

Study Drug: PEMBROLIZUMAB
Protocol Version: 08.14.2019
Protocol Number: COMIRB 16-1080
PI: Martin McCarter, MD

PROTOCOL NUMBER:	COMIRB 16-1080
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PROTOCOL TITLE:	Pembrolizumab and All-Trans Retinoic Acid Combination Treatment of Advanced Melanoma
VERSION DATE:	August 14, 2019
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STUDY REFERENCE NUMBER:	MISP 54054

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STATEMENT OF COMPLIANCE

This is an investigator-initiated study. The Principal Investigator (PI), **Martin McCarter, MD**, is conducting the study and acting as the sponsor. As the Sponsor-Investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/ or 21 CFR Part 812).

The PI will assure that no changes to the protocol will take place without documented approval from the Institutional Review Board (IRB). 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 about their obligations in meeting the above commitments.

Sponsor-Lead Principal Investigator: _____
Print/Type Name

Signed: _____ **Date:** _____

Site Principal Investigator: _____
Print/Type Name

Signed: _____ **Date:** _____

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LIST OF ABBREVIATIONS

ACRONYM	DESCRIPTION
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APL	acute promyelocytic leukemia
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATRA	all-trans retinoic acid
BCG	Bacillus Calmette-Guerin
CBC	complete blood count
CFR	Code of Federal Regulations
CNS	central nervous system
COMIRB	Colorado Multiple Institutional Review Board
CR	Complete Response
CrCl	creatinine clearance
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	cytolytic T-lymphocyte
CU	University of Colorado
DISC	University of Colorado-Denver Development and Informatics Service Center
DKA	diabetic ketoacidosis
dL	Deciliter
DSM	data and safety monitoring
DSMC	Data and Safety Monitoring Committee
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
EPO	Erythropoietin
ERC	Ethics Resource Center
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FSH	follicle-stimulating hormone
g	Gram
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	Gastrointestinal
GM-CSF	granulocyte-macrophage colony stimulating factor
HCG	human chorionic gonadotropin

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HIV	Human Immunodeficiency Virus
HLA	human leukocyte antigen
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
IFM	Interferon
IL	Interleukin
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	intrauterine device
IV	Intravenous
kg	Kilogram
L	Liter
m	Meter
mAb	monocolonal antibody
mcL	Microliter
MDSC	myeloid-derived suppressor cell
mg	Milligram
mL	Milliliter
mmol	Millimolar
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
OTC	over-the-counter
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PI	principal investigator
PK	Pharmacokinetics
po	by mouth
PT	prothrombin time
Q3W	every three weeks
RA-APL	retinoic acid-acute promyelocytic leukemia
RP2D	Recommended Phase 2 dose
SAE	serious adverse event
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
T1DM	Type 1 diabetes mellitus
TB	Tuberculosis
TSH	thyroid-stimulating hormone
UAP	unanticipated problem
UCCC	University of Colorado Cancer Center
ULN	upper limit of normal
US	United States

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1.0 PROTOCOL/TRIAL SUMMARY

Protocol Title	Pembrolizumab and All-Trans Retinoic Acid Combination Treatment of Stage IV Melanoma
Protocol Number	16-1080
Trial Objectives:	<p>Objectives:</p> <p>Primary Objective</p> <p>To identify the MTD and RP2D of the combination of pembrolizumab and ATRA.</p> <p>Secondary Objective</p> <ul style="list-style-type: none"> Describe the safety and toxicity of combined treatment with pembrolizumab and all-trans retinoic acid (ATRA) [brand name VESANOID] in melanoma patients. To assess the anti-tumor activity of the combination of pembrolizumab and all-trans retinoic acid (ATRA) [brand name VESANOID] in melanoma patients. <p>Exploratory Objective</p> <p>To determine the clinical outcomes with tumor-specific T cell responses.</p>
Trial Efficacy Endpoints:	<ol style="list-style-type: none"> Manipulation of MDSC subsets. Progression-free survival.
Trial Population:	<ul style="list-style-type: none"> 24 subjects to be treated Male and female subjects Ages 18-100
Trial Phase	I/IB
Clinical Indication	Stage IV Melanoma
Trial Type	Interventional
Type of Control	N/A
Description of Study Drug(s)	Pembrolizumab (Keytruda ®) will be administered Intravenous (IV) and Vesanoid will be administered orally.
Trial Blinding	Open Label Clinical Trial
Treatment Groups	One
Number of Trial Subjects	24

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Estimated Enrollment Period	1 year
Estimated Duration of Trial	5 years
Duration of Subject Participation	2 years
Estimated Average Length of Treatment Per Patient	VESANOID will be administered over 12 weeks. Pembrolizumab will be administered every 3 weeks until progression of disease, intolerance of therapy, or for up to two years.

This is a multi-center study to be conducted at the University of Colorado Cancer Center (UCHealth central campus) and Poudre Valley Hospital (UCHealth north campus). A complete and current listing of investigators, research personnel, and research facilities participating in this study will be maintained throughout the duration of this study on applicable study required forms such as an *FDA Form 1572*, the *COMIRB Research Personnel Form*, and/or a *UCCC Protocol Contact List*, incorporated herein by reference.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a Phase I/Ib investigator-initiated open label trial of the combination of VESANOID and pembrolizumab treatment.

A total of 24 evaluable patients will be recruited into the study. All the patients will receive 200mg Q3W pembrolizumab treatment plus the supplemental treatment of 150 mg/m² VESANOID orally for 3 days surrounding each of the first four infusions of pembrolizumab (day -1, day 0, day +1) for a total of 12 days of VESANOID treatment (Section 2.2 *Trial Schema/Diagram*).

To closely monitor DLTs, subjects will be recruited into the study using a cohort size of 6. The toxicity monitoring design is to inform de-escalation decisions based on safety if needed. DLTs will be assessed during the DLT assessment window of 21 days following the first dose of Vesanoide and Pembrolizumab (Cycle 1 Day 0 to Cycle 2 Day 0). Patients who withdraw from the study prior to completing the DLT assessment window for any reason other than a DLT will be replaced. See Section 6.1.1.2.3 for DLT definition.

After the first 6 subjects in cohort 1 complete the DLT period, the Sponsor-Investigator will review data pertaining to the dose de-escalation decision. Available adverse event data and laboratory assessments will be used to determine whether the Vesanoide dose should be continued at 150 mg/m² or whether the Vesanoide dose should be de-escalated to 100 mg/m² in the subsequent six subjects to be enrolled in cohort 2.

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Dose de-escalation will proceed in accordance with the following rules:

- 6 patients will be treated in cohort 1.
 - If 0-2 patients experience a DLT in cohort 1, the Vesanoïd dose will be maintained.
 - If ≥ 3 patients in cohort 1 experience a DLT, then dose de-escalation of Vesanoïd will proceed.
- 6 additional patients will be treated in cohort 2 at either the starting Vesanoïd dose (150 mg/m²) or the reduced Vesanoïd dose (100 mg/m²).
 - If 0-2 patients experience a DLT in cohort 2, the Vesanoïd dose will be maintained.
 - If ≥ 3 patients in cohort 2 experience a DLT, then the study will stop.
- If it is determined that the dose will be maintained from Cohort 2, then an additional cohort (cohort 3) of up to 12 patients (depending on the number of patients required to achieve the enrollment goal of 24 patients, but not to exceed 30 patients) will be treated at either the starting Vesanoïd dose (150 mg/m²), or the reduced Vesanoïd dose (100 mg/m²).

This trial will be conducted in compliance with this protocol, Good Clinical Practice, and local and federal regulations.

Anticipated total number of enrolled research subjects: up to 30 to allow for screen fails or withdrawals

Anticipated number to complete study: 24 (who receive at least one dose of VESANOïD and Pembrolizumab)

2.2 Trial Schema/Diagram

Proposed schedule for treatment and blood draws.

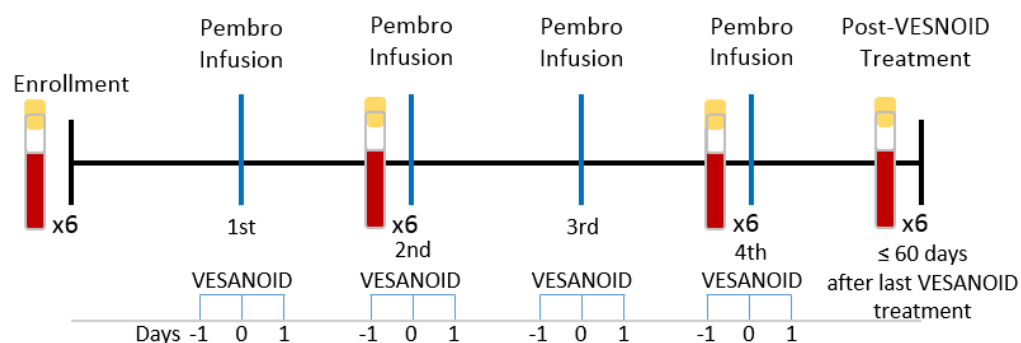


Figure 1. Diagram of the treatment and blood draw schedule for this study. Patients will receive pembrolizumab infusions every three weeks. Patients will also receive 3 days of VESANOïD treatment surrounding each of the first 4 infusions of pembrolizumab, beginning one day prior to the infusion (a total of 12 days of VESANOïD). Six tubes of peripheral blood (for a total of approximately 40 ml) will be drawn at enrollment, at the 2nd and 4th infusions, and within 60 days of the final VESANOïD dose for additional functional experiments.

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3.0 OBJECTIVE(S) & HYPOTHESIS (ES)

3.1 Primary Objective

To identify the MTD and RP2D of the combination of pembrolizumab and ATRA.

3.2 Secondary Objective:

- Describe the safety and toxicity of combined treatment with pembrolizumab and all-trans retinoic acid (ATRA) [brand name VESANOID] in melanoma patients.
- To assess the anti-tumor activity in terms of a). The reduction in MDSC (immunosuppressive myeloid –derived suppressor cells) frequency and suppressive function (measured as a continuous variable) in peripheral blood of advanced melanoma patients undergoing pembrolizumab and VESANOID combination therapy. b). progression free survival.

3.3 Exploratory Objective

To determine the clinical outcomes with tumor-specific T cell responses.

4.0 BACKGROUND & RATIONALE

4.1 Background

Melanoma elicits profound immune responses and is one of the few tumors for which immunotherapies have been successful (1). However, melanoma counters current immunotherapeutic approaches by inducing immune escape mechanisms, a critical barrier that may contribute to low response rates and treatment failure (1). Melanoma continues to be a leading cause of death among adult cancer patients (2, 3). Furthermore, the incidence of melanoma continues to increase across all age groups (4).

The antibody therapy pembrolizumab, specific for programmed cell death receptor 1 (PD-1), an inhibitory molecule expressed on activated T cells, has recently been shown to significantly improve overall survival and induce durable, long-lasting responses in approximately 45% of treated patients (5). Since pembrolizumab was granted approval as a first line treatment in metastatic melanoma patients, it has largely replaced Ipilimumab due to higher response rates with lower toxicities (5). While the results of this monumental study highlight a crucial advantage of immunotherapies in achieving long-term immunity that is resistant to disease relapse, increased response rates to pembrolizumab could further enhance survival and clinical outcomes for patients with advanced-stage melanoma. One proven mechanism of action for this drug is eliciting the frequency and function of tumor-specific T cells (6). However, tumor induced immunosuppression may limit the development of effective immune responses in some patients treated with pembrolizumab. Improving clinical responses to pembrolizumab by enhancing other immune-mediated mechanisms in a combinatorial approach is essential for the future evolution of immunotherapeutic strategies.

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MDSCs are a mixed population of immunosuppressive myeloid cells that are key contributors to tumor-induced immunosuppression. Increased numbers of MDSCs are associated with larger tumor burdens, increased tumor progression, and shorter overall survival in several cancers, including melanoma (7-10). These data suggest that targeting MDSCs may improve tumor-specific immune responses, increase clinical responses to immunotherapy, and ultimately increase survival in melanoma patients. In this proposal, we aim to decrease the frequency and/or function of MDSCs in melanoma patients treated with all-trans retinoic acid (ATRA).

4.1.1 Pharmaceutical and Therapeutic Background

All-trans retinoic acid (ATRA) is a vitamin A derivative that binds the retinoic acid receptor on MDSCs and differentiates immature monocytes into more mature dendritic cells (11). VESANOID is a standard treatment currently approved for patients with acute promyelocytic leukemia (APL).

VESANOID (tretinoin) is an FDA-approved commercially available retinoid that induces maturation of APL cells in culture. It is not approved in combination with pembrolizumab or for the treatment of patients with melanoma. It is available in a 10 mg soft gelatin capsule for oral administration. The recommended dose (for APL) is 45 mg/m²/day administered as two evenly divided doses until complete remission is documented.

Virtually all patients with APL experience some drug-related toxicity, especially headache, fever, weakness, and fatigue. These adverse effects are seldom permanent or irreversible nor do they usually require interruption of therapy. Some of the adverse events noted in patients with APL are associated with rapid tumor response and include hemorrhage, infections, gastrointestinal hemorrhage, disseminated intravascular coagulation, pneumonia, septicemia, and cerebral hemorrhage. There are no reported adverse side effects in patients with solid tumors treated with a short course of 150 mg/m² VESANOID combined with high dose IL-2 or a dendritic cell vaccine (12, 13).

4.1.2 Preclinical and Clinical Trial Data

Pre-clinical data suggest that VESANOID abrogates the suppressive effects of MDSCs isolated from both human cancer patients and mouse cancer models in vitro (14-16). Furthermore, mice treated with VESANOID have decreased frequencies of MDSCs and increased frequencies of dendritic cells that improve T cell responses against tumors (17-19).

Our preliminary research has identified a population of immunosuppressive MDSCs (Lineage negative, HLA-DR negative, CD11b positive, and CD33 positive) that are increased in Stage IV melanoma patients relative to healthy donors. To establish MDSCs as a potentially important contributor to immunosuppression in melanoma patients, we compared the frequency and function of immunosuppressive MDSCs in the peripheral blood of healthy donors, Stage I, and Stage IV melanoma patients (10). We found significant increases in the frequency of MDSCs in the peripheral blood of Stage IV

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melanoma patients compared to healthy donors. We showed that the frequency of these cells correlates with an increase in regulatory T cells and an increased level of IL-6 and IL-8 cytokines in the peripheral blood. Furthermore, patients with clinical disease progression had an increased frequency of these cells. We also found that patients with a high frequency of MDSCs had decreased overall survival and an increased risk of death (hazard ratio 4.83, $p = 0.016$). This increased risk of death was independent of other clinical factors including age, gender, and treatment regimens. Finally, we demonstrated that MDSCs isolated from Stage IV melanoma patients were significantly more immunosuppressive than those isolated from healthy donors. Overall, these data suggest that MDSCs may be a significant contributor to immunosuppression in melanoma patients and that targeting these cells in a combinatorial approach may improve immune responses against melanoma.

VESANOID induces the differentiation of immature monocytes into more mature cells of the dendritic cell lineage (15, 16, 20). In agreement with these results, our preliminary data suggest that VESANOID induces maturation of in vitro-derived MDSCs. We cultured monocytes from healthy donors with GM-CSF/IL-4 or GM-CSF/IL-6 to generate mature monocytes of the dendritic cell lineage (a control population) or MDSCs, respectively (21, 22). In contrast to the control population, MDSCs express low levels of HLA-DR and maintain high expression of CD14, consistent with the phenotype of an immature monocyte. Furthermore, MDSCs express increased levels of molecules that inhibit T cell responses such as Arginase I, NOX1, iNOS, and PD-L1. Conversely, MDSCs cultured with VESANOID are phenotypically more similar to the control dendritic cell population, expressing decreased levels of inhibitory molecules and CD14 and increased levels of HLA-DR. Most importantly, MDSCs derived in vitro with GM-CSF and IL-6 suppress T cell proliferation. However, treatment of these MDSCs with VESANOID eliminates their suppressive effects and restores T cell proliferation. Finally, MDSCs express higher levels of retinoic acid receptors RAR and RXR, suggesting that VESANOID treatment may selectively target these inhibitory cells. These preliminary data and our previous publications demonstrate that our research team has established the protocols necessary to accomplish the experiments outlined in this protocol.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Reducing immunosuppression by MDSCs during pembrolizumab treatment may maximize T cell activation and expansion, increasing the overall effectiveness and success of pembrolizumab treatment. This pilot clinical trial will demonstrate whether combinatorial immunotherapeutic approaches that target immunosuppressive MDSC's can augment tumor-specific T cells and benefit melanoma patients.

4.2.2 Rationale for Study Design/Dose Selection/Regimen/Modification

Pembrolizumab Dose Selection

Dosing of pembrolizumab has been evaluated in a variety of clinical settings. A population pharmacokinetic analysis has been performed using serum concentration time

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data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

All the patients will receive 200mg Q3W pembrolizumab treatment plus the supplemental treatment of 150 mg/m² VESANOID orally for 3 days surrounding each of the first four infusions of pembrolizumab (day -1, day 0, day +1) for a total of 12 days of VESANOID treatment (Section 2.2 *Trial Schema/Diagram*). The total daily dose of VESANOID may be taken anytime on the day before the pembrolizumab infusion (day -1) according to the patient's preferences, prior to the pembrolizumab infusion on the day of the infusion (day 0), and anytime on the day after the pembrolizumab infusion (day 1) according to the patient's preferences.

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VESANOID Dose Selection

Although VESANOID is a standard treatment for patients with acute promyelocytic leukemia, it has also been used to treat patients with solid tumors. We have selected the dose of VESANOID based on two prior clinical trials that combined VESANOID with other treatments. We have selected the same dose of VESANOID based on the pharmacokinetics and effects on MDSCs observed in these trials (11, 12). Renal cell carcinoma patients treated with VESANOID followed by high dose IL-2 had reduced frequencies of circulating MDSCs with reduced immunosuppressive function during the VESANOID phase of the treatment regimen (13). However, the subsequent high-dose IL-2 treatment abrogated these effects and resulted in a lack of clinical benefit overall (13). In another recent trial, VESANOID was used in combination with a dendritic cell vaccine targeting p53 mutations in small cell lung cancer patients (12). The survival outcomes have not yet been reported; however, the study demonstrated that the frequency and function of MDSCs was reduced following VESANOID treatment and that p53-specific T cell responses were increased in more patients receiving the combinatorial therapy compared to patients receiving the dendritic cell vaccine alone (12). These investigators performed a dose ranging pharmacokinetic analysis and correlated serum concentrations of ATRA with the desired target effect on MDSC's and determined that the optimal oral dose of ATRA was 150mg/m²/day. Lower doses of ATRA generally resulted in lower serum concentrations and less reliable effects on MDSC's. The authors also reported common side effects associated with the ATRA as dry skin, myalgia and headache that resolved when the ATRA was stopped. No specifics regarding the frequency or severity of these side effects were reported. (13)

De-escalation Design

The available data suggests that in order to target the MDSC's, sufficient serum concentrations of ATRA are necessary to have the desired effect. Based on prior reported investigations (13), the dose of 150mg/m²/day of ATRA was considered optimal and used in a subsequent trial with a similar design of three days of high dose ATRA around administration of a vaccine (12). The choice of a de-escalation design was based on feedback and concern for the potential toxicity associated with the short term higher doses of ATRA. In our prior trial combining three days of ATRA (150mg/m²/day) around administration of Ipilimumab, we noted headache as a significant common side effect that resolved with discontinuation of the ATRA. The de-escalation design was intended to aim for the effect on MDSC's yet allow for a dose reduction for side effects with the hope of still observing at least some effect on the intended target of MDSC's.

4.2.3 Efficacy Endpoints

We will monitor efficacy via two endpoints (1) manipulation of MDSC subsets and (2) progression free survival.

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4.2.3.1 *Biomarker Research*

We will track MDSC populations throughout the study and will analyze banked plasma for exploratory cytokine and potentially other biomarker analysis that correlate with MDSC's.

5.0 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Trial Participation Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Stage IV melanoma patients or patients who are being considered for pembrolizumab therapy.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Diagnosis of advanced melanoma (unresectable Stage III or Stage IV Melanoma).
2. Planned standard treatment with pembrolizumab.
3. Be willing and able to provide written informed consent for the trial.
4. State willingness to comply with all study procedures and be available for the duration of the trial.
5. Be ≥ 18 years of age on day of signing informed consent.
6. Have a performance status of 0 or 1 on the ECOG Performance Scale.
7. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

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Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	$\geq 1,500$ /mcL
Platelets	$\geq 100,000$ / mcL
Hemoglobin	≥ 9 g/dL or ≥ 5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine OR Measured or calculated ^a creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 X upper limit of normal (ULN) OR ≥ 60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN OR Direct bilirubin \leq ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN OR ≤ 5 X ULN for subjects with liver metastases
Albumin	≥ 2.5 mg/dL
^a Creatinine clearance should be calculated per institutional standard.	

8. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

9. Female subjects of childbearing potential (Section 6.5.2 - *Contraception*) must be willing to use an adequate method of contraception as outlined in Section 6.5.2 – *Contraception*, for the course of the study through 120 days after the last dose of study medication.

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

10. Male subjects of childbearing potential (Section 6.5.2- *Contraception*) must agree to use an adequate method of contraception as outlined in Section 6.5.2 - *Contraception*, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.

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2. 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 trial treatment.
3. Has a known history of active TB (Bacillus Tuberculosis).
4. Hypersensitivity to pembrolizumab or any of its excipients.
5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., \leq Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., \leq Grade 1 or at baseline) from adverse events due to a previously administered agent. Subjects with chronic conditions such as vision changes from plaque radiation therapy for ocular melanoma or prior hearing loss, that is not reasonably expected to be exacerbated by the investigational product may be included.

Note: Subjects with \leq Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

Note: Subjects with Grade 2 adrenal insufficiency or thyroid conditions who are not expected to resolve to baseline, are on a stable dose of medication may be included if it is not reasonably expected to be exacerbated by the investigational product, and asymptomatic whilst on treatment.

7. Has known active CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable, i.e. without evidence of progression for at least 4 weeks by repeat imaging (repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
8. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
9. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
10. Has known history of, or any evidence of active, non-infectious pneumonitis.

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11. Has an active infection requiring systemic therapy.
12. 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.
13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
14. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
15. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
17. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
18. Has received a live vaccine within 30 days of planned start of study therapy.

Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.
19. Has known sensitivity to retinoic acid derivatives.
20. Has a medical history of allogenic stem cell transplant or received a solid organ transplant.

6.0 STUDY AGENT AND TRIAL TREATMENT

6.1 Study Drug Description and Trial Treatments

The treatment to be used in this trial is outlined below in Table 2

Table 2 Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 0 of each 3 week cycle	Standard agent
All-trans retinoic acid	150 mg/m ²	Q3W	Oral	Day -1, 0, and 1 of each 3 week cycle (first four cycles)	Experimental agent

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6.1.1 Dose Selection/Modification and Study Drug Risks

6.1.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 (*Background and Rationale*).

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual or investigational brochure.

The selected dose of VESANOID is based on two prior studies (11, 12) and our own experience with VESANOID combined with ipilimumab. These trials combined VESANOID with other treatments. We have selected a dose based on the pharmacokinetics and effects on MDSCs observed in these trials (11, 12). Renal cell carcinoma patients treated with VESANOID followed by high dose IL-2 had reduced frequencies of circulating MDSCs with reduced immunosuppressive function during the VESANOID phase of the treatment regimen (13).

6.1.1.2 Dose Modification (Escalation/Titration/Other)

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor-Investigator. The reason for interruption should be documented in the patient's study record.

The toxicity profile of VESANOID and Pembrolizumab may overlap causing difficulty in determining the causative agent. Our investigators have many years of prior experience treating patients with Pembrolizumab and their clinical judgement will be used to assess the toxicity and any potential relationship.

Subjects who discontinue VESANOID treatment due to toxicity will be allowed to continue treatment with Pembrolizumab alone if the investigator feels the subject will continue to derive benefit from the treatment.

6.1.1.2.1 Pembrolizumab – Risks and Dosing Modification Guidelines

Pembrolizumab is generally well tolerated and demonstrates a favorable safety profile in comparison to chemotherapy. Pembrolizumab is an immunomodulatory agent, and based on this mechanism of action, immune-related adverse events (irAEs) are of primary concern. An irAE is defined as a clinically significant AE of any organ that is associated with study drug exposure, is of unknown etiology, and is consistent with an immune-related mechanism. If an irAE is suspected, a thorough evaluation should be conducted in an effort to possibly rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes before

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diagnosing an irAE. Serological, immunological, and histological (biopsy) data should be considered to support the diagnosis of an immune-related toxicity.

Immune-related AEs, including severe and fatal cases, have occurred in patients receiving pembrolizumab. Immune-related AEs can occur after discontinuation of treatment.

Immune-related AEs affecting more than one body system can occur simultaneously. In clinical studies, most immune-mediated ARs were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids, and/or supportive care.

Consultation with the appropriate medical specialist should be considered when investigating a possible irAE. These events can occur at times ranging from after the first dose of treatment to several months after the last dose of treatment. Mild irAEs are usually treated symptomatically and infrequently require dosing delays or discontinuation. Higher grade and persistent lower grade irAEs typically necessitate withholding or discontinuing treatment, and administration of systemic steroids or other immunosuppressive agents (such as tumor necrosis factor blockers) when systemic steroids are not effective. Early recognition of irAEs and initiation of treatment are critical to reduce the risk of complications because the majority of irAEs are reversible with the use of steroids and other immune suppressants (please reference the clinical protocol for additional information regarding the management of irAEs). Therefore, early recognition and initiation of treatment is critical to reduce complications.

For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 3.

Suggested supportive care measures for the management of adverse events related to pembrolizumab, including use of corticosteroids, are also outlined in Section 6.3 - *Rescue Medications & Supportive Care*.

In addition to the immune-related risks noted below, infusion-related reactions are also an important identified risk for pembrolizumab; however, they are not considered immune-mediated.

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Table 3 Dose Modification Guidelines for Pembrolizumab-Related Adverse Events

General instructions:				
<ol style="list-style-type: none"> 1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks. 2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks. 3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids. 				
Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	<ul style="list-style-type: none"> • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper 	<ul style="list-style-type: none"> • Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	<ul style="list-style-type: none"> • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper 	<ul style="list-style-type: none"> • Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with \geq Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

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Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	<ul style="list-style-type: none"> Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper 	<ul style="list-style-type: none"> Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	<ul style="list-style-type: none"> Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper 	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β -cell failure	Withhold	<ul style="list-style-type: none"> Administer insulin for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia until metabolic control is achieved 	<ul style="list-style-type: none"> Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	<ul style="list-style-type: none"> Administer corticosteroids to treat adrenal insufficiency and other hormone replacements as clinically indicated. 	<ul style="list-style-type: none"> Monitor patients for signs and symptoms of adrenal insufficiency and hypophysitis (including hypopituitarism)
	Grade 3 or 4	Withhold or permanently discontinue ¹		
Hyperthyroidism	Grade 2	Continue	<ul style="list-style-type: none"> Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate 	<ul style="list-style-type: none"> Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue ¹		
Hypothyroidism	Grade 2-4	Continue	<ul style="list-style-type: none"> Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care 	<ul style="list-style-type: none"> Monitor for signs and symptoms of thyroid disorders.

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Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Nephritis and Renal dysfunction	Grade 2	Withhold	<ul style="list-style-type: none"> Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper. 	<ul style="list-style-type: none"> Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	<ul style="list-style-type: none"> Based on severity of AE administer corticosteroids 	<ul style="list-style-type: none"> Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Severe skin reactions		Withhold or permanently discontinue based on the type of event. Events that require discontinuation include and not limited to: Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN)	<ul style="list-style-type: none"> Administer corticosteroids 	<ul style="list-style-type: none"> Monitor patients for suspected severe skin reactions and exclude other causes.
All other immune-related AEs	Intolerable/persistent Grade 2	Withhold	<ul style="list-style-type: none"> Based on type and severity of AE administer corticosteroids 	<ul style="list-style-type: none"> Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation		

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		include and not limited to: Guillain-Barre Syndrome, pancreatitis, encephalitis, sarcoidosis, and myasthenic syndrome-myasthenia gravis (including exacerbation)		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. NOTE: For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

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Management of Infusion Reactions:

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Following are treatment guidelines (Table 4) for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
<u>Grade 1</u> Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
<u>Grade 2</u> Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	<p>Stop Infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics</p> <p>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.</p> <p>Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.</p>	<p>Subject may be premedicated 1.5h (\pm 30 minutes) prior to infusion of pembrolizumab (Pembrolizumab) with:</p> <p>Diphenhydramine 50 mg po (or equivalent dose of antihistamine).</p> <p>Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).</p>
<u>Grades 3 or 4</u> Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	<p>Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine</p> <p>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Subject is permanently discontinued from further trial treatment administration.</p>	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

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6.1.1.2.2 VESANOID - Risks

Adverse events (both non-serious and serious) associated with VESANOID will be reported to the principal investigator, the University of Colorado Data Safety Monitoring Committee (DSMC), and COMIRB. The treating medical oncologist and principal investigator will decide if VESANOID dose should be decreased or if VESANOID treatment should be discontinued.

VESANOID Side Effects

Below is a comprehensive list of reported side effects for VESANOID. Much of the reported experience is in patients being treated for APL, which may differ for patients in this trial who do not have APL.

Potential Side Effects

Virtually all patients experience some drug-related toxicity, especially headache, fever, weakness, and fatigue. These adverse effects are seldom permanent or irreversible nor do they usually require interruption of therapy. Some of the adverse events are common in patients with APL, including hemorrhage, infections, gastrointestinal hemorrhage, disseminated intravascular coagulation, pneumonia, septicemia, and cerebral hemorrhage. The following describes the adverse events, regardless of drug relationship, that were observed in patients treated with VESANOID (tretinoin).

Typical Retinoid Toxicity

The most frequently reported adverse events were similar to those described in patients taking high doses of vitamin A and included headache (86%), fever (83%), skin/mucous membrane dryness (77%), bone pain (77%), nausea/vomiting (57%), rash (54%), mucositis (26%), pruritus (20%), increased sweating (20%), visual disturbances (17%), ocular disorders (17%), alopecia (14%), skin changes (14%), changed visual acuity (6%), bone inflammation (3%), visual field defects (3%).

Body as a Whole

General disorders related to VESANOID (tretinoin) administration and/or associated with APL included malaise (66%), shivering (63%), hemorrhage (60%), infections (58%), peripheral edema (52%), pain (37%), chest discomfort (32%), edema (29%), disseminated intravascular coagulation (26%), weight increase (23%), injection site reactions (17%), anorexia (17%), weight decrease (17%), myalgia (14%), flank pain (9%), cellulitis (8%), face edema (6%), fluid imbalance (6%), pallor (6%), lymph disorders (6%), acidosis (3%), hypothermia (3%), ascites (3%).

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Respiratory System Disorders

Respiratory system disorders were commonly reported in APL patients administered VESANOID (tretinoin). The majority of these events are symptoms of the RA-APL syndrome (see boxed WARNINGS). Respiratory system adverse events included upper respiratory tract disorders (63%), dyspnea (60%), respiratory insufficiency (26%), pleural effusion (20%), pneumonia (14%), rales (14%), expiratory wheezing (14%), lower respiratory tract disorders (9%), pulmonary infiltration (6%), bronchial asthma (3%), pulmonary edema (3%), larynx edema (3%), unspecified pulmonary disease (3%).

Ear Disorders

Ear disorders were consistently reported, with earache or feeling of fullness in the ears reported by 23% of the patients. Hearing loss and other unspecified auricular disorders were observed in 6% of patients, with infrequent (<1%) reports of irreversible hearing loss.

Gastrointestinal Disorders

GI disorders included GI hemorrhage (34%), abdominal pain (31%), other gastrointestinal disorders (26%), diarrhea (23%), constipation (17%), dyspepsia (14%), abdominal distention (11%), hepatosplenomegaly (9%), hepatitis (3%), ulcer (3%), and unspecified liver disorder (3%).

Cardiovascular and Heart Rate and Rhythm Disorders

Arrhythmias (23%), flushing (23%), hypotension (14%), hypertension (11%), phlebitis (11%), cardiac failure (6%) and for 3% of patients: cardiac arrest, myocardial infarction, enlarged heart, heart murmur, ischemia, stroke, myocarditis, pericarditis, pulmonary hypertension, secondary cardiomyopathy.

Central and Peripheral Nervous System Disorders and Psychiatric

Dizziness (20%), paresthesias (17%), anxiety (17%), insomnia (14%), depression (14%), confusion (11%), cerebral hemorrhage (9%), intracranial hypertension (9%), agitation (9%), hallucination (6%) and for 3% of patients: abnormal gait, agnosia, aphasia, asterixis, cerebellar edema, cerebellar disorders, convulsions, coma, CNS depression, dysarthria, encephalopathy, facial paralysis, hemiplegia, hyporeflexia, hypotaxia, no light reflex, neurologic reaction, spinal cord disorder, tremor, leg weakness, unconsciousness, dementia, forgetfulness, somnolence, slow speech.

Urinary System Disorders

Renal insufficiency (11%), dysuria (9%), acute renal failure (3%), micturition frequency (3%), renal tubular necrosis (3%), enlarged prostate (3%).

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Miscellaneous Adverse Events

Isolated cases of erythema nodosum, basophilia and hyperhistaminemia, Sweet's syndrome, organomegaly, hypercalcemia, pancreatitis and myositis have been reported.

Cardiovascular

Cases of thrombosis (both venous and arterial) involving various sites (e.g., cerebrovascular accident, myocardial infarction, renal infarct) have been reported rarely.

Hematologic

Rare cases of thrombocytosis have been reported.

Skin

Genital ulceration.

Miscellaneous Adverse Events

Rare cases of vasculitis, predominantly involving the skin, have been reported.

6.1.1.2.3 Dose Modifications for VESANOID

If patients experience grade 3 or 4 toxicity that is believed to be related to the VESANOID, then the VESANOID will be held until the toxicity resolves to grade 0 or 1. In the case where the grade 3 or 4 toxicity is believed to be related to Pembrolizumab, the dose modification guidelines in table 3 will be followed. If the toxicity appears to be related to a combination of Pembrolizumab and VESANOID, the VESANOID will be held and the guidelines in table 3 will be followed. After the toxicity has resolved, the VESANOID will either be restarted at the next scheduled time at a reduced dose of 100mg/m² or will be discontinued for serious toxicities. The decision to discontinue treatment will be based on what the treating physician feels is in the subjects' best interest. If the grade 3 or 4 toxicity returns, the VESANOID will be held indefinitely.

The severity of the adverse events will be rated on a scale of Grade 1-4 and reported according to the Data and Safety Monitoring Plan using CTCAE version 4.0. Medical oncologists at the University of Colorado Hospital Cutaneous Oncology Clinic specialize in melanoma and have extensive experience treating patients with immune-based therapies that cause immune-related adverse events. The Principal Investigator will be notified of all adverse events that occur during this trial and will work with the treating oncology team to determine the likelihood of VESANOID's contribution to the adverse event.

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VESANOID Related Toxicity

Significant VESANOID related toxicity is defined as any \geq grade 3 non-hematologic toxicity related to VESANOID, \geq grade 4 hematologic toxicity related to VESANOID or other grade VESANOID related adverse events that lead to treatment discontinuation. An exception is VESANOID related headache not optimally managed with supportive care therapies [acetaminophen, non-steroidal anti-inflammatory medication, or Imitrex (sumatriptan)] or that does not resolve within 72 hours of stopping the VESANOID. A patient's choice to stop all VESANOID, with or without a dose reduction, due to headache alone will not be considered a dose limiting toxicity.

Dose Limiting Toxicity and Study Discontinuation Criteria

The trial stopping criteria outlined in the table found in Section 6.6.5 - *Toxicity and Study Discontinuation Criteria* will be followed to avoid posing undue risk to additional patients. Twenty four (24) patients will potentially be recruited to further evaluate safety and assess preliminary efficacy.

Dose limiting toxicities are defined according to the AE profile observed during the first cycle (Cycle 1 Day 0 to Cycle 2 Day 0) of study drug administration. All AEs should be considered possibly related to the study drug unless such relationship can be definitively excluded.

Toxicity will be evaluated according to NCI CTCAE Version 4.0. A DLT will be defined as any of the following events that are considered by the investigator to be at least possibly related to treatment with Vesanoid and Pembrolizumab:

1. Any \geq grade 3 non-hematologic toxicity related to VESANOID, \geq grade 4 hematologic toxicity related to VESANOID or other grade VESANOID related adverse events that lead to treatment discontinuation. An exception is VESANOID related headache not optimally managed with supportive care therapies (acetaminophen or non-steroidal anti-inflammatory medication) or that does not resolve within 72 hours of stopping the VESANOID. A patient's choice to stop all VESANOID, with or without a dose reduction, due to headache alone will not be considered a dose limiting toxicity.
2. Any \geq grade 3 toxicity related to Pembrolizumab.

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The dose levels will be as follows:

Dose Level	Number of Patients	Vesanoid	Pembrolizumab
-1	6	100 mg/m ² PO on days -1, 0, and 1 every 3 weeks for the first 4 cycles	200 mg IV on Day 0 every 3 weeks
1 (Starting Dose)	6	150 mg/m ² PO on days -1, 0, and 1 every 3 weeks for the first 4 cycles	200 mg IV on Day 0 every 3 weeks

6.1.2 Timing of Dose Administration

Trial treatment with Pembrolizumab should be administered on Day 0 of each cycle after all procedures/assessments have been completed as detailed on the *Trial Schedule of Events Chart (Section 7.1)*. All trial treatments will be administered on an outpatient basis. VESANOID will be administered on day -1, 0 and 1 with each of the first four cycles of Pembrolizumab. VESANOID will be administered twice a day (75mg/m² each dose for a total dose of 150mg/m²).

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion every 3 weeks. Given the variability of infusion pumps from site to site, a window of -10 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -10 min/+10 min).

The Pharmacy Manual and investigational brochure contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

6.1.3 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor-Investigator, study personnel, and subject will know the treatment administered.

6.2 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the Sponsor-Investigator and/or the subject's primary physician.

6.2.1 Acceptable Concomitant Medications

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

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of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.5 – *Events of Clinical Interest (ECI)*.

6.2.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- 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 trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor-Investigator.

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 trial. Subjects may receive other medications that the investigator deems to be medically necessary.

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

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

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6.3 Rescue Medications & Supportive Care

6.3.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 6.1.1.2 - *Dose Modification (Escalation/Titration/Other)*.

6.4 Known Potential Benefits of the Trial

The risks to subjects are reasonable in relation to the anticipated benefits to subjects and/or society, and in relation to the importance of the knowledge that may reasonably be expected to result, thereby falling in favor of performing the study:

- To Subject: The potential benefit to the study subject is decreased immunosuppressive action of MDSC's and enhanced immunologic responses.
- To Society: The potential benefit to society is generalizable knowledge regarding utilization of combinational immunotherapies.
- Justify the importance of the knowledge gained: The potential knowledge to be gained includes a better understanding of mechanisms surrounding ongoing tumor induced immunosuppression. Information from this study may be used to further refine immunologic targets such as MDSC's.

6.5 Diet/Activity/Other Considerations

6.5.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

6.5.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

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Animal reproduction studies have not been conducted with pembrolizumab; however, blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. These results indicate a potential risk, based on its mechanism of action, that administration of pembrolizumab during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth. Human IgG4 is known to cross the placental barrier and pembrolizumab is an IgG4; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. Pembrolizumab is not recommended during pregnancy unless the clinical benefit outweighs the potential risk to the fetus. Women of childbearing potential should use effective contraception during treatment with pembrolizumab and for at least after the last dose of pembrolizumab.

For this trial:

- ***Male subjects will be considered to be of non-reproductive potential if*** they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).
- ***Female subjects will be considered of non-reproductive potential if they are either:***
 - (1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age 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. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);
OR
 - (2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;
OR
 - (3) has a congenital or acquired condition that prevents childbearing.
- ***Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner,*** respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:
 - (1) practice abstinence[†] from heterosexual activity;
OR
 - (2) use (or have their partner use) acceptable contraception during heterosexual activity.

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- ***Acceptable methods of contraception are[†]:***

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

6.5.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor-Investigator, DSMC, COMIRB, and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

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The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor-Investigator, DSMC, COMIRB, and to Merck. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the investigator, DSMC, COMIRB, and to Merck and followed as described above and in Section 7.4.2 – *Immediate Reporting of SAEs*.

6.5.4 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

6.6 Subject Withdrawal, Treatment Discontinuation, or Study Termination Criteria

6.6.1 Subject Withdrawal

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.2.6 - *Other Procedures*.

6.6.2 Subject Discontinuation

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent
- Confirmed radiographic disease progression (i.e. progressive disease per RECIST 1.1 as documented by tumor imaging at any time point). Subjects with disease progression indicated on imaging should discontinue all study treatment, but may continue pembrolizumab according to standard of care outside of the study at investigator discretion. Subjects with suspected clinical progression may continue study treatment at investigator discretion until there is radiographic confirmation of disease progression.
- Unacceptable adverse experiences as described in Section 6.1.1.2 (*Dose Modification (Escalation/Titration/Other)*)
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up

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- Administrative reasons

The End of Treatment (EOT) and Follow-up visit procedures are listed in Section 7.1 (*Trial Schedule of Events Chart*) and Section 7.2.7 (*Visit Requirements*). Additionally, all subjects will be followed for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.6.3 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed Complete Response (CR) that have had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for retreatment (200mg Q 3 weeks) for up to one additional year.

6.6.4 Discontinuation of Study Therapy after Disease Stability

Patients who achieve a partial response and prolonged disease stability may stay on Pembrolizumab (200mg Q3 weeks) for up to two years on study. In the absence of significant toxicity, the study drug may be discontinued at the discretion of the treating medical oncologist or Sponsor-Investigator after a prolonged period of disease stability. Subjects who then experience radiographic disease progression may be eligible for retreatment (200mg Q 3 weeks) for up to one additional year.

6.6.5 Toxicity and Study Discontinuation Criteria

The trial stopping criteria outlined in the Calculated Trial Stopping Criteria (Table 5) below will be followed to avoid posing undue risk to additional patients. Twenty-four patients will potentially be recruited in our study to evaluate DLTs and suggest RP2D. Toxicity is defined as AEs of grade 3 or higher. Historical data of similar patients show an overall grade 3 or 4 toxicity rate of approximately 14% for pembrolizumab treatment alone. It is estimated that the current trial (the combination) may increase toxicity rates an additional 10% compared to pembrolizumab alone. The DSMC will have oversight responsibilities for reviewing toxicities in patients associated with this trial.

Table 5 Calculated Trial Stopping Criteria

Number of Patients	Stopping Criteria	Dosing Action
6 (Cohort 1)	≥ 3	Dose de-escalate in Cohort 2 (dose level -1)
6 (Cohort 2)	≥ 3	Study Stop

If the grade 3 or 4 toxicity exceeds 33% the stopping criteria, the next 6 enrolled patients will be put on the lower dose.

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6.6.6 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete.
2. Poor adherence to protocol and regulatory requirements.
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects.

7.0 TRIAL SCHEDULE AND PROCEDURES

7.1 Trial Schedule of Events Chart

Trial Period:	Screening Phase	Treatment Cycles					Post-Treatment			
Treatment Cycle/Title:	Screening	1	2	3	4	5+	EOT ⁱ	Safety Follow-up 1	Safety Follow-up 2 ^b	Survival Follow-up
Scheduling Window (Days):	-28 to -1		± 7	± 7	± 7	± 7	± 7	30 days (±2 days) post last treatment or prior to starting new treatment	90 days (±7 days) post last treatment	Every 12 weeks (±14 days)
Administrative Procedures										
Informed Consent	x									
Inclusion/Exclusion Criteria	x									
Demographics and Medical History	x									
Prior and Concomitant Medication Review	x	x	x	x	x	x	x	x	x	x
Vesanoid Administration ^a		x	x	x	x					
Pembrolizumab Administration ^a		x	x	x	x	x				
Post-study anticancer therapy status							x	x	x	x
Survival Status								x	x	x
Clinical Procedures/Assessments										
Review Adverse Events		x	x	x	x	x	x	x	x	
Full Physical Examination	x									
Directed Physical Examination		x	x	x	x	x		x		
Vital Signs and Weight	x	x	x	x	x	x		x		
ECOG Performance Status	x	x	x	x	x	x	x			
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory										
Pregnancy Test – Urine or Serum β-HCG ^h	x									

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Trial Period:	Screening Phase	Treatment Cycles					Post-Treatment			
Treatment Cycle/Title:	Screening	1	2	3	4	5+	EOT ⁱ	Safety Follow-up 1	Safety Follow-up 2 ^b	Survival Follow-up
Scheduling Window (Days):	-28 to -1		± 7	± 7	± 7	± 7	± 7	30 days (±2 days) post last treatment or prior to starting new treatment	90 days (±7 days) post last treatment	Every 12 weeks (±14 days)
CBC with Differential ^g	x	x	x	x	x	x				
Comprehensive Serum Chemistry Panel ^{e & g}	x	x	x	x	x	x				
T3, FT4 and TSH ^g	x	x		x		x ^f				
Efficacy Measurements										
Tumor Imaging ^c	x					x	x			
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood										
Optional Archival or Newly Obtained Tissue Collection ^d	x							x	x	x
Correlative Studies Blood Collection	x		x		x	x ^j		x ^j		

^a Administered according to schedule outlined in table 2. Vesanoïd drug supply will be dispensed in clinic on Cycle 1 Day -1 for Cycle 1, Cycle 1 Day 0 for Cycle 2, Cycle 2 Day 0 for Cycle 3 and Cycle 3 Day 0 for Cycle 4.

^b To be completed only for subjects who have not initiated a new therapy. Can be collected at a regularly scheduled clinic visit or via patient contact by telephone.

^c Tumor imaging generally performed every 12 weeks per standard of care for the clinic and evaluated by RECIST 1.1 criteria (Section 11.3 - *Appendices*). Baseline tumor imaging should be completed within 28 days of starting treatment; however, exceptions may be approved after discussion with the principal investigator. Brain metastases that were radiated prior to starting the trial should be re-imaged at the standard 12 week frequency, or as deemed clinically appropriate, by the treating physician.

^d Optional additional tissue collection will be obtained from archival or future biopsies if available.

^e To include lactate dehydrogenase at screening.

^f To be collected every other cycle per standard of care for clinic.

^g Screening labs should be performed within 10 days of treatment initiation.

^h Within 72 hours prior to receiving the first dose of study medication.

ⁱ To be completed when it is decided that the subject will discontinue study treatment. Tumor imaging is only required at investigator's discretion. This visit can be combined with the first safety follow-up visit if the subject is planning to start a new treatment.

^j ≤ 60 days after last Vesanoïd treatment.

7.2 Trial Procedures

Section 7.1 - The *Trial Schedule of Events Chart* - summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be

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necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor/Principal-Investigator or treating physician for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

All trial procedures will be performed by the investigator, or a qualified designee (also an IRB approved research personnel for the study).

7.2.1 Administrative Procedures

7.2.1.1 *Informed Consent*

All subjects must first read, understand, and sign the IRB-approved informed consent form (ICF) before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study.

7.2.1.2 *Inclusion/Exclusion Criteria*

All inclusion and exclusion criteria will be reviewed to ensure that the subject qualifies for the trial.

7.2.1.3 *Medical History*

A medical history will be obtained and will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.2.1.4 *Prior Medications*

Prior medication taken by the subject within 28 days before the first dose of trial treatment, including any protocol-specified washout requirement, will be reviewed and recorded. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

7.2.1.5 *Concomitant Medications*

Medication, if any, taken by the subject during the trial will be recorded. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 6.2 (*Concomitant Medications/Vaccines (allowed & prohibited)*).

7.2.1.6 Disease Details and Treatments

7.2.1.6.1 Disease Details

Prior and current details regarding disease status will be obtained.

7.2.1.6.2 Prior Treatment Details

All prior cancer treatments including systemic treatments, radiation and surgeries will be reviewed.

7.2.1.6.3 Subsequent Anti-Cancer Therapy Status

All new anti-neoplastic therapy initiated after the last dose of trial treatment will be reviewed. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated, the subject will move into survival follow-up.

7.2.2 Clinical Procedures / Assessments

7.2.2.1 Adverse Event (AE) Monitoring

Each subject will be assessed to evaluate for potential new or worsening AEs as specified in the *Trial Schedule of Events Chart (Section 7.1)* and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 11.2 - *Appendices*). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 7.3 (*Adverse Events (AE) – Assessment, Recording and Reporting*) for detailed information regarding the assessment and recording of AEs.

7.2.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

7.2.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the *Trial Schedule of Events Chart (Section 7.1)*, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.2.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as

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specified in the *Trial Schedule of Events Chart (Section 7.1)*. Vital signs should include weight and other vital signs per standard of care.

7.2.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the *Trial Schedule of Events Chart (Section 7.1)*.

7.2.3 Efficacy Measurement

7.2.3.1 Tumor Imaging and Assessment of Disease

Following the standard of care for pembrolizumab treatment, imaging will be performed at the treating physician's discretion. The imaging will be reviewed by the investigator according to the RECIST criteria (version 1.1), to monitor the appearance of new metastatic lesions and the size of existing lesions.

7.2.4 Tumor Tissue Collection and Correlative Studies Blood Sampling

Plasma will be banked from every patient for cytokine analysis, potential biomarker and other correlative studies. Plasma will also be collected for potential analysis of plasma VESANOID levels in the event this could correlate with results from the immunologic analysis. Whenever possible, tumor samples will be cataloged and stored at the CU Melanoma Biorepository. Additional correlative studies may include genomic analysis.

7.2.5 Laboratory Procedures/Assessments

7.2.5.1 Standard safety laboratory tests.

Will be obtained as outlined in section 7.1 - *Trial Schedule of Events*.

7.2.5.2 Experimental lab draws.

Will be performed at regularly scheduled clinic visits as outlined in section 2.2 - *Trial Schema/Diagram*. Peripheral blood mononuclear cells (PBMCs) will be isolated and flow cytometry will be used to quantify MDSCs and T cells.

- **Baseline immune response determination.** Subjects in the study will be asked to provide 40 mls of blood prior to initiating treatment to evaluate baseline immune responses and immune cell frequencies.
- **Immune response monitoring.** Blood samples will be drawn prior to the administration of the 2nd and 4th doses of pembrolizumab and after the last dose of VESANOID for continued measurement of immune cell frequencies.
- **Cytokine analysis.** Up to 20 ml of plasma will be stored for up to five years following study completion for subsequent cytokine analysis.

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7.2.5.3 Specimen Analysis

Functional assays will be performed to assess the ability of isolated MDSCs to suppress T cell responses.

- **Determination of tumor-specific T cell response frequency.** Peripheral blood mononuclear cells (PBMCs) will be isolated over a ficoll gradient and cells will be banked to analyze the frequency of MDSCs and T cells using flow cytometry as previously published. PBMCs will be used to determine the frequency of tumor-specific T cell responses by stimulating the cells with a mixture of peptides derived from known melanoma tumor antigens including NYESO, gp100, and tyrosinase as well as measuring IFN-gamma production by flow cytometry.
- **T cell suppression assay.** The remaining PBMC will be used to perform T cell suppression assays using magnetically separated MDSC populations, comparing the suppressive function of MDSCs throughout treatment. Any remaining MDSCs will be flash frozen and banked for biomarker studies analyzing the expression of known suppressive molecules by real-time quantitative PCR.

7.2.5.4 Cytokine analysis.

Multiplex cytokine array will be used for subsequent cytokine analysis. Concentration of cytokines related to the function of MDSCs (GM-CSF, VEGF, MIP-1 alpha, MIP-1 beta, IL-10, IL-6, and IL-8) and T cells (IFN-gamma, TNF-alpha, IL-1-beta, IL-2, IL-4, IL-5, IL-12p70, IL-17) will be analyzed.

7.2.5.5 Biomarker analysis.

When available, representative histologic slides from each patient's primary or metastatic melanoma will be procured and submitted to QualTek for PD-L1 analysis. Correlations between baseline PD-L1 staining and MDSC assessments, progression free survival and clinical outcomes will be analyzed.

QualTek Molecular Laboratories
300 Pheasant Run, Newtown, PA 18940
(215) 504-7402

7.2.6 Other Procedures

7.2.6.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined below at *Assessing and Recording Adverse Events* (Section 7.3) and then proceed to the *Follow-Up Visits* of the study (Section 7.2.8.).

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7.2.7 Visit Requirements

Visit requirements are outlined in Section 7.1 - *Trial Schedule of Events Chart*. Specific procedure-related details are provided above in Section 7.2 - *Trial Procedures*.

7.2.7.1 Screening Period

There will be a screening period of up to 28 days after subjects sign informed consent.

7.2.7.2 Treatment Period

The treatment period is defined as the time that the patients are receiving VESANOID and/or Pembrolizumab treatment.

7.2.7.3 Post-Treatment Visits

7.2.7.3.1 Safety Follow-Up Visits

Subjects who discontinue trial treatment will move into the follow-up phase and other treatment decisions will be at the discretion of the treating physician.

The first safety follow-up visit will be conducted for all subjects 30 days after the last dose of trial treatment (VESANOID and/or pembrolizumab) or before the initiation of a new anti-cancer treatment, whichever comes first.

Should the subject not initiate a new anti-cancer treatment, the second safety follow-up visit will be conducted 90 days after the last dose of trial treatment.

All AEs that occur prior to the Safety Follow-Up Visits should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.2.7.3.2 Survival Follow-up

Subjects should be contacted at regularly scheduled clinic visits or by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. Every effort should be made to collect information regarding disease status and post-study anti-neoplastic treatment.

Patients will be followed for up to 2 years or until recurrence or death.

7.3 Adverse Events (AE) – Assessing, Recording and Reporting

7.3.1 Definition of AE

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

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7.3.2 Assessment of AE

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the study drug, is also an adverse event.

Adverse events may occur during the course of the use of the study drug in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an adverse event.

7.3.3 Reporting of AEs

All adverse events that occur after the consent form is signed but before treatment allocation must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment allocation through 90 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the adverse event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in Section 7.4 (*Serious Adverse Events (SAE) – Assessing, Recording and Reporting*). The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

7.4 Serious Adverse Events (SAE) – Assessing, Recording and Reporting

7.4.1 Definition and Assessment SAEs

A serious adverse event is any adverse event occurring at any dose or during any use of Pembrolizumab and VESANOID that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is another important medical event.

Refer to Table 6 for additional details regarding each of the above criteria.

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7.4.2 Immediate Reporting of SAEs

For the time period beginning when the consent form is signed until treatment allocation, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference section 7.4.3 below - *Protocol Specific Exceptions to Serious Adverse Event Reporting* for additional details) that occurs to any subject must be reported within 24 hours to the Sponsor-Investigator, within 2 business days to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220), within 5 business days to the DSMC, and in accordance with COMIRB reporting requirements (within 5 business days or during continuing review) if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference section 7.4.3 below - *Protocol Specific Exceptions to Serious Adverse Event Reporting* for additional details), whether or not related to the study drug, must be reported within 24 hours to the Sponsor-Investigator, within 2 business days to Merck Global Safety, within 5 business days to the DSMC, and in accordance with COMIRB reporting requirements (within 5 business days or during continuing review).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the study drug, that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported within 24 hours to the Sponsor-Investigator, within 2 business days to Merck Global Safety, within 5 business days to the DSMC, and in accordance with COMIRB reporting requirements (within 5 business days or during continuing review).

All subjects with serious adverse events must be followed up for outcome.

7.4.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

The suspected/actual events covered in this exception include any event that is disease progression of the cancer under study. Additionally, hospitalization related to convenience (e.g., transportation issues etc.) will not be considered a SAE.

7.5 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported be within 24 hours to the Sponsor-Investigator, within 2 working

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days to Merck Global Safety, within 5 business days to the DSMC, and in accordance with COMIRB reporting requirements (within 5 business days or during continuing review).

For the time period beginning when the consent form is signed until treatment allocation, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the investigator if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, must be reported within 24 hours to the Sponsor-Investigator, within 2 working days to Merck Global Safety, within 5 business days to the DSMC, and in accordance with COMIRB reporting requirements (within 5 business days or during continuing review).

Events of clinical interest for this trial include:

1. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, 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.

7.6 Reporting of Pregnancy and Lactation

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation through 120 days following cessation of the study drugs, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues

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to term, the outcome (health of infant) must also be reported. Such events must be reported within 24 hours to the Sponsor-Investigator, within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220), within 5 days to the DSMC and within 5 days to COMIRB.

7.7 Sponsor-Investigator Responsibility for Reporting Adverse Events

The Sponsor-Investigator will report all Adverse Events to regulatory authorities and COMIRB, in accordance with all applicable laws and regulations.

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7.7.1 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. 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 grade must also be evaluated for seriousness.

Table 6 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
	Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
	Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
	Grade 4	Life threatening consequences; urgent intervention indicated.
	Grade 5	Death related to AE
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of study drug product that:	
	†Results in death; or	
	†Is life threatening; or places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or	
	†Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of study drug and is documented in the patient's medical history.); or	

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	†Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new cancer (that is not a condition of the study) (although not serious per ICH definition, is reportable to the investigator within 24 hours and to Merck within 2 working days to meet certain local requirements); or	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the investigator and to Merck Global Safety, the DSMC, and COMIRB within 2 working days.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause study drug to be discontinued?	
Relationship to Study Drug	<p>Did study drug cause the adverse event? The determination of the likelihood that study drug caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information.</p> <p>The following components are to be used to assess the relationship between study drug and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely study drug caused the adverse event (AE):</p>	
	Exposure	Is there evidence that the subject was actually exposed to study drug such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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Relationship to Study Drug (continued)	The following components are to be used to assess the relationship between the test drug and the AE: (continued)	
	Dechallenge	<p>Was study drug discontinued or dose/exposure/frequency reduced?</p> <p>If yes, did the AE resolve or improve?</p> <p>If yes, this is a positive dechallenge. If no, this is a negative dechallenge.</p> <p>(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)</p>
	Rechallenge	<p>Was the subject re-exposed to study drug in this study?</p> <p>If yes, did the AE recur or worsen?</p> <p>If yes, this is a positive rechallenge. If no, this is a negative rechallenge.</p> <p>(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time).</p> <p>NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY STUDY DRUG, OR IF REEXPOSURE TO STUDY DRUG POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.</p>
	Consistency with Trial Treatment Profile	<p>Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding study drug or drug class pharmacology or toxicology?</p>
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).	
Yes, there is a reasonable possibility of Merck product relationship.	<p>There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.</p>	
No, there is not a reasonable possibility of Merck product relationship	<p>Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a subject with overdose without an associated AE.)</p>	

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8.0 STATISTICAL ANALYSIS PLAN

The primary goal of the study is to characterize the safety and establish the recommended phase 2 dose (RP2D) and preliminary efficacy evaluation with a total of 24 evaluable subjects. A modified 3+3 design with a cohort size of 6 with a continuous toxicity monitoring. The design is to inform de-escalation decisions based on safety if needed. For the purposes of this trial, a target toxicity rate of approximately 33% will be used to establish the RP2D. Table 7 below provides the probability of detecting the number of DLTs based on true toxicity rates with 24 subjects:

Table 7 Number of DLTs and the Corresponding Cumulative Probability for Several Toxicity Rates with 24 Subjects

True toxicity rate (%)	Corresponding Number of DLTs (# DLT)	Cumulative Probability for Detecting #DLT
20	5	0.66
25	6	0.56
30	7	0.56
35	8	0.53
40	10	0.65

Safety Analyses

All patients who received any protocol therapy will be employed for safety analyses. Patient incidence of all treatment-emergent AEs will be tabulated by dose and system organ class and preferred term. Tables of fatal adverse events, serious adverse events, treatment-related AEs, and adverse events leading to withdrawal from investigation product will also be provided. The MedDRA will be used to code adverse events and the NCI CTCAE version 4.0 will be used to grade severity of adverse events and laboratory toxicities.

Summary statistic will be provided for total number of subjects treated under each dose, average dose administered, and duration of treatment.

For select laboratory parameters, changes of laboratory values over time (eg, change from baseline summary statistics), grade shifts in laboratory values from baseline to worst on-study value, and grade 3 or higher laboratory toxicities will be summarized. The ECG measurements from this study will be performed as per standard of care for routine safety monitoring.

Efficacy analysis

The efficacy analysis population consists of all subjects who receive at least one cycle treatment (3-day doses of study treatment).

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Tcell subsets (CD4, CD8, Treg) and MDSC subsets (CD14+, CD15+) will be analyzed by flow cytometry at each of the blood draws time points and compared to whole blood cells, total lymphocytes and monocytes populations between time points and compared between pretreatment, on treatment and post treatment. T cell activation will be assessed by CD107 and IFN γ production in response to PMA and ionomycin and compared between pretreatment, on treatment and post treatment. MDSC functional assays will assess the ability of MDSC's to suppress stimulated T cell proliferation as a percent of positive control and will be compared between time points and compared between pretreatment, on treatment and post treatment.

Linear mixed effects models will be used to assess the frequency of MDSC subsets over times. Contrast statements will be used to estimate changes in the frequency of MDSC subsets and its suppressive function from baseline after treatment at different time points. For PFS endpoint, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided as appropriate. Subjects without efficacy evaluation data or without survival data will be censored at Day 1. The change in frequency of T cell subsets, the expression of activation markers, and the CTL response will be evaluated using paired t-test. Correlations between the frequencies of MDSCs and T cell subsets or expression of activation markers will be evaluated using Pearson or Spearman Correlation Coefficients at a specified time points. Alternatively, Intraclass correlation coefficients will be used to assess the potential correlations among those measurements over time.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

VESANOID will be supplied through the University of Colorado Cancer Center's investigational pharmacy. VERSANOID is supplied as 10 mg capsules, two-tone (lengthwise), orange-yellow and reddish-brown and imprinted VERSANOID 10 ROCHE. It is packaged in high-density polyethylene opaque bottles of 100 capsule with child-resistance closure.

Pembrolizumab (200mg dosing Q3 weeks) will be supplied by Merck.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor-Investigator, and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

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9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Returns and Reconciliation

The Sponsor-Investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount of VESANOID and Pembrolizumab dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product (study drug) will be destroyed at the site per institutional policy. It is the Sponsor-Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Ethics and Protection of Human Subjects

10.1.1 Ethical Standard

The PI will ensure that this study is conducted in full conformity with regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56. ICH E6 may also be followed to the extent it has been adopted by and is in accordance with FDA regulations.

10.1.2 Institutional Review Board (IRB)

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Colorado Multiple Institutional Review Board (COMIRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by COMIRB before the changes are implemented to the study. All changes to the consent form will COMIRB-approved.

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10.1.3 Informed Consent Process

10.1.3.1 Informed Consent Form(s) (ICF)

Informed Consent Form(s) (ICF) describing in detail the study drug, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/ administering study drug.

10.1.3.2 Informed Consent Procedures and Documentation

The informed consent process will be initiated prior to the individual's agreeing to participate in the study and continues throughout the subject's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the subjects and their families.

ICFs will be IRB-approved and the subject will be asked to read and review the document. The investigator, or qualified research study personnel, will explain the clinical trial to the subject and answer any questions that may arise. All subjects will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures being done specifically for the study.

The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The study allows the inclusion of non-English speaking and non-reading subjects. Witnesses to these consent processes will be individuals not associated with the trial and will not have a conflict of interest.

10.1.4 Subject and Data Confidentiality

Subject confidentiality is strictly held in trust by the Sponsor-Investigator, their staff, and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor-Investigator.

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The study monitor, other authorized representatives of the Sponsor-Investigator, representatives of the IRB or pharmaceutical company supplying study product or funding may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Colorado Cancer Center. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the University of Colorado Cancer Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Colorado Cancer Center.

10.1.5 Future Use of Stored Specimens

Any remaining specimens will be banked for future studies.

10.2 Data Management and Record Keeping

10.2.1 Clinical Data Collection and Management Responsibilities:

Clinical data collection is the responsibility of the site's clinical trial staff under the supervision of the PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Clinical data will be collected during each visit by the clinical provider and stored in a locked office or cabinet with access limited to the study coordinator and/or data manager. Age, gender, pathologic features of the melanoma, co-morbid conditions, and concomitant medications will be recorded.

All paper form source documents will be recorded neatly and legibly to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL. Clinical data will be used for the initial recording of clinical data. Corrections will be made legibly, initialed, and dated. Correction fluid and covering labels will not be used. Data quality will be monitored by random inspection of the completed forms by a research assistant and any problems will be discussed with the PI.

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10.2.2 Database:

Study data will be collected and managed using OnCore. OnCore is a secure web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages.

The database will be designed and maintained by the University of Colorado Cancer Center Clinical Protocol and Data Management (CPDM) team. The study/data coordinator will enter the data at the conclusion of each clinic visit.

10.2.3 Study Records Retention:

Study documents will be retained per applicable regulations, and/or institution policies. No records will be destroyed without the written consent of the Sponsor-Investigator, if applicable. It is the responsibility of the Sponsor-Investigator to determine when these documents no longer need to be retained.

10.2.4 Unanticipated Problems (UAP) including Protocol Deviations

10.2.4.1 Definition of UAP

This study will use the Office of Human Research Protection (OHRP) definition of a UAP, which considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

10.2.4.2 Definition of Protocol Deviation

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or SOP requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site personnel. As a result of deviations, corrective actions are to be developed by the site in compliance with this protocol and implemented promptly.

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It is the responsibility of the study team to use continuous vigilance to identify and report protocol deviations. All protocol deviations must be addressed in study source documents, and reported as required by COMIRB UAP Reporting Guidelines. The Sponsor-Investigator and study personnel are responsible for knowing and adhering to the IRB requirements. Further details about the handling of protocol deviations may be included in the study procedures manual.

10.2.4.3 Reporting a UAP

The study will follow COMIRB's guidance for UAP reporting and the DSMC's requirements (discussed below). AEs, noncompliance and protocol violations will be recorded and reported as required either promptly (within 5 days of Sponsor-Investigator's knowledge) or at the time of the study's continuing review.

10.3 Data and Safety Monitoring and Oversight

10.3.1 Data Safety Monitoring Committee and Plan

The Sponsor-Investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study subject safety for all clinical studies at the CU Cancer Center, which is the coordinating institution of this trial. A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all serious adverse events (SAEs), unanticipated problems (UAPs) and reportable adverse events (AEs)
- Has the authority to close and/or suspend trials for safety or trial conduct issues
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs, UAPs and reportable AEs are reported to the DSMC, IRB and the Sponsor-Investigator per protocol. All SAEs, UAPs and reportable AEs are to be reported to the DSMC within 5 business days of the investigator receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the investigator and appropriate staff at weekly meetings. Toxicity will be addressed in real time and communicated to the team, then submitted to DSMC as indicated. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed.

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The Sponsor-Investigator will provide a DSM report to the CU Cancer Center DSMC on a six-month basis. The DSM report will include a protocol summary; current enrollment numbers; summary of toxicity data to include specific SAEs, UAPs and AEs; any dose modifications; all protocol deviations; and protocol amendments. The DSM report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this six-month report by the DSMC will then be provided to the Sponsor-Investigator in a DSMC review letter. The Sponsor-Investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review.

10.3.2 Quality Control and Quality Assurance

10.3.2.1 Clinical Monitoring

Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with applicable regulatory requirement(s). Monitoring for this study will be performed by the CU Cancer Center Clinical Monitor on a regular basis, and pursuant to the Clinical Monitoring Plan (CMP), incorporated herein by reference. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports. As necessary, requests for data clarification or correction will be sent to the PI.

10.3.2.2 Independent Auditing.

Independent auditors from the UCCC DSMC will be allowed to audit this study. In addition, audits may be conducted at any time by appropriate regulatory authorities and/or the IRB.

The PI will be notified of any recommendation in order that he may alert all sub-investigators involved in the trial with regard to the action plan.

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11.0 APPENDICES

11.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. 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	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. <i>Am J Clin Oncol</i> 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

11.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (<http://ctep.cancer.gov/reporting/ctc.html>)

11.3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009 Jan;45(2):228-47.

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COMIRB
APPROVED
For Use
23-Oct-2019
23-Jul-2020

Principal Investigator: Martin McCarter, MD

COMIRB No: 16-1080

Version Date: August 14, 2019

Study Title: *Pembrolizumab and All-Trans Retinoic Acid Combination Treatment of Advanced Melanoma*

You are being asked to be in a research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Why is this study being done?

This study plans to learn more about melanoma treatment. Melanoma is one of the few tumors for which immunotherapy can be effective. Pembrolizumab is one type of immunotherapy approved by the Food and Drug Administration (FDA) for first line treatment in metastatic melanoma patients. ATRA is an All-trans retinoic acid and is commercially available Vitamin A derivative that is approved by the FDA as a standard treatment for leukemia. ATRA has also been shown to alter the immune response. ATRA has previously been used to treat different types of cancer; however, the combination of these two drugs for melanoma is considered experimental. We are hoping to learn if the combination of pembrolizumab and ATRA will be effective in treating melanoma.

This study will evaluate the effects of ATRA on tumor-induced immunosuppression. We believe that adding ATRA to standard pembrolizumab therapy will increase patients' responses to the immunotherapy. Throughout the rest of this consent form ATRA will be referred to as the "study drug". The doses of study drug that will be given on this study will start at a higher dose and may be reduced if subjects experience significant side effects. If certain serious or severe side effects are seen, the study will be stopped.

You are being asked to be in this research study because you have advanced melanoma and will receive pembrolizumab therapy as part of your standard melanoma treatment.

Other people in this study

Up to 30 people will participate in the study.

What happens if I join this study?

If you join the study, you will be asked to sign this consent form. You will be given a copy to keep and the original form will be kept at the clinic. You can withdraw from the study at any time and without giving a reason. This will not affect the standard medical care you receive.

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There are three (3) sections to this study:

1. Before starting the study (Screening)
2. During the study (Treatment)
3. Post-treatment (After last dose of ATRA and/or Pembrolizumab)

There are also optional parts of this study. These optional procedures are voluntary and are not required. You can still take part in the main study if you choose not to take part in the optional study procedures. You will be given the choice later in this consent form to decide if you would like to take part in these optional procedures.

This next section is an overview of what will be expected of you, and what you can expect if you take part in this study.

Study Procedures:

Below are the study procedures and schedule of events (when each procedure will take place). Some procedures you receive while taking part in this study are “standard of care procedures” for treatment of your disease.

If you have had some of these procedures recently, they may not need to be repeated.

Some procedures are required only for this research and are called “research procedures”, which are described here.

The time points when these study procedures will take place are specified in the next section called “Study Visits”.

- **Informed Consent** (research)

This informed consent form will be discussed with you and you will be given a copy of this document. If you join the study, you will be asked to sign this consent form before you receive any study related tests or procedures.

- **Medical and Cancer History**

Before you start the study, we will record your date of birth, race, ethnicity, and complete medical history. This history will look at the background and progress of your cancer and any treatments you have received for your disease.

- **Physical Examination**

A physical examination will be completed at the beginning of the study and throughout the duration of the study. After you join the study, we will assess if the study drug is affecting your bodily functions including lungs, heart, abdomen, extremities, skin, head (eyes, ears, noses, hair, etc.), and nervous system.

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- **Blood and Urine Samples**

One of the main components of the study is to collect blood samples for both safety testing and to look at your immune response to the drug combination. These will occur at the study visits as listed in the study visit descriptions later in this form. These tests will consist of some standard of care tests and some research tests and include:

- Pregnancy test - women who are able to become pregnant will be given either a urine or blood pregnancy test. A positive pregnancy test prior to being given the study drugs, will exclude you from starting or continuing to take part in the study.
- Complete blood count (CBC) with differential
- Comprehensive serum chemistry panel
- Thyroid function tests (T3, FT4 and TSH)
- Blood collection - to check for immune response (research)
- Lactase Dehydrogenase (LDH) (research)

Your doctor may order additional blood tests for planning treatment administrations, dose modification, or further evaluation.

- **CT**

A computed tomography scan uses x-rays to make detailed pictures of parts of the body and the structures inside the body.

- **MRI**

Magnetic resonance imaging is a test that uses a magnetic field and pulses of radio wave energy to make pictures of organs and structures inside the body.

- **Vital Signs**

We will collect your vital signs including blood pressure, heart rate, respiratory rate, body temperature and weight per standard of care.

- **Performance Status**

We will assess how well you are performing your daily activities.

- **Review of other medications**

Your study doctor will let you know which other medications you can and cannot take while taking part in this study. You will need to check with the study doctor before taking any new medications. From the time you first receive the study drugs through 30 days after the last dose, we will record other medications you may be taking.

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- **Review Adverse Events**

Some risks have been identified because of the disease process or through use of the study drugs. These are commonly called side effects and will be followed very closely by your doctor and study staff. More information about these will be provided in the Risk section of this consent form.

Study Visits:

1. SCREENING

After signing this consent form you will have the following done to see if you can be in this study:

- Review your medical history
- Review your current medications
- Full physical examination
- Vital signs
- Performance status
- Urine or serum pregnancy test to make sure you are not pregnant for women who can get pregnant (within 72 hours of your first dose of study drug)
- Blood tests – CBC with differential, comprehensive serum chemistry panel and thyroid function test
- Tumor imaging (CT or MRI) will be done
- Tumor tissue collections of archived and recent biopsies

2. TREATMENT

In addition to your standard treatment with pembrolizumab, all patients will also receive treatment with ATRA (both study drugs provided by Merck). The study drugs will be given on a 3 week treatment cycle.

Pembrolizumab:

You will receive an intravenous (IV) treatment of pembrolizumab every three weeks. You will receive a dose (200 mg) on the first day of each cycle.

ATRA:

You will receive an oral dose of ATRA every three weeks. You will receive three doses of 150 mg/m² at the beginning of the first four cycles. ATRA treatments will be given twice a day:

- on the day before pembrolizumab infusion (Day -1)
- the day of pembrolizumab infusion (Day 0)
- the day after pembrolizumab infusion (Day 1)

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Day -1 of treatment cycle 1

- You will be dispensed your ATRA supply for cycle 1 and receive a drug diary to record dosing information

Day 0 of treatment cycle 1

- Review of medications you are taking
- Review of Adverse Events (AEs)
- Directed physical examination
- Performance Status
- Vital signs including weight
- Blood tests – CBC with differential, comprehensive serum chemistry panel and thyroid function test
- You will take your Day 0 dose of ATRA once instructed and receive your pembrolizumab infusion
- You will be dispensed your ATRA supply for cycle 2 and receive a new drug diary to record dosing information

Day 0 of treatment cycle 2

- Review of medications you are taking
- Review of AEs
- Directed physical examination
- Performance Status
- Vital signs including weight
- Blood tests – CBC with differential and comprehensive serum chemistry panel
- Research blood samples
- You will return your drug bottles and diary from cycle 1
- You will take your Day 0 dose of ATRA once instructed and receive your pembrolizumab infusion
- You will be dispensed your ATRA supply for cycle 3 and receive a new drug diary to record dosing information

Day 0 of treatment cycle 3

- Review of medications you are taking
- Review of AEs
- Directed physical examination
- Performance Status
- Vital signs including weight
- Blood tests – CBC with differential, comprehensive serum chemistry panel and thyroid function test
- You will return your drug bottles and diary from cycle 2
- You will take your Day 0 dose of ATRA once instructed and

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receive your pembrolizumab infusion

- You will be dispensed your ATRA supply for cycle 4 and receive a new drug diary to record dosing information

Day 0 of treatment cycle 4

- Review of medications you are taking
- Review of AEs
- Directed physical examination
- Performance Status
- Vital signs including weight
- Blood tests – CBC with differential and comprehensive serum chemistry panel
- Research blood samples
- You will return your drug bottles and diary from cycle 3
- You will take your Day 0 dose of ATRA once instructed and receive your pembrolizumab infusion

Day 0 of treatment cycle 5+

- Review of medications you are taking
- Review of AEs
- Directed physical examination
- Performance Status
- Vital signs including weight
- Blood tests – CBC with differential and comprehensive serum chemistry panel
- Research blood samples will be collected within 60 days of last ATRA dose
- Thyroid function test will be collected every other cycle per standard of care for clinic
- Tumor imaging (CT or MRI) will generally be performed every 12 weeks per standard of care for clinic
- You will return your drug bottles and diary from cycle 4 at the cycle 5 day 0 visit
- You will continue to receive pembrolizumab infusions as long as you are receiving benefit or up to 2 years

3. AFTER TREATMENT FOLLOW-UP

End of Treatment (EOT) +/-7 days

- Review of medications you are taking
- Review of AEs
- Performance Status
- Post-study therapy status
- Tumor Imaging

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Safety Follow-up Visit (30 days after last treatment or prior to starting new treatment):

- Review of medications you are taking
- Review of AEs
- Directed physical exam
- Vital signs including weight
- Research blood samples will be collected within 60 days of last ATRA dose
- Post-study therapy status
- Survival status
- Archival tissue collection for newly obtained tissue - optional

Safety Follow-up Visit (90 days after last treatment unless a new anti-cancer treatment was initiated, can be collected at a regularly scheduled clinic visit or by telephone):

- Review of medications you are taking
- Review of AEs
- Post-study therapy status
- Survival status
- Archival tissue collection for newly obtained tissue - optional

Survival Follow-up Visit (every 12 weeks until end of study, can be collected at a regularly scheduled clinic visit or by telephone):

- Review medications you are taking
- Post-study therapy status
- Survival status
- Archival tissue collection for newly obtained tissue - optional

Optional Data and Specimen Banking for Future Research

Dr. Martin McCarter would like to collect archival tissue and some of the data, blood and tissue that is taken during the study but is not used for other tests. If you agree, the data and samples will be kept and may be used in future research to learn more about melanoma. The research that is done with your data and samples is not designed to specifically help you. It might help people who have melanoma and other diseases in the future. Reports about research done with your data and samples will not be given to you or your doctor. These reports will not be put in your health records. The research using your data and samples will not affect your care.

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The choice to let Dr. McCarter keep the data and samples for future research is up to you. No matter what you decide to do, it will not affect the care that you will receive as part of the study. If you decide now that your data and samples can be kept for research, you can

change your mind at any time and contact your study doctor to let him or her know that you do not want Dr. McCarter to use your data and samples any longer, and they will no longer be used for research. Otherwise, they may be kept until they are used up, or until Dr. McCarter decides to destroy them.

When your data and samples are given to other researchers in the future, Dr. McCarter will not give them your name, address, phone number or any other information that will let the researchers know who you are.

Sometimes data and samples are used for genetic research (about diseases that are passed on in families). Even if your data and samples are used for this kind of research, the results will not be told to you and will not be put in your health records. Your data and samples will only be used for research and will not be sold. The research done with your data and samples may help to develop new products in the future, but there is no plan for you to be paid.

Please read each sentence below and think about your choice. After reading each sentence, check “yes” or “no” and initial next to your selection. If you have questions, please talk to your doctor or nurse. Remember, no matter what you decide to do about the storage and future use of your data and samples, you may still take part in the study.

I give my permission for my data, blood and tissue to be stored in a central tissue bank at the University of Colorado Cancer Center for future use by the study investigators:

1. I give my permissions for my data, blood and tissue samples taken during the study to be kept by Dr. McCarter for use in future research to learn more about how to prevent, detect, or treat melanoma.
☐ Yes ☐ No _____Initials
2. I give my permissions for my archival tissue samples to be kept by Dr. McCarter for use in future research to learn more about how to prevent, detect, or treat melanoma.
☐ Yes ☐ No _____Initials

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3. I give my permissions for my data, blood and tissue samples to be used for research about other health problems (for example: causes of heart disease, osteoporosis, and diabetes).
☐ Yes ☐ No _____ Initials
4. I give my permission for my study doctor (or someone he or she chooses) to contact me in the future to ask me to take part in more research.
☐ Yes ☐ No _____ Initials

How long will I be in the study?

Your study participation is expected to last at least 2 years. The amount of time you participate in this study will depend on how your disease responds and how you tolerate the treatment. You will continue in the study until there is evidence that your disease has relapsed, your side effects are too severe, you request to stop participation, the study doctor feels that you will not benefit from further dosing, you do not follow the study instructions, or (for women) you become pregnant.

What are the possible discomforts or risks?

As with any study drug, side effects may occur when taking this study drug. While taking part in this study, and being treated with the study drugs, you will be watched carefully for any side effects. Some side effects may go away after you stop taking the study drug. Some side effects can be long lasting and may never go away or may even lead to death.

You should talk to your study doctor about any side effects or discomfort you may have. The study doctor may give you some medicine that will help with some side effects. The study doctor may also interrupt or discontinue the study drug.

You will be notified by your study doctor of any new side effects seen in other patients that occur during the time you are on the study. This may affect you wanting to continue in this research study.

Based on animal studies and/or other studies with similar types of drugs, side effects or discomforts you may experience while in this study include:

Risks of Pembrolizumab (KEYTRUDA)

Pembrolizumab, which is approved in the USA and some other countries, is available by prescription to treat several different cancers, but may not be approved to treat your type of cancer.

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Pembrolizumab works by helping your immune system to fight your cancer.

However, pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects. These side effects may be serious (i.e. causing hospitalization or be life-threatening), may result in death, and/or may occur after you stop taking pembrolizumab. These side effects can affect more than one of your normal organs and tissues at the same time.

VERY COMMON, SOME MAY BE SERIOUS (i.e. causing hospitalization, **life-threatening** or where noted, may cause **death**) – occurring in more than 20 people out of 100 people:

- Itching of the skin
- Loose or watery stools
- Cough

COMMON, SOME MAY BE SERIOUS (i.e. causing hospitalization, **life-threatening**, or where noted, may cause **death**) occurring in at least 5 but less than 20 people out of 100 people:

- Joint pain
- Rash
- Fever
- Back pain
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, have infrequent or hard stools
- Low level of salt in the blood that may cause you to feel tired, confused, headache, muscle cramps or upset stomach

UNCOMMON, SOME MAY BE SERIOUS - i.e. causing hospitalization, **life-threatening**, or where noted, may cause **death**) – occurring in at least 1 to less than 5 people out of 100 people:

- Inflammation of the lungs so you may feel short of breath and cough. Rarely this might lead to **death**.
- Too much thyroid hormone so you may feel anxious, angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools
- Infusion reaction, where you may feel dizzy or faint, flushed, get a rash, have a fever, feel short of breath, experience a decrease in your blood pressure at the time of receiving your infusion (IV) or just after, or pain at the site of infusion

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- Inflammation of the bowels/gut that can cause severe stomach pain with loose or watery stools, or stools that are black, tarry, sticky or stools with blood or mucus
- A condition called Stevens Johnson Syndrome (SJS) or Toxic Epidermal Necrosis (TEN). This condition involves inflammation of the skin, which may cause peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e. peeling, itching and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body, which can cause severe infection. These severe conditions can rarely lead to **death**.

RARE, SOME MAY BE SERIOUS (i.e. causing hospitalization, **life-threatening**, or where noted, may cause **death**) – in less than 1 out of 100 people:

- Inflammation of the nerves that may cause
 - Pain
 - Weakness or tingling in the hands and feet, and may spread to the legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis
- Inflammation of the muscles so you may feel weak or have pain in the muscles, sometimes referred to as myasthenic syndrome
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels)
 - Severe pain in the top part of your belly that may move to the back
 - Sick to your stomach
 - Vomiting that gets worse when you eat
- Inflammation of the eye
 - Redness of the eye
 - Blurred vision
 - Sensitivity to light
 - Have eye pain
 - See floaters
 - Have headaches
- Inflammation of the liver
 - Upset stomach and vomiting
 - Feel like not eating
 - Feel tired
 - Mild fever
 - Pain in the right side of your belly
 - Yellow eyes and skin
 - Dark urine
- Inflammation of the pituitary gland (a gland in the head)
 - Headaches

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- Upset stomach
 - Changes in behavior
 - Double vision
 - Few to no menstrual cycles
 - Weakness
 - Vomiting
 - Dizziness or fainting
- Adrenal glands (glands on top of the kidneys) may not produce enough hormone
 - Tiredness
 - Weight loss
 - Muscle weakness
 - Feeling faint
 - Joint, muscle and belly aches
 - Nausea
 - Vomiting
 - Loose or watery stools
 - Fever
 - Salt craving
 - Darkening of the skin like a suntan
- Type 1 Diabetes, a condition that can cause too much sugar in the blood which may make you:
 - Feel thirstier than usual
 - Frequent urination
 - Weight Loss
 - May need regular insulin shots
- Inflammation of the kidney, you may:
 - pass less urine
 - have cloudy or bloody urine
 - swelling
 - low back pain
- Inflammation of the middle layer of your heart (myocarditis)
 - Difficulty pumping blood throughout your body
 - Chest pain
 - Shortness of breath
 - Swelling of the legs
 - Fast or irregular heartbeat (that may cause dizziness or fainting)
 - **Death**
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your:
 - heart rate
 - blood pressure
 - body temperature

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- metabolism (the rate at which food is converted into energy)
- A condition that may make you feel weak and tired and might have drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing
- Formation of small clusters of immune cells (granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs
- Inflammation of the brain which may include:
 - Confusion
 - Fever
 - Disorientation
 - Memory problems
 - Seizures (fits)
 - Changes in personality and behavior
 - Difficulty speaking
 - Weakness or loss of movement in some parts of your body
 - Loss of consciousness

Additionally, since pembrolizumab was approved in September 2014, the following side effects have been reported by people receiving pembrolizumab. These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of this side effect:

- Inflammation of the joints which may include joint pain, stiffness and/or swelling
- Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin and brain. This may include fever, rash, inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures, and even coma.

Risks of ATRA

ATRA is approved by the Food and Drug Administration for the treatment of leukemia. Patients with acute promyelocytic leukemia (APL) treated with ATRA every day for many weeks at a time reported the following:

In this study, you will receive a higher dose of ATRA for a shorter period of time than patients with APL. The most common side effect of ATRA treatment is a limited headache that typically resolves when ATRA treatment stops.

COMMON SIDE EFFECTS – in 30 people out of 100 people

- Which may include the following symptoms:
 - Headache
 - Fever

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- Dry skin
- Dry mouth and nose
- Bone pain
- Nausea and vomiting
- Rash
- Mouth sores
- Itching
- Sweating
- Eyesight changes
- Flu-like symptoms such as malaise and chills
- Bleeding problems
- Vulnerability to infections
- Swelling of feet or ankles
- Bone and joint pain
- Chest discomfort
- Abdominal pain

LESS COMMON SIDE EFFECTS – in 10 to 29 people out of 100 people

- Weight increase
- Heart rate irregularities
- Flushing
- Poor appetite
- Weight loss
- Earache or feeling of fullness in the ears
- Diarrhea
- Dizziness
- Constipation
- Numbness and tingling in hands and feet
- Anxiety
- Heartburn
- Low blood pressure
- Insomnia
- Depression
- High blood pressure
- Confusion

RARE BUT SERIOUS SIDE EFFECTS – in 3 people out of 100 people

- Brain disease, damage, or malfunction (encephalopathy)
- Cardiac arrest
- Inflammation of the blood vessels (vasculitis)
- Neurologic reaction
- Stroke

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Risks of Having an IV Inserted in Your Vein

In this study, we will insert a needle, connected to a plastic tube, into a vein in your arm. You will feel some pain when we first insert the tube into your vein. You may have some redness, swelling, or bruising where the tube goes under your skin. In some cases, this type of tube can cause an infection where it goes under the skin. In rare cases, it can cause a blood clot in the vein.

Risks of Having Blood Taken

In this study, depending on study visit, we will need to get about $\frac{3}{4}$ of a cup (24 tubes) of blood from you over the course of the study. We will get blood by putting a needle into one of your veins and letting the blood flow into a vacuum tube. You may feel some pain when the needle goes into your vein. A day or two later, you may have a small bruise where the needle went under the skin.

Computed Tomography (CT) Risk

As part of this study, we will perform a CT scan. CT is a way of taking detailed pictures inside your body by using X-rays. X-rays are a type of radiation.

You get some radiation from your environment. You get radiation from bricks and concrete, from some foods, and from radon gas, which is an invisible gas that seeps out of the ground. The amount of radiation that this CT scan will deliver to your body (give you) is about the same as you would get from living in your environment. This is an estimate.

The amount of radiation you get could be higher or lower, depending on the machine, the power setting, and your body weight. Exposure to radiation at high levels increases a risk of developing cancer. There is no evidence of such risks for diagnostic procedures.

Risks of Having an MRI

In this study, we will take Magnetic Resonance Images (MRI's) of your affected area. The MRI machine uses powerful magnetic waves to take pictures inside the body. The waves themselves are not harmful, but they can cause metal to heat up and electronics to stop working. **You should NOT have an MRI if you have metal or electronic devices inside your body. Heart pacemakers and insulin pumps are examples of electronic devices.**

The MRI machine is a small round tube. It might make you uncomfortable if you do not like tight spaces.

The most common side effect of having an MRI is flashing lights in the eyes. This is caused by the magnetic waves and is not harmful. Some people also experience

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warmth and reddening of the skin. This usually goes away after a few minutes.

If you are pregnant, be sure to tell the person giving you the MRI.

Risk of Loss of Confidentiality

There is a risk that people outside of the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

Reproductive Risks

The use of the study drugs in pregnant females and nursing mothers has not been studied. The effects of the study drugs on human eggs and sperm has not been studied. The risks to a human fetus are unknown. However, based on the way the drugs work, it cannot be ruled out that there is potential for the study drugs to cause birth defects in humans. If the study drugs are taken during pregnancy, they may cause birth defects or death to an unborn baby.

Females must not become pregnant while taking the study drugs. Women who are able to get pregnant must use effective birth control while taking pembrolizumab and for at least 4 months after the last dose of pembrolizumab.

Before you begin study treatment, your doctor will discuss acceptable forms of birth control with you.

The study may also include risks that are unknown at this time.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about the effects of Pembrolizumab and the study drug on your disease. However, there is no guarantee that your health will improve if you join this study. Also, there could be risks to being in this study. If there are risks, these are described in the section describing the discomforts or risks.

Are there alternative treatments?

There may be other ways of treating your Melanoma. These other ways include:

- You may choose to receive treatment with another experimental therapy
- You may choose to receive treatment with another approved therapy
- You may choose to receive comfort/palliative care
- You could also choose to get no treatment at all

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You should talk to your doctor about your choices. Make sure you understand all of your choices before you decide to take part in this study. You may leave this study and still have these other choices available to you.

Who is paying for this study?

Merck is providing funding support for this trial. This research is being sponsored by the University of Colorado Cancer Center.

Dr. Karl Lewis (investigator) has a significant financial interest due to his role as an Advisory Board Member with Merck & Co., Inc.. Merck & Co., Inc. is the sponsor of this study and the manufacturer of one of the study drugs (pembrolizumab).

Dr. Rene Gonzalez (investigator) and Dr. Karl Lewis (investigator) have financial interests with Roche/Genetech. Roche/Genetech is the manufacturer of one of the study drugs (ATRA). Please feel free to ask any questions you have about this matter.

Will I be paid for being in the study?

You will not be paid to be in the study.

Will I have to pay for anything?

Merck will pay for the cost of the Pembrolizumab, ATRA and research blood work. The sponsor will also pay for any tests or procedures that are related to the research study.

You will need to pay for any tests and procedures that are considered standard of care. These include the CT scans, MRIs and some clinic visits and laboratory tests. You may be responsible for co-payments and deductibles that are standard for your insurance coverage.

Ask your study doctor to discuss the costs that will or will not be covered by the sponsor. This discussion should include the costs of treating possible side effects. Otherwise, you might have unexpected expenses from being in this study.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

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If you leave this study, you will still receive your normal medical care. The only medical care that you will lose is the medical care you are getting as part of this study. You might be able to get that same kind of medical care outside of the study. Ask your study doctor.

If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

Can I be removed from this study?

The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason. Also, the sponsor may stop the study at any time.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study you should call your study investigator immediately. Dr. Martin McCarter's phone number is (303) 724 2728. You may also call Dr. Schuster at 970-493-6337, Dr. Rene Gonzalez at (720) 848-0564 or Dr. Karl Lewis at (720) 848-0584.

If you are hurt by this research, we will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Who do I call if I have questions?

The researcher carrying out this study is Martin McCarter, MD. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Dr. McCarter at (303) 724-2728 or Dr. Schuster at (970)493-6337. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Dr. McCarter at (303) 724-2728 or Dr. Schuster at (970) 493-6337 with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at (303) 724-1055.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who will see my research information?

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The University of Colorado Denver (UCD) and its affiliated hospital(s) have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy.

This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver
- University of Colorado Hospital
- University of Colorado-North Poudre Valley Hospital

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the UCD and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

*Martin McCarter, MD
University of Colorado Denver Anschutz Medical
Campus 12631 E. 17th Avenue, Mail Stop C325
Aurora, CO 80045*

*Steven Schuster, MD
UCH-North Poudre Valley Hospital
2121 E. Harmony Road, Suite 170*

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Fort Collins, CO 80528

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB).
- The study doctor and the rest of the study team.
- Merck who is the company paying for this research study.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals, but we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator.

The investigator (or staff acting on behalf of the investigator) will use your information for the research outlined in this consent form. They will also make *all or some* of the following health information about you collected in this study available to:

Merck - the company providing Pembrolizumab and VESANOID and QualTek laboratories for biomarker analysis.

Some of the research procedures involve genetic testing or the use of your genetic information. Your genetic information will not be released to others.

Information about you that will be seen, collected, used and disclosed in this study:

- Name and Demographic Information (age, sex, ethnicity, address, phone number, etc.
- Portions of your previous and current Medical Records that are relevant to this study, including but not limited to Diagnosis(es), History and Physical, laboratory or tissue studies, radiology studies, procedure results
- Research Visit and Research Test records
- Tissue samples and the data with the samples.

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- Billing or financial information

What happens to Data, Tissue, Blood and Specimens that are collected in this study?

Scientists at the University of Colorado Denver and the hospitals involved in this study work to find the causes and cures of disease. The data, tissue, blood and specimens collected from you during this study are important to this study and to future research. If you join this study:

- The data, tissue, blood, or other specimens given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study your data, tissue, blood, or other specimens collected from you.
- If data, tissue, blood, or other specimens are in a form that identifies you, UCD or the hospitals involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

HIPAA Authorization for Optional Additional Study Procedures –

In this form, you were given the option to agree to additional, optional research procedures. You must also give us your permission, under HIPAA rules, to use and disclose the information collected from these optional procedures, as described above.

Some of these optional procedures may involve genetic testing or the use of your genetic information. Your genetic information will not be released to others.

If you decline to give us permission to use and disclose your information, you cannot take part in these optional procedures, but you can still participate in the main study. Please initial next to your choice:

_____ I give permission for my information, from the optional procedures I have agreed to above, to be used and disclosed as described in this section.

_____ I **do not** give permission for my information for any optional procedures to be used and disclosed; I understand that I will not

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participate in any optional procedures.

Agreement to be in this study and use my data

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study: I will get a signed and dated copy of this consent form.

Signature: _____ Date: _____

Print Name: _____

Consent form explained by: _____ Date: _____

Print Name: _____

A signature line for a witness is required for consent of non-reading subjects and consent using a short form.

Witness Signature: _____ Date: _____

Witness Print Name: _____

Witness of Signature

Witness of consent process: _____