# CLINICAL STUDY PROTOCOL

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| **Protocol Title:** | Neoadjuvant Immunotherapy with Intratumoral Tavokinogene Telseplasmid (Tavo) plus Electroporation in Combination with Intravenous Nivolumab in Patients with Operable Locally-Regionally Advanced Melanoma |
| **MCC Number:** | 20313 |
| **Compound Number:** | Tavokinogene telseplasmid (tavo) with Electroporation (EP)<br>Nivolumab, an anti-programmed cell death 1 (anti-PD-1) antibody |
| **Study Phase:** | II |
| **Sponsor Name:** | Moffitt Cancer Center |
| **Source of Funding:** | OncoSec Medical Incorporated |

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| **Protocol Number** | MCC 20313 |
| **Amendment No. (if applicable)** | NA |
| **IND Number(s):** | 19502 |

# PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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| **Protocol Number** | MCC 20313 |
| **Version and Date** | v.26JUL2023 |
| **Amendment No. (if applicable)** | NA |
| **Regulatory Agency Identifier Number(s):** | |

## STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the Supporting Agency Terms. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed of their obligation to meet the above commitments.

**Principal Investigator:** Ahmad Tarhini, MD, PhD **Print/Type Name**

**Signed:** _____ **Date:** See signature

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# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

**Protocol Title:** Neoadjuvant Immunotherapy with Intratumoral Tavokinogene Telseplasmid (tavo) plus Electroporation in Combination with Intravenous Nivolumab in Patients with Operable Locally-Regionally Advanced Melanoma.

**Short Title:** Neoadjuvant Immunotherapy of Tavo-EP and Nivolumab in Operable Melanoma

**Rationale:** Treatment of advanced melanoma has recently been transformed by the approval of several novel agents (immune checkpoint inhibitors and molecular-targeted agents) that are more effective than conventional chemotherapy. Despite the clinical benefit in the responding subgroup to anti-programmed cell death protein 1 (PD-1) agents (nivolumab, pembrolizumab), the numbers indicate that a significant rate of subjects still do not respond to treatment, thus new agents are needed to increase the tumor response in advanced melanoma to improve response rates. A combination therapy of an anti-PD-1 drug with an agent capable of driving an effective T cell response, such as interleukin-12 (IL-12) may increase the immunogenicity and cytotoxic T lymphocytes (CTL) activity leading to an enhanced response.

Intratumoral injection of tavokinogene telseplasmid (tavo; IL-12 plasmid) followed by in vivo electroporation (tavo-EP or GenPulse® tavo), the investigational therapy, is a gene therapy approach designed to produce a localized expression of the pro-inflammatory cytokine IL-12 in the tumor microenvironment. The current study is designed to evaluate the safety and efficacy of neoadjuvant immunotherapy of intratumoral tavo-EP in combination with intravenous (IV) nivolumab followed by surgery and adjuvant phase with nivolumab monotherapy in subjects with operable, locally-regionally advanced melanoma. Neoadjuvant evaluation of anti-PD-1 agent nivolumab in combination with tavo may improve the clinical outcome in these subjects as it can transform poorly infiltrated/non-inflamed tumors into immunologically active lesions.

**Objectives and Endpoints:**

| Objectives | Endpoints |
|---|---|
| Primary | |
| • To assess the complete pathologic response rate (pCR) of intratumoral tavo-EP in combination with IV nivolumab (collectively 'the combined treatment') in subjects with operable locally-regionally advanced melanoma. | • pCR defined as proportion of subjects with no viable tumor on histologic assessment at definitive surgery |
| Secondary | |
| • To assess<br>(a) radiologic/clinical preoperative response rate, | • Objective response rate (ORR) assessed by Investigator based on Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 at 12 weeks of |

| Objectives | Endpoints |
|---|---|
| (b) Relapse Free Survival (RFS) and<br>(c) Overall Survival (OS). | Neoadjuvant phase (preoperative, unconfirmed)<br>• Duration of response (DOR)<br>• RFS<br>• Immune best overall response rate (iBORR) assessed by Investigator based on iRECIST (optional)<br>• OS |
| • To assess safety and tolerability of the combined treatment as neoadjuvant therapy in subjects with operable locally-regionally advanced melanoma. | • Frequency, duration and severity of adverse events (AEs) and serious adverse events (SAEs);<br>• Number of subjects with events of clinical interest (ECIs);<br>• Number of subjects who discontinued due to AEs<br>• Incidence and shifts of clinically significant laboratory abnormalities; safety laboratory evaluations includes complete blood count (CBC), blood biochemistry and urinalysis. |
| Exploratory | |
| • Immune monitoring | • Characterization of the tumor microenvironment and assessment of the immune phenotype and function pre- and post-combination therapy |

**Overall Design:**

This will be a Phase 2, Simon 2 stage minimax, open-label, single-arm study of neoadjuvant treatment of intratumoral tavo-EP plus nivolumab IV. Eligible subjects will be those with pathological diagnosis of operable locally-regionally advanced melanoma.

The Treatment period will be comprised of 3 phases:

Neoadjuvant Phase (Up to 3 x 4-week cycles, total 12 weeks): At each cycle, intratumoral tavo-EP willbe administered (on Days 1 and 8) concurrently with 480 mg nivolumab IV infusion on Day 8 ofeach cycle (tavo-EP will be administered prior to nivolumab infusion). NOTE: At the discretion of the treating physician investigator and as discussed with the patient as a means of maximizinglocal effects of tavo, an optional additional cycle of tavo-EP can be administered during the 3rd week (Day 15) of each of the 3 neoadjuvant cycles in the absence of limiting toxicities.

Definitive Surgery Phase: Surgery may be scheduled about 2-4 weeks after the last dose of nivolumab following radiologic and clinical assessment at that point. Pathologic response will be determined by institutional pathologist. Under certain circumstances, the definitive surgery may be delayed and done after completion of additional cycles of neoadjuvant therapy if decided by the treating physician investigators (surgeon and medical oncologist) to be in the best interest of the patient (or can be done earlier if study intervention(s) was discontinued due to AEs or other reasons).

Adjuvant Phase: Adjuvant therapy with nivolumab monotherapy will begin approximately 2-4 weeks following definitive surgery, but can be later as clinically indicated to allow medical clearance for systemic therapy; recovery from surgery is required (Day 1 of Cycle 4 will be determined by the treating investigator once the subject is cleared to initiate systemic therapy). Nivolumab (480 mg IV infusion on Day 1 of each 4-week cycle) will be administered for up to 9 cycles during the Adjuvant phase.

Follow up:

- All subjects will be followed for 4 weeks after last dose of nivolumab at End of Study (EOS) visit.
- In the absence of disease progression, data from standard of care imaging will be captured every 3 months for 2 years post-surgery and every 6 months thereafter for up to 3 years post-surgery.
- Long-term survival status will be performed every 6 months (by phone) for up to 5 years from study registration, unless the study is terminated early.

**Protocol Monitoring Committee (PMC) review:** Moffitt **PMC** will monitor safety and efficacy parameters as specified in the **PMC** section later in this protocol.

**Disclosure Statement:** This is a single group treatment study with 1 arm that has no masking.

**Number of Subjects:** Up to 33 subjects; in Simon minimax Stage 1, up to 22 subjects can be enrolled. If the number of pCR in Stage 1 meet the pre-specified number (N≥3 /22), enrollment for Stage 2 will include an additional 11 subjects (for a total of 33 subjects).

**Study Duration:** For each subject, the total duration of study participation will be 1 year (excluding the Screening period), plus long-term follow-up of up to 5 years (until death, subject withdraws consent or the study was terminated):

- Screening period: up to 4 weeks
- Neoadjuvant phase: 12 weeks (Up to 3 x 4-week cycles)
- Definitive surgery phase: approximately 2-4 weeks
- Adjuvant phase: up to 36 weeks (Up to 9 4-week cycles)
- Follow-up: up to 5 years

**Data Monitoring Committee:** Yes

## 1.2. Schema

| | |
|---|---|
| **Neoadjuvant Phase** (Up to 3 x4-week cycles; 12 weeks) | • Intra-tumoral TAVO-EP on Days 1, 8 and 15 (optional) of each 4-week cycle.<br>• Nivolumab 480 mg IV infusion on Day 8 of each 4-week cycle.<br>• On Day 8, TAVO-EP will be administered prior to nivolumab infusion. |
| **Definitive Surgery Phase** | • Surgery approximately 2-4 weeks after the last dose of nivolumab.<br>• Pathologic response will be determined by the institutional pathologist.<br>• Surgery may be done sooner or delayed if clinically indicated based on disease status and recovery from adverse events as determined by the treating physician investigator to be in the patient's best interest. |
| **Adjuvant Phase** (Up to 9 x4-week cycles) | • Recovery from surgery is required (Cycle 4 Day 1 is determined by the treating physician investigator once the patient is cleared to initiate adjuvant systemic therapy; Approximately 2-4 weeks following definitive surgery but can be later as clinically indicated to allow medical clearance for systemic therapy).<br>• Nivolumab 480 mg IV infusion on Day 1 of every 4-week adjuvant cycle, up to 9 cycles. |
| **Follow-Up Phase** | • Subjects will follow up 4 weeks after the last dose of nivolumab (End of Study visit).<br>• Long term follow-up in accordance with the standard of care.<br>• Long term follow-up status either in clinic or via phone, but must collect information on disease status (relapse or not) and survival. |

NOTE: At the discretion of the treating physician investigator and as discussed with the patient as a means of maximizing local effects of tavo, an optional additional cycle of tavo-EP can be administered during the 3rd week (Day 15) of each of the 3 neoadjuvant cycles in the absence of limiting toxicities.

## 1.3. Schedule of Activities (SoA)

| Period/Procedure | Screening | Neoadjuvant Phase | | | | | | | | | Definitive Surgery Phase | | | Adjuvant Phase | EOS / Early Discontinuation Visit [21] | Long term follow-up [22] ☎ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | Cycle 2 | | | Cycle 3 | | | Pre-Surgery | Surgery [18] | Post-Surgery Recovery [19] | Cycles 4-12 [20] | | |
| Study Day/ Day on cycle (1 cycle = 4 weeks) | ≤-28 | 1 | 8 | 15 | 1 | 8 | 15 | 1 | 8 | 15 | | | | Day 1 | 4 weeks after last dose | ~ every 6 months |
| Visit Window | | ±2 days | | | | | | | | | | | ±7 days | ±3 days | ±3 days | |
| Informed consent | X | | | | | | | | | | | | | | | |
| Demographic and Medical History [1] | X | | | | | | | | | | | | | | | |
| Inclusion/Exclusion criteria review | X | | | | | | | | | | | | | | | |
| Concomitant medications [2] | X | X | | | X | | | X | | | X | | X | X | X | |
| ECOG Performance status | X | X | | | | | | | | | X | | X | X | X | |
| Overall Survival status | | | | | | | | | | | | | | | | X |
| Physical exam and weight | X | X | | | X | | | X | | | X | | X | X | X | |
| Vital signs [3] | X | X | X | X | X | X | X | X | X | X | X | | X | X | X | |
| Disease staging [4] | X | | | | | | | | | | | | | | | |
| Disease Evaluation by RECIST v1.1 / iRECIST [5] | X | | | | | | | | | | X | | | | X, if disease progression | |
| Lesion Photographs & clinical | X | | | | X | | | X | | | X | | | | X, if disease progression | |

| Period/Procedure | Screening | Neoadjuvant Phase | | | | | | | | | Definitive Surgery Phase | | | Adjuvant Phase | EOS / Early Discontinuation Visit [21] | Long term follow-up [22] ☎ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | Cycle 2 | | | Cycle 3 | | | Pre-Surgery | Surgery [18] | Post-Surgery Recovery [19] | Cycles 4-12 [20] | | |
| **Study Day/ Day on cycle (1 cycle = 4 weeks)** | **≤-28** | **1** | **8** | **15** | **1** | **8** | **15** | **1** | **8** | **15** | | | | **Day 1** | **4 weeks after last dose** | **~ every 6 months** |
| measurements [6] | | | | | | | | | | | | | | | | |
| CBC with Differential [7] | X | X | | | X | | | X | | | X | | | X (Cycles 6, 9, 12) | X | |
| Blood chemistry [8] | X | X | | | X | | | X | | | X | | | X (Cycles 6, 9, 12) | X | |
| Thyroid Function [9] | X | X | | | X | | | X | | | X | | | X (Cycles 6, 9, 12) | X | |
| HIV, Hepatitis B & C, PT, PTT [10] | X | | | | | | | | | | | | | | | |
| Pregnancy test [11 | X | | | | | | | | | | | | | | X | |
| Urinalysis [12] | X | X | | | X | | | X | | | X | | | X (Cycles 6, 9, 12) | X | |
| **Imaging Procedures** | | | | | | | | | | | | | | | | |
| Imaging [13] | X | | | | | | | | | | X | | | Per standard of care | X, if disease progression & possible | Per standard of care |
| **Drug Administration** | | | | | | | | | | | | | | | | |
| Bi-dimensional tumor measurement for tavo dose calculation and tumor | X | | | | X | | | | | | | | | | | |

| Period/Procedure | Screening | Neoadjuvant Phase | | | | | | | | | Definitive Surgery Phase | | | Adjuvant Phase | EOS / Early Discontinuation Visit [21] | Long term follow-up [22] ☎ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | Cycle 2 | | | Cycle 3 | | | Pre-Surgery | Surgery [18] | Post-Surgery Recovery [19] | Cycles 4-12 [20] | | |
| **Study Day/ Day on cycle (1 cycle = 4 weeks)** | **≤-28** | **1** | **8** | **15** | **1** | **8** | **15** | **1** | **8** | **15** | | | | **Day 1** | **4 weeks after last dose** | **~ every 6 months** |
| response[14] | | | | | | | | | | | | | | | | |
| tavo-EP [25] | | X | X | X | X | X | X | X | X | X | | | | | | |
| Pain Assessment [15] | | X | X | X | X | X | X | X | X | X | | | | | | |
| Nivolumab | | | X | | | X | | | X | | | | | X | | |
| AE assessment [16] | X | X | X | X | X | X | X | X | X | X | X | | X | X | X | |
| Immune Monitoring [17] | | | | | | | | | | | | | | | | |
| Fixed tumor biopsy [24] | X | | X | | X | | | | | | | X | | | X (if disease progression & possible) | |
| Fresh tumor biopsy [24] | X | | X | | X | | | | | | | X | | | | |

AE = adverse events; CBC = Complete Blood Count; ECOG = Eastern Cooperative Oncology Group; EOS = End of Study; EP = Electroporation; HIV = Human Immunodeficiency Virus; iRECIST = immune Response Evaluation Criteria in Solid Tumors; RECIST = Response Evaluation Criteria in Solid Tumors

## Notes to Schedule of Assessments:

1. Medical history of the prior 3 years including any co-morbid conditions requiring active treatment as well as significant surgeries. Information on all interventions (systemic therapy, surgery, radiation treatment)

related to the subject's melanoma cancer will also be collected. Prior immunotherapy dosing concentration and cycle numbers should be captured.

2. Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. All concomitant medications received within 30 days before the first dose of study intervention (Cycle 1, Day 1) through 30 days after the last dose of study intervention should be recorded.
3. Vital signs to include heart rate, respiratory rate, temperature, blood pressure (systolic and diastolic). Height to be obtained at Screening only.
4. Disease staging should be collected at screening for this protocol.
5. Assessment by RECIST v1.1 will be done locally by the investigator (a) before the first dose of study intervention on scans performed as part of routine clinical management if they are of diagnostic quality and performed ≤28 days before study enrollment and (b) within 2 week prior to definitive surgery (preferred to be as close to surgery as possible).
6. Photographs and unidimensional clinical measurements are required at screening and within 28 days of tavo dosing. All lesions will be indicated by pen and numbered before being photographed. This provides the baseline map of ALL accessible lesions with baseline defined as the period between signing the informed consent form and prior to completion of Cycle 1. Target and non-target as well as new lesion will be identified by a lesion number which must remain the same throughout the study. Measurable lesions that are target lesions must be measured by the site and data entered into electronic data capture (EDC)
7. CBC w/differential to include: Hemoglobin, Platelets, Red Blood Cell, White Blood Cell, Basophils (Absolute; Abs), Eosinophils (Abs), Lymphocytes (Abs), Monocytes (Abs), Neutrophils (Abs) and Hematocrit.
8. Serum Chemistry to include: sodium, potassium, $CO_2$ or bicarbonate, chloride, albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), total bilirubin, blood urea nitrogen (BUN), calcium, creatinine, non-fasting glucose, magnesium, phosphorus, and total protein, serum chemistry and hematology do not need to be repeated if the Screening evaluations occurred within 10 days of the C1D1, unless a clinically significant change in the interim is suspected.
9. Thyroid function will include free T3, FT4 and TSH (will not need to be re-tested at C1D1 if screening evaluations were done within 10 days of C1D1).
10. Virology including HIV 1/2 antibodies, HBsAg, HCV RNA (qualitative). Also, PT, PTT. These tests will be done only if considered clinically indicated by the treating physician.
11. Only if considered clinically indicated by the treating physician and only for women of childbearing potential (i.e., postmenopausal women and women who have had a hysterectomy, oophorectomy are not of child- bearing potential). Local urine test must be performed within 72 hours prior to first study treatment and if positive, a serum test s required. An EOS urine pregnancy test will be performed and if positive, a serum test will be done.
12. Urinalysis will be done only if clinically indicated.
13. Tumor imaging will be performed in accordance with the standard of care as determined by the treating physician(s) and ideally should be done with the same imaging technique (computed tomography [CT ] or magnetic resonance imaging [MRI]; PET-CT preferred including diagnostic CT component if possible) to be used in a given subject throughout the study.

Baseline MRI brain is required to rule out metastatic disease if determined to be clinically indicated by the treating physician(s). CT should include the chest, abdomen and pelvis (and head and neck and all extremities if clinically indicated due to metastatic lesions or lymphadenopathy). All imaging will be assessed locally by the Investigator.

Imaging will be performed in accordance with the standard of care as determined by the treating physician(s) at (a) screening imaging (can utilize scans performed 28 days prior to subject signing the informed consent form with a confirmatory scan within 28 days prior to Cycle 1 Day 1); (b) within a week prior to definite surgery. Thereafter, post-surgery, imaging will be performed per standard of care (e.g., every 3 months for 2 years, every 6 months (± 1 week) for 3 years) and as clinically indicated up to 5 years from study entry.

14. Accessible tumors for treatment will be measured in millimeter and ¼ tumor volume will be calculated in centimeter for each tumor selected for treatment: ¼ tumor volume = [(longest diameter in cm) (perpendicular diameter in cm)$^2$]/8; a minimum of 0.1 mL per lesion for lesions <0.1 cm$^3$ in ¼ volume will be administered. The maximum plasmid injection volume per subject per day will not exceed 20 mL.
15. Intratumoral tavo-EP associated pain assessment: monitoring of pain will be performed by treating physician or designee (registered nurse, nurse practitioner, physician assistant) as part of the assessment on Days 1 and 8 of each tavo-EP treatment visit (at the start of each treatment and 5-7 minutes after EP procedure). Subjects will use a numeric pain rating scale to rate their pain with a start and stop time to capture any pain associated with EP procedure and duration. Any pain 5-7 minutes after the EP treatment will be evaluated on the pain scale and documented as an AE per the NCI-CTCAE v5.0
16. AEs occurring after signing consent will be recorded
17. Immune Monitoring details are documented in Section 10.5. Coagulation assessment (done locally) to be evaluated within 24 hours prior to biopsy collections if deemed clinically indicated. Coagulation assessment includes prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR). Biopsy (core or punch 3-5 mm) will be done at screening, Day 8 of cycle 1 and Day 1 of Cycle 2. Further, tumor will be removed at definitive surgery and some tissue will be allocated to immune monitoring; blood and fecal sample collection will be done at screening, Day 1 of Cycle 2, and then Day 1 of Cycles 6, 9 and 12 (±1 week) before treatment administration, and at disease progression (± 2-4 weeks). Please notice that PT and PTT will be done only if considered clinically indicated by the treating physician.
18. Refer to Appendix 8 (Section 10.8) for suggested guidelines on surgical management and techniques. These are important standard of care surgical guidelines and all investigators are strongly urged to consider them in the management of their patients. Under certain circumstances, the definitive surgery may be delayed and done after completion of additional cycles of neoadjuvant therapy if decided by the treating physician investigators (surgeon and medical oncologist) to be in the best interest of the patient (or earlier if study intervention(s) was discontinued due to AEs or other reasons).
19. Post-surgery visit will take place approximately 2-4 weeks after surgery; subjects must be cleared by the treating physician investigator for systemic standard of care adjuvant treatment with nivolumab every 4 weeks; the Post-surgery recovery visit may serve as the start of the Adjuvant Phase, but initiation of systemic adjuvant therapy can be later as clinically indicated to allow medical clearance for systemic therapy..
20. Adjuvant Treatment will include up to 9 cycles of nivolumab.
21. End of Study Visit will be conducted for all enrolled subjects. EOS Visit will be conducted 4 weeks ±3 days after the last dose of study intervention (whether combination of intratumoral tavo-EP and

nivolumab or nivolumab alone). Subjects who withdraw from the study prematurely will undergo same assessments as EOS visit. Imaging at EOS will be in accordance with the standard of care as determined by the treatingphysician(s).

22. Long term overall survival follow up may be via a phone call.
23. Following enrollment/registration on the study, patients should begin protocol treatment within 7 business days.
24. Research biopsy and research blood samples scheduled for Day 8 of Cycle 1 should be obtained before the nivolumab infusion scheduled for that day.
25. Optional Day 15: At the discretion of the treating physician investigator and as discussed with the patient as a means of maximizing local effects of tavo, an optional additional cycle of tavo-EP can be administered during the 3rd week (Day 15) of each of the 3 neoadjuvant cycles in the absence of limiting toxicities. The checked procedures on the calendar would be required only if the optional Day 15 injections were opted for.

**NOTE:** The Investigator/Sub-Investigators are expected to make every reasonable effort to comply with the study calendar and schedule of activities. However, if a cycle is missed or a subject's study treatment and/or testing days need to be rescheduled due to the subject's inability to comply with the study calendar (i.e., COVID-19 related events, hospitalizations, business and vacation travel plans, illness, transportation issues, holidays, family emergencies, etc.), an additional window of ± one week is available for rescheduling of study treatment and procedures per the discretion of the Sub- Investigator, and as needed discussed with the Investigator.

**NOTE:** Existing FFPE tumor samples from previous and future (while on study) melanoma tumor biopsies should be requested if available and should be submitted for research purposes. Up to 20 unstained slides may be requested if available. Provision of less than 20 slides is acceptable based on availability. This applies primary melanoma tumor lesions and metastatic melanoma tumor lesions. These should be requested in addition to the protocol indicated research biopsies.

**NOTE:** Effective July 26, 2023, blood and fecal biospecimens will no longer be collected on study.
**Rationale:** (1) All patients have completed the neoadjuvant phase of the study; (2) OncoSec is no longer able to support this study or biospecimen collections.

# 2. INTRODUCTION

## 2.1. Study Rationale

The therapeutic landscape for advanced melanoma has recently been transformed by the approval of several novel agents (immune checkpoint inhibitors and molecular-targeted agents) that are more effective than conventional chemotherapy (Michielin, 2015; Redman, 2016). Despite the clinical benefit in the responding subgroup to anti-PD-1 agents (nivolumab, pembrolizumab), the numbers indicate that significant rate of subjects still do not respond to treatment, thus new agents are needed to increase the tumor response in advanced melanoma to improve response rates. A combination therapy of an anti-PD-1 drug with an agent capable of driving an effective T cell response, such as IL-12 may increase the immunogenicity and CTL activity to enhance response.

Intratumoral injection of tavokinogene telseplasmid (tavo; IL-12 plasmid) followed by in vivo electroporation (tavo-EP or ImmunoPulse® tavo), the investigational therapy, is a gene therapy approach designed to produce a localized expression of pro-inflammatory cytokine IL-12 in the tumor microenvironment. The current study is designed to evaluate the safety and efficacy of neoadjuvant immunotherapy with intratumoral tavo-EP in combination with IV nivolumab followed by surgery and adjuvant phase with nivolumab in subjects with operable locally-regionally advanced melanoma. Neoadjuvant evaluation of anti-PD-1 agent nivolumab in combination with tavo may improve the clinical outcome in these subjects as it can transform poorly infiltrated/non-inflamed tumors into immunologically active lesions.

## 2.2. Background

Human IL-12 is a 70 kilodalton protein consisting of two subunits linked by a disulfide bond (Kobayashi, 1989). It is a potent pleotropic cytokine, capable of driving cell-mediated immunity through multiple parallel mechanisms, including activation of natural killer (NK) cells and CTLs as well as inhibition of regulatory T cells and myeloid-derived suppressor cells (MDSCs) (Kobayashi, 1989; Brunda, 1993; Steding, 2011). Also, as a potent inducer of interferon-gamma (IFN-γ), IL-12 can drive upregulation of antigen processing and presentation machinery (APM) within tumors (Zika, 2005; Kerkar, 2011).

Intratumorally injected tavo is taken up by tumor cells by electroporation (short electrical pulses to increase membrane permeability) using the OncoSec Medical System (OMS), a medical device consisting of a handle and sterile disposable electrode applicator tips containing a circular 6 stainless steel needle array (with diameter of either 0.5 cm or 1.0 cm) (OMS Applicator) and an electric pulse device (OMS Generator). EP is a physical method of delivery of compounds to tissues in vivo and was first reported to transfect cells in vivo with plasmid DNA in 1991 when reporter gene expression was seen in skin cells of mice (Titomirov, 1991). EP exposes target tissue to a sequence of brief electrical pulses of controlled voltage and duration, leading to transient increased permeability of the cell membrane. This allows for enhanced movement of molecules, such as plasmid DNA, into the intracellular space.

The tavo nonclinical program consists of a battery of in vivo tumor models, biodistribution studies and non-GLP toxicology studies. The tavo-EP clinical development program includes 9 clinical studies in 153 subjects with different malignancies with data available for 153 subjects in

the clinical database, of whom 106 received tavo-EP as monotherapy and 47 received tavo-EP in combination with IV pembrolizumab.

A detailed description of nonclinical and clinical studies, chemistry, pharmacology, efficacy, and safety is provided in the tavo Investigator's Brochure (IB).

Nivolumab (OPDIVO; Bristol-Myers Squibb Company) is a fully human IgG4 anti-PD-1 blocking monoclonal antibody that has shown clinical activity in subjects with advanced melanoma, non-small cell lung cancer, renal cell cancer, colorectal cancer, bladder cancer, head and neck cancer and other advanced malignancies (Topalian, 2012). In the adjuvant setting, nivolumab was associated with an improved recurrence-free survival (RFS) compared with ipilimumab (HR 0.65; CI: 0.51-0.83; P < 0.001) in a phase 3 study (CHECKMATE-238) that randomized 906 subjects with resected Stage IIIB-IV melanoma to either one year of nivolumab (3 mg/kg every 2 weeks) or ipilimumab (10 mg/kg every 3 weeks times 4 doses followed by every 12 weeks). Furthermore, the rate of treatment-related Grade 3-4 toxicity was 14.4% with nivolumab versus 42.6% in subjects treated with ipilimumab (Weber, 2017). Nivolumab was recently approved in the US as an adjuvant treatment for subjects with completely resected melanoma with lymph node involvement or metastatic disease. For additional information refer to the Package Insert (OPDIVO®, 2018).

## 2.3. Benefit/Risk Assessment

As indicated above, anti-PD-1 monoclonal antibody nivolumab was recently approved by the FDA for the treatment of melanoma in the adjuvant setting based on improvement in RFS in a randomized, double-blind study CHECKMATE-238. The most common adverse reactions in the study (reported in at least 20% of nivolumab-treated subjects) were fatigue, diarrhea, rash, musculoskeletal pain, pruritus, headache, nausea, upper respiratory infection, and abdominal pain. The most common immune-mediated adverse reactions were rash (16%), diarrhea/colitis (6%), and hepatitis (3%). For information about the known and expected benefits and risks and reasonably expected AEs of nivolumab refer to the Package Insert (OPDIVO®, 2018).

Anti-tumor activity of intratumoral tavo-EP demonstrated that intratumoral tavo-EP leads to significant increases in intratumoral IL-12 concentration without systemic IL-12 exposure, or systemic immune-related toxicities. Moreover, intratumoral tavo-EP in melanoma has been shown to not only increase intratumoral expression of IL-12 but also genes related to innate immunity, antigen presentation and anti-tumor adaptive immune responses. Efficacy data with tavo-EP in combination with anti-PD-1 monoclonal antibody pembrolizumab (OMS-I102) in subjects with melanoma that has low tumor infiltrating lymphocytes (TILs) showed a BORR of 50% (11/22); a CR of 41% (9/22); a disease control rate (DCR; CR + PR + stable disease [SD]) of 59% (13/22); progression free survival (PFS) of 57% at 15 months; and duration of response (DOR) of 100% (11/11) (Algazi, 2016; Algazi, 2016 AACR; Algazi, 2017).

The most frequently reported treatment-related adverse event (AE) is transient pain in association with the EP procedure. Other common treatment-related AE (incidence of ≥10% of subjects) treated with intratumoral tavo-EP as monotherapy were pain, injection site inflammation and injection site discoloration, most of which have been Grade 1 or 2 in severity. One tavo-EP monotherapy subject experienced a treatment-related serious adverse drug reaction (ADR), a Grade 3 cellulitis and 1 subject died due to tumor hemorrhage assessed by the

Investigator as unlikely related to study treatment. Two monotherapy subjects discontinued the study due to treatment related procedural pain.

For the combination therapy study (tavo-EP with pembrolizumab; CC-15852/OMS-I102), the common study treatment-related TEAEs (incidence of >10%) were fatigue, dizziness, myalgia, injection site pain, pruritus, nausea, procedural pain, arthralgia, and diarrhea, all of which have been Grade 1 or 2. No deaths have been reported among subjects. One subject reported a Grade 3 cellulitis assessed by the investigator as related to tavo-EP and unlikely related to pembrolizumab. Two subjects discontinued treatment due to AE; 1 subject experienced Grade 2 diarrhea, assessed by the investigator as not related to tavo-EP and possibly related to pembrolizumab; 1 subject experienced 2 AEs, a Grade 2 confusional state assessed by the investigator as possible related to tavo-EP and pembrolizumab, and a Grade 1 paresthesia, assessed by the investigator as not related to tavo-EP and pembrolizumab.

Most subjects report discomfort and/or pain associated with EP, even with administration of local anesthesia, oral pain killers, and anxiolytics. The BP-associated pain, described as an "electrical shock" or "sharp punch" is experienced only during administration of the EP pulses and is transient. It is recommended that the area be iced or treated with a topical numbing agent. Individuals should be properly informed to prepare for the EP discomfort and pain sensation before treatment in procedures where general anesthesia is not indicated or desired. For subjects with low pain thresholds or with large treatment areas requiring multiple EPs, the subject may receive Ativan (Iorazepam) as prophylaxis.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of intratumoral tavo-EP may be found in the IB.

# 3. OBJECTIVES AND ENDPOINTS

| Objectives | Endpoints |
|---|---|
| Primary | |
| • To assess the complete pCR of intratumoral tavo-EP in combination with IV nivolumab (collectively 'the combined treatment') in subjects with operable locally-regionally advanced melanoma. | • pCR defined as proportion of subjects with no viable tumor on histologic assessment at definitive surgery. |
| Secondary | |
| • To assess<br>(a) radiologic/clinical preoperative response rate,<br>(b) RFS and<br>(c) OS. | • ORR assessed by Investigator based on RECIST v1.1 at 12 weeks during the Neoadjuvant phase (preoperative, unconfirmed).<br>• Duration of response (DOR)<br>• RFS<br>• iBORR assessed by Investigator based on iRECIST (optional).<br>• OS |
| • To assess safety and tolerability of the combined treatment as neoadjuvant therapy in subjects with operable locally-regionally advanced melanoma. | • Frequency, duration and severity of AEs and SAEs.<br>• Number of subjects with ECIs.<br>• Number of subjects who discontinued due to AEs.<br>• Incidence and shifts of clinically significant laboratory abnormalities; safety laboratory evaluations includes CBC, blood biochemistry and urinalysis. |
| • To assess the risk of surgical delay (either due to toxicity and/or tumor progression). | • Definitive surgery will be planned at about 12 weeks. Patients will be monitored for surgical delay (either due to toxicity and/or tumor progression). |
| Exploratory | |
| • Immune monitoring. | • Characterization of the tumor microenvironment and assessment of |

| Objectives | Endpoints |
|---|---|
| | immune phenotypes and function associated with treatment |

# 4. STUDY DESIGN

## 4.1. Overall Design

This will be a Phase 2, Simon 2 stage minimax, open-label, single-arm study of neoadjuvant treatment of intratumoral tavo-EP plus nivolumab IV. Eligible subjects will be those with pathological diagnosis of operable locally-regionally advanced melanoma. The purpose and procedures of the study will be fully explained to potential subjects. Those wishing to enroll in the study will sign a written informed consent prior to initiating any study-related evaluations or procedures. Screening must be completed within 28 days prior to initiation of the study treatment (i.e. Cycle 1 Day 1; C1D1).

The Treatment period will be comprised of 3 phases:

Neoadjuvant Phase (Up to 3 x 4-week cycles, total 12 weeks): At every cycle, intratumoral tavo-EP will be administered (on Days 1 and 8) concurrently with 480 mg nivolumab IV infusion on Day8 of each cycle (tavo-EP will be administered prior to nivolumab infusion).

Definitive Surgery Phase: Surgery may be scheduled about 2-4 weeks after the last dose of nivolumab following radiologic and clinical assessment at that point. Pathologic response will be determined by institutional pathologist. Refer to Appendix 8 (Section 10.8) for suggested guidelines on surgical management and techniques. These are important standard of care surgical guidelines and all investigators are strongly urged to consider them in the management of their patients. Under certain circumstances, the definitive surgery may be delayed and done after completion of additional cycles of neoadjuvant therapy if perceived by the treating physician investigators (surgeon and medical oncologist) to be in the best interest of the patient (or earlier if study intervention(s) was discontinued due to AEs or other reasons).

Adjuvant Phase: Adjuvant therapy with nivolumab monotherapy will begin approximately 2-4 weeks following definitive surgery; recovery from surgery is required (Day 1 of Cycle 4 will be determined by the treating investigator once the subject is cleared to initiate systemic therapy). Nivolumab (480 mg IV infusion on Day 1 of each 4-week cycle) will be administered for up to 9 cycles during the Adjuvant phase.

In Simon minimax Stage 1, up to 22 subjects can be enrolled. If the number of responders in Stage 1 meet the pre-specified number (N≥3 //22), enrollment for Stage 2 will include an additional 11 subjects (for a total of 33 subjects).

All subjects will be followed for 4 weeks after last dose of nivolumab at EOS visit; data from standard of care imaging will be captured (every 3 months for 2 years post-surgery and every 6 months thereafter for up to 3 years post-surgery); long-term survival status will be determined every 6 month (by phone) for up to 5 years unless the study is terminated early.

Written IND safety reports will be submitted to the FDA by the IND sponsor, for serious, unexpected suspected adverse reactions within 15 calendar days of learning of its occurrence. If the event is fatal or is deemed to be life threatening, the report will be made within 7 calendar days. The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the IRB, which, in turn will make a final determination. If the IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

## 4.2. Scientific Rationale for Study Design

Pooled data from 4 ongoing neoadjuvant therapy studies at 3 large melanoma centers participating in the International Neoadjuvant Melanoma Consortium indicated that neoadjuvant targeted and immunotherapy are associated with a high pCR rate in stage III melanoma (Tetzlaff, 2018). Preliminary data suggest pCR correlates with improved RFS, particularly in those with pCR with immunotherapy (Menzies, 2017). Neoadjuvant evaluation of anti-PD-1 agent nivolumab in combination with tavo may improve the clinical outcome in subjects with advanced operable melanoma as it can transform poorly infiltrated/non-inflamed tumors into immunologically active lesions. The response rate (both pathologic and radiologic) in this setting is important to define to guide the field on the best approach for managing clinically evident operable disease. It will also provide needed data that would guide future nivolumab-based active combinations that may have important applicability in this setting.

The pCR rate (defined as no viable tumor on histologic assessment at surgery) is the most clinically meaningful endpoint with this immunotherapeutic agent given the implications on both the operability of the disease and on survival. The preoperative radiologic response rate will also be informative and clinically meaningful and such responses are expected to translate into durable survival benefits based on the current experience with nivolumab.

## 4.3. Justification for Dose

### 4.3.1. Tavo Dose Selection Rationale

**Dose:** Phase 1 clinical study to evaluate the safety and efficacy of a single cycle of intratumoral tavo-EP as a monotherapy in subjects with unresectable or metastatic melanoma showed 19 of 24 (79%) subjects enrolled on this study had additional sites of disease outside of the treated lesions (distant disease), and these subjects were therefore evaluated for distant response to therapy. In 53% there was evidence of a systemic response resulting in either stable disease, or objective regression of untreated lesions. In addition, in 3/19 subjects (15%) all of the distant lesions regressed completely in either the absence of any other systemic antitumor therapy (n=2) or following treatment with dacarbazine (n=1). Thus, the tavo selected dose (concentration of 0.5 mg/mL at a dose volume of approximately ¼ of the calculated lesion volume) is based on the dose cohort that yielded the highest proportion of responders.

**Intratumoral administration:** Systemic administration of IL-12 in multiple clinical studies in recombinant form (Atkins, 1997; Leonard, 1997; Hurteau, 2001) or via IL-12-expressing adoptive cell therapies (Rosenberg, 2015; National Cancer Institute, 2017) led to widespread, severe immune-related toxicities and death, but little or no anti-cancer efficacy in nearly all solid tumor indications.

To mitigate these toxicities, a multitude of localized delivery approaches have been explored (Sangro, 2004; van Herpen, 2004; Heinzerling, 2005; Mahvi, 2007; Anwer, 2010; Anwer, 2013; Linette, 2013; Nemunaitis, 2013; Nemunaitis, 2014; Lebel, 2015; Lebel, 2016; 2016; McArthur, 2016). The best efficacy demonstrated to date by any of these approaches was 20-50% ORR; these responses were accompanied by systemic Grade 3 or higher drug-related SAEs in 16-50%

of subjects across all indications tested (Linette, 2013; Nemunaitis, 2013; Nemunaitis, 2014; Lebel, 2015; Lebel, 2016; 2016; McArthur, 2016). In all studies where significant IL-12-related efficacy was achieved, related toxicities led to removal of at least some subjects from therapy or, in several cases, halt of the studies (Atkins, 1997; Leonard, 1997; Hurteau, 2001; Heinzerling, 2005; Mahvi, 2007; Anwer, 2010; Rudman, 2011; Anwer, 2013; Linette, 2013; Nemunaitis, 2013; Nemunaitis, 2014; Lebel, 2015; Rosenberg, 2015; Lebel, 2016; 2016; McArthur, 2016; National Cancer Institute, 2017).

As a monotherapy in advanced melanoma, ImmunoPulse® tavo yielded 33% best ORR, with 62% of subjects showing regression of untreated lesions (Daud, 2014; Daud, 2014). Yet, in contrast to other monotherapies yielding comparable objective responses (Nemunaitis, 2013; Nemunaitis, 2014; KEYTRUDA®, 2015; Lebel, 2015; Lebel, 2016; 2016; McArthur, 2016; OPDIVO®, 2018), ImmunoPulse® tavo treatment has not resulted in any systemic drug-related SAEs (Daud, 2008; Daud, 2014; Daud, 2014; Pierce, 2014; Bhatia, 2015; Pierce, 2015).

**Regimen:** Assessment of treatment on Days 1 and 8 at 4-week intervals will be evaluated in this study in neoadjuvant settings. Since IL-12 has an estimated half-life of 2-12 hours (Atkins, 1997; Portielje, 2005; Arkenau, 2011; Bhatia, 2015), any IL-12 that may enter the systemic circulation would be cleared within the 4-week cycle duration, and thus, cumulative increases in IL-12 should not be of concern when applying a 4-week cycle frequency with tavo and EP for co-localization of placement.

### 4.3.2. Electroporation Parameters Rationale

Of the methods available for in vivo gene delivery, EP is associated with high transfection efficiency and is a clinically developed platform (Potter, 2003).

Exposure of cells or tissue to brief, controlled electrical pulses at a specified electrical voltage causes a transient increase in cell membrane permeability, allowing macromolecules such as DNA to enter the cell and be expressed (i.e., transfection) (Gehl, 2003). EP-mediated transfection with plasmid DNA (pDNA) represents a non-viral gene therapy. EP has been used extensively to deliver pDNA to cartilage, blood, muscle, epithelial and loose connective tissue (Grossin, 2003; Weissinger, 2003; Kunieda, 2004; Hirao, 2008; Yuan, 2008). EP has also been applied to tumors to enhance the uptake of immunomodulatory genes (Lohr, 2001; Yamashita, 2001; Li, 2002; Lucas, 2002).

Electrical conditions utilized for electrochemotherapy have historically been used to deliver immunomodulatory genes to tumor tissues (Lucas, 2002). The reasoning behind this is the short-duration high-intensity pulses result in less tissue damage and fewer muscle contractions than traditional long-duration lower-intensity gene therapy conditions (Arena, 2012). Ultimately, using these pulses results in a shorter duration of expression, which is inconsequential as activation of the immune system results in the eventual destruction of transfected tumor cells. Commonly, this has resulted in the use of 6 pulses at a field strength (E+) of 1500 volt/cm and pulse width of 100 µs at 300 msec intervals, which are the parameters used by the OMS system.

### 4.3.3. Nivolumab Dose Selection Rationale

Nivolumab will be administered according to the approved label. The recommended dose of nivolumab is 480 mg every 4 weeks (Q4W) over 30 minutes infusion. This dose was recently approved in the United States for the adjuvant treatment of high-risk melanoma patients.

## 4.4. End of Study Definition

A subject is considered to have completed the study if he/she has completed all phases of the study including the end of study (EOS) visit.

The end of the study is defined as the date of the last survival contact of the last subject in the study.

# 5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1. Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

**Age**

1. Subject must be ≥ 18 years of age inclusive, at the time of signing the informed consent.

**Type of Subject and Disease Characteristics**

2. Histologic diagnosis of melanoma belonging to the following American Joint Committee on Cancer (AJCC) 8th edition TNM stages (Tx or T1-4) and (N1b, N1c, N2b, N2c, N3b or N3c) and/or (M1a)
3. Must be considered surgically operable and may present as any of the following groups:
    a. Primary melanoma with clinically apparent regional lymph node metastases, confirmed by pathological diagnosis.
    b. Clinically detected recurrence of melanoma at regional lymph node basin(s), confirmed by pathological diagnosis.
    c. Clinically or histologically detected primary melanoma involving multiple regional nodal groups, confirmed by pathological diagnosis.
    d. Clinically detected single site of nodal metastatic melanoma arising from an unknown primary, confirmed by pathological diagnosis.
    e. Subjects with in transit or satellite metastases with or without lymph node involvement are allowed if they are considered surgically resectable at Screening by the treating surgical oncologist.
    f. Subjects with distant cutaneous/subcutaneous, soft tissue or nodal metastases with or without regional lymph node involvement are allowed if they are considered potentially surgically resectable and can be biopsied at Screening by the treating surgical oncologist. Elevated LDH is not an exclusion.
4. Subjects are eligible for this study either at presentation for primary melanoma with concurrent regional nodal and/or in-transit or distant metastasis, or at the time of clinically detected nodal, in transit, or distant recurrence.
5. Subjects must be evaluated by standard-of-care full body imaging studies including positron emission tomography – computed tomography (PET-CT ;preferred; including diagnostic CT component if possible) or CT (if PET-CT cannot be done) as well as magnetic resonance imaging (MRI) of the brain (or CT if MRI cannot be done) as part of the initial clinical work-up at Screening (no more than 4 weeks prior to Cycle 1, Day 1).
6. Have measurable disease based on RECIST v1.1, with at least one anatomically distinct lesion. Lesion or lesions must meet all the following baseline criteria:
    a. Accessible for electroporation

b. Must be measured in at least one dimension (longest diameter in the plane of measurement is to be recorded)
c. Greater than 3 mm

**Sex**

7. Male and Female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male subjects:

Male subjects of childbearing potential must be surgically sterile, or must agree to use adequate method of contraception during the study and at least 5 months following the last day of study drug administration.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject

b. Female subjects:

Women of childbearing potential must have negative serum or urine pregnancy test within 72 hours prior to receiving the first study drug administration. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

For women of childbearing potential, must be willing to use an adequate method of contraception from 30 days prior to the first study drug administration and 5 months following last day study drug administration (either tavo or nivolumab); acceptable methods include hormonal contraception (oral contraceptives – as long as on stable dose, patch, implant, and injection), intrauterine devices, or double barrier methods (e.g. vaginal diaphragm/vaginal sponge plus condom, or condom plus spermicidal jelly), sexual abstinence or a vasectomized partner. Women may be surgically sterile or at least 1-year post-last menstrual period.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

**Informed Consent**

8. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

## 5.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

**Medical Conditions**

1. Subject has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer. Also,

includes patients who are considered disease-free for at least 3 years from the last definitive treatment for a second malignancy.

2. Subjects who have Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies at Screening). HIV testing at screening is not required unless considered clinically indicated by the treating physician.
3. Subjects who have active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected at Screening); *Note: Subjects who have been vaccinated against Hepatitis B and who are positive only for the Hepatitis B surface antibody are permitted to participate in the study.* Hepatitis B and C testing at screening is not required unless considered clinically indicated by the treating physician.
4. Subject has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug. The use of physiologic doses of corticosteroids may be approved after consultation with the Principal Investigator.
5. Subject has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
6. Subject has a history of interstitial lung disease.
7. Subject has an active infection requiring systemic therapy.
8. Subject has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
9. Subject has not recovered (i.e., > Grade 1 at Cycle 1, Day 1) from AEs due to a previously administered agent.

   *Note: Subjects with ≤Grade 2 neuropathy or ≤Grade 2 alopecia are an exception to this criterion and may qualify for the study.*
   *Note: If subject underwent major surgery or radiation therapy of >30 Gy, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study combination therapy.*
10. Subject has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.
11. Subjects who are pregnant or breast feeding or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 5 months after the last dose of trial treatment.

**Prior/Concomitant Therapy**

12. Subjects with electronic pacemakers or defibrillators

13. Subjects who have received a live-virus vaccination within 30 days of the first dose of treatment. Seasonal flu vaccines that do not contain live virus are permitted
14. Subjects who have received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks prior to study Cycle 1, Day 1.
15. Previous treatment with anti-PD1 or anti-PDL1 immunotherapy.

**Prior/Concurrent Clinical Study Experience**

16. Participation in another clinical study and systemic therapy within 30 days of Cycle 1, Day 1.

*Note: Subjects participating in an observational study are an exception to this criterion and may qualify for the study with Principal Investigator approval.*

**Organ Function Assessments**

17. ECOG Performance Status: >1
18. Inadequate organ function as defined below. All screening laboratories should be performed within 10 days of treatment initiation.

| **System** | **Laboratory Value** |
|---|---|
| Hematological | |
| Absolute neutrophil count (ANC) | $<1.5 \times 10^9$/L |
| Platelets | $<100 \times 10^9$/L |
| Hemoglobin | <9 g/dL or <5.6 mmol/L |
| Renal | |
| Creatinine* OR | >1.5 × the upper limit of normal (ULN) OR |
| Measured or calculated creatinine clearance (CrCl)<br><br>Glomerular filtration rate (GFR) can also be used instead of creatinine or CrCl | ≥60 mL/min for subject with creatinine levels ≤1.5 × institutional ULN |
| Hepatic | |
| Total bilirubin | >1.5 × ULN OR direct bilirubin >ULN for subjects with total bilirubin levels ≤ 1.5× ULN |
| Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) | >2.5 × ULN OR >5 × ULN for subjects with liver metastases |
| Coagulation¥ | |

| | |
|---|---|
| International Normalized Ratio (INR) or Prothrombin Time (PT) | >1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants |
| Activated Partial Thromboplastin Time (aPTT) | |
| * Creatinine clearance should be calculated per institutional standard.<br>¥PT, INR and PTT will be done only if considered clinically indicated by the treating physician. | |

**Other Exclusions**

19. Subject has severe hypersensitivity (≥Grade 3) to nivolumab and/or any of its excipients

## 5.3. Screen Failures

Subjects who fail to meet the entrance criteria at any time during the screening period are defined as screen failures. All screen failures will be recorded on the screening failure log, which documents the site number and screening number and reason(s) for screen failure. The screening failure log will be kept in the Investigator's Site File.

Re-screening/re-assessment outside the Screening period will be possible on a case-by-case basis following approval by the principal investigator. Subjects allowed to be re-screened, will be determined a screen failure after the second screening confirmed the subject is ineligible.

## 5.4 Registration Procedures

Patients will be registered after meeting all entry requirements and providing a signed informed consent document. The date of the PI/treating physician signature on the eligibility checklist confirming that the patient meets the eligibility criteria is the registration date.

### 5.4.1 Enrollment

Eligible patients will be enrolled on study centrally at Moffitt Cancer Center by the Study Coordinator.

When all required test results are available, complete the eligibility checklist and provide the checklist and the supporting documentation to the IRB approved investigator for review and sign-off. Once the investigator (or Sub-Investigator) has signed the eligibility checklist, enrollment may proceed.

Following enrollment, patients should begin protocol treatment within 7 business days. Issues that would cause treatment delays should be discussed with the Principal Investigator.

# 6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

## 6.1. Study Intervention(s) Administered

On days when both intratumoral tavo and IV nivolumab are administered, every effort will be made not to administer the treatments to the same arm or location. It is recommended that tavo will be administered first.

| | **tavo-EP** | | **Nivolumab** |
|---|---|---|---|
| **Intervention Name** | Tavokinogene telseplasmid | Electroporation | Nivolumab |
| **Type** | Biologic | Device | Biologic |
| **Dose Formulation** | 1.5 mL vials at a concentration of 0.5 mg/mL | | 4 mL and 10 ml vials at a concentration of 10 mg/mL solution for IV infusion |
| **Unit Dose Strength(s)** | mg | | mg |
| **Dosage Level(s)** | Tavo will be injected on Days 1 and 8 every 4 weeks at a dose volume of ¼ of the calculated lesion volume with a minimum dose volume per lesion of 0.1 mL for lesions of volume <0.4 $cm^3$<br>NOTE: At the discretion of the treating physician investigator and as discussed with the patient as a means of maximizing local effects of Tavo, an optional additional cycle of Tavo can be administered during the 3rd week (Day 15) of each of the 3 neoadjuvant cycles in the absence of limiting toxicities. | See Section 6.1.1. | 480 mg Q4W over 30 minutes<br>**NOTE:** Every effort will be taken to ensure that the infusion duration be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time of 25 to 40 minutes).<br>In patients who poorly tolerate the planned infusion time, the infusion time may be extended as clinically indicated by the treating team. Future infusion times may also be extended as determined to be clinically indicated by the treating physician. |
| **Route of Administration** | Intratumoral injection | Electroporation | IV infusion |

| | tavo-EP | | Nivolumab |
|---|---|---|---|
| **IMP and NIMP** | | | Approved |
| **Sourcing** | GMP-grade tavo is manufactured, packaged and provided centrally on behalf of the study supporter. | Provided centrally by the study supporter. | Provided locally by the study site. |
| **Packaging and Labeling** | Study Intervention will be provided in vials. Each vial will be labeled as required per country requirement. | See Section 6.1.1. | Study Intervention will be provided in vials. Each vial will be labeled as required per country requirement. |
| **Current/Former Name(s) or Alias(es)** | ImmunoPulse tavo<br>Tavokinogene telseplasmid | | OPDIVO |

### 6.1.1. Medical Devices

The OMS, a medical EP device system, consists of 3 main components: (1) an Electroporation Generator that generates electric pulses, (2) a sterile Applicator Tip containing needle array, and (3) an Applicator Handle that connects to the Electroporation Generator at the proximal end and connects to the Applicator Tip at the distal end. The Applicator Tip contains a circular 6 needle array and comes in two models characterized by the needle array diameter: 0.5 cm and 1.0 cm. The needle length is 1.5 cm for both models and the needle insertion depth is adjustable by the user between 0 and 1.5 cm. An OncoSec Printer may be optionally used to generate a real-time event log of the electroporation treatment information used during the treatment.

Upon user activation of the attached Foot Switch, the OMS Electroporation Generator delivers controlled electrical pulses in a square wave pulse pattern yielding optimal transmembrane potential for electroporation to occur. EP pulses occur between 6 hexagonal opposing needle electrodes. After the first pulse, the polarity between the opposing needle electrode pairs is reversed and the needle pair is pulsed again. After the initial paired pulse, the pulse delivery is rotated clockwise to the next opposing needle pairs until a total of 6 pulses are delivered to complete the EP sequence.

OncoSec filed a Device Master File (MAF) with the Food and Drug Administration (FDA) with information on the electrical safety and electromagnetic compatibility, biocompatibility, sterility, software, packaging, etc.

Additional details regarding handling of the device are provided in the OncoSec Medical System Operator's Manual.

## 6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Unopened drug product (tavo) sterile vials should be stored in the packaging received from OncoSec in a secure, continuously temperature monitored and alarmed freezer in

the pharmacy or other appropriate secure location at a nominal temperature of -20ºC. Temperature variation is allowed to a maximum temperature of -10°C. Any temperature excursions greater (warmer) than -10°C must be reported to the principal investigator and later to OncoSec. Refer to the Pharmacy Manual.

3. The OMS Applicator and Tips will be supplied by OncoSec and should be stored in ambient conditions in a restricted area with limited access and may only be used on subjects who have been properly consented and enrolled into the investigational studies. Refer to the Operators Manual.
4. Only subjects enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
5. Please refer to the Study Pharmacy Manual for tavo plasmid preparation and storage instructions. Briefly, Tumor size will be used to calculate the total dose per lesion and per subject. The number of vials needed for each intratumoral injection must be thawed at room temperature for approximately 5-10 minutes and mixed vigorously prior to drawing the solution using a sterile tuberculin syringe of appropriate size (0.3 mL to 10 mL), with a 25-gauge to 30-gauge 5/8-inch needle and needle cap. Additional plasmid solution can be withdrawn as needed to prime the syringe and deliver accurate dose(s) to the subject. Each treatment syringe should be visually inspected prior to injection, checking that the suspension is homogeneous. If the suspension does not appear homogeneous, the syringe should be discarded and new plasmid for treatment prepared. Unused portions of each vial will be discarded into approved biohazard containers and disposed of as per institutional requirements. The prepared formulation must be administered within 8 hours after thawing at room temperature.
6. Nivolumab will be prepared per manufacturer's instructions and should be stored as per the product's package insert.
7. The investigator is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

## 6.3. Study Intervention Compliance

Subject compliance with study intervention will be assessed at each visit. Compliance will be based on accountability records and an inventory of used/unused supplies. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

## 6.4. Concomitant Therapy

All treatments that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Any medications that belong to corticosteroids, immunosuppressant and/or hormonal replacement therapies that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
-

Both local and systemic analgesics and anxiolytics, as well as topical and/or injected anesthetics are recommended prior to the intratumoral tavo-EP procedure. Other methods, including conscious sedation, are also permitted and will be employed per Investigator discretion and standard institutional practices. Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Principal Investigator.

The Principal Investigator should be contacted if there are any questions regarding concomitant or prior therapy.

### 6.4.1. Prohibited Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The Investigator should discuss any questions regarding this with the Principal Investigator. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the subject's primary physician. However, the decision to continue the subject on study therapy or vaccination schedule requires the mutual agreement of the Investigator, the Principal Investigator and the subject.

Listed below are specific restrictions for concomitant therapy or vaccination during the course of the study:

- Antineoplastic -systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Investigational agents other than nivolumab and tavo-EP
- Radiation therapy (Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the Investigator's discretion)
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

- Systemic glucocorticoids (in dosing exceeding 10 mg daily of prednisone equivalent) for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the principal investigator. *Note: Topical steroids are permitted. Inhaled steroids are allowed for management of asthma.*

Subjects who, in the assessment by the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study.

All treatments that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

The Exclusion Criteria describes other medications that are prohibited in this study.

There are no prohibited therapies during the post-treatment follow-up period.

## 6.5. Intervention after the End of the Study

No study extension is planned.

## 6.6. Stopping Rules and Toxicity Management Guidelines

### 6.6.1. Tavo

The concentration of tavo is 0.5 mg/mL. Decision in the total number of injected lesions will be made at the discretion of the Principal Investigator and/or treating physician. Considerations will include the number of tumor lesions accessible for injection and electroporation and each subject's ability to tolerate the procedure.

Death(s) within 30 days of last dose of combination treatment on study, that are considered at least possibly related to study treatment, will result in temporary suspension of enrollment and dosing until assessed by **PMC**.

If a subject experiences a Grade 4 hematological or non-hematological AE, combination treatment of tavo-EP and nivolumab will be discontinued until toxicity resolves to Grade ≤1 or baseline levels. Consult the principal investigator if a subject experiences a Grade 3 hematological or non-hematological AE that is not resolved within 1 treatment cycle. If the AE resolves during the cycle such that Days 1 and 8 may take place within the allowed ±2-day window, then continuation of treatment may take place. Alternatively, combined treatment will be restarted on Day 1 of the next scheduled treatment cycle. The next treatment cycle may begin sooner than scheduled per Investigator's discretion following discussion with the principal investigator. If the hematological toxicity does not resolve within 12 weeks of last treatment, permanent discontinuation should be considered for any severe or life-threatening event. Subject missing 2 intratumoral tavo-EP treatments in the neoadjuvant phase will be allowed to continue nivolumab (as monotherapy) treatment up to a total of 12 cycles (3 combination cycles and 9 monotherapy cycles). Missed doses are permitted for inclement weather/acts of nature.

Please notice that tissue ulceration or cellulitis infections related to Tavo injection and/or EP are included under Events of Clinical Interest. Further, the occurrence of any > grade 2 skin ulcerations must lead to the discontinuation of injection and EP at that site.

### 6.6.2. Nivolumab

It is recommended to continue treatment with nivolumab for clinically stable subjects with initial evidence of disease progression until disease progression is confirmed.

Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Guidelines for permanent discontinuation or withholding of doses are described in Table 1. Detailed guidelines for the management of immune-related adverse reactions are described in Nivolumab package insert.

If during the neoadjuvant phase, nivolumab is withheld or discontinued, tavo-EP can be administered as monotherapy (up to 3 4-week cycles) after discussion with principal investigator.

**Table 1 Recommended treatment modifications for nivolumab**

| **Immune-related adverse reaction** | **Severity** | **Treatment modification** |
|---|---|---|
| Immune-related pneumonitis | Grade 2 pneumonitis | Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete |
| | Grade 3 or 4 pneumonitis | Permanently discontinue treatment |
| Immune-related colitis | Grade 2 diarrhea or colitis | Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete |
| | Grade 3 diarrhea or colitis | Withhold dose(s) until symptoms resolve and management with corticosteroids is complete |
| | Grade 4 diarrhea or colitis | Permanently discontinue treatment |
| Immune-related hepatitis | Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin | Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete |
| | Grade 3 or 4 elevation in AST, ALT, or total bilirubin | Permanently discontinue treatment |
| Immune-related nephritis and renal dysfunction | Grade 2 or 3 creatinine elevation | Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete |
| | Grade 4 creatinine elevation | Permanently discontinue treatment |

| Immune-related adverse reaction | Severity | Treatment modification |
|---|---|---|
| Immune-related endocrinopathies | Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis,<br>Grade 2 adrenal insufficiency<br>Grade 3 diabetes | Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy[a] as long as no symptoms are present |
| | Grade 4 hypothyroidism<br>Grade 4 hyperthyroidism<br>Grade 4 hypophysitis<br>Grade 3 or 4 adrenal insufficiency<br>Grade 4 diabetes | Permanently discontinue treatment |
| Immune-related skin adverse reactions | Grade 3 rash | Withhold dose(s) until symptoms resolve and management with corticosteroids is complete |
| | Grade 4 rash | Permanently discontinue treatment |
| | Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) | Permanently discontinue treatment (see section 4.4) |
| Other immune-related adverse reactions | Grade 3 (first occurrence) | Withhold dose(s) |
| | Grade 3 myocarditis | Permanently discontinue treatment |
| | Grade 4 or recurrent Grade 3; persistent Grade 2 or 3 despite treatment modification; inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day | Permanently discontinue treatment |

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0).
Source: Nivolumab package insert 2018

# 7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

## 7.1. Discontinuation of Study Intervention

It may be necessary for a subject to permanently discontinue study intervention prior to planned completion of treatment regimen (see Section 6.6 for stopping rules and toxicity management). If study intervention is permanently discontinued, the subject will remain in the study to be evaluated for up to 30 days post last dose of study intervention. See the SoA (Section 1.3 ) for data to be collected at the time of discontinuation of study intervention (30 days post last dose of study intervention).

### 7.1.1. Temporary Discontinuation

See Section 6.6 for stopping rules and toxicity management.

## 7.2. Subject Discontinuation/Withdrawal from the Study

Subjects are free to discontinue their participation in the study at any time and without prejudice to further treatment. The Investigator must withdraw any subject from the study if that subject requests to be withdrawn, or if it is determined that continuing in the study would result in a significant safety risk to the subject.

Subjects who discontinue study drug or are withdrawn from the study prior to the first efficacy endpoint will not be replaced.

The subject's participation in the study may be discontinued due to the following reasons:

- Request of Investigator
- Life-threatening event or death
- Subject withdrew consent
- Subject is lost-to-follow-up

The subject may discontinue study medication due to the following reasons:

- Request of Investigator
- AE
- Treatment failure
- Subject is non-compliant with study procedures or study protocol
- Request of regulatory authority
- Pregnancy
- Other (to be specified in the electronic case report form; eCRF)

## 7.3. Lost to Follow up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 in Section 10.1.8.

# 8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the investigator immediately upon occurrence or awareness to determine if the subject should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

## 8.1. Efficacy Assessments

Planned time points for efficacy assessments are provided in the SoA.

### 8.1.1. Complete Pathologic Response (pCR)

The primary endpoint of this study is pCR, defined as no viable tumor on histologic assessment at definitive surgery (Tetzlaff, 2018). pCR will be evaluated locally by a certified surgical pathologist.

### 8.1.2. Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and immune RECIST (iRECIST)

Secondary efficacy endpoints will be evaluated using RECIST v1.1 (Eisenhauer, 2009) as described in Section 10.7.1 (required) and iRECIST (optional), as described in Section 10.7.2.

Radiographic imaging will be assessed locally by the Investigator during the neoadjuvant phase (preoperative, unconfirmed); during the adjuvant phase, radiographic imaging and local assessments will be done only if feasible (as tumor is resected during surgery).

Disease staging will be collected at original diagnosis and at screening for this protocol, prior to any treatment initiation.

### 8.1.3. Lesion Photographs and Unidimensional Clinical Measurements

Lesions photographs and unidimensional clinical measurements will be done as specified in SoA. Lesions will be numbered identically for each visit, each lesion will also be labelled as target, non-target, or new lesions (Table 8). At all study visits, lesion photography will always be done with a caliper/ruler and lesion identification on all accessible clinically measure lesions.

## 8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

### 8.2.1. Medical History and Concomitant Medications

Any diseases in the prior three years including any co-morbid conditions requiring active treatment as well as significant surgeries will be documented in the medical history of the eCRF. Abnormal physical examination finding and/or the diagnosis of concomitant disease resulting from assessment at screening must be also documented in the medical history section.

Information on all interventions (systemic therapy, surgery, radiation treatment) related to the subject's melanoma cancer will also be collected.

Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. Corticosteroids, immunosuppressant and/or hormonal replacement therapies that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates

### 8.2.2. Eastern Cooperative Oncology Group (ECOG) Performance Status

The ECOG Performance Status will be used to assess subjects' performance status by the same study staff (Table 2 ). The performance status will be assessed as specified in the SoA (Section 1.3).

**Table 2 ECOG Performance Status**

| **ECOG PERFORMANCE STATUS** | |
|---|---|
| **Grade** | **ECOG** |
| **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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours |
| **3** | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours |
| **4** | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair |
| **5** | Dead |

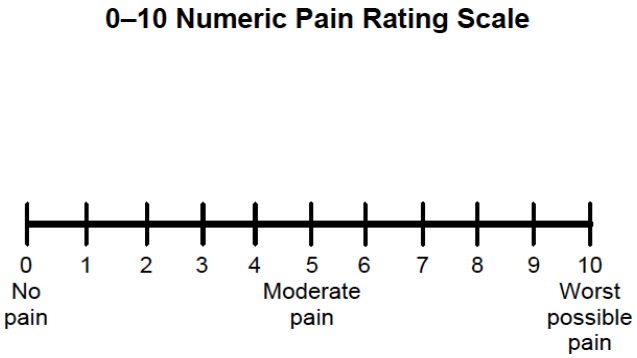
### 8.2.3. Durable Procedural Pain Assessment

Based on clinical data, it is expected that subjects will experience a transient pain associated with the procedure of EP that dissipates shortly thereafter. EP-associated pain assessment monitoring

will be performed by the treating physician or designee (registered nurse, nurse practitioner, physician assistant) on Days 1 and 8 of each tavo-EP treatment visit before the EP procedure and 5 minutes after EP procedure. Only pain that persists five minutes after the end of EP procedure will be evaluated on numeric pain rating scale Figure 1 and documented as an AE per the CTCAE v5.0.

Numeric pain rating scale measures the intensity or magnitude of sensations and subjective feelings and the relative strength of attitudes and opinions about specific stimuli, on a scale of 0 to 10 with a score of zero denoting "no pain at all" and a score of 10 denoting "worst possible pain" (Duncan, 1989; Holdgate, 2003; Johnson, 2005; Krebs, 2007).

**Figure 1 Numeric Pain Rating Scale**




### 8.2.4. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

### 8.2.5. Vital Signs

- Vital signs will be measured will include heart rate, respiratory rate, temperature, and blood pressure (systolic and diastolic).
- Blood pressure and heart rate will be done at rest as per standard practice at the investigational site.
- Significant findings noticed after the start of study medication and findings that worsen significantly, which meet the definition of an AE must be recorded on the AE eCRF.
- Height to be obtained at Screening only.

### 8.2.6. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or principal investigator.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the investigator notified.
  - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the protocol and the SoA.
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in subject management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

## 8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

AE will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the subject to discontinue the study intervention (see Section 6.6).

### 8.3.1. Time Period and Frequency for Collecting AE, SAE and ECI Information

All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).

Table 3 below summarizes the different observation periods for AEs, SAEs, and ECIs.

**Table 3: Adverse Event Observation Periods**

| Type of Event | Adverse Event | Serious Adverse Event | ECI with study intervention |
|---|---|---|---|
| Reporting period | From consent until 30 days after the end of treatment | From consent until 30 days after the last dose of study treatment for all SAEs, and any time after the end of study for SAEs believed to be related to study intervention | From consent until 30 days after the last dose of study treatment, or 30 days after the initiation of a new anti-cancer therapy, whichever is earlier |
| Reporting Timelines to the Study supporter | Entered into the clinical database on an ongoing basis | Within 24 hours | Within 24 hours |

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.

The Investigator is responsible for ensuring that all AEs observed by the Investigator or reported by subjects are properly captured in the subject's medical records and reported in the eCRF.

Investigators are not obligated to actively seek AE, ECI or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Study supporter.

### 8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

During the study, subjects should be assessed for possible ECIs prior to each dose. Laboratory results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If laboratory results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

### 8.3.3. Follow-up of AEs, ECIs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and ECIs (as defined in Section 10.3.3), will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

### 8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor-investigator will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- Any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the study drug, must be submitted on an SAE form and assessed by PI in order to determine reporting criteria to regulatory authorities, IRB, **PMC**, FDA. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator (or designee; sub-investigator) must assess and record the relationship ofeach SAE to each specific study treatment (if there is more than one study treatment),complete the SAE Report Form, and submit the completed form.
- Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.
- All SAE must be recorded on a MedWatch 3500 Form. SAE reports and any other relevant safety information are to be forwarded as follows,

  MedWatch 3500 Reporting Guidelines:

  Note: MedWatch 3500 forms and other information related to MedWatch reporting are available at http://www.fda.gov/medwatch/index.html.

  A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA. Investigators will cross reference this submission according to local regulations to the Investigational Compound Number (IND, CSA, etc.) at the time of submission.

- An investigator (or designee; sub-investigator) will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets. All adverse events regardless of CTCAE grademust also be evaluated for seriousness.
- **Reporting Requirements for IND holder:**
    - For Investigator-sponsored IND studies, reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR, Part 312.32. Events meeting the following criteria need to be submitted to the FDA as Expedited IND Safety Reports.
    - 7 Calendar-Day Telephone or Fax Report:

      The Sponsor-Investigator is required to notify the FDA of a fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of investigational agents. An unexpected adverse event is one that is not already described in the most recent Guidance for Investigator section of the Investigator's Brochure. Such reports are to be telephoned or faxed to the FDA, within 7 calendar days of the first learning of the event.
    - 15 Calendar-Day Written Report:

      The Sponsor-Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious unexpected adverse event that is considered reasonably or possibly related to the use of investigational agent.

      Written IND Safety Reports with analysis of similar events are to be submitted to the FDA, within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 Form but alternative formats (e.g., summary letter) are acceptable.

      FDA Fax number of IND Safety Reports: 1-(800)-FDA-1078.

      The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the IRB, which, in turn will make a final determination. If the IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

      All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

### 8.3.5. Pregnancy

- Details of all pregnancies in female subjects and, if indicated, female partners of male subjects will be collected after the start of study intervention and until through 5

months following cessation of study intervention, or 30 days following cessation of study intervention if the subject initiates new anticancer therapy, whichever is earlier.

- If a pregnancy is reported, the investigator should inform the Sponsor-invstigator within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

### 8.3.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following disease related events (DREs) are common in subjects with melanoma and can be serious/life threatening:

- Disease progression; if disease progression occurs, record the date first documented in the EOS visit eCRF. Signs and symptoms related to PD should be reported in the appropriate eCRF as an AE or as an SAE if the event in question meets the criteria for seriousness.

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of a SAE. These events will be recorded on the corresponding eCRF page in the subject's CRF within the appropriate time frame.

In addition, the following will not be considered AEs

- Worsening of a pre-existing medical condition, (i.e., diabetes, migraine headaches, gout). However, it should be considered an AE if there is either a significant increase in severity, frequency, or duration of the condition or an association with significantly worse outcomes.
- Interventions for pretreatment conditions (i.e., elective cosmetic surgery) or medical procedures that were planned before study enrollment are not considered AEs.

*NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):*

- *The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual subject.*

  OR

- *The Investigator considers that there is a reasonable possibility that the event was related to study intervention.*

### 8.3.7. Medical Device Incidents (Including Malfunctions)

Medical devices are being provided for use in this study for the purposes of electroporation. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 6.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Appendix 3 of the protocol.

#### 8.3.7.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any incident at any time after a subject has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the Sponsor-invastigator who will notify the study supporter.

The method of documenting Medical Device Incidents is provided in Appendix 6.

#### 8.3.7.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 8.3.3). This applies to all subjects, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

#### 8.3.7.3. Prompt Reporting of Medical Device Incidents to Study Supporter

- Medical device incidents will be reported to the Sponsor via email within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident.
- The same individual will be the contact for the receipt of medical device reports and SAE.

#### 8.3.7.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the Sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

## 8.4. Biomarkers

- Collection of samples for other biomarker research is also part of this study. Tumor biopsies (fixed and fresh) as well as blood and fecal samples will be collected as specified in SoA and Appendix 5 (Section 10.5).
- The main objective of the Immune Monitoring is to characterize the tumor microenvironment and assess the immune phenotype and function pre- and post-study intervention (tavo-EP in combination with nivolumab) prior to as well as post-surgery.
- Samples may be stored according to local regulations following the last subject's last visit for the study at a facility selected by the Sponsor to enable further analysis.

# 9. STATISTICAL CONSIDERATIONS

## 9.1. Statistical Hypotheses

This is a Phase 2 single-agent, open-label study. The primary endpoint of this study is the complete pCR at definitive surgery. It is anticipated that combination regimen will improve the pCR from an estimated 10% to 30%.

## 9.2. Sample Size Determination

The statistical power calculations are based on the Simon 2-stage minimax design (Simon, 1989) A total of 33 eligible subjects will be enrolled into this study in a 2-stage design. In the first stage, up to 22 subjects can be accrued. If there are ≤ 2 responses in these 22 patients, the study will be stopped. Otherwise if ≥3 responses are observed, the study will proceed to Stage 2, in which an additional 11 subjects will be accrued for a total of 33 subjects. If 7 or more responses are observed in 33 subjects, the conclusion will be that the therapy is worthy of further investigation. When the true response rate of 30% (alternative hypothesis) is tested against the null hypothesis response rate of 10%, this design yields a Type I error rate of 0.05 and power of 90%.

## 9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

| Population | Description |
|---|---|
| All Subjects as Treated (ASaT) / Safety | All enrolled subjects who received at least 1 dose of either study intervention (tavo or nivolumab) |

## 9.4. Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. The SAP may modify the plans outlined in the protocol; however, any major modifications will also be reflected in a protocol amendment.

Since this is an open-label, single arm clinical study, descriptive summary statistics will be employed to analyze the data.

The standard summary statistics for continuous variables are sample size (n), mean, standard deviation, median, minimum and maximum. The standard summary statistics for categorical variables are frequencies and percentages. Time to event variables will be summarized using the Kaplan-Meier method. Where confidence limits are appropriate, the confidence level will be 95% (two-sided), unless otherwise stated. The only test of statistical significance will be performed according to the pre-defined analysis of the Simon 2-stage design.

Individual data (including relevant derived variables) will be presented by parameter in listings. Results of statistical analyses, descriptive summary statistics and supportive listings will also be presented.

Baseline values are defined as the last valid value prior to study drug administration. Baseline safety data will be presented along with subsequent safety values assessed during or after drug administration.

Statistical analyses will be performed using SAS® v9.4 or higher (SAS Institute, Cary NC, USA).

### 9.4.1. Subject Disposition

A detailed description of subject disposition will be provided. It will include:

- The number of subjects who were included in the safety analysis sets
- A summary of subjects who complete the protocol
- A summary of reasons for subject discontinuation
- A summary of reasons for subject with treatment failure
- An account of all identified protocol violations

All subject enrolled in the study will be accounted for in the summation.

### 9.4.2. Demographic and Baseline Characteristics

Demographic characteristics including age, gender, race, and ethnicity will be presented in the form of tabular summary statistics for all ASaT analysis set. Other subject baseline characteristics including weight, height, body mass index (BMI), initial stage of disease, and performance status will be presented similarly.

### 9.4.3. Efficacy Analyses

| Endpoint | Statistical Analysis Methods |
|---|---|
| Primary | Primary efficacy analyses will be performed on ASaT Population.<br>The pCR will be estimated based on the proportion of subjects with no viable tumor on histologic assessment at definitive surgery. The estimated pCR will be accompanied by a 2-sided 95% exact binomial confidence interval (CI). Refer to statistical analysis plan (SAP) for detail. |
| Secondary | DOR, PFS, iPFS, iBORR and OS (time to events endpoints) will be summarized descriptively using Kaplan-Meier methods. The censoring rules will be defined in the SAP. The ORR, BORR, and iBORR (categorical endpoints) will be summarized in a similar fashion as pCR. These will be assessed by Investigator based on Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 at 12 weeks of Neoadjuvant phase (preoperative, unconfirmed). Refer to SAP for detail. Further, the risk of surgical delay (either due to toxicity and/or tumor progression) will be assessed. Surgery will be planned at about 12 weeks and any delays beyond the protocol allowed window will be monitored and reported. |

### 9.4.4. Safety Analyses

The safety assessment will be based on the frequency of AEs, on the observation of clinically significant abnormalities of laboratory values, concomitant medication use, vital signs, pain assessment, and physical examination data in the ASaT/Safety analysis set.

Adverse events: Overall AE as well as AE classified by system organ class and preferred terminology will be summarized. Additionally, AE will be summarized by severity and relation to study intervention. SAEs and AEs leading to discontinuation will also be tabulated.

Other safety data: These data will be summarized by presenting the proportions of subjects with clinically significant abnormalities or changes from baseline values. Laboratory data will be presented in data listings and summarized.

The following laboratory abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

• Any laboratory test result that is clinically significant or meets the definition of an SAE

• Any laboratory abnormality that required the subject to have study drug discontinued or interrupted

• Any laboratory abnormality that required the subject to receive specific corrective therapy

### 9.4.5. Other Analyses

Immune monitoring exploratory analysis will be described in the SAP finalized before database lock.

## 9.5. Interim Analyses

No formal interim analyses are planned for this study. Because a Simon 2-stage minimax design will be employed, response rate data will be assessed at Stage 1 to determine whether enrollment should proceed to Stage 2 per the defined stopping rules.

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

### 10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

### 10.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The research record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study if required by sponsor-investigator or IRB.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

Subjects who are rescreened are required to sign a new ICF.

### 10.1.3. Data Protection

- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

### 10.1.4. Dissemination of Clinical Study Data

A clinical study report will be developed by the Sponsor-investigator at completion of data analysis. This report will be a clinical and statistical integrated report, according to the ICH E3 guidelines.

Sponsor will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

### 10.1.5. Data and Safety Monitoring

Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly by the MCC Clinical Monitoring Core for accuracy, completeness, and source verification of data entry, validation of appropriate informed consent process, reporting of SAEs, and adherence to the protocol, Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements.

### 10.1.6. Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic CRF (eg, OnCore).
- The Sponsor must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Sponsor must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator per ICH-GCP and local regulations or institutional policies. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Study Supporter.
- Study documents should be retained for a minimum of 10 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 10 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when there is no longer a need for these documents to be retained. Permission must be acquired from the State of Florida for document destruction after the 10-year minimum record-retention period described above has elapsed.

### 10.1.7. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

### 10.1.8. Study and Site Closure

The Study Supporter reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Study Supporter. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Study Supporter or Investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study intervention development

### 10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Study Supporter before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor-investigator will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Study Supporter will generally support publication only in their entirety and not as individual site data.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

### 10.1.10. Confidentiality and Privacy

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP and regulatory and institutional requirements for the protection of confidentiality of participants.

## 10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 4 will be performed as indicated in the study calendar (SoA).
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 of the protocol.

  Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

**Table 4: Protocol-Required Safety Laboratory Assessments**

| | |
|---|---|
| **Hematology** | |
| White blood cell count (WBC) with differential (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils)<br>Hemoglobin<br>Platelet count | Red blood cell (RBC)<br>RBC Indices:<br>MCV, MCH<br>Hematocrit<br>Coagulation factors, including PT or INR and aPTT (Screening only if deemed clinically indicated) |
| **Clinical Chemistries**[a] | |
| Alanine Aminotransferase (ALT)<br>Alkaline phosphatase<br>Total bilirubin (fractionated)<br>Calcium<br>Sodium<br>Potassium<br>Chloride<br>Glucose (non-fasting)<br>Phosphates | Aspartate Aminotransferase (AST)<br>Albumin<br>Blood urea nitrogen (BUN)<br>Creatinine<br>Magnesium<br>$CO_2$ or bicarbonate<br>Lactate dehydrogenase (LDH)<br>Total protein |
| **Urinalysis** | |
| Basic Urinalysis (dipstick, including macroscopic appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen; prior to each administration of study intervention treatment). | Urinalysis includes dipstick and microscopic examinations when findings are abnormal |
| **Other Laboratory Assessments** | |
| Prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR)<br>Human chorionic gonadotropin (hCG) pregnancy test as needed for women of childbearing potential[a]<br>HIV 1/2 antibodies, HBsAg, HCV RNA (qualitative)[b]<br>Thyroid function: free T3, FT4 and thyroid stimulating hormone (TSH) | |

a For female subjects of child-bearing potential, local urine test must be performed within 72 hours prior to first dose of study intervention and if positive, a serum test is required. Similarly, at EOS urine pregnancy test will be performed locally and if positive, a serum test is required .

b Polymerase chain reaction is required and must be negative for HCV RNA in subjects positive for HCV antibody

# 10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## 10.3.1. Definition of AE

| **AE Definition** |
|---|
| • An AE is any untoward medical occurrence in a subject or clinical study subject, temporally associated with the use of study intervention, whether or not considered related to the study intervention.<br>• NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. |

| **Events <u>Meeting</u> the AE Definition** |
|---|
| • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease).<br>• Worsening of a pre-existing medical condition, (i.e., diabetes, migraine headaches, gout) should be considered an AE if there is either an increase in severity, frequency, or duration of the condition or an association with significantly worse outcomes.<br>• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. |

| **Events <u>NOT</u> Meeting the AE Definition** |
|---|
| • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.<br>• The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.<br>• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.<br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br>• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. |

### 10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

| **A SAE is defined as any untoward medical occurrence that, at any dose:** |
|---|
| **1. Results in death** |
| **2. Is life-threatening**<br>The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. |
| **3. Requires inpatient hospitalization or prolongation of existing hospitalization**<br>In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.<br>Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. |
| **4. Results in persistent disability/incapacity**<br>• The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br>• This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption. |
| **5. Is a congenital anomaly/birth defect** |
| **6. Other situations:**<br>• Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.<br>• Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. |

### 10.3.3. Definition of Events of Clinical Interest

| **Events of Clinical Interest for tavo-EP are by the Sponsor defined as:** |
|---|
| • Immune-related ECIs are AEs of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon |

- An overdose of study intervention, that is not associated with clinical symptoms or abnormal laboratory results
- An elevated AST or ALT laboratory value that is greater than or equal to 3 × ULN and an elevated total bilirubin lab value that is greater than or equal to 2 × ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2 × ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).*

- Tissue ulceration or cellulitis infections related to Tavo injection and/or EP.
- Delay in definitive surgery beyond the protocol allowed windows.

### 10.3.4. Definition of Suspected and Unsuspected Adverse Reaction

**Suspected adverse reactions are defined as:**

- Any AE for which there is a reasonable possibility that the study intervention caused the AE. For the purposes of Sponsor regulatory safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the study intervention and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a study intervention

**Unexpected Adverse events are defined as:**

- AE which is not listed in the IB of the study intervention or is not listed at the specificity or severity that has been observed

### 10.3.5. Recording and Follow-Up of AE and/or SAE

**AE and SAE Recording**

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the Investigator to send photocopies of the subject's medical records to the principal investigator in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the principal investigator. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the principal investigator.

**AE and SAE Recording**

- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of Intensity**

AE severity will be evaluated by the Investigator in accordance with the NCI CTCAE v5.0. For AEs that are not adequately addressed in the NCI CTCAE, the Investigator should classify the intensity of the AE using the following guidelines:

- Grade 1: Mild: Aware of sign or symptom, but easily tolerated; no intervention needed
- Grade 2: Moderate: Discomfort enough to cause interference with usual activity, minimal non-invasive intervention indicated (e.g., short course of antibiotics)
- Grade 3: Severe: Medically significant but not immediately life-threatening; incapacitation with inability to work or do usual activity
- Grade 4: Life-threatening: Refers to an event in which the subject was at risk of death at the time of the event, as judged by the Investigator; urgent/emergent intervention indicated. This category should not be used for an event that hypothetically might have caused death if it were more severe.
- Grade 5: Fatal outcome.

It will be left to the Investigator's clinical judgment to determine whether an AE is of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw consent from treatment due to what she/he perceives as an intolerable AE. If either of these situations arises, the subject should be strongly encouraged to undergo an end-of-study assessment and be under medical supervision until symptoms cease or the condition becomes stable. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

**Assessment of Causality**

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE as follows:

| CAUSALITY | ASSESSMENT CRITERIA<br>(all points should be reasonably complied with) |
|---|---|
| **Not related** | An AE with sufficient evidence to accept that there is improbable relationship to investigational product administration (e.g., no temporal relationship to drug administration) and the disease, other drugs or other events provide plausible explanation) |
| **Possibly related** | An AE with a reasonable time sequence to administration of the investigational product, but which could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear |

| Assessment of Causality | |
|---|---|
| **Related** | An AE occurring in a plausible time relationship to investigational product administration, and which cannot be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (de-challenge) and rechallenge (if necessary), are clinically reasonable |

- A “"reasonable possibility”" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator’s Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to principal investigator. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to principal investigator.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow-up of AEs and SAEs**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by principal investigator to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

### 10.3.6. Reporting of SAEs

**SAE Reporting to Study Supportervia an Electronic Data Collection Tool**

- The primary mechanism for reporting an SAE to Study Supporter will be the electronic data collection tool (i.e., MedWatch 3500 form or Oncore SAE form) in accordance with Moffitt

**SAE Reporting to Study Supportervia an Electronic Data Collection Tool**

Cancer Center local regulations. The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the principal investigator by telephone.
- OncoSec Contacts for SAE reporting:

| **Oncosec Medical Representative:** |
| --- |
| Terrence Chew, MD |
| Email: safety@oncosec.com |

## 10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

**Definitions:**

**Woman of Childbearing Potential (WOCBP)**

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

**Women in the following categories are not considered WOCBP**

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     – A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

**Contraception Guidance:**

Acceptable methods include hormonal contraception (oral contraceptives – as long as on stable dose, patch, implant, and injection), intrauterine devices, or double barrier methods (e.g. vaginal diaphragm/ vaginal sponge plus condom, or condom plus spermicidal jelly), sexual abstinence or

a vasectomized partner. Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

**Collection of Pregnancy Information**

**Male subjects with partners who become pregnant**

- The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study.
- After obtaining the necessary signed ICF from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor-investigator within 24 hours of learning of the partner's pregnancy. The Sponsor will attempt to follow the female partner to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. The Sponsor will follow the female partner until birth or termination of pregnancy when possible. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

**Female Subjects who become pregnant**

- The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a subject's pregnancy.
- The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the Sponsor. The subject will be followed until birth or termination of pregnancy. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

## 10.5: Collection of Human Samples for Immune Monitoring

Immune Monitoring tumor biopsies (fixed and fresh) as well as blood and fecal samples will be collected during this study to characterize the tumor microenvironment and to assess the immune phenotype and function pre- and post-combination therapy of tavo-EP and nivolumab.

Eligible subjects at all participating sites will take part in this immune monitoring. Fresh tumor biopsies will be collected at North America sites only. Biopsies should not proceed if (a) tumor is inaccessible or (b) biopsy is not thought to be in the subject's best interest, (c) the tumor is a target lesion and the biopsy is being collected between C1D1 and definitive surgery, or (d) non-target lesion (unless there is no change in LD and >15% of tumor volume). Biopsies do not need to be done if either the site investigator or person performing the biopsy judges that no tumor is accessible for biopsy that meet the size/volume requirements or that biopsy poses too great of a risk to the subject and will not be noted as a deviation. (If the only tumor accessible for biopsy is also the only lesion that can be used for RECIST v1.1 response evaluation, then the subject may be exempt from biopsy after discussion with the principal investigator and no deviation is documented). Other minor deviations will be recorded for subjects with procedures not done.

The samples will be collected during the study as specified in the SoA and shipped to the central laboratory, for storage, or to OncoSec or third-party vendors for analyses (including but not limited to immune-based assays, protein biomarkers and gene expression profiling, and RNA-seq).

Sample collection methods and handling at the study site are described below for each type of sample.

***Tumor Biopsies***

In addition to fixed biopsies, fresh biopsies are to be collected as specified in the SoA. Thus two tumor biopsies will be acquired from any accessible treated RECIST v1.1 measurable or non-target lesions >10 mm and/or untreated cutaneous lesions >5 mm. These biopsies will be placed into a shipping media ("fresh") and fixed in 10% formalin. Possible use include but is not limited to the following: Assess PD-L1 and immune marker levels in the tumor microenvironment (tumor, stroma and immune infiltrate) by chromogenic and multispectral immunohistochemistry (IHC) workflows. DNA and RNA may also be extracted from these fixed tumor biopsies and used to interrogate intratumoral gene expression by NanoString, RNA-seq analysis as well as epigenetic analysis with an Illumina Methylation Array workflow. The DNA from the biopsy may be used to detect levels of pIL-12 by qPCR, changes in clonality or antigen-specific TCR sequences with an Adaptive Biotechnologies analysis and the potential mutation load and neo-antigen repertoire in the tumor by whole exome sequencing. The fresh biopsy may be used in a flow cytometric assay to determine the frequency of PD-$1^{hi}$CTLA-$4^{hi}$ cells in the live $CD45^{+}CD3^{+}CD8^{+}$ gate (Daud, 2016) or to establish and culture tumor and TIL lines that may be used in functional immune assays.

If reasonable for subject therapy, at least 1 distal, non-target lesion shall be left untreated with biopsies taken at timepoints before and after treatment as described above. If only one biopsy is possible, the sample should be a fixed biopsy. For collection of tumor biopsies, the lesion should be accessible and of an appropriate size. The biopsy should be done under sterile conditions with adequate tissue to be collected: one 5 mm punch, core, or excisional biopsy. Prior to biopsy

Collection and if considered clinically indicated, coagulation assessment will be done including prothrombin time (PT), partialthromboplastin time (PTT), and international normalized ratio (INR).

Handling instructions for tissue biopsy are as follows:

Fixed Biopsy: A Fixed Tumor Biopsy Collection Kit should be used at all study time points for the collection of fixed tumor samples. Place the tumor tissue sample in the formalin container and close the cap tightly. After 12-24 hours, the tissue shall be placed in PBS (+ 0.01% azide) and stored at ambient temperatures until shipment.

Fresh Biopsy: Insert the fresh tissue sample into a pre-chilled container with XVIVO-15 media and immediately place on ice. The sample must remain cold and on ice until ready for overnight 4°C shipment to the central laboratory.

**NOTE:** Existing FFPE tumor samples from previous and future (while on study) melanoma tumor biopsies should be requested if available and should be submitted for research purposes. Up to 20 unstained slides may be requested if available. Provision of less than 20 slides is acceptable based on availability. This applies primary melanoma tumor lesions and metastatic melanoma tumor lesions. These should be requested in addition to the protocol indicated research biopsies.

***Blood Sampling***

Blood collected from the subject as outlined in the SoA may be used to evaluate changes in the subject's peripheral immune cells and circulating levels of pIL-12 by qPCR. Peripheral blood mononuclear cells (PBMC) isolated with BD's CPT tube (see details below) may be used in flow cytometric and ELISpot workflows to interrogate immune phenotype, tetramer frequencies and immune function. Blood will be collected for serum isolation and analysis of protein signatures.

Please refer to 'Human Sampling for Immune Monitoring manual' for details on blood sampling collection. Briefly, blood sampling will be collected for immuno-assays at the same time of blood chemistry collections as follows:

1. One 2.5 mL PAXgene™ RNA Vacutainer Tube
2. One 2.5 mL PAXgene™ DNA Blood Collection Tube
3. Nine 8.0 mL Vacutainer CPT Tubes

*Handling for item 3 above: the CPT Tube should be at room temperature (18-25°C) and centrifuged within two hours of blood collection for best results. The cells in the upper phase (the plasma above the gel barrier) are to be re-suspended by inverting the unopened CPT tube gently 5 to 10 times before proceeding with shipment of processed blood at 4°C.* ***Samples should be shipped same day as collection.***

4. One 3.0 mL Vacutainer Serum Tube, Increased Silica Act Clot Activator

*Handling instructions for item 4 above: Allow for the blood to clot by leaving it undisturbed at room temperature for 30 minutes. Remove the clot by centrifuging at 1,300 x g for 10 minutes in a centrifuge. Serum will be aliquoted and frozen, then shipped (if necessary) frozen where they will be stored at -80C.* ***Samples should be shipped same day as collection.***

***Fecal Sampling***

Approximately 2 grams of fecal matter will be collected by the subject using Norgen Biotek's Stool Nucleic Acid Collection and Transport tubes. If the subject cannot provide this sample at the clinical site, a kit will be provided to go home with the subject. Samples can be stored at room temperature up to 72 hours until ambient shipment to the laboratory where they will be

stored at -80°C. These samples will subsequently be used for 16S rDNA and/or metagenome sequencing, allowing for the elucidation of microbial composition and genome structure.

Subjects will be instructed to:

Avoid any contact between the stool sample and urine.

- Pass stool directly onto the provided plastic wrap (if stool is loose, subjects will use a provided large clean container) placed under the seat of the toilet.
- Scoop stool sample from three sites using the spoon attached in the cap and place the stool into the tube until the liquid reaches the “Fill To This Line” (Do not over fill).
- Tighten the cap and shake gently until the stool is thoroughly mixed with the preservative before returning the tube to the clinician or placing the tube in the shipping envelope.
- Samples collected at home will be stored in a sealed shipping envelope at room temperature for up to 72 hours, while the courier service will be notified for next day pickup.

## 10.6. Appendix 6: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

### Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all Sponsor medical devices provided for use in the study (see Section 6.1.1 ) for the list of Sponsor medical devices).

| **Medical Device Incident Definition** |
|---|
| • A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject/user/other person or to a serious deterioration in his/her state of health.<br>• Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel. |

**It is sufficient that:**

- An **incident** associated with a device happened.

  AND

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

| **Examples of Incidents** |
|---|
| • A subject, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.<br>• A subject's study intervention is interrupted or compromised by a medical device failure.<br>• A misdiagnosis due to medical device failure leads to inappropriate treatment.<br>• A subject's health deteriorates due to medical device failure. |

## Documenting Medical Device Incidents

| Medical Device Incident Documenting |
| --- |
| • Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form of the eCRF.<br>• For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 3.<br>• The eCRF will be completed as thoroughly as possible and signed by the investigator before transmittal to the Sponsor or designee.<br>• It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by the Sponsor) at the time of the initial AE or SAE report and describes any corrective or remedial actions taken to prevent recurrence of the incident.<br>• A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence. |

## 10.7. Summary of Response Evaluation Criteria for Solid Tumors (RECIST) and Immune RECIST (iRECIST)

**NOTE:** Response evaluation by RECIST is required per protocol and it is optional by iRECIST.

### 10.7.1. RECIST v1.1

Tumor response will be evaluated according to RECIST guidelines (Therasse, 2000) using tumor imaging (see Section 10.7.3 for tumor imaging details).

Assessment by RECIST v1.1 will be done as specified in the SoA. If during the neoadjuvant phase, a treatment delay results in shifting cycles, imaging and tumor evaluation will be shifted accordingly. Lesions will be numbered identically for each visit as Target and non-target, new lesions (see definitions in Table 8).

In support of RECIST v1.1, when more than one accessible and measurable tumor is present at baseline, all lesions (those with the longest diameter(s)/ organ that are measurable in the physicians' discretion) up to 2 cutaneous lesions assessed by photography and up to 5 visceral or subcutaneous lesions (2 per organ), assessed by radiology, with a maximum of 7 lesions total should be identified as measurable representative Target Lesions. A target lesion may be a treated or untreated lesion.

An 'accessible lesion' is defined as a cutaneous or subcutaneous lesion that can be reached from the surface with the electroporation needle array (with depth of up to 1.5 cm from the surface). Measurable lesions include non-lymph node longest axis ≥10 mm (on CT, PET-CT, MRI, or calipers/rulers), non-lymph node longest axis ≥20 mm (on X-ray) and lymph node short axis ≥15 mm. All lesions will be indicated by pen and numbered before being photographed. This provides the baseline map of ALL accessible lesions with baseline defined as the period between signing the ICF and prior to completion of Cycle 1. Each lesion will be identified by a lesion number which must remain the same throughout the study. Measurable lesions that are target lesions must be measured by the site and data entered into electronic data capture (EDC).

Each subject will be assigned a response category (Table 5): complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD).

Preoperative response rate (unconfirmed) will be assessed during the Neoadjuvant phase (preoperative, unconfirmed).

**Table 5 Response Evaluation Criteria in Solid Tumors v1.1**

| RECIST v1.1 Response Criteria | Target Lesions | Non-Target Lesions |
|---|---|---|
| **Complete Response (CR)**[1] | Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be "0" if there are target nodes). There can be no appearance of new lesions. | Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis). |
| **Partial Response (PR)**[1] | At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions. | Non-target lesions must be non-PD. |
| **Stable Disease (SD)** | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started. | Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits. |
| **Progressive Disease (PD)** | At least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥5 mm, or the appearance of one or more new lesions. | Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. |

[1] Subjects will meet the primary endpoint (BORR) if they attain a confirmed CR or PR over the 24 weeks with the combination treatment with a 4-week confirmatory scan per RECIST v1.1.

#### 10.7.1.1. Evaluation of Overall Response with RECIST v1.1

The overall response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria (Table 6).

**Table 6 Overall Response Definitions using RECIST v1.1**

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response | Best Response for this Category Also Requires |
|---|---|---|---|---|
| CR | CR | No | CR | Normalization of tumor markers, tumor nodes <10 mm |
| CR | Non-CR/ Non-PD | No | PR | |
| CR | Not all evaluated | No | PR | |
| PR | Non-PD / No all evaluated | No | PR | |
| SD | Non-PD | No | SD | Documented at least once ≥4 weeks from baseline |
| Not all evaluated | Non-PD | No | NE | |
| PD | Any | Any | PD | |
| Any | PD* | Any | PD | |
| Any | Any | Yes | PD | |

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression

Source: (Seymour, 2017)

**Other definitions**

- Duration of response (DOR)
- Relapse free survival (RFS) – RFS is defined as the time, in months, from the first dosing date until the date of disease relapse (i.e., the date of the tumor imaging) or death from any cause. RECIST v1.1 will be used to determine the dates of relapse as this methodology is accepted by regulatory authorities. This will be further detailed in the SAP.
- Overall survival (OS) - OS is defined as the time from diagnosis until death from any cause. Subjects without a confirmed date of death will be censored at the last date when the subject was known to be alive.

### 10.7.2. Immune-Related RECIST (iRECIST)

iRECIST will be used to assess a secondary endpoint (refer to Section 3) according to recently published consensus guidelines for iRECIST (Seymour, 2017).

Assessment by iRECIST will be done at 12-week intervals as specified in the SoA. Lesions will be numbered identically for each visit as Target and non-target, new lesions (see definitions in Table 8).

Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST v1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

Unlike RECIST v1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (immune unconfirmed progression) and iCPD (immune confirmed progression).

For target lesions, iCR, iPR, and iSD can all be assigned after iUPD has been documented, if iCPD was not confirmed (Table 7). iUPD is defined by RECIST v1.1 criteria for progressive disease; iUPD can be assigned multiple times as long as iCPD is not confirmed at the next assessment. Progression is confirmed in the target lesion category if the next imaging assessment after iUPD (4–8 weeks later) confirms a further increase in sum of measures of target disease from iUPD, with an increase of at least 5 mm. However, the criteria for iCPD (after iUPD) are not considered to have been met if CR, PR, or SD criteria (compared with baseline and as defined by RECIST v1.1) are met at the next assessment after iUPD. The status is reset (unlike RECIST v1.1, in which any progression precludes later CR, PR, or SD). iCR, iPR, or iSD should then be assigned; and if no change is detected, then the timepoint response is iUPD.

The assessment of non-target lesions at each timepoint follows similar principles. iUPD (but not iCPD) can have been documented before iCR or when the criteria for neither CR nor PD have been met (referred to as non-iCPD/non-iUPD) and can be assigned several times, as long as iCPD was not confirmed. iUPD is defined by RECIST v1.1 criteria; however, iUPD can be assigned multiple times as long as iCPD is not confirmed at the next assessment. Progressive disease in the non-target lesion category is confirmed if subsequent imaging, done 4–8 weeks after iUPD, shows a further increase from iUPD. The criteria for iCPD are not judged to have been met if RECIST v1.1 criteria for complete response or non-iCR/non-iUPD are met after a previous iUPD. The status is reset (unlike RECIST v1.1) and iCR, or non-iCR/non-iUPD is assigned; if no change is detected, the timepoint response is iUPD.

iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST v1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions
  - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
  - Continued unequivocal progression in non-target disease with an increase in tumor burden
  - Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST v1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). The prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as immune best overall response (iBORR) providing that iCPD is not documented at the next assessment after iUPD.

The event date to be used for calculation of progression-free survival (iPFS) should be the first date at which progression criteria are met (i.e., the date of iUPD) provided that iCPD is confirmed at the next assessment. If iUPD occurs, but is disregarded because of later iSD, iPR, or iCR, that iUPD date should not be used as the progression event date

**Table 7 iRECIST Time Point response**

| **Target Lesions*** | **Non-Target Lesions*** | **New Lesions*** | **Time Point Response** | |
|---|---|---|---|---|
| | | | **No prior iUPD**** | **Prior iUPD**; ***** |
| iCR | iCR | No | iCR | iCR |
| iCR | Non-iCR/Non-iUPD | No | iPR | iPR |
| iPR | Non-iCR/Non-iUPD | No | iPR | iPR |
| iSD | Non-iCR/Non-iUPD | No | iSD | iSD |
| iUPD with no change OR decrease from last time point | iUPD with no change OR decrease from last TP | Yes | NA | New lesions (NL) confirms iCPD if NLs were previously identified and increase in size (≥5 mm in sum of measure (SOM) for new lesion, target (NLT) or any increase for new lesion, non-target; NLNT) or number. If no change in NLs (size or number) from last time point, remains iUPD |
| iSD | iUPD | No | iUPD | Remains iUPD unless iCPD confirmed based in further increase in size of non-target disease (need not meet RECIST v1.1 criteria for unequivocal PD) |
| iUPD | Non-iCR/Non-iUPD | No | iUPD | Remains iUPD unless iCPD confirmed based on:<br>o further increase in SOM of at least 5 mm, otherwise remains iUPD |
| iUPD | iUPD | No | iUPD | Remains iUPD unless iCPD confirmed based on further increase in:<br>o previously identified T lesion iUPD sum of measure ≥5 mm and / or<br>o NT lesion iUPD (prior assessment - need not be unequivocal PD) |
| iUPD | iUPD | Yes | iUPD | Remains iUPD unless iCPD confirmed based on further increase in:<br>• previously identified Target lesion iUPD ≥5 mm and / or<br>• previously identified non-target lesion iUPD (need not be unequivocal) and /or<br>• size or number of new lesions previously identified |
| Non-iUPD/PD | Non-iUPD/PD | Yes | iUPD | Remains iUPD unless iCPD confirmed based on |

| | | | | |
|---|---|---|---|---|
| | | | | ○ increase in size or number of new lesions previously identified |

TP = time-point; NT = non-target, T = target; NL = new lesions; iUPD = unconfirmed immune PD; iCPD = confirmed immune PD; SOM = sum of measures. iCR – immune complete response; iPR – immune partial response; iSD – immune stable disease

* Using RECIST v1.1 principles. If no PSPD occurs, RECIST v1.1 and iRECIST categories for CR, PR and SD would be the same.

** in any lesion category.

*** previously identified in assessment immediately prior to this time point.

Source: (Seymour, 2017)

### 10.7.3. Measurable Disease and Lesions Definitions

Table 8 provides definitions for measurable disease and lesions, target and non-target lesions. At all study visits, each lesion will always be assessed with the same method.

**Table 8 Definitions of Measurable Disease and Lesions**

| Parameter | Definitions |
|---|---|
| **Measurable disease** | Measurable tumor lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter [LD] to be recorded) as ≥20 mm with chest x-ray and as ≥10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥10 mm by CT scan). *Malignant lymph nodes* must be ≥15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion. These should be recorded and measured prior to treatment at Cycle 1 Day 1 (C1D1; baseline). |
| **Non-measurable disease** | All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated. |
| **Target lesions** | All measurable lesions up to a maximum of 7 lesions total (and a maximum of 2 lesions per organ) with 2 cutaneous lesions assessed by photography and up to 5 visceral or subcutaneous lesions assessed by radiology. Measurable lesions should be representative of all involved organs and should be identified as target lesions and recorded and measured at baseline. Target lesions will be selected based on their size (lesions with the LD) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). At baseline, the sum of the LD for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the |

| | |
|---|---|
| | objective tumor response. After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used. |
| **Non-target lesions** | All other lesions (or sites of disease) including any measurable lesions over and above the 7 target lesions should be identified as non-target lesions and should also be recorded at baseline. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. "multiple enlarged pelvic lymph nodes" or "multiple liver metastases"). Bone lesions may be measurable if ≥ 1 cm on MRI. Measurements of these lesions are not required, but the presence or absence of each will be noted throughout follow-up. It is recommended that bone lesions be followed closely by investigators by comments and measurements whenever possible for retrospective review. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent". |

Source: (Seymour, 2017)

### 10.7.4. Tools for Tumor Assessments

#### 10.7.4.1. Tumor Imaging for Evaluation of Response

Radiographic imaging will be done at frequency specified in SoA.

Tumor imaging is strongly preferred to be acquired by CT. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. MRI is the strongly preferred modality for imaging the brain.

The same method of assessment and the same imaging technique will be used to characterize each identified and reported lesion at baseline and during the study. Ideally the same scanner, and the use of contrast should be used in a subject throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

*Note: for the purposes of assessing tumor imaging, the term "investigator" refers to the local investigator at the site.*

## 10.8. Surgical Considerations

The investigators are expected to make every effort to comply with the surgical procedures within the time windows allowed in this study protocol. However, under certain circumstances and as discussed between the sub-investigator(s) (both surgeon and medical oncologist) and the principle investigator, an alteration in the surgical schedule/timing is allowed. These include (but are not limited to) the following:

- A 4-week window between the baseline biopsy and the first dose of study intervention is allowed.
- The definitive surgery may be a lymphadenectomy, resection of lymphatic metastases and/or resection of newly appearing distant oligometastases, as clinically indicated.
- The definitive surgery may be divided into more than one surgical procedure, scheduled at different time points as clinically/surgically indicated.
- Under certain circumstances, the definitive surgery may be delayed and done after completion of additional cycles of neoadjuvant therapy (or earlier if study intervention(s) was discontinued due to adverse events or other reasons).
- If for some reason, the baseline biopsy or definitive surgery could not be completed due to un-anticipated factors such as patient refusal, this will be documented in the subject medical record and OnCore.
- For the baseline biopsy required on this study, patients will undergo a standard core needle technique (16 gauge or thicker), punch biopsy, open technique, or other technique at the discretion of the treating physician investigator(s). The choice of specific surgical technique will be at the discretion of the surgeon or medical oncologist and actual techniques will be the same as those used as therapeutically or diagnostically indicated to surgically treat or confirm the clinical suspicion of recurrent or metastatic disease in any patient undergoing conventional evaluation and treatment (standard of care) within 4 weeks prior to initiating study drug(s) (baseline biopsy).

**NOTE**: The surgical guidelines are general and may be followed or modified at the discretion of the expert surgical oncologist on the case as clinically indicated and depending on the specifics of the individual surgical case.

### 10.8.1. Primary Excision or Primary Cutaneous Melanoma

All patients with initial presentation of melanoma $T_{1-4}$ will be treated by wide excision of the primary. Definitive surgery will include wide excision of the primary and lymphadenectomy.

For patients with known primary cutaneous melanoma lesion and no history of wide local excision of that primary lesion, an adequate wide excision of the primary lesion (minimum margin 1 cm if anatomically feasible) is recommended. The wide local excision will be done at the time of complete lymphadenectomy. Patients with nodal relapse after an inadequate primary excision will undergo wide excision at the time of complete lymphadenectomy. The recommendation for adequate wide excision is the same for patients enrolled at the time of lymph node recurrence as for those enrolled at the time of initial treatment of the primary. For

lesions whose Breslow's thickness is > 1 mm, a 2 cm minimum margin is preferred when anatomically feasible (i.e., for lesions of the trunk and proximal extremities). For subungual melanoma, a distal interphalangeal amputation with histologically negative margins constitutes an adequate wide excision. The specimen shall be excised to include skin and all subcutaneous tissue down to the muscular fascia. Fascia may be included at the discretion of the operating surgeon. Closure of the defect may be via primary closure, split thickness skin graft, or rotation-flap at the discretion of the surgeon.

### 10.8.2. Regional Lymphadenectomy

#### 10.8.2.1. Head and Neck Lesions

- Face, ear and anterior scalp: Modified radical neck or radical neck dissection.
- Submandibular and anterior neck: Modified radical or radical neck dissection.
- Posterior scalp, posterior neck and uppermost trunk (areas that drain to posterior cervical triangle): Modified posterior triangle neck dissection with suboccipital nodes (to yield a minimum of 8 nodes).

#### 10.8.2.2. Upper Extremity

Axillary node dissection for levels I and II. Level III nodes should be dissected if they are clinically involved. The pectoralis minor muscle may be divided or sacrificed at the surgeon's discretion.

#### 10.8.2.3. Lower Extremity

Superficial inguinal node dissection will be performed. A deep inguinal node dissection will be at the discretion of the surgeon, but if performed, the established guidelines should be followed as closely as possible.

#### 10.8.2.4. Lymphadenectomy for Nodal Recurrence

Regional node recurrences will be treated using the appropriate lymphadenectomy procedure. Whenever possible, diagnosis of regional node recurrence will be made using punch or open biopsy technique (if done as part of a clinically indicated baseline diagnostic procedure) to provide baseline pathologic material needed for evaluation of treatment effect. At the time of the definitive lymphadenectomy, the biopsy site will be included in the operative specimen.

### 10.8.3. Surgery for Distant Cutaneous/Subcutaneous or Nodal Metastases

Patients with Stage IV (i.e. M1a only) melanoma metastatic to skin, subcutaneous sites, or distant lymph nodes are allowed. All sites are to be resected with histologically negative margins.

## 10.9. Appendix 9: Abbreviations

| Abbreviation/Term | Definition |
|---|---|
| µg | Microgram |
| µL | Microliter |
| µs | Microsecond |
| Abs | Absolute |
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| AJCC | American Joint Committee on Cancer |
| ALT | Alanine Aminotransferase |
| ANC | Absolute Neutrophil Count |
| APM | Antigen Presenting and Processing Machinery |
| aPTT | Activated Partial Thromboplastin Time |
| ASaT | All Subjects as Treated |
| AST | Aspartate Aminotransferase |
| BMI | Body Mass Index |
| BUN | Blood Urea Nitrogen |
| C1D1 | Cycle 1, Day 1 |
| CBC | Complete Blood Count |
| CI | Confidence Interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| cm | Centimeter |
| CR | Complete Response |
| CrCl | Creatinine Clearance |
| CRF | Case Report Form |
| CT | Computerized Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events (version 5.0) |
| CTL | Cytotoxic T Lymphocytes |
| DCR | Disease Control Rate |
| **PMC** | Protocol Monitoring Committee |
| DNA | Deoxyribonucleic Acid |
| DOR | Duration of Response |
| DRE | Disease Related Events |
| ECI | Events of Clinical Interest |

| Abbreviation/Term | Definition |
|---|---|
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture System |
| EOS | End of Study |
| EP | Electroporation |
| FDA | Food and Drug Administration |
| FSH | Follicle Stimulating Hormone |
| GCP | Good Clinical Practice |
| GFR | Glomerular Filtration Rate |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human Immunodeficiency Virus |
| HRT | Hormonal Replacement Therapy |
| IB | Investigator's Brochure |
| iBOR | Immune Best Overall Response |
| iBORR | Immune Best Overall Response Rate |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| iCPD | Immune Confirmed Progressive Disease |
| iCR | Immune Complete Response |
| IEC | Independent Ethics Committees |
| IFN | Interferon |
| IHC | Immunohistochemical Method |
| IL-12 | Interleukin-12 |
| IL-2 | Interleukin-2 |
| IND | Investigational New Drug application |
| INMC | International Neoadjuvant Melanoma Consortium |
| INR | International Normalized Ratio |
| iPFS | Immune Progression Free Survival |
| iPR | Immune Partial Response |
| irAE | Immune-related Adverse Event |
| IRB | Institutional Review Board |
| iRECIST | Immune Response Evaluation Criteria in Solid Tumor |
| iSD | Immune Stable Disease |

| Abbreviation/Term | Definition |
|---|---|
| iUPD | Immune Unconfirmed Progressive Disease |
| IV | Intravenous |
| LD | Longest Diameter |
| LDH | Lactate dehydrogenase |
| MAF | Master File |
| MDSCs | Myeloid-Derived Suppressor Cells |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligram |
| mL | Milliliter |
| mm | Millimeter |
| MRI | Magnetic Resonance Imaging |
| NCI | National Cancer Institute |
| NK | Natural Killer (NK cells) |
| NL | New Lesions |
| OMS | OncoSec Medical Electroporation Therapy System |
| ORR | Objective Response Rate |
| OS | Overall Survival |
| PBMC | Peripheral Blood Mononuclear Cell |
| pCR | Complete pathological response |
| PD | Progression of Disease |
| PD-1 | Programmed Cell Death Protein 1 |
| pDNA | plasmid DNA |
| PET | Positron Emission Tomography |
| pIL-12 | Plasmid Interleukin-12 |
| PR | Partial Response |
| PT (AE) | Preferred Term |
| PT (lab) | Prothrombin Time |
| PTT | Partial Thromboplastin Time |
| RBC | Red Blood Cell |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RFS | Relapse/Recurrence Free Survival |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |

| Abbreviation/Term | Definition |
|---|---|
| SD | Stable Disease |
| SJS | Stevens-Johnson syndrome |
| SoA | Schedule of Activities |
| SOM | Sum of Measure |
| SUSAR | Serious Unexpected Suspected Adverse Reaction |
| tavo | Tavokinogene telseplasmid expressing Interleukin-12 |
| tavo-EP | Tavokinogene telseplasmid with electroporation |
| TEAE | Treatment Emergent Adverse Event |
| TEN | Toxic Epidermal Necrolysis |
| TIL | Tumor Infiltrating Lymphocytes |
| TRAE | Treatment-related Adverse Events |
| TSH | Thyroid Stimulating Hormone |
| ULN | Upper Limit of Normal |
| US | United States |
| WBC | White Blood Cell |
| WOCBP | Woman of Childbearing Potential |

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