozolomide is excreted in human breast milk; thus, breast-feeding is prohibited while receiving temozolomide. Female subjects of childbearing potential must use highly effective contraception to avoid pregnancy while they are receiving temozolomide and for 6 months after cessation of temozolomide treatment, and pregnancy testing should be performed monthly during temozolomide treatment and for 6 months after cessation of treatment. Temozolomide can have genotoxic effects. Therefore, male subjects receiving temozolomide should be advised to take contraceptive measures during and for 6 months after cessation of temozolomide treatment and to seek advice on cryoconservation of sperm prior to treatment, because of the possibility of irreversible infertility due to temozolomide.

6.3.1 Temozolomide Dose and Schedule

Temozolomide will be administered orally at an initial dose of 200 mg/m^2 daily for 5 consecutive days every 28 days in a manner consistent with prescribing information or approved summary of product characteristics (SmPC) and standard procedures of the local institution. Treatment will be continued until the occurrence of disease progression as defined in the study protocol, intolerable toxicity or for 2 cycles after complete response.

Body surface area (BSA) in m^2 may be calculated using the Du Bois formula,

$$BSA = 0.007184 \times W^{0.425} \times H^{0.725}$$

or the Mosteller formula,

$$BSA = (W \times H / 3600)^{0\,5}$$

where weight (W) is in kg and height (H) is in cm.

6.3.2 Repeat Dosing and Dose Modification

Repeat dosing and dose modifications will be made according to the following criteria [35]:

- Repeat dosing is allowed 28 days or more after each prior dose provided that absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L.
- A dose reduction by 25% will be made if a CTCAE Grade 3 or 4 hematologic toxicity occurs.
- A dose reduction by 50% will be made if a CTCAE Grade 3 or 4 non-hematologic toxicity occurs.
- A dose reduction by 25% will be made if a delay in repeat dosing of 14 days or more is necessary.
- In the event of a dose reduction, re-escalation is not permitted.

Subjects with CTCAE Grade 3 or 4 laboratory abnormalities will have weekly laboratory testing until values have returned to ≤ CTCAE Grade 2.

In the event of a dosing delay, all subsequent study events should be delayed commensurately.

6.3.3 Toxicity Requiring Study Drug Discontinuation

Any CTCAE Grade 3 non-hematologic or a CTCAE Grade 4 hematologic toxicity having an onset at any time from the first dose of temozolomide and up to 28 days after the last dose and that is persistent for 14 days or longer will constitute a toxicity requiring study drug discontinuation.

The requirement of more than 2 dose reductions also constitutes a toxicity requiring study drug discontinuation.

Subjects experiencing a toxicity requiring study drug discontinuation will permanently discontinue study treatment with temozolomide. Those subjects without objective evidence of disease progression at the time of treatment discontinuation may continue Response Follow-up at the discretion of the Investigator (protocol Section 7.3.2) and may be eligible to enter the crossover portion of the study (protocol Section 7.4); all other subjects discontinuing study treatment due to toxicity will enter the Survival Follow-up phase of the study (protocol Section 7.7).

6.3.4 Concomitant Medications

Appropriate medications for prophylaxis or treatment of side effects of temozolomide may be used at the discretion of the Investigator.

6.4 Talimogene Laherparepvec

Talimogene laherparepvec, a genetically modified oncolytic virus, is an intralesional agent for injection into cutaneous, subcutaneous, soft tissue, or superficial or palpable nodal melanoma lesions.

6.4.1 Warnings and Precautions

Talimogene laherparepvec is a live, attenuated herpes simplex virus and may cause life-threatening disseminated herpetic infection in patients who are immunocompromised. Do not administer talimogene laherparepvec to subjects with a history of primary or acquired immunodeficiency, leukemia, lymphoma, infection with a human immunodeficiency virus or who are on immunosuppressive therapy.

Adequate and well controlled studies with talimogene laherparepvec have not been conducted in pregnant women. As an appropriate precaution in compliance with current Heads of Medicines Agencies Clinical Trials Facilitation Group (HMA CTFG) guidelines for highly effective contraception, female subjects of childbearing potential should use highly effective contraception to prevent pregnancy during treatment with talimogene laherparepvec and for 6 months after cessation of study treatment, and pregnancy testing should be performed monthly during treatment with talimogene laherparepvec and for 6 months after cessation of treatment. All subjects should be advised to use a latex condom during sexual contact to prevent possible transmission of talimogene laherparepvec.

6.4.2 Talimogene Laherparepvec Dose and Schedule

Talimogene laherparepvec will be administered by intralesional injection at an initial 21-day interval followed by 14-day intervals in a manner consistent with prescribing information or approved summary of product characteristics (SmPC) and standard procedures of the local institution. Ultrasound may be used for measurement of subcutaneous, soft tissue, or superficial or palpable nodal lesions for determining dose of talimogene laherparepvec and to guide injection of these lesions. Treatment will be continued until the occurrence of complete response, disease progression as defined in the study protocol or intolerable toxicity.

- If there is persistent infection or delayed healing of injection site(s), consider the risks and benefits of talimogene laherparepvec before continuing treatment.

- Consider the risks and benefits of talimogene laherparepvec before continuing treatment in patients who develop immune-mediated events.

- Consider the risks and benefits of talimogene laherparepvec in patients in whom plasmacytoma develops during treatment.

- Obstructive airway disorder has been reported following talimogene laherparepvec treatment. Use caution when injecting lesions close to major airways.

6.4.3 Repeat Dosing and Dose Modification

After the initial 21-day interval administration of talimogene laherparepvec should be continued at 14-day intervals until there are no injectable lesions to treat. Dose modification should follow prescribing information.

6.4.4 Toxicity Requiring Study Drug Discontinuation

Onset of any Grade 3 non-hematologic or a Grade 4 hematologic toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) occurring at any time from the first dose of talimogene laherparepvec and up to 28 days after the last dose that is persistent for 14 days or longer will constitute a toxicity requiring study drug discontinuation.

A delay of dosing by more than 4 weeks due to the occurrence of an adverse event that is considered related to talimogene laherparepvec, will also constitute a toxicity requiring study drug discontinuation. This includes delay due to immune-mediated events.

Subjects experiencing a toxicity requiring study drug discontinuation will permanently discontinue study treatment with talimogene laherparepvec. Those subjects without objective evidence of disease progression at the time of treatment discontinuation may continue Response Follow-up at the discretion of the Investigator (protocol Section 7.3.2) and may be eligible to enter the crossover portion of the study (protocol Section 7.4); all other subjects discontinuing study treatment due to toxicity will enter the Survival Follow-up phase of the study (protocol Section 7.7).

6.4.5 Concomitant Medications

Talimogene laherparepvec is sensitive to acyclovir. Acyclovir or other antiherpetic viral agents may interfere with the effectiveness of talimogene laherparepvec. No drug interaction studies have been reported with talimogene laherparepvec.

7 STUDY PROCEDURES AND EVALUATIONS

The timing and requirements for study evaluations are summarized in the Schedule of Study Events (**Appendix A**) and described in detail below.

As soon as a potential subject is considered for this study and prior to any other study procedures, the subject will have the nature of the study explained to them, and will be asked to provide written informed consent and authorization to access medical records needed for study documentation. Informed consent must be obtained prior to any procedures that do not form a part of the subject's normal care.

All subjects will have study evaluations at Screening, at study Day 1 prior to initiation of study treatment (i.e., baseline), at the end of each Treatment Cycle and at the end of each Treatment Course. Subjects receiving PV-10 will also have study evaluations one week after any PV-10 administration. Detailed measurement of lesions using calipers, CT and / or MRI for determination of tumor response will be performed at the end of the Initial Treatment Course and at 12-week intervals thereafter.

All Screening visit procedures are to be completed within 21 days prior to study Day 1 to allow for reporting of laboratory and radiology results prior to initiation of study treatment.

Informed consent may be conducted up to 30 days prior to study Day 1.

To avoid unnecessary invasive procedures, baseline data from imaging (CT, MRI or PET/CT) acquired within 30 days prior to study Day 1 may be used in lieu of equivalent study-specific imaging at Screening (baseline radiologic imaging may be obtained up to 45 days prior to study Day 1 for Stage III subjects with cutaneous-only disease).

All subjects will be randomized after completion of Screening, within 14 days prior to study Day 1, and will commence their assigned treatment on study Day 1. Designation of Target Lesions must occur prior to randomization. If Study Lesion measurements have been performed more than 7 days prior to Day 1, they must be repeated on Day 1.

Subjects receiving PV-10 who do not have disease progression as defined in the study protocol (protocol Section 4.3.1) can be re-administered PV-10 as needed at 28-day (4 week) intervals until complete response, disease progression, intolerable adverse events, discontinuation of treatment at subject request or withdrawal of consent. No individual lesion should be treated within less than 28 days (4 weeks) from prior treatment of that lesion so that response of the lesion can be accurately assessed.

Subjects receiving dacarbazine or temozolomide who do not have disease progression as defined in the study protocol (protocol Section 4.3.1) will continue to be eligible for treatment with dacarbazine or temozolomide, respectively, every 4 weeks until complete response, disease progression, intolerable adverse events, discontinuation of treatment at subject request or withdrawal of consent. Subjects receiving dacarbazine or temozolomide

who have a complete response will receive 2 additional treatments at 4-week intervals after documentation of the complete response.

Subjects receiving talimogene laherparepvec who do not have disease progression as defined in the study protocol (protocol Section 4.3.1) will continue to be eligible for treatment with talimogene laherparepvec every 2 weeks until complete response, disease progression, intolerable adverse events, discontinuation of treatment at subject request or withdrawal of consent.

Photodocumentation of Study Lesions will be performed at Screening; at study Day 1 prior to initiation of study treatment (i.e., baseline); at the end of each Treatment Cycle; and at all subsequent evaluations. Additional photographic documentation will be performed at intermediate times if disease progression is clinically identified or suspected. Specifications for study photography are found in **Appendix E**. Only study personnel who have completed photodocumentation training may perform study photography.

Radiologic documentation of non-cutaneous Study Lesions (i.e., subcutaneous, soft tissue, and superficial or palpable nodal Study Lesions) will be performed at Screening and at all subsequent comprehensive assessments of progression status to accurately identify, track and confirm status of these Study Lesions. Computed tomography (CT) is recommended for non-cutaneous Study Lesions located in the chest, abdomen and pelvis. If non-cutaneous Study Lesions are located beyond the chest, abdomen and pelvis (e.g., in an extremity or the head or neck) scanning by CT (preferred) or by magnetic resonance imaging (MRI) must include all affected body regions. Consistent scanning methodology should be used throughout the study interval for each Study Lesion. Specifications for radiologic imaging are found in **Appendix D.**

Laboratory tests will be performed at Screening; at study Day 1 prior to initiation of study treatment (i.e., baseline); at the end of each Treatment Cycle; and at Final Follow-up. Laboratory specimens from each specified evaluation will be sent to a central laboratory. Duplicate laboratory testing that is necessary to determine if chemotherapy can be administered (i.e., CBC, CMP) may be performed at a local laboratory in addition to central laboratory testing.[3]

Female subjects of childbearing potential must have a serum pregnancy test within 21 days prior to initiation of study treatment.

[3] In the event of disagreement in results between the local laboratory and the central laboratory with regard to test values affecting treatment decisions, it will not be a protocol violation if treatment is given based on within-range results from the local laboratory that subsequently prove to be out of range as analyzed by the central laboratory or if treatment is delayed based on out-of-range results from the local laboratory that subsequently prove to be within-range as analyzed by the central laboratory.

Female subjects of childbearing potential must have a negative urine pregnancy test within 48 hours prior to administration of study treatment at monthly intervals during the treatment phase of the study and for 6 months after cessation of study treatment (all study arms).

Comprehensive assessment of disease status will be performed at Screening; **comprehensive assessment of progression status** will be performed at the end of the Initial Treatment Course and every 12 weeks thereafter, and at Final Follow-up. These assessments will include assessment for the presence of visceral and nodal metastases by CT and / or MRI imaging. Subjects with suspected brain metastases should be assessed by MRI of the brain at Screening, at the end of each Treatment Course, on subsequent Response Follow-up visits and/or Final Follow-up as indicated clinically.[4] Subjects for whom Final Follow-up occurs less than 8 weeks after prior scanning (CT and/or MRI) will not undergo additional imaging at Final Follow-up. Subjects will also undergo physical examination for visible or palpable cutaneous, subcutaneous, soft tissue, and superficial or palpable nodal metastases at these times.

Clinical evaluation will be performed at 28-day intervals during the treatment and response follow-up phases of the study, commencing at the end of the first Treatment Cycle, and at any unscheduled visits during follow-up. This will continue through Week 37 (for subjects receiving PV-10 or chemotherapy) or Week 38 (for subjects receiving talimogene laherparepvec) undergoing long-term Response Follow-up. This evaluation is supplanted by comprehensive assessment of progression status at 12-week intervals (protocol Section 4.3.3). **Subjects exhibiting clinical evidence of progression** (i.e., meriting change of study therapy) **will undergo Final Follow-up assessment** for documentation of progression status (protocol Section 7.6).

Investigators should use **consistent measurement methods** (i.e., study-specific calipers provided by the Sponsor and repeatable scan settings) throughout the study interval for each subject to facilitate comparison of the subject's data over the course of the study (see **Appendix D**).

Assessment and documentation of adverse events and concomitant medications should be done at each study evaluation. Adverse events occurring after signing the informed consent form but before initiation of study treatment on Study Day 1 will be recorded on the Adverse Events CRF.

Unscheduled visits are permitted at the Investigator's discretion to evaluate adverse events and possible disease progression.

[4] To avoid unnecessary procedures, data from equivalent imaging acquired within 30 days prior to study Day 1 may be used in lieu of CT and/or MRI imaging at Screening. If MRI is contraindicated or not standard care CT may be performed in lieu of MRI.

Event windows vary during the course of the study interval:

- Evaluations for study Day 1 and subsequent evaluations through the end of the treatment phase of the study are to be done within 2 days before or after the specified study day. Exceptions to this window are:
    - Study Lesion measurement at study Day 1 may be done up to 7 days before the specified time; and
    - CT and MRI imaging, which may be done up to 7 days before or after the specified time.
- Long-term Response Follow-up assessments and Survival Follow-up assessments are to be carried out within 14 days before or after the specified time.

7.1 Screening and Randomization (all subjects)

7.1.1 Screening

Potential subjects will undergo the following screening procedures within 21 days prior to initiation of study treatment on study Day 1; informed consent and baseline radiology may be performed up to 30 days prior to study Day 1 (baseline radiology may be obtained up to 45 days prior to study Day 1 for Stage III subjects with cutaneous-only disease).

- Informed consent
- Histological or cytological confirmation of melanoma; this can be based on a previous diagnostic biopsy; no new biopsies are required
- Documentation of BRAF mutation status; if documentation is not available, BRAF testing must be done using the methodology that is standard for the Investigator's institution; testing may be omitted if testing is not standard care or targeted therapy is unavailable or not standard care
- Demographics, including gender, age, race and ethnicity
- Medical history and physical examination, including melanoma history
- Documentation of baseline medications, including nutritional supplements and herbal preparations
- Height, weight and vital signs (including heart rate, blood pressure and temperature)
- ECOG performance status
- Laboratory tests:
  - Complete blood count (CBC), including differential white cell count and platelet count
  - Comprehensive metabolic panel (CMP), including albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, blood urea nitrogen (BUN), calcium, carbon dioxide, chloride, creatinine, random glucose, potassium, total protein and sodium
  - Estimated creatinine clearance (CrCl) or estimated glomerular filtration rate (eGFR)
  - Lactate dehydrogenase (LDH)
  - Thyroid function test (TFT), including total T3 or free T3 (serum triiodothyronine), total T4 or free T4 (serum thyroxine) and TSH (serum thyrotropin)
  - Pregnancy test (serum βHCG, only female subjects of childbearing potential)
- Designation of Target Lesions
- Body mapping of Study Lesions
- Photodocumentation of Study Lesions
- Study Lesion measurement
- Study Lesion dose calculation (estimation of total PV-10 dose)
- Radiologic imaging of chest, abdomen and pelvis (and any other body regions with non-cutaneous Study Lesions)
- MRI of brain if clinically indicated

- Assessment of adverse events (adverse events occurring after signing the informed consent form but before initiation of study treatment on Study Day 1 will be recorded on the Adverse Events CRF)

7.1.2 Randomization

Randomization will occur after all Screening procedures are complete and within 14 days prior to initiation of study treatment on study Day 1.

7.2 Initial Treatment Course

After randomization subjects will follow study procedures during the treatment phase of the study according to their assigned study drug.

Subjects will commence the initial Treatment Course within 21 days of initiation of Screening.

7.2.1 PV-10 Arm

Subjects assigned to receive PV-10 will undergo the following procedures during the Treatment Course.

7.2.1.1 Treatment Cycle 1: Beginning of Cycle ("Week 1 / Day 1")

All subjects will undergo the following procedures to begin the first Treatment Cycle:

- Assessment of adverse events (adverse events occurring after signing the informed consent form but before initiation of study treatment on Study Day 1 will be recorded on the Adverse Events CRF)
- Symptom self-assessment (Skindex-16)
- Review of baseline medical conditions and symptoms
- Grading of lesion bleeding, ulceration and infection (per CTCAE criteria)
- Review of concomitant medications
- Weight and vital signs
- ECOG performance status
- Laboratory tests (CBC, CMP, TFT)
- Pregnancy test (urine βHCG, only female subjects of childbearing potential)
- Photodocumentation of Study Lesions
- Study Lesion measurement (if prior measurements done more than 7 days before Day 1)
- Study Lesion dose calculation
- Administration of PV-10 to all Study Lesions
- Observation for post-treatment adverse events

7.2.1.2 Treatment Cycle 1: Treatment Follow-up ("Week 2")

Subjects who received PV-10 at the preceding visit will undergo the following procedures one week after beginning the first Treatment Cycle:

- Review of concomitant medications
- Assessment of adverse events
- Note: these assessments may be conducted remotely (e.g., telephonically)

7.2.1.3 Treatment Cycle 1: End of Cycle ("Week 5")

All subjects will undergo the following procedures at the end of the first Treatment Cycle:

- Symptom self-assessment (Skindex-16)
- Review of medical conditions and symptoms
- Clinical evaluation
- Grading of lesion bleeding, ulceration and infection (per CTCAE criteria)
- Review of concomitant medications
- Assessment of adverse events
- Weight and vital signs
- ECOG performance status
- Laboratory tests (CBC, CMP, TFT)
- Pregnancy test (urine βHCG, only female subjects of childbearing potential)
- Photodocumentation of Study Lesions

7.2.1.4 Treatment Cycle 2: Beginning of Cycle ("Week 5")

Upon completion of follow-up assessments for the end of the first Treatment Cycle all subjects will undergo the following procedures to begin the second Treatment Cycle:

- Subjects requiring PV-10 at this visit
  - Study Lesion measurement
  - Study Lesion dose calculation
  - Administration of PV-10
  - Observation for post-treatment adverse events
- Subjects not requiring PV-10 at this visit
  - No additional study procedures

7.2.1.5 Treatment Cycle 2: Treatment Follow-up ("Week 6")

Subjects who received PV-10 at the preceding visit will undergo the following procedures one week after beginning the second Treatment Cycle:

- Review of concomitant medications
- Assessment of adverse events
- Note: these assessments may be conducted remotely (e.g., telephonically)

7.2.1.6 Treatment Cycle 2: End of Cycle ("Week 9")

All subjects will undergo the following procedures at the end of the second Treatment Cycle:

- Symptom self-assessment (Skindex-16)
- Review of medical conditions and symptoms
- Clinical evaluation
- Grading of lesion bleeding, ulceration and infection (per CTCAE criteria)
- Review of concomitant medications
- Assessment of adverse events
- Weight and vital signs
- ECOG performance status
- Laboratory tests (CBC, CMP, TFT)
- Pregnancy test (urine βHCG, only female subjects of childbearing potential)
- Photodocumentation of Study Lesions

7.2.1.7 Treatment Cycle 3: Beginning of Cycle ("Week 9")

Upon completion of follow-up assessments for the end of the second Treatment Cycle all subjects will undergo the following procedures to begin the third Treatment Cycle:

- Subjects requiring PV-10 at this visit
  - Study Lesion measurement
  - Study Lesion dose calculation
  - Administration of PV-10
  - Observation for post-treatment adverse events
- Subjects not requiring PV-10 at this visit
  - No additional study procedures

7.2.1.8 Treatment Cycle 3: Treatment Follow-up ("Week 10")

Subjects who received PV-10 at the preceding visit will undergo the following procedures one week after beginning the third Treatment Cycle:

- Review of concomitant medications
- Assessment of adverse events
- Note: these assessments may be conducted remotely (e.g., telephonically)

7.2.1.9 Treatment Cycle 3: End of Cycle ("Week 13")

All subjects will undergo the following procedures at the end of the third Treatment Cycle:

- Symptom self-assessment (Skindex-16; subjects transitioning to Response Follow-up, Final Follow-up or Survival Follow-up will complete final self-assessment at this visit)
- Review of medical conditions and symptoms
- Grading of lesion bleeding, ulceration and infection (per CTCAE criteria)
- Review of concomitant medications
- Assessment of adverse events
- Weight and vital signs
- ECOG performance status
- Laboratory tests (CBC, CMP, TFT)
- Pregnancy test (urine βHCG, only female subjects of childbearing potential)
- Photodocumentation of Study Lesions
- Comprehensive assessment of progression status (RECIST)
  - Radiologic imaging of chest, abdomen and pelvis (and any other body regions with non-cutaneous Study Lesions)
  - MRI of brain (if clinically indicated)
  - Histological or cytological confirmation of CR (if indicated)
  - Evaluation for distant metastases
  - Evaluation of Target Lesions (Target Lesion measurement)
  - Evaluation of Non-Target Lesions

Completion of these procedures constitutes completion of a Treatment Course.

7.2.2 Comparator Arm (Chemotherapy)

Subjects assigned to the comparator arm and receiving chemotherapy (dacarbazine or temozolomide) will undergo the following procedures during the Treatment Course.

7.2.2.1 Treatment Cycle 1: Beginning of Cycle ("Week 1 / Day 1")

All subjects will undergo the following procedures to begin the first Treatment Cycle:

- Assessment of adverse events (adverse events occurring after signing the informed consent form but before initiation of study treatment on Study Day 1 will be recorded on the Adverse Events CRF)
- Symptom self-assessment (Skindex-16)
- Review of baseline medical conditions and symptoms
- Grading of lesion bleeding, ulceration and infection (per CTCAE criteria)
- Review of concomitant medications
- Weight and vital signs
- ECOG performance status
- Laboratory tests (CBC, CMP, TFT)
- Pregnancy test (urine βHCG, only female subjects of childbearing potential)
- Photodocumentation of Study Lesions
- Calculation of body surface area (BSA)
- Administration of dacarbazine (850 mg/m^2 IV) or temozolomide (200 mg/m^2 PO daily for 5 days)

7.2.2.2 Treatment Cycle 1: End of Cycle ("Week 5")

All subjects will undergo the following procedures at the end of the first Treatment Cycle:

- Symptom self-assessment (Skindex-16)
- Review of medical conditions and symptoms
- Clinical evaluation
- Grading of lesion bleeding, ulceration and infection (per CTCAE criteria)
- Review of concomitant medications
- Assessment of adverse events
- Weight and vital signs
- ECOG performance status
- Laboratory tests (CBC, CMP, TFT) and duplicate local laboratory tests (CBC, CMP)
- Pregnancy test (urine βHCG, only female subjects of childbearing potential)
- Photodocumentation of Study Lesions

- Assessment of dose tolerance [5]

7.2.2.3 Treatment Cycle 2: Beginning of Cycle ("Week 5")

Upon completion of follow-up assessments for the end of the first Treatment Cycle all subjects will undergo the following procedures to begin the second Treatment Cycle:

- Subjects receiving dacarbazine or temozolomide
  - Calculation of BSA
  - Administration of dacarbazine or temozolomide

7.2.2.4 Treatment Cycle 2: End of Cycle ("Week 9")

All subjects will undergo the following procedures at the end of the second Treatment Cycle:

- Symptom self-assessment (Skindex-16)
- Review of medical conditions and symptoms
- Clinical evaluation
- Grading of lesion bleeding, ulceration and infection (per CTCAE criteria)
- Review of concomitant medications
- Assessment of adverse events
- Weight and vital signs
- ECOG performance status
- Laboratory tests (CBC, CMP, TFT) and duplicate local laboratory tests (CBC, CMP)
- Pregnancy test (urine βHCG, only female subjects of childbearing potential)
- Photodocumentation of Study Lesions
- Assessment of dose tolerance [6]

[5] Dose delay or dose reduction is required per protocol Sections 6.2.2 (dacarbazine) or 6.3.2 (temozolomide) if a CTCAE Grade 3 or Grade 4 hematologic or non-hematologic toxicity is present at this visit. In the event of a dose delay, all subsequent study events should be delayed by the duration of the dose delay.

[6] Dose delay or dose reduction is required per protocol Sections 6.2.2 (dacarbazine) or 6.3.2 (temozolomide) if a CTCAE Grade 3 or Grade 4 hematologic or non-hematologic toxicity is present at this visit. In the event of a dose delay, all subsequent study events should be delayed by the duration of the dose delay.

7.2.2.5 Treatment Cycle 3: Beginning of Cycle ("Week 9")

Upon completion of follow-up assessments for the end of the second Treatment Cycle all subjects will undergo the following procedures to begin the third Treatment Cycle:

- Subjects receiving dacarbazine or temozolomide
  - Calculation of BSA
  - Administration of dacarbazine or temozolomide

7.2.2.6 Treatment Cycle 3: End of Cycle ("Week 13")

All subjects will undergo the following procedures at the end of the third Treatment Cycle:

- Symptom self-assessment (Skindex-16; subjects transitioning to Response Follow-up, Final Follow-up or Survival Follow-up will complete final self-assessment at this visit)
- Review of medical conditions and symptoms
- Grading of lesion bleeding, ulceration and infection (per CTCAE criteria)
- Review of concomitant medications
- Assessment of adverse events
- Weight and vital signs
- ECOG performance status
- Laboratory tests (CBC, CMP, TFT) and duplicate local laboratory tests (CBC, CMP)
- Pregnancy test (urine βHCG, only female subjects of childbearing potential)
- Photodocumentation of Study Lesions
- Assessment of dose tolerance [7]
- Comprehensive assessment of progression status (RECIST)
  - Radiologic imaging of chest, abdomen and pelvis (and any other body regions with non-cutaneous Study Lesions)
  - MRI of brain (if clinically indicated)
  - Histological or cytological confirmation of CR (if indicated)
  - Evaluation for distant metastases
  - Evaluation of Target Lesions (Target Lesion measurement)
  - Evaluation of Non-Target Lesions

Completion of these procedures constitutes completion of a Treatment Course.

[7] Dose delay or dose reduction is required per protocol Sections 6.2.2 (dacarbazine) or 6.3.2 (temozolomide) if a CTCAE Grade 3 or Grade 4 hematologic or non-hematologic toxicity is present at this visit. In the event of a dose delay, all subsequent study events should be delayed by the duration of the dose delay.

7.2.3 Comparator Arm (Talimogene Laherparepvec)

Subjects assigned to the comparator arm and receiving talimogene laherparepvec will undergo the following procedures during the Treatment Course.

7.2.3.1 Treatment Cycle 1: Beginning of Cycle ("Week 1 / Day 1")

All subjects will undergo the following procedures to begin the first Treatment Cycle:

- Assessment of adverse events (adverse events occurring after signing the informed consent form but before initiation of study treatment on Study Day 1 will be recorded on the Adverse Events CRF)
- Symptom self-assessment (Skindex-16)
- Review of baseline medical conditions and symptoms
- Grading of lesion bleeding, ulceration and infection (per CTCAE criteria)
- Review of concomitant medications
- Weight and vital signs
- ECOG performance status
- Laboratory tests (CBC, CMP, TFT)
- Pregnancy test (urine βHCG, only female subjects of childbearing potential)
- Photodocumentation of Study Lesions
- Study Lesion measurement (if prior measurements done more than 7 days before Day 1)
- Study Lesion dose calculation
- Administration of talimogene laherparepvec to Study Lesions

7.2.3.2 Treatment Cycle 1: Middle of Cycle ("Week 4")

Subjects will undergo the following procedures three weeks after beginning the first Treatment Cycle:

- Review of concomitant medications
- Assessment of adverse events
- Weight and vital signs
- Subjects requiring talimogene laherparepvec at this visit
  - Study Lesion measurement
  - Study Lesion dose calculation
  - Administration of talimogene laherparepvec to Study Lesions
- All subjects will return in two weeks for assessment

7.2.3.3 Treatment Cycle 1: End of Cycle ("Week 6")

All subjects will undergo the following procedures five weeks after beginning the first Treatment Cycle:

- Symptom self-assessment (Skindex-16)
- Review of medical conditions and symptoms
- Clinical evaluation
- Grading of lesion bleeding, ulceration and infection (per CTCAE criteria)
- Review of concomitant medications
- Assessment of adverse events
- Weight and vital signs
- ECOG performance status
- Laboratory tests (CBC, CMP, TFT)
- Pregnancy test (urine βHCG, only female subjects of childbearing potential)
- Photodocumentation of Study Lesions

7.2.3.4 Treatment Cycle 2: Beginning of Cycle ("Week 6")

Upon completion of follow-up assessments for the end of the first Treatment Cycle all subjects will undergo the following procedures to begin the second Treatment Cycle:

- Subjects requiring talimogene laherparepvec at this visit
  - Study Lesion measurement
  - Study Lesion dose calculation
  - Administration of talimogene laherparepvec to Study Lesions
- All subjects will return in two weeks for assessment

7.2.3.5 Treatment Cycle 2: Middle of Cycle ("Week 8")

Subjects will undergo the following procedures two weeks after beginning the second Treatment Cycle:

- Review of concomitant medications
- Assessment of adverse events
- Weight and vital signs
- Subjects requiring talimogene laherparepvec at this visit
  - Study Lesion measurement
  - Study Lesion dose calculation
  - Administration of talimogene laherparepvec to Study Lesions
- All subjects will return in two weeks for assessment

7.2.3.6 Treatment Cycle 2: End of Cycle ("Week 10")

All subjects will undergo the following procedures four weeks after beginning the second Treatment Cycle:

- Symptom self-assessment (Skindex-16)
- Review of medical conditions and symptoms
- Clinical evaluation
- Grading of lesion bleeding, ulceration and infection (per CTCAE criteria)
- Review of concomitant medications
- Assessment of adverse events
- Weight and vital signs
- ECOG performance status
- Laboratory tests (CBC, CMP, TFT)
- Pregnancy test (urine βHCG, only female subjects of childbearing potential)
- Photodocumentation of Study Lesions

7.2.3.7 Treatment Cycle 3: Beginning of Cycle ("Week 10")

Upon completion of follow-up assessments for the end of the second Treatment Cycle all subjects will undergo the following procedures to begin the third Treatment Cycle:

- Subjects requiring talimogene laherparepvec at this visit
  - Study Lesion measurement
  - Study Lesion dose calculation
  - Administration of talimogene laherparepvec to Study Lesions
- All subjects will return in two weeks for assessment

7.2.3.8 Treatment Cycle 3: Middle of Cycle ("Week 12")

Subjects will undergo the following procedures two weeks after beginning the third Treatment Cycle:

- Review of concomitant medications
- Assessment of adverse events
- Weight and vital signs
- Subjects requiring talimogene laherparepvec at this visit
  - Study Lesion measurement
  - Study Lesion dose calculation
  - Administration of talimogene laherparepvec to Study Lesions
- All subjects will return in two weeks for assessment

7.2.3.9 Treatment Cycle 3: End of Cycle ("Week 14")

All subjects will undergo the following procedures at the end of the third Treatment Cycle:

- Symptom self-assessment (Skindex-16; subjects transitioning to Response Follow-up, Final Follow-up or Survival Follow-up will complete final self-assessment at this visit)
- Review of medical conditions and symptoms
- Grading of lesion bleeding, ulceration and infection (per CTCAE criteria)
- Review of concomitant medications
- Assessment of adverse events
- Weight and vital signs
- ECOG performance status
- Laboratory tests (CBC, CMP, TFT)
- Pregnancy test (urine βHCG, only female subjects of childbearing potential)
- Photodocumentation of Study Lesions
- Comprehensive assessment of progression status
  - Radiologic imaging of chest, abdomen and pelvis (and any other body regions with non-cutaneous Study Lesions)
  - MRI of brain (if clinically indicated)
  - Histological or cytological confirmation of CR (if indicated)
  - Evaluation for distant metastases
  - Evaluation of Target Lesions (Target Lesion measurement)
  - Evaluation of Non-Target Lesions

Completion of these procedures constitutes completion of a Treatment Course.

7.3 Response Assessment Upon Completion of a Treatment Course

Upon completion of a Treatment Course (i.e., 3 Treatment Cycles), subsequent study procedures, evaluations and treatments will be determined by subject status at the end of the Treatment Course (i.e., complete response, partial response, stable disease or disease progression).

7.3.1 Subjects with Partial Response or Stable Disease

7.3.1.1 Extended Treatment (PV-10)

- Subjects in the PV-10 arm with partial response or stable disease after completing a Treatment Course will receive additional treatment (i.e., immediately commence Extended Treatment Course) until the occurrence of disease progression as defined in the study protocol, intolerable toxicity, subject request to discontinue treatment, serious intercurrent or worsening concurrent medical conditions, or complete response is achieved.

- Subjects will undergo the procedures delineated in protocol Section 7.2.1; however, the assessments conducted at the end of the prior Treatment Course (Initial or Extended) do not need to be repeated at the commencement of an Extended Treatment Course if the Extended Treatment Course commences within 2 days of the completion of the prior Treatment Course.

7.3.1.2 Extended Treatment (Chemotherapy)

- Subjects in the comparator arm (dacarbazine or temozolomide) with partial response or stable disease after completing a Treatment Course will receive additional cycles of dacarbazine or temozolomide (i.e., immediately commence Extended Treatment Course) until the occurrence of disease progression as defined in the study protocol, intolerable toxicity, subject request to discontinue treatment, serious intercurrent or worsening concurrent medical conditions, or for 2 cycles after complete response.

- Subjects will undergo the procedures delineated in protocol Section 7.2.2; however, the assessments conducted at the end of the prior Treatment Course (Initial or Extended) do not need to be repeated at the commencement of an Extended Treatment Course if the Extended Treatment Course commences within 2 days of the completion of the prior Treatment Course.

7.3.1.3 Extended Treatment (Talimogene Laherparepvec)

- Subjects in the comparator arm (talimogene laherparepvec) with partial response or stable disease after completing a Treatment Course will receive additional cycles of talimogene laherparepvec (i.e., immediately commence Extended Treatment Course) until the occurrence of disease progression as defined in the study protocol, intolerable toxicity, subject request to discontinue treatment, serious intercurrent or worsening concurrent medical conditions, or complete response is achieved.

A. All subjects will undergo the **following procedures at two week intervals** during Extended Treatment, commencing at initiation of an Extended Treatment Course:

   - Review of concomitant medications
   - Assessment of adverse events
   - Weight and vital signs
   - Study Lesion measurement
   - Study Lesion dose calculation
   - Administration of talimogene laherparepvec to Study Lesions

   Note that assessments conducted at the end of a prior Treatment Course (Initial or Extended) do not need to be repeated at the commencement of an Extended Treatment Course if the Extended Treatment Course commences within 2 days of the completion of the prior Treatment Course.

B. All subjects will undergo the following **additional procedures at 4 week intervals** during Extended Treatment (i.e., in addition to those specified at 2 week intervals):

   - Symptom self-assessment (Skindex-16)
   - Review of medical conditions and symptoms
   - Clinical evaluation
   - Grading of lesion bleeding, ulceration and infection (per CTCAE criteria)
   - ECOG performance status
   - Laboratory tests (CBC, CMP, TFT)
   - Pregnancy test (urine βHCG, only female subjects of childbearing potential)
   - Photodocumentation of Study Lesions

C. All subjects will undergo the following **additional procedures at 12 week intervals** during Extended Treatment (i.e., in addition to those specified at 2 and 4 week intervals):

   - Comprehensive assessment of progression status (RECIST)
     - Radiologic imaging of chest, abdomen and pelvis (and any other body regions with non-cutaneous Study Lesions)
     - MRI of brain (if clinically indicated)

- Histological or cytological confirmation of CR (if indicated)
- Evaluation for distant metastases
- Evaluation of Target Lesions (Target Lesion measurement)
- Evaluation of Non-Target Lesions

Completion of these procedures constitutes completion of an Extended Treatment Course of talimogene laherparepvec.

7.3.1.4 Repetition of Extended Treatment

Before commencing additional treatment subjects should be evaluated for dose tolerance (see protocol Sections 6.1.5, 6.2.3. 6.3.3 or 6.4.4 for PV-10, dacarbazine, temozolomide or talimogene laherparepvec, respectively).

Subjects continuing to exhibit partial response or stable disease at the conclusion of an Extended Treatment Course should repeat extended treatment until complete response or disease progression.

Commencement of study events scheduled for Response Follow-up or Survival Follow-up will be delayed by the number of weeks the subject remains in Extended Treatment.

7.3.2 Subjects with Complete Response

Subjects with complete response at the end of an Initial or Extended Treatment Course will enter Response Follow-up and be followed until disease progression, withdrawal of consent or study termination. These subjects will undergo the following procedures during Response Follow-up.

7.3.2.1 Clinical Evaluation (every 4 weeks)

The following evaluations will be performed:

- Review of medical conditions and symptoms
- Clinical evaluation
- Grading of lesion bleeding, ulceration and infection (per CTCAE criteria)
- ECOG performance status
- Photodocumentation of Study Lesions (or Study Lesion locations if lesions no longer present)
- Histological or cytological confirmation of CR (if indicated)

These evaluations will be discontinued 37 weeks after initial study treatment.

7.3.2.2 Response Assessment (every 12 weeks)

The following response assessments will be performed:

- Review of medical conditions and symptoms
- Grading of lesion bleeding, ulceration and infection (per CTCAE criteria)
- Weight and vital signs
- ECOG performance status
- Photodocumentation of Study Lesions (or Study Lesion locations if lesions no longer present)
- Comprehensive assessment of progression status (RECIST)
  - Radiologic imaging of chest, abdomen and pelvis (and any other body regions with non-cutaneous Study Lesions)
  - MRI of brain (if clinically indicated)
  - Histological or cytological confirmation of CR (if indicated)
  - Evaluation for distant metastases
  - Evaluation of Target Lesions (Target Lesion measurement)
  - Evaluation of Non-Target Lesions

Note that Response Assessments will coincide with every 3rd Clinical Evaluation through Week 37 (for subjects receiving PV-10 or chemotherapy) or Week 38 (for subjects receiving talimogene laherparepvec). At those time points, only the assessments required for Response Assessment will be performed.

Response assessments will continue until disease progression, subject withdrawal or study termination.

7.3.3 Subjects with Disease Progression

7.3.3.1 Subjects Receiving PV-10

Subjects who meet the study definition of disease progression will discontinue study treatment, undergo Final Follow-up assessment (protocol Section 7.6) and enter the Survival Follow-up portion of the study (protocol Section 7.7).

7.3.3.2 Subjects in the Comparator Arm

Subjects who have completed at least 1 Treatment Cycle of dacarbazine, temozolomide or talimogene laherparepvec and who meet the study protocol definition of disease progression (protocol Section 4.3.1) but do not have evidence of visceral metastases or a decline in ECOG status to ≥ 3 may enter the crossover portion of the study and be treated with PV-10 (protocol Section 7.4). These subjects must meet all study inclusion and exclusion criteria for clinical laboratories, thyroid function, concurrent or intercurrent illness and pregnancy at the time of crossover. Informed consent must be obtained prior to commencement of crossover treatment.

Subjects who meet the study definition of disease progression but are not eligible to enter the crossover portion of the study or who elect not to enter the crossover portion of the study will discontinue study treatment, undergo Final Follow-up assessment (protocol Section 7.6) and enter the Survival Follow-up portion of the study (protocol Section 7.7).

7.4 Crossover Treatment and Follow-up

Subjects eligible for and electing to crossover from the comparator arm to PV-10 (see protocol Section 4.6) will be treated with PV-10 using a schedule equivalent to that used with subjects enrolled into the main PV-10 study arm (i.e., protocol Section 7.2).

7.4.1 Crossover Treatment Cycle 1: Beginning of Cycle ("Week 1 / Day 1")

- Informed consent
- Assessment of adverse events (adverse events occurring after signing the informed consent form but before initiation of study treatment on Study Day 1 will be recorded on the Adverse Events CRF)
- Symptom self-assessment (Skindex-16)
- Review of medical conditions and symptoms
- Grading of lesion bleeding, ulceration and infection (per CTCAE criteria)
- Review of concomitant medications
- Weight and vital signs
- ECOG performance status
- Laboratory tests (CBC, CMP, TFT)
- Pregnancy test (urine βHCG, only female subjects of childbearing potential)
- Photodocumentation of Study Lesions (prior to initiation of PV-10 treatment)
- Study Lesion measurement
- Study Lesion dose calculation
- Administration of PV-10 (to Study Lesions)
- Observation for post-treatment adverse events

7.4.2 Crossover Treatment Cycle 1: Treatment Follow-up

Subjects will undergo the following procedures one week after beginning the first Crossover Treatment Cycle:

- Review of concomitant medications
- Assessment of adverse events
- Note: these assessments may be conducted remotely (e.g., telephonically)

7.4.3 Crossover Treatment Cycle 1: End of Cycle

All subjects will undergo the following procedures four weeks after beginning the first Crossover Treatment Cycle:

- Symptom self-assessment (Skindex-16)
- Review of medical conditions and symptoms
- Clinical evaluation
- Grading of lesion bleeding, ulceration and infection (per CTCAE criteria)
- Review of concomitant medications
- Assessment of adverse events
- Weight and vital signs
- ECOG performance status
- Laboratory tests (CBC, CMP, TFT)
- Pregnancy test (urine βHCG, only female subjects of childbearing potential)
- Photodocumentation of Study Lesions

7.4.4 Crossover Treatment Cycle 2: Beginning of Cycle

Upon completion of follow-up assessments for the end of the first Crossover Treatment Cycle all subjects will undergo the following procedures to begin the second Crossover Treatment Cycle:

- Subjects requiring PV-10 at this visit
  - Study Lesion measurement
  - Study Lesion dose calculation
  - Administration of PV-10
  - Observation for post-treatment adverse events
- Subjects not requiring PV-10 at this visit
  - No additional study procedures

7.4.5 Crossover Treatment Cycle 2: Treatment Follow-up

Subjects who received PV-10 at the preceding visit will undergo the following procedures one week after beginning the second Crossover Treatment Cycle:

- Review of concomitant medications
- Assessment of adverse events
- Note: these assessments may be conducted remotely (e.g., telephonically)

7.4.6 Crossover Treatment Cycle 2: End of Cycle

All subjects will undergo the following procedures four weeks after beginning the second Crossover Treatment Cycle:

- Symptom self-assessment (Skindex-16)
- Review of medical conditions and symptoms
- Clinical evaluation
- Grading of lesion bleeding, ulceration and infection (per CTCAE criteria)
- Review of concomitant medications
- Assessment of adverse events
- Weight and vital signs
- ECOG performance status
- Laboratory tests (CBC, CMP, TFT)
- Pregnancy test (urine βHCG, only female subjects of childbearing potential)
- Photodocumentation of Study Lesions

7.4.7 Crossover Treatment Cycle 3: Beginning of Cycle

Upon completion of follow-up assessments for the end of the second Crossover Treatment Cycle all subjects will undergo the following procedures to begin the third Crossover Treatment Cycle:

- Subjects requiring PV-10 at this visit
  - Study Lesion measurement
  - Study Lesion dose calculation
  - Administration of PV-10
  - Observation for post-treatment adverse events
- Subjects not requiring PV-10 at this visit
  - No additional study procedures

7.4.8 Crossover Treatment Cycle 3: Treatment Follow-up

Subjects who received PV-10 at the preceding visit will undergo the following procedures one week after beginning the third Crossover Treatment Cycle:

- Review of concomitant medications
- Assessment of adverse events
- Note: these assessments may be conducted remotely (e.g., telephonically)

7.4.9 Crossover Treatment Cycle 3: End of Cycle

All subjects will undergo the following procedures four weeks after beginning the third Crossover Treatment Cycle:

- Symptom self-assessment (Skindex-16)
- Review of medical conditions and symptoms
- Grading of lesion bleeding, ulceration and infection (per CTCAE criteria)
- Review of concomitant medications
- Assessment of adverse events
- Weight and vital signs
- ECOG performance status
- Laboratory tests (CBC, CMP, TFT)
- Pregnancy test (urine βHCG, only female subjects of childbearing potential)
- Photodocumentation of Study Lesions
- Comprehensive assessment of progression status (RECIST)
  - Radiologic imaging of chest, abdomen and pelvis (and any other body regions with non-cutaneous Study Lesions)
  - MRI of brain (if clinically indicated)
  - Histological or cytological confirmation of CR (if indicated)
  - Evaluation for distant metastases
  - Evaluation of Target Lesions (Target Lesion measurement)
  - Evaluation of Non-Target Lesions

Completion of these procedures constitutes completion of a Crossover Treatment Course.

7.4.10 Response Assessment Upon Completion of a Crossover Treatment Course

At the completion of a Crossover Treatment Course (i.e., 3 Crossover Treatment Cycles), subsequent study procedures, evaluations and treatments will be determined by subject status at the end of the Treatment Course (i.e., complete response, partial response, stable disease or disease progression).

7.4.10.1 Subjects with Partial Response or Stable Disease

Subjects with partial response or stable disease after completing a Crossover Treatment Course will receive additional treatment until the occurrence of disease progression as defined in the study protocol, intolerable toxicity, subject request to discontinue treatment, serious intercurrent or worsening concurrent medical conditions, or complete response is achieved.

Subjects will undergo the procedures delineated in protocol Sections 7.4.1 to 7.4.9; however, the assessments conducted at the end of the prior Treatment Course do not need to be

repeated at the commencement of the next Treatment Course if the next Treatment Course commences within 2 days of the completion of the prior Treatment Course.

7.4.10.2 Subjects with Complete Response

Subjects with complete response at the end of a Crossover Treatment Course will enter Response Follow-up and be followed until disease progression, withdrawal of consent or study termination. These subjects will undergo the procedures delineated in protocol Section 7.3.2.

7.4.10.3 Subjects with Disease Progression

Subjects who meet the study definition of disease progression will discontinue study treatment, undergo Final Follow-up assessment (protocol Section 7.6) and enter the Survival Follow-up portion of the study (protocol Section 7.7).

7.5 Treatment Discontinuation

A Subject's assigned study treatment will be permanently discontinued without objective evidence of disease progression in Study Lesions under the following circumstances:

1. The treatment exhibits unacceptable toxicity (i.e., toxicity requiring study drug discontinuation, as defined in protocol Sections 6.1.5, 6.2.3, 6.3.3 or 6.4.4 for PV-10, dacarbazine, temozolomide or talimogene laherparepvec, respectively).

2. The Principal Investigator thinks that the best interest of the subject requires a change of therapy, including palliative surgery.

3. Serious concurrent or intercurrent illness or significant worsening of concurrent or intercurrent illness.

4. The subject is not compliant with protocol procedures.

5. The subject requests treatment discontinuation.

6. The subject withdraws consent.

7. The subject is lost to follow-up.

8. Administrative reasons (if this is designated, an explanation must be provided).

Subjects in the comparator arm who discontinue study treatment due to unacceptable toxicity may continue Response Follow-up at the discretion of the Investigator (protocol Section 7.3.2) and may be eligible to enter the crossover portion of the study (protocol Section 7.4).

Subjects without objective evidence of disease progression who discontinue study treatment due to subject request to discontinue treatment or serious intercurrent or significant worsening of concurrent illness may continue Response Follow-up at the discretion of the Investigator (protocol Section 7.3.2).

Subjects who discontinue study treatment for any of the remaining circumstances will be withdrawn from active participation in the study and should, if possible, undergo Final Follow-up assessment (protocol Section 7.6).

7.6 Subject Withdrawal and Final Follow-up (Termination Visit)

Subjects will be withdrawn from active participation in the study due to disease progression and should undergo Final Follow-up assessment prior to entry into the survival portion of the study (protocol Section 7.7).

Subjects withdrawn from active participation in the study due to clinical progression, increase in melanoma-related symptoms or change of melanoma therapy (including due to toxicity requiring study drug discontinuation, sections 6.1.5, 6.2.3, 6.3.3 and 6.4.4) will be deemed to have experienced disease progression at the time of withdrawal; these subjects should undergo Final Follow-up assessment prior to entry into the survival portion of the study (protocol Section 7.7). Subjects in the comparator arm withdrawing due to toxicity may be eligible for crossover (protocol Section 4.6).

Subjects withdrawn from active participation in the study due to serious concurrent or intercurrent illness or significant worsening of concurrent or intercurrent illness should resume active participation if possible upon resolution or stabilization of their concurrent or intercurrent illness. Subjects that cannot resume active study participation should undergo Final Follow-up assessment, if possible, prior to entry into the survival portion of the study (protocol Section 7.7), and will be censored from response and safety assessment using the date of their last assessment for progression.

Subjects withdrawn from active participation in the study due to non-compliance with protocol procedures or request for treatment discontinuation will be censored from response and safety assessment using the date of their last assessment for progression; if possible, these subjects should undergo Final Follow-up assessment prior to entry into the survival portion of the study (protocol Section 7.7).

Subjects withdrawn from active participation in the study due to withdrawal of consent, loss to follow-up or for administrative reasons will be censored from all assessments using the date of their last assessment for progression; these subjects will not undergo Final Follow-up assessment nor enter the survival portion of the study (protocol Section 7.7).

Subjects participating in Final Follow-up assessment at time of withdrawal from active participation in the study (i.e., Termination Visit) should undergo the following procedures.

- Symptom self-assessment (Skindex-16; subjects will complete final self-assessment at this visit)
- Review of medical conditions and symptoms
- Grading of lesion bleeding, ulceration and infection (per CTCAE criteria)
- Assessment of adverse events
- Height, weight and vital signs
- ECOG performance status
- Laboratory tests (CBC, CMP, TFT)
- Pregnancy test (urine βHCG, only female subjects of childbearing potential)
- Photodocumentation of Study Lesions
- Comprehensive assessment of progression status (RECIST)
    - Radiologic imaging of chest, abdomen and pelvis (and any other body regions with non-cutaneous Study Lesions) [8]
    - MRI of brain (if clinically indicated)
    - Histological or cytological confirmation of CR (if indicated)
    - Evaluation for distant metastases
    - Evaluation of Target Lesions (Target Lesion measurement)
    - Evaluation of Non-Target Lesions

These Termination Visit procedures are not required if subject withdrawal coincides with the end of a Treatment Course (i.e., procedures are redundant with those scheduled for the end of a Treatment Course, including those during Extended or Crossover Treatment).

7.7 Survival Follow-up

Survival Follow-up will be done at 12 week intervals commencing at the date of the subject's withdrawal from active participation in the study and will continue every 12 weeks thereafter until the subject's death or study termination. Documentation of survival may be in the form of a subject clinic visit or other personal contact; telephone contact with the subject, subject's immediate family or legal representative or medical care providers; review of medical records; or other unequivocal evidence of the subject's survival status.

Survival Follow-up will be discontinued and subject status censored for those subjects withdrawing consent using the date of their last confirmation of survival.

Survival Follow-up is to be attempted at the specified times for subjects who appear to be lost to follow-up until survival status can be determined or until the end of the study.

[8] Subjects for whom Final Follow-up occurs less than 8 weeks after a prior CT or MRI will not undergo additional CT or MRI imaging at Final Follow-up.

Subjects whose survival status cannot be determined will be censored using the date of their last confirmation of survival.

7.8 Study Modifications

Any modification of the study protocol will be made only with the approval of the Sponsor and Principal Investigator.

There will be no alterations or changes in this protocol without the written consent of the Sponsor, except as required in medical emergencies. Any other changes in the protocol will be implemented as an amendment to the protocol. The Sponsor will generate all protocol amendments. Amendments will be in writing and signed by the Principal Investigator to document his/her agreement. The Principal Investigator will have all relevant protocol amendments approved by his or her IRB/IEC as required under applicable institutional regulations and local and national laws and regulations. Until an amendment has been approved by the IRB/IEC, the existing protocol is to be followed unless otherwise instructed by the Sponsor. Depending on the nature of the amendment, enrollment may be curtailed until the amendment has been approved by the IRB/IEC. The Sponsor will inform Investigators if this is required at the time the amendment is issued.

7.9 Study Oversight

The Sponsor will designate a regional Lead Investigator from the Principal Investigators in each key geographic area where the study is implemented (e.g., a Lead Investigator for North America, South America, Oceana, Asia, Europe, etc). The regional Lead Investigator will represent the interests of each Principal Investigator located within his or her designated geographic area, and will serve as a resource for coordination of study efforts and study oversight within that designated geographic area.

7.10 Study Termination

If the Lead Investigator(s) or Sponsor discover conditions during the study that indicate the study should be terminated, a recommendation to terminate the study may be made after consultation between the Sponsor and Lead Investigator(s). Similarly, if a Principal Investigator discovers conditions of concern during the study he or she should notify the Lead Investigator, who will investigate such concerns together with the Sponsor. If the Sponsor determines that study termination is appropriate, the study will be terminated under an appropriate schedule designed so as not to jeopardize the health of any subject.

If the Clinical Trial Data Monitoring Committee (CTDMC) discovers conditions during the study that indicate the study should be terminated, a recommendation to terminate the study may be made after consultation between the Sponsor and the CTDMC. If the Sponsor determines that study termination is necessary, the study will be terminated under an appropriate schedule designed so as not to jeopardize the health of any subject.

Both the Sponsor and each Principal Investigator reserve the right to terminate the study at the Principal Investigator's Institution, according to the terms specified in the study contract with the Principal Investigator's Institution. In such cases the Principal Investigator is to notify his or her IRB/IEC in writing of the study's completion or early termination, and send a copy of the notification to the Sponsor.

8 ADVERSE EVENTS

All adverse events (AE) and suspected adverse drug reactions (ADR) encountered during the reporting interval for the clinical study will be reported on the adverse events Case Report Form (CRF). 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)

A suspected adverse drug reaction (ADR) is any adverse event associated with the use of a drug and a suspected causal relationship:

> "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)

An unexpected adverse reaction is defined as:

> "An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product)". ICH-E2A: Clinical Safety Data Management, Definitions and Standards for Expedited Reporting

Serious unexpected adverse reactions (SUSARs) are subject to regulatory reporting to authorities and study sites and other bodies, according to local requirements (please refer to protocol Section 8.2).

All adverse events occurring after signing the informed consent form and within 28 days of study drug administration (i.e., PV-10, dacarbazine, temozolomide or talimogene laherparepvec), or that occur at any time during the study interval that may be at least possibly related to such administration, should be followed until resolution or until they have met one of the criteria described in protocol Section 8.1. This may require obtaining clinical blood samples for appropriate laboratory tests until values return to baseline levels or performing follow-up physical examinations until resolution or stabilization of identified abnormalities.

Any adverse events that are ongoing at the time of subject withdrawal from the study must be followed until resolution or for a period of at least 28 days from the last dose of study drug. Any adverse events that lead to discontinuation of a subject from the study must be followed until one of the criteria met in section 8.1 is met.

Any serious adverse events that occur within 28 days of the last dose of study medication must be reported to the Sponsor and followed to conclusion.

Follow-up adverse event data for subjects who have discontinued active study participation may be obtained by telephone contact with the subject, the subject's immediate family or legal representative or medical care providers; review of medical records; or other unequivocal evidence of the subject's health status.

In the event of the initiation of new anticancer therapy, adverse events should be reported up to the date the subject commences new therapy.

8.1 Adverse Event Reporting

All adverse events that occur during the reporting interval for the clinical study, whether or not associated with administration of the study 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. Subject number, age, gender, site number, and country of occurrence.

2. Product administration (dose, start and stop date of administration).

3. The specific type of reaction reported in standard medical terminology.

4. The maximum severity/grade of the adverse event. Severity will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.03 (CTCAE) until 31 March 2018. CTCAE version 5.0 will be utilized for AE grading beginning on 1 April 2018. The Sponsor will provide the Investigator with the CTCAE in electronic format. A copy of the CTCAE version 5.0 can be downloaded from the NCI website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If severities are not defined in this scale, the intensity of each adverse event should be graded as follows:

CTCAE Grade	Severity	Definition
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observation only; intervention not indicated
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL NOTE: Must be reported as a Serious Adverse Event (SAE) if event is medically significant, inpatient hospitalization or prolongation of existing hospitalization or disabling or incapacity occurred. See protocol Section 8.2.
4	Life-threatening	Life-threatening consequences; urgent intervention indicated NOTE: Must be reported as a Serious Adverse Event (SAE). See protocol Section 8.2.
5	Death	Death related to AE NOTE: Must be reported as a Serious Adverse Event (SAE). See protocol Section 8.2.

A semicolon indicates "or" within the description of the grade.
Instrumental ADL (Activities of Daily Living) refer to preparing meals, shopping, using the telephone, managing money, etc.
Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

5. The duration of the adverse event (start and stop dates).

6. The drug/treatment relationship (assessed by the Investigator).

An assessment should be made of the causal relationship of the adverse event to the study drug or treatment, i.e., according to the following definitions:

Unrelated: There is evidence that the adverse event definitely has an etiology other than the assigned study drug or treatment.

Unlikely To be Related: The adverse event does not follow a plausible temporal relationship to the study drug or treatment but could not be

clearly explained by either the subject's clinical status or concomitant medication(s).

Possibly Related: The adverse event follows reasonable temporal relationship to the study 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 study drug or treatment and is not reasonably explained by either the subject's clinical status or concomitant medication(s). Confirmations by dechallenge and/or rechallenge is not required.

Certain Related: The adverse event occurs in a plausible temporal relationship to the study drug or treatment, and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study drug or treatment (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

7. The outcome/status, coded:

   [1] Recovered / resolved
   [2] Recovering / resolving
   [3] Not recovered / not resolved
   [4] Death
   [5] Unknown

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

The reporting period for adverse events commences upon signing the informed consent form.

8.2 Serious Adverse Events

Criteria for a serious adverse event (SAE) or serious adverse drug reaction (SADR):

Any untoward medical event or adverse reaction that at any dose:

- Results in death
- Is life threatening (at the time when the event occurred)
- Requires hospitalization or prolongation of existing hospitalization
- Results in significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is a significant important medical event (according to ICH-GCP)

If there is an AE or ADR within the trial which meets at least one criterion for seriousness, the SAE report form must be filled in as completely as possible by the site and submitted via electronic Case Report Form within 24 hours after getting knowledge of the event. If the electronic Case Report Form is unavailable, the "Serious Adverse Event" form and the instructions on completion are provided in the investigator's study manual. The "Instructions for Completing the SAE Form" give more detailed guidance on the reporting of SAEs, significant overdose cases, and AEs initially reported as non-serious which become serious.

Reporting of a suspected SAE should not be delayed in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the initial report.

If a SAE meets the criteria for a SUSAR, it is subject to regulatory reporting according to local regulations. Criteria for a SUSAR are:

- event is serious;
- event is unexpected; and
- event has at least a suspected causal relationship to the study drug.

The assessment of expectedness will be done by the Sponsor and the Medical Monitor.

Even if the regulatory reporting can be conducted by designees, the Sponsor is responsible for notification of and reporting to FDA and other governmental regulatory authorities having jurisdiction over the study, and for informing all participating Principal Investigators in a written safety report of any adverse event deemed at least possibly related to use of the study drug that is both serious and unexpected (SUSAR) according to local requirements.

The Principal 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 Sponsor with a complete written history of the adverse event and keep his/her IRB/IEC informed of all adverse events occurring during the course of the study if required according to the local IRB's/IEC's rules and regulations.

If the Principal Investigator detects a serious adverse event in a study subject occurring more than 28 days after the last dose of study medication, and considers the event at least possibly related to study treatment, he or she should contact the Sponsor to determine how the event should be documented and reported.

8.3 Pregnancy

Any pregnancy diagnosed during the study interval, or that occurs within 28 days after the last dose of study medication, must be reported immediately to the Principal Investigator. The Principal Investigator will notify the Sponsor or designee by following the procedures described in Section 8.2. The outcome of all such pregnancies (i.e., spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be documented and followed up on a form that will be provided by the Sponsor. The pregnancy will be followed to term and the outcome, including any premature termination, must be reported to the Sponsor. All live births must be followed for a minimum of 30 days or to the first well-baby visit. All reports of congenital abnormalities/birth defects and spontaneous abortions/miscarriages should be reported as an SAE. Elective abortion procedures, without complications, should not be considered as adverse events.

9 DATA MANAGEMENT, QUALITY ASSURANCE AND QUALITY CONTROL

The study will be conducted according to ICH GCP consolidated guidelines (E6) and applicable regulatory requirements. The Sponsor will assure that the written Standard Operating Procedures (SOPs) are implemented to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

Each Principal Investigator shall ensure that the handling and storage of all study records and data, including photographs of study participants, at his or her study site complies with all data management and confidentiality regulations and policies in effect at his or her institution, including those regulating storage, sharing and retention of subject-identifiable data.

9.1 Data Collection, Reporting, and Subject Confidentiality

Data for each subject will be clearly recorded in the subject's source documents.

Data from the study must be transcribed from each subject's primary records and reported to the Sponsor on case report forms (CRFs) (and subject diaries, if applicable) which are identified by subject number. Case report forms (and subject diaries, if applicable) will be provided by the Sponsor for each subject enrolled. The Principal Investigator will ensure that the CRFs are correctly completed.

Subject identity and study information (CRFs, photographs, adverse event correspondence, etc.) will be kept confidential to the extent provided by law. Subjects and Investigators must be aware that the Sponsor, the FDA or other governmental regulatory authorities having jurisdiction over the study may inspect relevant parts of the subject medical records and other source documents.

Study radiologic imaging data will be uploaded to a secure server (**Appendix D**), which will allow access by authorized study staff, the Sponsor, authorized representatives of the Sponsor and the IRC.

Study photographic data must not be stored on computers or servers of study staff or their institution. Study photographs will be uploaded to a secure server (**Appendix E**), which will allow access by authorized study staff, the Sponsor, authorized representatives of the Sponsor and the IRC. The Investigator will be provided with reference prints of study photographs. At the end of the study, study photographs will be transferred to digital storage media for archiving with CRFs in the site file and the Trial Master File.

9.2 Quality Control

The Principal Investigator will permit a representative of the Sponsor to conduct study-related monitoring, IRB / IEC review, and regulatory inspections, providing access to

relevant source data /documents and CRFs at regular intervals throughout the study. These inspections are for the purpose of verifying adherence to the protocol and the completeness and exactness of the data being recorded, as well as compliance with Good Clinical Practices as defined in Title 21 of the United States Code of Federal Regulations Parts 50, 54, 56, 312, and Part 11, ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

Sponsor-authorized quality assurance personnel may carry out audits for which the Principal Investigator must provide support.

The study will be supervised by a Sponsor-authorized monitor. The study monitor will contact the Principal Investigator regularly to discuss the progress of the study and to check study documents, including the informed consent forms, for completeness and consistency.

The study monitor will cross-check the data entered in the CRFs with the source data at the study site and examine source documents in order to verify adherence to the study protocol.

The CRFs will be checked for completeness and correctness by the study monitor and data management department of the Sponsor-authorized data management vendor, [redacted], according to applicable SOPs, and any queries will be resolved by the Investigator.

All clinical data will be captured via electronic data capture (EDC) using a web-based tool. The EDC software [redacted] will be used for data capture. [redacted] is compliant with all legislation relevant to electronic data capture (e.g., FDA 21 CFR Part 11, GCP).

Authorized site staff will enter and edit the data via a secure network, with secure access features (username and password). A complete electronic audit trail will be maintained. The Principal Investigator will approve the data using an electronic signature (Ref: 21 CFR Part 11), and this approval is used to confirm the accuracy of the data recorded.

Electronic CRFs will be used for all subjects. The Investigator's data will be accessible from the Investigator's site throughout the trial. The eCRFs must be kept current to reflect subject status at each phase during the course of the trial. The eCRF will not capture personalized data. The Investigator must make a separate confidential record of personalized details (name and initials) on the subject identification and enrollment log. All changes to data are done by the Investigator and/or the Investigator's authorized site staff through the EDC system.

It is the responsibility of the Principal Investigator of the respective site to ensure that all subject discontinuations or changes in study or other medications entered on the subject's eCRF are also made on the subject's medical records.

The eCRFs for any subject leaving the study should be completed at the time of the final visit or shortly thereafter.

9.3 Data Management

Overall data management will be performed by the Sponsor-authorized data management vendor, [redacted], according to [redacted] SOPs.

The IRC for study will be established and managed by the Sponsor-authorized vendor, [redacted], according to Sponsor-approved IRC charters and [redacted] SOPs. The IRC will consist of three subcommittees: a radiology IRC; a dermatology IRC; and an Endpoint Assessment Committee (EAC) IRC that incorporates the respective assessments of the radiology IRC and dermatology IRC to determine primary and secondary endpoints for each study subject. The determinations of each subcommittee will be reported to [redacted] for incorporation into the clinical study report (CSR).

9.4 Study Data Documents and Record Retention

It is the responsibility of the Principal Investigator and study staff to maintain a comprehensive file of all subject documents relevant to the study. Such documentation should include:

- Source Documents – all documents substantiating the data reported to the Sponsor with regard to laboratory data, diagnostic tests and procedures, treatment regimens and study evaluations
- Screening Log – this log must include the reason any subject was screened for the study and found to be ineligible
- Investigational Product Accountability Record (IPAR) or equivalent
- Informed Consent Forms – signed by each subject
- IRB / IEC approval letters and correspondence
- Study protocol and any study amendments
- All versions of the PV-10 Investigator Brochure in effect during the study
- All serious adverse event (SAE) notifications and correspondence

The Principal Investigator shall maintain the records of drug disposition, subject screening logs, signed informed consent forms, case report forms, all correspondence, and supporting source documentation for a minimum period of two years following the marketing approval or two years after the formal discontinuation of the clinical development of the investigational product.

The Sponsor shall retain copies of study records for a minimum period of fifteen years after completion of the study.

9.5 Study Reports, Use of Information and Publication

CRFs will be used by the Sponsor to prepare a final clinical study report of the study results. This final report will be submitted to the study's Lead Investigator(s) for signature. The Sponsor and each Principal Investigator will maintain copies of the final approved report.

All information concerning the Sponsor, its operations, patent applications, formulas, manufacturing processes, basic scientific data and formulation information supplied by the Sponsor and not previously published, are considered confidential and will remain the sole property of the Sponsor. The Principal Investigator agrees to use this information only in conducting this study and will not use it for other purposes without the Sponsor's prior written consent.

The data generated by this clinical study are the property of the Sponsor and should not be disclosed without prior written permission from the Sponsor. The data may be used for presentation or publication at the Sponsor's discretion or for submission to governmental regulatory agencies. The study results may be published and/or presented by the Principal Investigator and/or study Investigators upon written agreement from the Sponsor. The study personnel shall be listed on each publication.

10 STATISTICAL AND ANALYTICAL CONSIDERATIONS

The statistical analyses will be reported using summary tables, figures, and data listings. Unless otherwise noted, all statistical testing will be two-sided and will be performed at the 0.05 significance level. Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. All summary tables will be presented by treatment group. Baseline summaries will also include a total summary column. All individual subject data (in anonymized form) will be presented by subject in data listings.

Data from the crossover phase will be summarized separately. Unless otherwise specified, data collected prior to the first dose of PV-10 in crossover will be associated with the comparator treatment and data collected after the first dose of PV-10 in crossover will be associated with the PV-10 treatment.

All primary and secondary endpoints involving disease response and progression will be based on the IRC determination. In addition, other secondary and exploratory analyses will be conducted based on patient reported outcome or Investigator determination.

10.1 Determination of Sample Size

Historical data on treatment of melanoma with DTIC, TMZ and talimogene laherparepvec illustrate a similar pattern of response for these drugs, with the majority of patients experiencing progression within 2-4 months (i.e., at the first comprehensive assessment for progression). While the majority of these clinical data are derived from Stage IV patients, there is minimal or no evidence indicating differential response of earlier-stage versus later-stage patients to these drugs. In comparison with these data, PV-10 appears favorably in terms of response rate and PFS, as illustrated in the following table.

Comparison of Melanoma Study Data:

Agent	N	Median Age (yrs)	Stage IV	CR	PR	ORR	Median PFS (months)	% Progressed after 6 Months
PV-10 †	80	70	34%	26%	25%	51%	NA	67%¶
DTIC [a]	252	56	97%	1%	10%	10%	2.6	79%
DTIC [b]	338	52	96%	0%	5%	5%	1.6	96%
DTIC [c]	149	59	79%	3%	9%	12%	1.5	95%
DTIC [d]	430	NR	100%	1%	9%	10%	2.2	78%
TMZ [c]	156	58	76%	3%	11%	14%	1.9	88%
TMZ [d]	429	NR	100%	2%	12%	14%	2.3	75%
TMZ [e]	22	59	23%	9%	5%	14%	NR	NR
Investigator Choice [f]	155	63	99%	0%	4%	4%	2.7	83%
Talimogene Laherparepvec [g,h]	295	63	70%	11%	16%	26%	NR	NR

† Data from phase 2 trial of PV-10; response assessed at 4-week intervals from week 8 to week 24 then at weeks 36 and 52 using modified RECIST criteria. The median PFS was not reached during the study interval for Stage III subjects (the mean PFS for Stage III subjects was at least 9.5 months). The median PFS for stage IV subjects was 2.0 months (2.5 months mean PFS). Subjects could not receive additional melanoma treatment after week 16.

¶ Percentage of ITT population progressed after 6 months. Among subjects with Stage III disease, 58% had disease progression after 6 months.

[a] Data from comparator arm of ipilimumab + DTIC phase 3 trial (Robert et al.); response assessed at 12-week intervals using RECIST criteria [17].

[b] Data from comparator arm of vemurafenib vs DTIC phase 3 trial (Chapman et al.); response assessed at 6-week intervals to week 12 then every 9 weeks thereafter using RECIST criteria [18].

[c] Data from randomized trial of temozolomide vs dacarbazine (Middleton et al.); response assessed at 4-week intervals using WHO criteria [34].

[d] Data from randomized trial of extended-schedule temozolomide vs dacarbazine (Patel et al.); response assessed at 9-week intervals using RECIST criteria [84].

[e] Data from phase 2 trial of neoadjuvant temozolomide in resectable melanoma patients (Shah et al.); response assessed at 4-week intervals using RECIST criteria [85].

[f] Data from phase 2 trial of pembrolizumab vs chemotherapy in ipilimumab-refractory melanoma (Ribas et al.); response assessed at 12-week intervals using RECIST criteria [86].

[g] Data from phase 3 trial of talimogene laherparepvec vs GM-CSF (Andtbacka et al.); response assessed using modified WHO criteria [37].

[h] Data from patterns of response in phase 3 trial of talimogene laherparepvec (Andtbacka et al.) [87].

While none of these literature reports provide a detailed breakout of PFS data by disease stage, Chapman et al. [18] show that "tumor best response" characteristics for Stage III subjects closely overlap those of Stage IV subjects in both the vemurafenib and DTIC study arms, supporting a hypothesis that disease progression with these systemic therapies is not strongly correlated with stage. A Cox regression analysis by Middleton et al. [34] indicated that site of metastatic disease (i.e., hepatic and any other, subcutaneous only, or other) was a prognostic factor for PFS and OS; however, data on PFS for these subgroups are not presented. In a small study primarily of Stage III patients Shah et al. [85] concluded that "the response proportion to temozolomide in the neoadjuvant setting … was not different than in

the metastatic setting." Differences in PFS by disease stage observed in the phase 2 PV-10 study appear to be related to differences in baseline disease burden and early progression of non-study disease in Stage IV subjects that led to early termination of a substantial fraction of these subjects before the effects of PV-10 could be fully assessed. Melanoma patients refractory to ipilimumab receiving chemotherapy (investigator's choice of paclitaxel plus carboplatin, paclitaxel, carboplatin, dacarbazine or temozolomide) exhibited response rates and duration of response comparable to naïve patients [86].

In the phase 3 study of talimogene laherparepvec vs GM-CSF, Andtbacka et al. [37] report a higher CR and ORR than that shown here for chemotherapy, although the study endpoints did not include PFS. It was noted that 68% of patients achieving ORR had response duration of $\geq$ 9 months (equating to 23% of ITT patients); DRR (duration of response lasting $\geq$ 6 months) was reported to be 16.3% with a median TTR of 4.1 months. Of responders, 54% met criteria for disease progression prior to response (PPR). Andtbacka et al. [87] show that about 40% of these PPRs were due to progression of existing lesions (per modified WHO criteria). Median time to treatment failure (TTF) was 8.2 months. Durable response occurred predominantly among Stage III patients (33% DRR vs 16.3% for ITT) and in treatment naïve patients (24% vs 10% for second line or greater). Thus, while it is impossible to comprehensively compare the potential treatment benefit of talimogene laherparepvec to that of dacarbazine and temozolomide, it appears that objective response rates and PFS are within a factor of two and it is appropriate to model the comparator arm using point estimates for these parameters.

For this study, the overall type I error probability is 0.05 (two-sided) and the type II error probability used to compute sample size is 0.10 (corresponding to 90% power). Subjects will be randomized using a 2:1 treatment allocation (i.e. two-thirds of the subjects will receive PV-10).

The sample size calculations are based on a group sequential design with one interim analysis after 50% of the total number of events have occurred. The interim analysis will use an alpha level of 0.00001 and the final analysis will be performed using an alpha level of 0.05 (i.e., there is no adjustment necessary). However, for the purposes of sample size calculations, an O'Brien-Fleming stopping boundary was used, with an alpha level of 0.005 at the interim analysis and an alpha level of 0.048 at the final analysis [88]. Assuming a 4.0 month median PFS for the comparator arm and a hazard ratio of 0.58 (corresponding to a median PFS of 6.9 months for the PV-10 arm), the required number of events (disease progression or death) is 161. Assuming an accrual period of 48 months and an additional follow-up period of 12 months after the last subject is enrolled, the calculated total sample size is 180 subjects. Allowing for a dropout rate of approximately 20% gives an adjusted total sample size of 225 (i.e., 75 in the comparator arm and 150 in the PV-10 arm).

These calculations were carried out using the SEQDESIGN procedure in SAS® version 9.2.

10.2 Analysis Populations

The following analysis populations will be used for efficacy analyses:

- The Intent-To-Treat (ITT) population is defined as all randomized subjects. Treatment assignment will be based on the randomized treatment. This is the primary population for efficacy analyses.

- The Efficacy Evaluable (EE) population will include all ITT subjects who receive at least one dose of study medication; have Stage IIIB, Stage IIIC or Stage IV M1a recurrent, satellite or in-transit cutaneous, subcutaneous, soft tissue, or superficial or palpable nodal melanoma metastases; have at least 1 measurable Target Lesion consisting of at least one cutaneous lesion (each lesion ≥ 10 mm in longest diameter or up to 5 lesions having a sum of longest diameters ≥ 10 mm), and / or at least one subcutaneous or soft tissue lesion (each lesion ≥ 10 mm in longest diameter by CT or MRI), and / or at least one superficial or palpable nodal lesion (each lesion ≥ 15 mm in short axis diameter by CT or MRI); have no lesion > 50 mm longest diameter; and have no more than 50 total lesions at enrollment.

The Safety Population will include all subjects who received any amount of study drug. Treatment assignment will be based on the treatment actually received.

10.3 Study Population

10.3.1 Subject Disposition

Subject disposition information will be summarized for all subjects by treatment group. Summaries will include: the number of subjects screened, the number of subjects in each analysis population, the number of subjects in each geographic region, the number of subjects who cross over from the comparator arm to the PV-10 arm, and the primary reason for discontinuation.

10.3.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics, including age, gender, ethnicity, race, height, weight, ECOG performance status, prior immunotherapy status (failure or naïve), BRAF V600 mutation status (positive, wild-type, unknown), medical history, and melanoma disease characteristics, will be summarized for the Safety, ITT, and EE populations using descriptive statistics. Additional characteristics may be included as needed.

10.3.3 Concomitant Medications

Verbatim terms on case report forms will be mapped to Anatomical/Therapeutic/Chemical (ATC) class and Generic Drug Names using the World Health Organization (WHO) dictionary.

Concomitant medications will be summarized by WHO ATC class and preferred name. These summaries will present the number and percentage of subjects using each medication.

10.4 Efficacy Analyses

The primary efficacy analysis will be based on the ITT population. Additional supportive efficacy analyses will be performed using the EE population.

The IRC determination of disease progression and tumor response will be used for all primary and secondary efficacy analyses involving disease response or progression. Exploratory analyses using the Investigator determination will also be performed.

All time to event analyses will be reported in time units of months. The conversion from days to months will be: months = (days / 365.25) • 12.

10.4.1 Primary Efficacy Endpoint

The primary endpoint of PFS is defined as the time from randomization to the first documentation of disease progression (as determined by the IRC) or death, whichever comes first. Subjects without documentation of disease progression or death at the time of analysis will be censored at the date of the last comprehensive assessment of progression status that documents a lack of progression.

A comprehensive assessment of progression status consists of study lesion measurement; evaluation for visceral, distant cutaneous, subcutaneous, soft tissue and nodal metastases; radiologic imaging of chest, abdomen and pelvis (and any other body regions with non-cutaneous Study Lesions); and MRI of the brain (if clinically indicated).

The following conventions will apply:

- Subjects who die prior to the first disease assessment will not be censored and his or her PFS value will equal the time to death.

- Subjects with no documentation of death or progression and with no post-baseline comprehensive assessments of progression status will be censored with a PFS value of 1 day.

- Any subject who crosses over from the comparator arm to PV-10, prior to documented progression, will be censored at the date of the last comprehensive assessment of progression status that is prior to the first dose of PV-10, regardless of whether or not the subject subsequently progressed. (This would be a protocol violation and is not expected to occur since progression status qualifying for crossover will be reviewed and approved by the sponsor and verified by the IRC.)

- Subjects with documented disease progression after discontinuing study drug for any other reason will not be censored. His or her PFS value will be the time from randomization to the first documentation of disease progression.

10.4.2 Secondary Efficacy Endpoints

The following list defines the secondary efficacy endpoints for which a hierarchical testing procedure will be applied, listed in the order in which they will be tested:

- Complete response rate (CRR) defined as the proportion of subjects achieving a best overall response of CR. Confirmation of response is not required. Response assessment will be conducted at the end of the Initial Treatment Course and every 12 weeks thereafter until disease progression or study discontinuation occurs.

- Overall survival (OS) is defined as the time from randomization until death. Survival status of all ITT subjects will be assessed by telephone, personal contact (e.g., clinic visit) or other unequivocal documentation of subject status at 12-week intervals commencing at the time of study withdrawal. Subjects without documentation of death at the time of analysis will be censored at the date of last contact. Subjects in the comparator arm who cross over to PV-10 will not be censored at the time of crossover.

In addition the following secondary endpoint will be analyzed but will not be subject to the hierarchical testing procedure:

- Duration of complete response is defined as the time from the first documentation of CR to the first documentation of progressive disease or death, whichever comes first. Subjects without documentation of disease progression or death at the time of analysis will be censored at the date of the last comprehensive assessment of progression status that documents a lack of progression. This endpoint only applies to subjects who achieve a complete response.

10.4.3 Primary Efficacy Analysis

The stratified log-rank test, stratified by prior immunotherapy status (failure or naïve), will be used to test the null hypothesis that the PFS distributions in the 2 treatment arms are equal. A Cox regression analysis with a fixed effect for treatment arm and stratified by prior immunotherapy status (failure or naïve) will be used to estimate the hazard ratio and its 95% confidence interval. Kaplan-Meier estimates will be plotted and tabulated at selected time points. The median value and a 95% confidence interval will also be provided (assuming the median can be estimated).

10.4.4 Secondary Efficacy Analyses

Each of the secondary time-to-event endpoints (duration of CR and overall survival) will be analyzed using the same methods described above for the primary analysis of PFS. For the analysis of OS, crossover will be ignored. Addition exploratory analyses of OS are described below.

The complete response rate along with its exact 95% confidence interval will be tabulated by treatment arm. An exact confidence interval for the difference between the rates in the two treatment arms will also be provided. Fisher's exact test will be used to test the null hypothesis of no difference between the two treatment arms.

10.4.5 Multiplicity Adjustments

In order to maintain an overall type I error rate of 0.05, taking into account the primary and secondary analyses, a fixed-sequence testing procedure will be used, starting with the primary analysis and continuing with the analysis of each of the secondary endpoints in the *a priori* order specified above. If the primary analysis results in $p < 0.05$, it will be considered significant and the process continues with the first secondary endpoint; if the primary analysis results in $p \geq 0.05$, the process stops and none of the endpoints are considered significant. This process continues until the first analysis (in the pre-specified order) resulting in $p \geq 0.05$, in which case the process stops and this analysis and all subsequent analyses are considered non-significant. Note that all of the secondary analyses will be conducted and reported – this sequential procedure will be used to determine which of the analyses are considered to be statistically significant.

10.4.6 Examination of Subgroups and Covariates

Subgroups of the ITT population will be defined based on the following criteria:

- Gender (male, female)
- Age group (< 65 years, ≥ 65 years)
- Previous nodal disease (yes, no)
- Previous immunotherapy (failure versus naïve)
- Targeted therapy candidacy (failure, not candidate, unknown candidacy)
- Previous chemotherapy (failure versus naïve)
- Therapy class (PV-10, chemotherapy, oncolytic virus)
- Geographic region (North America, South America, Oceana, Asia, Europe)
- Number of lesions treated (≤ median, > median)

The primary efficacy analysis will be repeated for each of the subgroups. In addition, a Cox regression model with effects for treatment arm and each subgroup variable will be used to assess the treatment effect adjusted for all of these covariates. For the number of lesions treated, the actual number will be used as the covariate in the Cox model, rather than the

grouping based on the median. The hazard ratio and confidence interval for each effect in the model will be provided.

10.4.7 Sensitivity Analyses

A sensitivity analysis will be conducted using the following modification to the definition of PFS:

- Subjects who progress (or die without documentation of progression) more than 24 weeks after the most recent preceding comprehensive assessment of progression status will be censored at the date of the last preceding comprehensive assessment.

Analyses of this modified PFS endpoint will be carried out using the ITT and EE Populations.

A summary of the observed assessment schedules in the two treatment arms will be provided. For each subject, the time in weeks between successive comprehensive assessments of progression status will be computed. These inter-assessment intervals, which should be approximately 12 weeks in duration, will be summarized using descriptive statistics.

For subjects who die without documentation of disease progression, the time from the last comprehensive assessment of progression status to death will be calculated and summarized by treatment arm.

10.4.8 Exploratory Analyses

Exploratory analyses will be conducted for the following endpoints:

1. Change from Baseline to each visit where the variable is assessed in each of the Skindex-16 self-assessment instrument domain scores: symptoms (items 1 – 4), emotions (items 5 – 11), and functioning (items 12 – 16).

2. Change in Investigator assessed lesion bleeding, using the CTCAE grading schema for “skin and subcutaneous tissue disorders – other, bleeding.” Change will be assessed from Baseline to each visit where clinical evaluation or assessment of progression status is performed.

3. Change in Investigator assessed lesion ulceration, using the CTCAE grading schema for “skin and subcutaneous tissue disorders – skin ulceration.” Change will be assessed from Baseline to each visit where clinical evaluation or assessment of progression status is performed.

4. Change in Investigator assessed lesion infection, using the CTCAE grading schema for “infections and infestations – skin infection.” Change will be assessed from

Baseline to each visit where clinical evaluation or assessment of progression status is performed.

The following exploratory objective response and survival endpoints will also be analyzed:

1. PFS based on the Investigator assessment of disease progression.

2. CRR based on the Investigator assessment of disease response. Confirmation of response is not required.

3. Objective response rate (ORR) defined as the proportion of subjects achieving a best overall response of CR or PR, using the IRC determination of disease response. Confirmation of response is not required.

4. ORR based on the Investigator assessment of disease response. Confirmation of response is not required.

5. OS in the comparator arm with subjects censored at the time of crossover to PV-10.

6. OS in the comparator arm for subjects who cross over to PV-10, with OS calculated from the time of crossover to PV-10.

7. CRR and ORR in the comparator arm for subjects who cross over to PV-10, with response rate calculated from the time of crossover to PV-10

Change in disease impacts will be assessed using the Skindex-16 instrument [89-90]. The Skindex-16 consists of 16 items, each of which is scored on a 7-point Likert scale. Each item score will be transformed to a 0 to 100 scale by subtracting the minimum possible score, dividing by 6, and multiplying by 100. If the possible scores are 1-7, the transformed scores will be calculated as $[(S - 1)/6] \times 100$, where S is the raw score. If the possible scores are 0-6, the transformed scores will be calculated as $(S/6) \times 100$. Each domain score (i.e., symptoms, items 1 – 4; emotions, items 5 – 11; and functioning, items 12 – 16) is calculated as the average of the non-missing transformed items in the domain. An item with multiple answers is considered missing. If more than 25% (> 25%) of the items in a domain are missing, the domain score will be missing.

The change from Baseline in the three Skindex-16 domain scores will be summarized by visit during the Initial Treatment Course. These changes will be analyzed using a mixed model repeated measures (MMRM) analysis. The model will include fixed effects for treatment group, visit, the treatment-by-visit interaction, prior immunotherapy (failure or naïve), and the baseline domain score. An unstructured covariance matrix will be used and the Kenward-Roger method will be used to approximate the degrees of freedom. Least square means for each treatment group, and for the difference between treatment groups, at the end of the Initial Treatment Course, will be tabulated along with 95% confidence intervals. Only those

subjects with both a baseline score and at least one post-baseline score will be included in this analysis.

An additional sensitivity analysis of the Skindex-16 domain scores using last observation carried forward (LOCF) to impute missing values will be provided. An ANCOVA model with fixed effects for treatment group, prior immunotherapy (failure or naïve), and the Skindex-16 baseline domain score will be used to compare the treatment groups.

For other visits descriptive summaries will be provided. Subjects in the comparator arm who cross over to PV-10 will be summarized separately from the point of crossover.

Lesion bleeding, lesion ulceration, and lesion infection will be assessed on a 6-point scale (0, 1, 2, 3, 4, 5) based on the CTCAE grades, with a score of "0" indicating absence of the condition. Descriptive summaries will be provided by visit, and will include the distribution of scores as well as summary statistics. For each of the visits in the Initial Treatment Course, the Cochran-Mantel-Haenszel (CMH) mean score test, using the observed change from Baseline values as the scores and stratified by prior immunotherapy status (failure or naïve), will be used to compare the treatment groups. Subjects in the comparator arm who cross over to PV-10 will be summarized separately from the point of crossover.

The response rate endpoints (CRR and ORR) will be analyzed in the same way as described above for the secondary CRR endpoint.

PFS based on the Investigator assessment will be analyzed in the same way as described above for the primary PFS endpoint.

For the OS endpoints, Kaplan-Meier estimates will be plotted and tabulated at selected time points. The median value and a 95% confidence interval will also be provided (assuming the median can be estimated).

10.5 Safety Analyses

All safety analyses will be based on the Safety Population. For subjects in the comparator arm, safety assessments occurring after initial crossover to PV-10 will be summarized separately from assessments occurring prior to crossover. For adverse events, the onset date will be used to determine whether the event is before or after crossover. Adverse events that start prior to crossover and continue after crossover will be considered pre-crossover.

10.5.1 Exposure to Study Drug

A summary of exposure to each study medication (PV-10, DTIC, TMZ and talimogene laherparepvec) will be provided. For each medication, this will include summaries of the number of cycles received and the average dose received.

10.5.2 Adverse Events

All adverse event summaries will be restricted to Treatment Emergent Adverse Events (TEAE), which are defined as those AEs that began after the first dose of study medication and those existing AEs that worsened after first dose of study medication. Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using MedDRA (version 17.1 or higher).

Summaries of the following types will be presented:

- Subject incidence of TEAEs and total number of unique TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and highest severity.
- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and closest relationship to study drug (Related/Not Related).
- Subject incidence of serious TEAEs and total number of unique serious TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs leading to discontinuation of study drug by MedDRA system organ class and preferred term.

Additional summaries of adverse events may be included as needed.

10.5.3 Clinical Laboratory Evaluation

Laboratory parameters will be summarized using descriptive statistics at baseline and at each post-baseline time point. Changes from baseline will also be summarized. Baseline is defined as the last non-missing value prior to the first dose of study medication.

Shift tables (i.e., low-normal-high at baseline versus low-normal-high at follow-up in a 3-by-3 contingency table) will be provided to assess changes in laboratory values from baseline to each post-baseline time point.

Selected laboratory parameters will be graded according to CTCAE criteria. Shift tables assessing changes from baseline in CTCAE grade will be presented.

10.5.4 Vital Signs

Vital signs will be summarized using descriptive statistics at baseline and at each post-baseline time point. Changes from baseline will also be summarized. Baseline is defined as the last non-missing value prior to the first dose of study medication.

Vital sign results will be reviewed for clinically notable abnormalities according to the criteria shown below. Subjects exhibiting clinically notable vital sign abnormalities will be listed and the number and percent of subjects with abnormalities will be tabulated by visit.

Parameter	Low Threshold	High Threshold
Systolic blood pressure	< 85 mm Hg	≥ 160 mm Hg
Diastolic blood pressure	< 50 mm Hg	≥ 100 mm Hg
Heart rate	< 45 bpm	> 100 bpm

mm Hg: millimeters of mercury; bpm: beats per minute

10.6 Timing of Final Analysis

For this event-driven study, it is expected that the final data analysis will occur once 161 events (disease progression or death) have been documented and reviewed by the IRC. However, in order to avoid waiting an unreasonable amount of time, due to a low event rate in either arm, if 161 events have not occurred within 24 months after the last subject is randomized, then the final analysis will occur at that time. Therefore the primary analysis will be conducted at the earlier of the following two time points:

- After a total of 161 subjects have experience disease progression (in both arms combined); or
- Twenty-four months after the last subject is randomized.

11 ETHICAL, REGULATORY AND LEGAL CONSIDERATIONS

11.1 Declaration of Helsinki

The study will be conducted in accordance with the Declaration of Helsinki (1964), including all amendments up to and including the Fortaleza revision (2013), as described in **Appendix I**.

11.2 Statement of Good Clinical Practices

The study will be conducted in adherence to the study protocol, Good Clinical Practices as defined in Title 21 of the United States Code of Federal Regulations Parts 50, 54, 56, 312, and Part 11 as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

11.3 Institutional Review Board / Independent Ethics Committee Oversight

This protocol and the informed consent form (ICF) will be submitted to an institutional review board (IRB) or independent ethics committee (IEC) prior to initiation of the study and the study will not start until the IRB or IEC has approved the documents.

11.4 Informed Consent

The protocol and informed consent documentation for this study must conform to institutional regulations and local and national laws and regulations.

Before inclusion in the study, each prospective subject will be given a full explanation of the purpose of the study, the procedures to be carried out and the potential hazards. Once this essential information is provided to the subject and once the Investigator believes that the subject understands the implications of participating in the study, the subjects will be required to read, sign and date a properly executed written ICF prior to enrollment. Subjects will be assured that they may withdraw from the study at any time without jeopardizing their medical care. They will be given a copy of their ICF.

If an amended or revised ICF is introduced during the study, each subject's further consent should be obtained.

11.5 Indemnity

The indemnity agreement between the Sponsor, the Principal Investigator, and the Principal Investigator's Institution that is applicable to study PV-10-MM-31 shall apply to all work conducted under this protocol.

11.6 Financial Disclosure

All clinical Investigators participating in clinical studies subject to FDA Regulation Title 21 CFR Part 54 – Financial Disclosure by Clinical Investigators are required prior to study initiation to submit a completed Clinical Investigator Financial Disclosure Form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, clinical Investigator is defined as any Investigator or sub-investigator who is directly involved in the treatment or evaluation of research subjects, including the spouse and any dependent child of the Investigator, but not that of any sub-investigators. These requirements apply to both United States and non-United States clinical Investigators conducting covered clinical studies.

Any new Investigators or sub-investigators added to the covered clinical study during its conduct must also submit a completed Clinical Investigator Financial Disclosure Form. At the conclusion of the covered clinical study and one year after completion of his or her participation in the study, Investigators and sub-investigators will be required to complete another Clinical Investigator Financial Disclosure Form.

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APPENDIX A: SCHEDULE OF STUDY EVENTS

Schedule of Study Events – PV-10 Arm			**Treatment Course: Initial[1], Extended[2] or Crossover[3]**							**Response Follow-Up[4]**		**Final Follow-Up** (Termination Visit)	**Survival Follow-Up** (q12w)
	Screen	Randomize	Cycle 1		Cycle 2		Cycle 3						
Time Points	Wk -3 to 0	Wk -2 to 0	Wk 1	Wk 2	Wk 5	Wk 6[5]	Wk 9	Wk 10[5]	Wk 13	q4w[6]	q12w		
Day	-21 to 1	-14 to 1	1	8	29	36	57	64	85				
Event Window (Days)				±2	±2	±2	±2	±2	±2	±14	±14		±14
Informed Consent	X[7]		X[7]										
Histological or Cytological Confirmation of Melanoma	X												
Documentation of BRAF V600 Mutation Status	X[8]												
Randomization		X[9]											
Symptom Self-Assessment (Skindex 16)			X[10]		X[10]		X[10]		X[11]			X[12]	
Demographics, Medical History and Physical Exam	X												
Review of Medical Conditions and Symptoms			X		X		X		X	X	X	X	
Grading of Lesion Bleeding, Ulceration and Infection			X[13]		X[13]		X[13]		X	X	X	X	
Concomitant Medications	X		X		X		X		X				
Adverse Events	X[14]		X[14]	X	X	X	X	X	X			X	
Height and Weight[15]	X		X		X		X		X		X	X	
Vital Signs[16]	X		X		X		X		X		X	X	
ECOG Performance Status	X		X		X		X		X	X	X	X	
Laboratory Tests (CBC, CMP, TFT, LDH[17])	X		X		X		X		X			X	
Pregnancy Test, Serum[18]	X												
Pregnancy Test, Urine[18]			X		X		X		X			X	
Designation of Target Lesions	X												
Body Mapping of Study Lesions	X												
Photodocumentation of Study Lesions	X		X		X		X		X	X	X	X	
Study Lesion Measurement	X		X[19]		X		X						
Clinical Evaluation[20]					X		X			X			
Comprehensive Assessment of Progression Status[21]									X[22]		X	X	
Histological or Cytological Confirmation of CR[23]									X	X	X	X	
Study Lesion Dose Calculation	X		X		X[24]		X[24]						
PV-10 Administration			X		X[24]		X[24]						
Observation for Post-Treatment Adverse Events[25]			X		X[24]		X[24]						
Evaluation for Distant Metastasis	X								X		X	X	
Radiologic imaging of Chest, Abdomen and Pelvis (and any other body regions with non-cutaneous Study Lesions)[26]	X[27]								X[28]		X	X[29]	
MRI of brain[30]	X[27]								X[28]		X	X[29]	
Survival Follow-Up													X

Footnotes are located on the following page.

Footnotes for PV-10 Arm Study Events Schedule:

[1] See protocol Section 7.2.
[2] See protocol Section 7.3.
[3] See protocol Section 7.4.
[4] Subjects deteriorating to PD status during Response Follow-up will undergo Final Follow-up and begin Survival Follow-up.
[5] This visit applies only to subjects receiving PV-10 at Weeks 5 or 9, respectively.
[6] Evaluation q4w will be discontinued at week 37.
[7] Informed consent may be obtained up to 30 days prior to study Day 1. Subjects entering Crossover must be re-consented prior to initiation of PV-10 treatment.
[8] If documentation of BRAF mutation status is not available, BRAF testing must be done using the methodology that is standard for the Investigator's institution; testing may be omitted if testing is not standard care or targeted therapy is unavailable or not standard care.
[9] Randomization will occur after completion of all Screening procedures and within 14 days prior to initiation of study of treatment on study Day 1.
[10] Self-assessment to be conducted prior to treatment administration.
[11] Subjects transitioning to Response Follow-up, Final Follow-up or Survival Follow-up will complete their final self-assessment at this visit.
[12] Subjects withdrawn from a Treatment Course will complete final self-assessment at this visit.
[13] Grading of lesion bleeding, ulceration and infection per CTCAE criteria; must be conducted prior to administration of study treatment.
[14] Adverse events occurring after signing the informed consent form but before initiation of study treatment on Study Day 1 will be recorded on the Adverse Events CRF.
[15] Height at Screening and Final Follow-up only.
[16] Heart rate, blood pressure, temperature.
[17] Central laboratory testing at all time points; LDH at Screening only.
[18] Female subjects of childbearing potential only. Urine pregnancy test within 48 hours prior to administration of study treatment and monthly for 6 months after final dose of study treatment.
[19] If Study Lesion measurements have been performed more than 7 days prior to Day 1, they must be repeated on Day 1.
[20] Evaluation of clinical changes in disease status indicative of progression (i.e., meriting change of study therapy).
[21] Assessment of: Target Lesion and overall disease burden; nodal, distant or visceral metastasis; and symptomatic signs of progression.
[22] Subjects with CR will start Response Follow-Up. Subjects with PR or SD status will repeat Treatment Course (Extended Treatment). Subjects with PD status will begin Survival Follow-Up.
[23] Histological or cytological confirmation of complete response is recommended in cases where it is difficult to distinguish residual disease from normal tissue. In such cases at least one representative residual lesion location should be investigated (e.g., by fine needle aspirate/biopsy, punch biopsy, excisional biopsy or incisional biopsy) before assigning a status of complete response. Assessment of tissue may be performed using histopathology or cytology.
[24] Applicable to subjects with residual disease; dose calculation for residual disease; administration to all residual disease.
[25] See protocol Section 6.1.3.
[26] CT is recommended for non-cutaneous Study Lesions located in the chest, abdomen and pelvis.
[27] Baseline data from imaging acquired within 30 days prior to study Day 1 may be used in lieu of equivalent study-specific imaging at Screening (baseline scans may be obtained up to 45 days prior to study Day 1 for Stage III subjects with cutaneous-only disease).
[28] This event may be done up to 7 days before or after specified time.

[29] Not required if prior scan within 8 weeks of this visit.
[30] Only if clinically indicated; if MRI is contraindicated or not standard care, CT scan may be performed instead.

Schedule of Study Events – Comparator Arm (Dacarbazine or Temozolomide)			**Treatment Course: Initial[1] or Extended[2]**							**Response Follow-Up[3]**		**Final Follow-Up** (Termination Visit)	**Survival Follow-Up** (q12w)
	Screen	Randomize	Cycle 1		Cycle 2		Cycle 3						
Time Points	Wk -3 to 0	Wk -2 to 0	Wk 1	Wk 2[4]	Wk 5	Wk 6[4]	Wk 9	Wk 10[4]	Wk 13	q4w[5]	q12w		
Day	-21 to 1	-14 to 1	1	8	29	36	57	64	85				
Event Window (Days)				±2	±2	±2	±2	±2	±2	±14	±14		±14
Informed Consent	X[6]												
Histological or Cytological Confirmation of Melanoma	X												
Documentation of BRAF V600 Mutation Status	X[7]												
Randomization		X[8]											
Symptom Self-Assessment (Skindex 16)			X[9]		X[9]		X[9]		X[10]			X[11]	
Demographics, Medical History and Physical Exam	X												
Review of Medical Conditions and Symptoms			X		X		X		X	X	X	X	
Grading of Lesion Bleeding, Ulceration and Infection			X[12]		X[12]		X[12]		X	X	X	X	
Concomitant Medications	X		X		X		X		X				
Adverse Events	X[13]		X[13]		X		X		X			X	
Height and Weight[14]	X		X		X		X		X		X	X	
Vital Signs[15]	X		X		X		X		X		X	X	
ECOG Performance Status	X		X		X		X		X	X	X	X	
Laboratory Tests (CBC, CMP, TFT, LDH[16])[17]	X		X		X		X		X			X	
Pregnancy Test, Serum[18]	X												
Pregnancy Test, Urine[18]			X		X		X		X			X	
Designation of Target Lesions	X												
Body Mapping of Study Lesions	X												
Photodocumentation of Study Lesions	X		X		X		X		X	X	X	X	
Study Lesion Measurement	X		X[19]										
Clinical Evaluation[20]					X		X			X			
Comprehensive Assessment of Progression Status[21]									X[22]		X	X	
Histological or Cytological Confirmation of CR[23]									X	X	X	X	
Study Lesion Dose Calculation	X												
Assessment of Dose Tolerance					X		X		X				
Calculation of Body Surface Area (BSA)			X		X[24]		X[24]						
Study Drug Administration			X		X[24]		X[24]						
Evaluation for Distant Metastasis	X								X		X	X	
Radiologic imaging of Chest, Abdomen and Pelvis (and any other body regions with non-cutaneous Study Lesions)[25]	X[26]								X[27]		X	X[28]	
MRI of brain[29]	X[26]								X[27]		X	X[28]	
Survival Follow-Up													X

Footnotes are located on the following page.

Footnotes for Comparator Arm (Dacarbazine or Temozolomide) Study Events Schedule:

[1] See protocol Section 7.2.
[2] See protocol Section 7.3.
[3] Subjects deteriorating to PD status during Response Follow-up will undergo Final Follow-up and begin Survival Follow-up.
[4] This visit applies only to subjects receiving PV-10.
[5] Evaluation q4w will be discontinued at week 37.
[6] Informed consent may be obtained up to 30 days prior to study Day 1.
[7] If documentation of BRAF mutation status is not available, BRAF testing must be done using the methodology that is standard for the Investigator's institution; testing may be omitted if testing is not standard care or targeted therapy is unavailable or not standard care.
[8] Randomization will occur after completion of all Screening procedures and within 14 days prior to initiation of study of treatment on study Day 1.
[9] Self-assessment to be conducted prior to treatment administration.
[10] Subjects transitioning to Response Follow-up, Final Follow-up or Survival Follow-up will complete their final self-assessment at this visit.
[11] Subjects withdrawn from a Treatment Course will complete final self-assessment at this visit.
[12] Grading of lesion bleeding, ulceration and infection per CTCAE criteria; must be conducted prior to administration of study treatment.
[13] Adverse events occurring after signing the informed consent form but before initiation of study treatment on Study Day 1 will be recorded on the Adverse Events CRF.
[14] Height at Screening and Final Follow-up only.
[15] Heart rate, blood pressure, temperature.
[16] LDH at Screening only.
[17] Central laboratory tests at all time points; local laboratory tests (CBC and CMP) at the end of each Treatment Cycle (i.e., Weeks 5, 9 and 13).
[18] Female subjects of childbearing potential only. Urine pregnancy test within 48 hours prior to administration of study treatment and monthly for 6 months after final dose of study treatment.
[19] This assessment unnecessary for subjects randomized to dacarbazine or temozolomide.
[20] Evaluation of clinical changes in disease status indicative of progression (i.e., meriting change of study therapy).
[21] Assessment of: Target Lesion and overall disease burden; nodal, distant or visceral metastasis; and symptomatic signs of progression.
[22] Subjects with CR will start Response Follow-Up. Subjects with PR or SD status will repeat Treatment Course (Extended Treatment). Subjects with PD status will transition to Crossover, if eligible. If not eligible or elect not to transition to Crossover, Subjects will begin Survival Follow-Up.
[23] Histological or cytological confirmation of complete response is recommended in cases where it is difficult to distinguish residual disease from normal tissue. In such cases at least one representative residual lesion location should be investigated (e.g., by fine needle aspirate/biopsy, punch biopsy, excisional biopsy or incisional biopsy) before assigning a status of complete response. Assessment of tissue may be performed using histopathology or cytology.
[24] Applicable to subjects with residual disease; continued treatment for 2 cycles after complete response is recommended.
[25] CT is recommended for non-cutaneous Study Lesions located in the chest, abdomen and pelvis.
[26] Baseline data from imaging acquired within 30 days prior to study Day 1 may be used in lieu of equivalent study-specific imaging at Screening (baseline scans may be obtained up to 45 days prior to study Day 1 for Stage III subjects with cutaneous-only disease).
[27] This event may be done up to 7 days before or after specified time.
[28] Not required if prior scan within 8 weeks of this visit.

[29] Only if clinically indicated; if MRI is contraindicated or not standard care, CT scan may be performed instead.

Schedule of Study Events – Comparator Arm (Talimogene Laherparepvec)			**Treatment Course: Initial[1]**							**Treatment Course: Extended[2]**			**Response Follow-Up[3]**		**Final Follow-Up** (Termination Visit)	**Survival Follow-Up** (q12w)
	Screen	Randomize	Cycle 1		Cycle 2			Cycle 3								
Time Points	Wk -3 to 0	Wk -2 to 0	Wk 1	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	q2w	q4w	q12w	q4w[4]	q12w		
Day	-21 to 1	-14 to 1	1	22	36	50	64	78	92							
Event Window (Days)				±2	±2	±2	±2	±2	±2				±14	±14		±14
Informed Consent	X[5]															
Histological or Cytological Confirmation of Melanoma	X															
Documentation of BRAF V600 Mutation Status	X[6]															
Randomization		X[7]														
Symptom Self-Assessment (Skindex 16)			X[8]		X[8]		X[8]		X[9]		X[8]	X[8,9]			X[10]	
Demographics, Medical History and Physical Exam	X															
Review of Medical Conditions and Symptoms			X		X		X		X		X	X	X	X	X	
Grading of Lesion Bleeding, Ulceration and Infection			X[11]		X[11]		X[11]		X		X[11]	X[11]	X	X	X	
Concomitant Medications	X		X	X	X	X	X	X	X	X	X	X				
Adverse Events	X[12]		X[12]	X	X	X	X	X	X	X	X	X			X	
Height and Weight[13]	X		X	X	X	X	X	X	X	X	X	X		X	X	
Vital Signs[14]	X		X	X	X	X	X	X	X	X	X	X		X	X	
ECOG Performance Status	X		X		X		X		X		X	X	X	X	X	
Laboratory Tests (CBC, CMP, TFT, LDH[15])[16]	X		X		X		X		X		X	X			X	
Pregnancy Test, Serum[17]	X															
Pregnancy Test, Urine[17]			X		X		X		X		X	X			X	
Designation of Target Lesions	X															
Body Mapping of Study Lesions	X															
Photodocumentation of Study Lesions	X		X		X		X		X		X	X	X	X	X	
Study Lesion Measurement	X		X[18]	X	X	X	X	X		X	X	X				
Clinical Evaluation[19]					X		X				X		X			
Comprehensive Assessment of Progression Status[20]									X[21]			X		X	X	
Histological or Cytological Confirmation of CR[22]									X			X	X	X	X	
Study Lesion Dose Calculation	X		X	X[23]	X[23]	X[23]	X[23]	X[23]		X[23]	X[23]	X[23]				
Study Drug Administration			X	X[23]	X[23]	X[23]	X[23]	X[23]		X[23]	X[23]	X[23]				
Evaluation for Distant Metastasis	X								X			X		X	X	
Radiologic imaging of Chest, Abdomen and Pelvis (and any other body regions with non-cutaneous Study Lesions)[24]	X[25]								X[26]			X		X	X[27]	
MRI of brain[28]	X[25]								X[26]			X		X	X[27]	
Survival Follow-Up																X

Footnotes are located on the following page.

Footnotes for Comparator Arm (Talimogene Laherparepvec) Study Events Schedule:

[1] See protocol Section 7.2.
[2] See protocol Section 7.3.
[3] Subjects deteriorating to PD status during Response Follow-up will undergo Final Follow-up and begin Survival Follow-up.
[4] Evaluation q4w will be discontinued at week 38.
[5] Informed consent may be obtained up to 30 days prior to study Day 1.
[6] If documentation of BRAF mutation status is not available, BRAF testing must be done using the methodology that is standard for the Investigator's institution; testing may be omitted if testing is not standard care or targeted therapy is unavailable or not standard care.
[7] Randomization will occur after completion of all Screening procedures and within 14 days prior to initiation of study of treatment on study Day 1.
[8] Self-assessment to be conducted prior to treatment administration.
[9] Subjects transitioning to Response Follow-up, Final Follow-up or Survival Follow-up will complete their final self-assessment at this visit.
[10] Subjects withdrawn from a Treatment Course will complete final self-assessment at this visit.
[11] Grading of lesion bleeding, ulceration and infection per CTCAE criteria; must be conducted prior to administration of study treatment.
[12] Adverse events occurring after signing the informed consent form but before initiation of study treatment on Study Day 1 will be recorded on the Adverse Events CRF.
[13] Height at Screening and Final Follow-up only.
[14] Heart rate, blood pressure, temperature.
[15] LDH at Screening only.
[16] Central laboratory tests at all time points.
[17] Female subjects of childbearing potential only. Urine pregnancy test monthly within 48 hours prior to administration of study treatment and monthly for 6 months after final dose of study treatment.
[18] If Study Lesion measurements have been performed more than 7 days prior to Day 1, they must be repeated on Day 1.
[19] Evaluation of clinical changes in disease status indicative of progression (i.e., meriting change of study therapy).
[20] Assessment of: Target Lesion and overall disease burden; nodal, distant or visceral metastasis; and symptomatic signs of progression.
[21] Subjects with CR will start Response Follow-Up. Subjects with PR or SD status will commence Extended Treatment. Subjects with PD status will transition to Crossover, if eligible. If not eligible or elect not to transition to Crossover, Subjects will begin Survival Follow-Up.
[22] Histological or cytological confirmation of complete response is recommended in cases where it is difficult to distinguish residual disease from normal tissue. In such cases at least one representative residual lesion location should be investigated (e.g., by fine needle aspirate/biopsy, punch biopsy, excisional biopsy or incisional biopsy) before assigning a status of complete response. Assessment of tissue may be performed using histopathology or cytology.
[23] Applicable to subjects with residual disease.
[24] CT is recommended for non-cutaneous Study Lesions located in the chest, abdomen and pelvis.
[25] Baseline data from imaging acquired within 30 days prior to study Day 1 may be used in lieu of equivalent study-specific imaging at Screening (baseline scans may be obtained up to 45 days prior to study Day 1 for Stage III subjects with cutaneous-only disease).
[26] This event may be done up to 7 days before or after specified time.
[27] Not required if prior scan within 8 weeks of this visit.
[28] Only if clinically indicated; if MRI is contraindicated or not standard care, CT scan may be performed instead.

APPENDIX B: PV-10 DOSING TABLE

Recommended dose of PV-10 for each lesion. If the indicated volume cannot be injected into a lesion, the actual injected amount should be recorded. Irregularly shaped lesions (i.e., lesions that are flat, elongated or otherwise irregular in shape) may require less than the indicated volume.

Longest Diameter (mm)	Recommended PV 10 Dose (mL)
≤ 5	**0.15**
6	**0.16**
7	**0.19**
8	**0.23**
9	**0.29**
10	**0.36**
11	**0.46**
12	**0.56**
13	**0.68**
14	**0.82**
15	**1.0**
16	**1.2**
17	**1.4**
18	**1.6**
19	**1.9**
20	**2.2**
21	**2.5**
22	**2.9**
23	**3.3**
24	**3.7**
25	**4.2**
26	**4.7**
27	**5.2**
28	**5.8**
29	**6.5**
30	**7.2**
31	**7.9**
32	**8.7**
33	**9.5**
34	**10.4**
35	**11.3**
36	**12.3**
37	**13.4**
38	**14.5**
39 to 50	**15.0**

APPENDIX C: CLINICALLY SIGNIFICANT PHOTOSENSITIVITY DRUGS

Antibiotics	• Fluoroquinolones, *including*:	• Ciprofloxacin (4 hr)[1] • Clinafloxacin (7 hr) • Enoxacin (6 hr) • Grepafloxacin (12 hr) • Levofloxacin (8 hr) • Lomefloxacin (6 hr) • Norfloxacin (4 hr) • Ofloxacin (8 hr) • Sparfloxacin (30 hr)
	• Nalidixic acid (7 hr)	
	• Sulphonamides, *including*:	• Sulfacetamide (13 hr) • Sulfadiazine (17 hr) • Sulfadoxine (8 days) • Sulfamethizole (8 hr) • Sulfamethoxazole (12 hr) • Sulfasalazine (10 hr) • Sulfisoxazole (7 hr)
	• Tetracyclines, *including:*	• Demeclocyline/ Demethylchlortetracycline (11-17 hr) • Doxycycline (12-22 hr) • Minocycline (11-33 hr)
Antifungals	• Griseofulvin (24 hr)	
Diuretics and Cardiovascular Agents	• Amiodarone (107 days) • Frusemide/Furosemide (2 hr) • Quinidine (8 hr)	
	• Thiazides, *including*:	• Bendroflumethiazide (9 hr) • Chlorothiazide (2 hr) • Hydrochlorothiazide (15 hr)
Non-Steroidal Anti-Inflammatory Drugs	• Azapropazone (14 hr) • Naproxen (13 hr) • Piroxicam (50 hr) • Tiaprofenic acid (3 hr)	
Calcium Channel Antagonists	• Nifedipine (5 hr)	
Psoralens	• 5-methoxypsoralen (2 hr) • 8-methoxypsoralen (1 hr)	
Psychoactive Drugs	• Phenothiazides, *including*:	• Chlorpromazine (30 hr) • Thioridazine (25 hr)
	• Protriptyline (92 hr)	
Retinoids	• Etretinate (16 days) • Isotretinonin (20 hr)	
Photodynamic Therapy Agents	• Foscan (32 hr) • Photofrin (9 days) • Verteporfin (6 hr)	
Botanicals	• St Johns Wort (36 hr)	

[1]Elimination half life in hours or days as shown

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APPENDIX D: SPECIFICATIONS FOR IMAGING

Detailed specifications for obtaining optimal radiologic imaging for this study are described in the Image Acquisition Protocol (IAP) that will be distributed to each study site prior to site qualification. A secure, validated, compliant web server set up at [redacted] is used for secure transfer of study radiologic images by study sites using [redacted] web-based portal, [redacted]. Remote access to all images by the Sponsor is also provided. Only individuals approved by the Sponsor have access to the website.

The following general considerations apply to study imaging.

Consistent Methodology

Consistent scanning methodology should be used throughout the study interval for each Study Lesion in a particular subject (e.g., to the extent possible, Study Lesions measured at baseline by computed tomography (CT) should be followed throughout the study interval using CT, while those measured at baseline by magnetic resonance imaging (MRI) should be followed throughout the study interval using MRI).

Computed Tomography (CT)

Computed tomography is recommended for non-cutaneous Study Lesions located in the chest, abdomen and pelvis.

To ensure sufficient resolution for lesion detection and assessment, a spiral (helical) CT scanner should be used. A multi-detector helical scanner with eight detector rows or more is preferred but not mandatory. The scan must be contiguous. Slice thickness should be no more than 8 mm, preferably 5 mm to allow accurate assessment of 10 mm lesions (maximum diameter in axial plane).

- Scanning of the chest, abdomen and pelvis are required at screening to document the existence or absence of lesions so that an accurate baseline can be established for subsequent assessment of possible disease progression.

- If non-cutaneous Study Lesions (i.e., subcutaneous, soft tissue or nodal Study Lesions) are located beyond the chest, abdomen and pelvis (e.g., in an extremity or the head or neck) scanning must include all affected body regions.

- Additional investigative scanning of other areas that may be involved based on signs and symptoms of disease is also appropriate.

To allow for comparison over time, to the extent possible the same scanning technique and contrast media (CM) administration should be used for a particular subject at baseline and on all subsequent examinations.

- Intravenous CM should be used unless contraindicated for medical reasons such as allergy. Sufficient quantity of CM should be used to allow detection and measurement of visceral or nodal melanoma 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.

Subjects who develop contraindications to CM after baseline contrast CT is done may receive subsequent non-contrast CT or MRI (enhanced or non-enhanced) at the discretion of the Investigator in consultation with the radiologist to optimize potential for comparison with prior scans, if possible. If alternate approaches are not possible the subject will be considered not evaluable from that point forward. Care must be taken in interpretation of data from different imaging modalities since apparent size and sensitivity in detection of lesions can vary substantially between modalities.

All images collected should be included in the resultant data set, along with operational details such as window settings. Data must be provided to the Sponsor in a portable electronic format (i.e., DICOM) for review and analysis. Files should be de-identified with regard to subject name and any personal identifying codes (such as Social Security number, Medicare number or medical record number) to the extent possible, and should include identification of the study protocol number, assigned subject ID and subject initials (if initials are allowed).

FDG-PET/CT

FDG-PET/CT scanning may be used at the Investigator's discretion to confirm disease progression and should be optimized for the evaluation of melanoma and the site of suspected disease.

All images collected should be included in the resultant data set, along with operational details used for data collection. Data are to be provided to the Sponsor in a portable electronic format (i.e., DICOM) for review and analysis. Files should be de-identified with regard to subject name and any personal identifying codes (such as Social Security number or medical record number) to the extent possible, and should include identification of the study protocol number, assigned subject ID and subject initials (if initials are allowed).

Magnetic Resonance Imaging (MRI)

If MRI is performed, the scanning sequences used should be optimized for the evaluation of melanoma and the site of suspected disease, and equivalent modalities should be used at all evaluations to allow for comparison of disease status over time. Generally, T1, T2 and post

gadolinium-enhanced axial imaging sequences are required, and fat-suppression sequences are preferred if possible.

- Scanning of the head is recommended in cases of suspect brain metastases; if MRI is contraindicated, CT scan may be performed instead.

- If non-cutaneous Study Lesions (i.e., subcutaneous, soft tissue or nodal Study Lesions) are located beyond the chest, abdomen and pelvis (e.g., in an extremity or the head or neck) scanning must include all affected body regions.

All images collected should be included in the resultant data set, along with operational details used for data collection. Data are to be provided to the Sponsor in a portable electronic format (i.e., DICOM) for review and analysis. Files should be de-identified with regard to subject name and any personal identifying codes (such as Social Security number, Medicare number or medical record number) to the extent possible, and should include identification of the study protocol number, assigned subject ID and subject initials (if initials are allowed).

MRI is not recommended for evaluation of Study Lesions located in the chest.

Ultrasound (US)

Ultrasound measurement may not be used for reporting of lesion diameters for the purpose of assessment of outcome.

New Nodal, Soft Tissue or Visceral Lesions

New unequivocal nodal, soft tissue or visceral lesions identified on follow-up in a location not scanned at baseline will be deemed to denote disease progression at the time of detection.

New equivocal nodal, soft tissue or visceral lesions (e.g., small unconfirmed lesions) should be followed to clarify whether they represent new disease. If determined to be unequivocal on subsequent follow-up then disease progression will be deemed to have occurred at the time of initial observation.

Suspicious new nodal disease in the absence of other unequivocal evidence of progression should be confirmed by histopathology or PET/CT prior to classification as disease progression and withdrawal of the subject from the study. If confirmed, the date of progression will be deemed to have occurred at the date of initial observation.

Equivocal distant metastatic disease in the absence of other evidence of progression should be confirmed by histopathology or radiology, or by clinical evaluation, at least 4 weeks after initial discovery, prior to withdrawal of the subject from the study. If confirmed, the date of progression will be deemed to have occurred at the date of initial observation.

APPENDIX E: PHOTODOCUMENTATION OF STUDY LESIONS

Serial Photographic Documentation of Melanoma

All photographic equipment and supplies will be provided by [redacted]

Image Capture

- ID card and color card: two each
- Close-up view with millimeter scale of each Target Lesion: two each per lesion
- Anatomical view of the Target Lesion areas: two each of each lesion area

Equipment

- Camera: Canon SL1 digital SLR camera body
- Lens: Canon
- Flash: [redacted] ringflash with ranging lights
- Millimeter scale attachment
- Subject ID Card/Color Card Holder
- Standardized background material

Procedures

In the series of clinical photographs spanning the duration of the study, the only variable allowed to change is the skin condition itself. Therefore, anything extraneous to the condition (background distractions, etc.) is to be eliminated from the photographic field, starting with the entry visit through the final visit. The necessity of good end of study photographs should be stressed to subjects to ensure cooperation. Lighting, framing, exposure, and reproduction ratios must be held constant. In the end, the images should read like a time-lapse movie.

1. The supplied equipment is to be used exclusively for this study. No modification, adjustments, or repairs of the camera equipment are to be undertaken without the expressed instruction of [redacted].

2. The supplied standardized background material is to be used. Do not use wrinkled or crimped material.

3. The supplied camera system consists of a preset, standardized lens magnification and f/stop for close-up view of Target Lesions and another preset, standardized lens magnification and f/stop for anatomical (global) view of lesion area.

4. For close-up views of Target Lesions, the millimeter scale attached to the base of the camera ensures accurate focal distance. The millimeter scale is removed for anatomical views, and proper focal distance is determined by moving the camera closer or further from the subject until the green ranging lights converge into one green dot centered on

the region to be photographed. Any doubt as to the correctness of the photographic technique should result in an immediate re-shoot.

5. Each photographic session includes an exposure series of:

    a. Subject ID, which will include the following legible information in black indelible ink (two exposures):

        Protocol number
        Date
        Center number
        Visit name
        Subject's initials (if initials are allowed)
        Subject's ID number
        Photographer's initials
        Color card

    b. Close-up view of the subject's cutaneous Target Lesions (two exposures per lesion). The supplied reference labels (numbered 1–5) should be placed directly above and to the left of each Target Lesion (1–5, respectively) and should be visible in each photograph. Equivalent close-up views of location of any subcutaneous, soft tissue or nodal Target Lesions should be taken; however, this view is optional if there is no visible evidence of the subcutaneous, soft tissue or nodal Target Lesion.

    c. Anatomical view of the subject's Target Lesion area (two exposures per area such that the global area around all Target Lesions is photographed). Repeat if necessary to capture anatomical views of all Target Lesion areas.

    d. If Non-Target Lesions are not completely visible in the anatomical views of Target Lesions, capture additional anatomical views of the subject's Non-Target Lesions (two exposures per area until the global areas around all Non-Target Lesions are photographed).

6. For New Lesions identified at follow-up visits, the photographic session must include an exposure series of:

    a. Close-up view of all New Lesions (two exposures per lesion). Supplied reference labels (numbered N1–N5) should be placed directly above and to the left of each New Lesion (N1–N5, respectively) and should be visible in each photograph. However, this view is optional if there is no visible evidence of a subcutaneous, soft tissue or nodal New Lesion.

    b. Anatomical view of the subject's New Lesion area (two exposures per area such that the global area around all New Lesions is photographed). Repeat if necessary to capture anatomical views of all New Lesion areas.

7. A secure, validated, compliant web server set up at [redacted] is used for secure transfer of study images by study sites. Images are to be transferred the day they are recorded. Remote access to all images by the Sponsor is also provided. Only individuals approved by the Sponsor have access to the website.

8. [redacted] will provide each study site with the necessary hardware as well as technical support as needed. All supplied photographic equipment remains the property of the Sponsor.

9. Any questions or problems regarding the photographic portion of this study are to be forwarded to the assigned Project Manager at [redacted].

[redacted]

APPENDIX F: ECOG PERFORMANCE STATUS

Definitions of ECOG Performance Status (Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-55):

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

APPENDIX G: RESPONSE EVALUATION CRITERIA FOR SOLID TUMORS

One (1) to 5 measurable lesions will be defined as Target Lesions. All other disease will be defined as Non-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 the diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more Unequivocal New Lesions is also considered progression.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s).
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions. To achieve ‘unequivocal progression’ on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit change of study therapy. The appearance of one or more Unequivocal New Lesions is also considered progression.

Pathological lymph nodes are to be measured and followed based on their short axis. Lymph nodes with a short axis ≥ 15 mm are considered measurable and assessable as Target Lesions. Lymph nodes with a short axis < 10 mm are considered non-pathological. Pathological lymph nodes that shrink to < 10 mm short axis are considered normal.

The study protocol differs from RECIST in the following ways:

Parameter	RECIST	Protocol	Basis for Difference
Target Lesion Location	Up to 5 total, up to 2 per organ	Up to 5 total	All disease sites for eligible patients are in the skin, lymph nodes or soft tissue; allowing up to 5 Target Lesions without anatomical restriction assures more thorough assessment of representative tumor burden in the study patient population
Minimum Size of Target Lesions	≥ 10 mm	≥ 10 mm in aggregate (cutaneous lesions only)	Stage IIIB – Stage IV M1a patients frequently have multiple cutaneous lesions < 10 mm but may not have a single cutaneous, subcutaneous or soft tissue lesion ≥ 10 mm or a single pathological superficial or palpable lymph node ≥ 15 mm (short axis)

Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-247.

APPENDIX H: SKINDEX-16 QUESTIONNAIRE

Skindex16
a MMChren,1997
Protocol PV-10-MM-31 Subject Number: ___ ___ ___ ___ Visit Date: ___ ___/ ___ ___ ___/ ___ ___

DERMATOLOGY SURVEY

This survey concerns the skin condition which has bothered you the most during the past week.

Skindex16 - United States/English - Mapi.
ID6862 / Skindex16_AU2.0_eng-USori.doc

Skindex16 Protocol PV-10-MM-31 Subject Number: ___ ___ ___ ___ Visit Date: ___ ___ / ___ ___ ___ / ___ ___
a MMChren,1997

THESE QUESTIONS CONCERN THE SKIN CONDITION WHICH HAS BOTHERED YOU THE MOST DURING THE PAST WEEK

During the past week, how often have you been bothered by:	Never Bothered ↓						Always Bothered ↓
1. Your skin condition **itching**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
2. Your skin condition **burning** or **stinging**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
3. Your skin condition **hurting**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
4. Your skin condition **being irritated**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
5. The **persistence / reoccurrence** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
6. **Worry** about your skin condition (For example: that it will spread, get worse, scar, be unpredictable, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
7. The **appearance** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
8. **Frustration** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
9. **Embarrassment** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
10. **Being annoyed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
11. **Feeling depressed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
12. The effects of your skin condition on your **interactions with others** (For example: interactions with family, friends, close relationships, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
13. The effects of your skin condition on your **desire to be with people**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
14. Your skin condition making it hard to **show affection**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
15. The effects of your skin condition on your **daily activities**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
16. Your skin condition making it hard to **work or do what you enjoy**	☐0	☐1	☐2	☐3	☐4	☐5	☐6

Have you answered every item? Yes ☐ No ☐

Skindex16 - United States/English - Mapi.
ID6862 / Skindex16_AU2.0_eng-USori.doc

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
59th WMA General Assembly, Seoul, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA 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 in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic

interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison

with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. 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 adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue

influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, 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, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed

with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as

beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX J: LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
ADR	adverse drug reaction
AE	adverse event
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
ALT	alanine transaminase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate transaminase
ATC	Anatomical/Therapeutic/Chemical class
BCG	Bacillus Calmette-Guérin
bpm	beats per minute
BRAF	gene encoding the B-Raf protein
BSA	body surface area
BUN	blood urea nitrogen
°C	degrees Celsius
ca.	*circa* (“approximately”)
CBC	complete blood count
CCR	complete response rate
CDER	FDA Center for Drug Evaluation and Research
CFR	Code of Federal Regulations (United States)
$C_{initial}$	initial concentration (extrapolated)
Cm	centimeter
cm^3	cubic centimeter
CM	contrast media
CMH	Cochran-Mantel-Haenszel mean score test
CMP	comprehensive metabolic panel
CMS	Centers for Medicare and Medicaid Services (United States)
CPMP	Committee for Proprietary Medicinal Products
CR	complete response
CrCl	creatinine clearance (estimated)
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTDMC	Clinical Trial Data Monitoring Committee
CTLA-4	cytotoxic T lymphocyte antigen-4
CYP	cytochrome P450 (enzymes)
DICOM	Digital Imaging and Communications in Medicine
DOP2	Division of Oncology Products 2 (FDA)
DRR	durable response rate (response lasting $\geq$ 6 months)
DTIC	dacarbazine

EAC	endpoint assessment committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EE	Efficacy Evaluable
e.g.	*exempli gratia* (“for example”)
eGFR	estimated glomerular filtration rate
EORTC	European Organisation for Research and Treatment of Cancer
et al.	*et alii* (“and others”)
°F	degrees Fahrenheit
FDA	Food and Drug Administration (United States)
FDG	Fludeoxyglucose (^{18}F)
g	gauge
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM-CSF	Granulocyte-macrophage colony-stimulating factor
Gy	Gray (unit of absorbed radiation)
H	height (cm)
HMA CTFG	Heads of Medicines Agencies Clinical Trials Facilitation Group
HPLC	high performance liquid chromatography
hr	hour
I	iodide
^{131}I	^{131}iodide isotope
IAP	Image Acquisition Protocol
ICF	informed consent form
ICH	International Conference on Harmonisation
IC_{50}	concentration of an inhibitor that causes a 50% decrease in response
ID	identification number
i.e.	*id est* (“that is”)
IEC	independent ethics committee
IFN	interferon
IL	intralesional
IL-2	interleukin-2
ILI	isolated limb infusion
ILP	isolated limb perfusion
IND	Investigational New Drug Application
IPAR	Investigational Product Accountability Record
IPI	ipilimumab
IRB	institutional review board
IRC	Independent Review Committee
ITT	intent-to-treat
IV	intravenous
IWRS	interactive web-based response system
$k_{D/A}$	distribution / absorption phase rate constant
k_E	elimination phase rate constant

kg	kilogram
L	liter
LDH	lactate dehydrogenase
LOCF	last observation carried forward
m^2	square meter
MedDRA	Medical Dictionary for Regulatory Activities
MEK	a protein kinase implicated in grow of melanoma
mg	milligram
min	minute
min^{-1}	per minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
MMRM	mixed model repeated measures
mRECIST	modified Response Evaluation Criteria in Solid Tumours
MRI	magnetic resonance imaging
NCI	National Cancer Institute (United States)
NE	not evaluable
No.	number
NOAEL	no observed adverse effect level
OR	objective response
ORR	objective response rate
OS	overall survival
p	statistical probability value
PD	progressive disease
PET	positron emission tomography
PFS	progression free survival
PK	pharmacokinetic
PO	per os (“by mouth”)
PPR	progression prior to response
PR	partial response
PV-10	rose bengal disodium in 0.9% saline for injection
q2w	every two weeks
q4w	every four weeks
q12w	every twelve weeks
RB	rose bengal disodium
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SADR	serious adverse drug reaction
SAE	serious adverse event
SD	stable disease
SLR	single lens reflex camera
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	serious unexpected adverse reaction

T1	spin-lattice relaxation time (MRI)
$t_{1/2}$	half-life
$t_{1/2,D/A}$	distribution / absorption half-life
$t_{1/2,E}$	elimination phase half-life
T2	spin-lattice relaxation time (MRI)
T3	serum triiodothyronine
T4	serum thyroxine
TEAE	Treatment Emergent Adverse Events
TFT	thyroid function test
TMZ	temozolomide
TSH	thyroid stimulating hormone (serum thyrotropin)
TTF	time to treatment failure
TTR	time to response
UGT	uridine diphosphate glucuronosyltransferase (enzymes)
U.S.	United States
US	ultrasound
USA	United States of America
ULN	upper limit of normal
USP	United States Pharmacopoeia
VEM	vemurafenib
V_L	lesion volume
V_{PV-10}	volume of PV-10
W	weight (kg)
Wk	week
w/v	weight/volume
WHO	World Health Organisation
WMA	World Medical Association
yrs	years
βHCG	beta human chorionic gonadotropin
μg	microgram
π	Pi (3.14159)