Mayo Clinic Cancer Center

Pilot study to test the safety and efficacy of the combination of imiquimod and pembrolizumab for the treatment of metastatic melanoma.

Study Chair: [redacted]

Statistician: [redacted]

√Study contributor(s) not responsible for patient care.

Drug Availability

Commercial Agents: Imiquimod
Drug Company Supplied: Pembrolizumab

Document History	
Activation	12/20/2017
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Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted]
Drug administration, infusion pumps, nursing guidelines	[redacted]
Forms completion and submission	[redacted]
Protocol document, consent form, regulatory issues	[redacted]
Serious Adverse Events	[redacted]

*No waivers of eligibility per NCI

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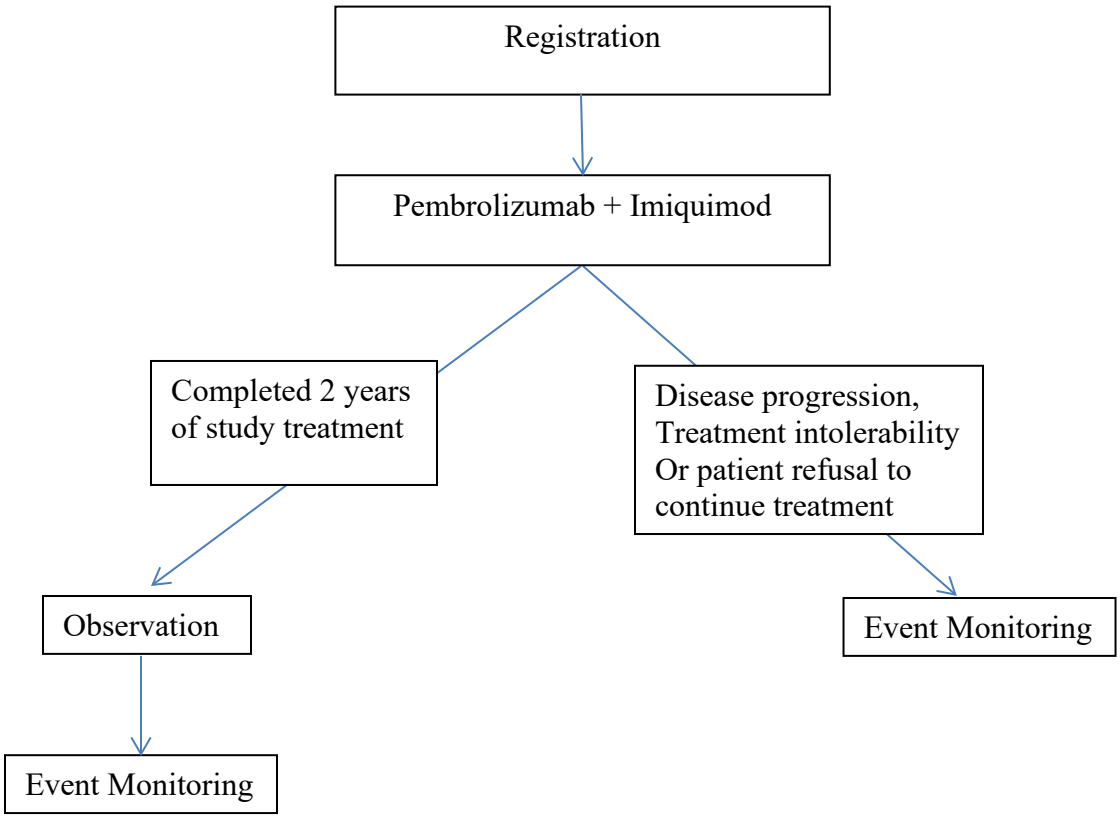
Schema



Generic name: Pembrolizumab Brand name(s): Keytruda Mayo Abbreviation: MK-3475 Availability: Investigational	Generic name: Imiquimod Brand name(s): Aldara Mayo Abbreviation: IMQ Availability: Commercial

1.0 Background

1.1 Melanoma is the fifth most common cancer in men and sixth most common in women in the United States with an estimated ten thousand deaths a year. Recent advances in systemic therapy for metastatic melanoma have dramatically improved outcomes; however, the majority of patients ultimately die from their disease.

1.2 One of the major breakthroughs for the treatment of metastatic melanoma is the immunotherapy pembrolizumab (MK-3475). Pembrolizumab has demonstrated dramatic clinical activity in patients with metastatic melanoma inducing response rates in ~20-40% of patients. In addition, the majority of these responses are durable which will likely result in significant improvement in long-term survival for patients. Despite the success of pembrolizumab in a large minority of patients, the majority of patients ultimately go on to progress and require additional therapy.

1.3 Approximately 20-30% of patients with metastatic melanoma have metastatic cutaneous lesions that are amenable to treatment with the combination of systemic therapy with topical or injectable therapy.

1.4 Pharmaceutical and Therapeutic Background on Pembrolizumab

1.41 The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

1.42 The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD 1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown

during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

1.43 Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

1.5 Pharmaceutical and Therapeutic Background on Imiquimod

1.51 Imiquimod is a toll-like receptor seven (TLR7) agonist that activates the innate arm of the immune system. Imiquimod stimulates immune cells to secrete pro-inflammatory cytokines such as interferon-α (IFN-α), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). Cells activated by imiquimod include natural killer cells, macrophages and B-lymphocytes. Overall imiquimod acts on several levels, which appear to synergistically underlie the profound antitumoral activity of the compound. (1)

1.6 Preclinical and clinical Trial Data

1.61 The clinical trial data for pembrolizumab for the treatment of patients with metastatic melanoma has been previously published in detail. In summary, pembrolizumab induces durable remissions in a sizable minority of patients with metastatic melanoma (20-40%) with an acceptable safety profile of less than 10% grade 3 or 4 adverse events.

1.62 Imiquimod is a toll-like receptor 7 (TLR7) agonist approved for the treatment of basal cell carcinoma and genital warts. Imiquimod was tested in a randomized phase three study of patients with superficial basal cell carcinoma. (2) In this study, imiquimod induced histologic clearance in 80% of patients compared with 3% in the control arm with less than 10% of patients experiencing a severe (grade 3 or 4) adverse event. In the setting of genital warts, imiquimod 5% cleared 72-

84% of warts with a complete remission rate of 40-70% with few recurrences (5-19%). (3)

1.63 There are several reports demonstrating the clinical activity of imiquimod in treating cutaneous melanoma. In 2000, imiquimod 5% induced a complete remission in one patient with lentigo maligna melanoma. [1] In 2002, topical imiquimod 5% induced a complete remission in a patient with invasive melanoma however the patient did eventually develop lymph node metastases. [2] Also in 2002, Bong et al reported 3 patients with cutaneous metastases treated topical imiquimod with excellent responses in 2/3 of patients with the third patient achieving a response when combining imiquimod with intra-lesional interleukin-2. [3] Taken together, topical imiquimod is effective at controlling some patients with cutaneous melanoma but not at preventing distant metastases.

1.64 Topical imiquimod certainly has clinical activity in cutaneous melanoma metastases, however, often times additional immune modulation is necessary to achieve a complete response or prevent distant spread. With this in mind, Green et al performed a phase 1/2 study combining imiquimod with intralesional interleukin-2 in 13 patients demonstrating an overall response rate of 50% and complete response rate of 40%. [4] In a separate study, the combination of imiquimod 5% with BCG demonstrated complete remissions in 2 out of 3 patients. [5] In another case series of 11 patients with in-transit melanoma, 100% of patients responded to a combination of intra-lesional IL-2, imiquimod, and a topical retinoid. [6] Taken together, there is ample evidence that imiquimod is an effective at treating local cutaneous melanoma metastases however there are high rates of distant failure providing the rational for combining imiquimod with systemic therapy.

1.7 Rationale

1.71 Approximately 20% of patients with metastatic melanoma are burdened with surgically unresectable cutaneous disease. The standard of care for these patients is systemic therapy as there are no FDA approved agents to apply directly to the skin. While systemic therapy can sometimes generate response in patients' cutaneous lesions, a topical therapy that could assist the systemic therapy would be highly desirable.

1.72 Multiple topical agents have been utilized to treat cutaneous melanoma with variable success. Imiquimod is a topical immune modulator thought to activate the toll-like receptor (TLR) pathway and help the body produce interferon locally to increase the activity of the immune system. Imiquimod is approved for the use of variety of skin disorders including basal cell carcinoma, actinic keratosis, and genital warts. Several studies have explored the efficacy of imiquimod to treat cutaneous melanoma and have demonstrated activity. There are no studies combining the use of imiquimod with pembrolizumab.

1.73 A case series reports successfully treated two patients with the combination of ipilimumab and imiquimod[7]. In both patients, cutaneous tumors substantially grew while on ipilimumab only to regress after the addition of imiquimod. Both patients tolerated the combination well and both patients have a durable remission of 9-12 months.

1.8 Rationale for Trial and Selected Subject Population

1.81 Despite recent improvement in the treatment of metastatic melanoma, the majority of patients still die from their disease providing a clear need to improve upon current treatments.

1.82 More specifically anti-PD1 agents such as pembrolizumab are capable of stimulating the patient's immune system by inhibiting the PD1/PDL1 axis. Given the ability of pembrolizumab to stimulate the patient's immune system, combining pembrolizumab with additional immune stimulation has the potential to provide additive or synergistic benefit when compared to single agent pembrolizumab.

1.83 Patients with metastatic melanoma and cutaneous metastases provide a unique opportunity to combing both topical and systemic therapy. We have previously demonstrated that the combination of imiquimod and ipilimumab is both safe and effective in two patients (under review).

1.84 The potential benefit of the combination of imiquimod and pembrolizumab remains to be tested in controlled studies.

1.9a Rationale for Fixed Dose of Pembrolizumab

1.9a1 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.

1.9a2 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.

1.9b Rationale for dose of Imiquimod

The dose of imiquimod 5% applied Monday-Friday was selected on the basis of previous clinical studies demonstrating acceptable toxicity and efficacy profile in other skin conditions.

1.9c Rationale for Clinical Endpoints

1.9c1 As mentioned above, this is a pilot study to test both the safety and efficacy of the combination of pembrolizumab and imiquimod. Both safety and efficacy will be assessed individually.

1.9c11 Clinical Efficacy Endpoint- The expected single agent response rate of pembrolizumab is ~40% in the front line setting and ~25% when given after progression on ipilimumab. Given the small number of patients to be enrolled onto this trial, we will construct a 90% confidence interval for the proportion of patients who have a CR or PR on two consecutive evaluations at least 6 weeks among all the patients enrolled on this trial.

1.9c12 Clinical Safety Endpoint - Given the non-overlapping toxicities of pembrolizumab and imiquimod, we expect serious toxicities to occur at a rate similar to each drug individually. For example, pembrolizumab induces serious adverse events in ~10% of patient and imiquimod induces serious adverse events in 1-3% of patients. Therefore we expect ~10-13% of patient to experience a serious adverse event.

1.9d Biomarker Research

One of the largest unmet needs in improving the therapeutic potential of pembrolizumab is identifying reliable predictive biomarkers. In this study, the biomarker research will be exploratory in nature and will include assessing total tumor RNA through RNA seq and PDL1 expression through the use of immunohistochemistry. Attempts will then be made to associate molecular markers with clinical outcomes.

2.0 Goals

2.1 Primary

To gain preliminary data of the anti-tumor activity and safety profile of the combination of imiquimod and pembrolizumab in patients with unresectable cutaneous melanoma.

2.3 Correlative Research

To compare and contrast (in a hypothesis generating manner) the biomarker profiles of patients who have a confirmed CR or PR by RECIST criteria with patients who do not. Immunologic markers to be assessed include tumor-infiltrating lymphocytes (TIL), tumor expression of programmed death ligand one (PDL1), and toll-like receptor 7.

3.0 Patient Eligibility

3.1 Registration – Inclusion Criteria

3.11 Age ≥18 years.

3.12 Histological confirmation of Stage IIIB, IIIC, IVM1a, IVM1b, or IVM1c that is not suitable for surgical resection.

3.13 Patients must not have received prior pembrolizumab or other anti-PD1/PDL1 therapies for their metastatic disease.

3.14 At least one cutaneous lesion that is amenable to treatment with topical imiquimod.

3.15 Measurable disease by RECIST as defined in Section 11.0.

3.16 ECOG Performance Status (PS) of 0 or 1 (Appendix I).

3.17 The following laboratory values obtained ≤14 days prior to registration.

- Absolute neutrophil count (ANC) ≥1500/mm^3
- Platelet count ≥100,000/mm^3
- Hemoglobin >9.0 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment).
- Serum total bilirubin ≤ 1.5 X ULN or Direct bilirubin ≤ (ULN) for subjects with total bilirubin levels > 1.5 ULN
- Aspartate transaminase (AST) ≤2.5 x ULN or ≤ 5 x ULN for subjects with liver metastases.
- Albumin ≥2.5mg/dL
- Creatinine ≤1.5 X upper limit of normal (ULN)
  NOTE: Measured or calculated (per institutional standard) creatinine clearance is acceptable ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN. Calculated creatinine clearance can be used in place of creatinine or CrCl and must be ≥45 ml/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:

Creatinine clearance for males = $\dfrac{\textbf{(140 - age)(weight in kg)}}{\text{(72)(serum creatinine in mg/dL)}}$

Creatinine clearance for females = $\dfrac{\textbf{(140 - age)(weight in kg)(0.85)}}{\textbf{(72)(serum creatinine in mg/dL)}}$

3.18 Negative urine or serum pregnancy test done ≤72 hours prior to first treatment, for women of childbearing potential only.

If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

3.19a Provide informed written consent.

3.19b Willing to return to enrolling institution for follow-up.

3.19c Willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion in appropriate low risk cutaneous lesions.

NOTE: If the tissue biopsy is deemed to be of increased risk for the patient, the biopsy should not be performed and is optional.

NOTE: Newly-obtained is defined as a specimen obtained up to 42 days prior to registration where no anti-cancer therapy after the specimen was obtained and registration.

3.2 Registration – Exclusion Criteria

3.21 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

NOTE: Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy. Abstain from heterosexual activity is also acceptable method of contraception for males.

3.22 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.23 Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

3.24 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.25 Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm or used an investigational device ≤ 4 weeks from registration.

3.26 History of myocardial infarction ≤6 months, or congestive heart failure requiring use of ongoing maintenance therapy for life-threatening ventricular arrhythmias.

3.27 Known history of active TB (Bacillus Tuberculosis)

3.28 Hypersensitivity to pembrolizumab or any of its excipients.

3.29a Prior anti-cancer monoclonal antibody (mAb) ≤ 4 weeks prior to registration or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks prior to registration

3.29b Prior chemotherapy, targeted small molecule therapy, or radiation therapy ≤ 2 weeks prior to registration or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

Note: Subjects with ≤ 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.

3.29c Known secondary malignancy that has progressed within the last 3 years 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.

3.29d Known central nervous system (CNS) metastases and/or carcinomatous meningitis.

3.29e 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 (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

3.29f History of (non-infectious) pneumonitis that required steroids or current pneumonitis.

3.29g Active infection requiring systemic therapy.

3.29h 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.

3.29i Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

3.29j Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

3.29k Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

3.29l Received a live vaccine ≤30 days prior to registration.

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.

4.0 Test Schedule

Tests and Procedures	≤28 Days prior to Registration	Day 1 (+/-3 days) of each cycle	End of Treatment	Observation	
				Every 12 (+/-2) weeks for months 24 thru 36 post registration	at progression
History and Physical Examination, wt, PS	X	X	X	X	X
Height	X				
Adverse Events Assessment	X	X	X	X	X
Pregnancy Test – Urine or Serum –HCG[1]		X[6]			
CBC w/diff	X[2]	X	X	X	X
Renal Profile: Sodium, Potassium, Chloride, Bicarbonate, Creatinine, Bun, Glucose	X[2]	X	X	X	X
Albumin, bilirubin total and direct, alkaline phosphatase, total protein, AST, and ALT	X[2]	X			
FT4 and TSH	X	X	X		
Disease Evaluation[3]	X	X[4]	X	X	X
Research Tissue Collection[R]		X[5]			
Photograph of lesions	X	X	X	X	X

1. For women of childbearing potential only. Must be done ≤72 hours prior to registration.
2. ≤14 Days prior to Registration
3. Radiographic tumor imaging assessments must include CT scan, PET/CT, or MRI of the chest, abdomen, and pelvis. CT scan or MRI of the brain with contrast will only be performed if symptoms or signs of CNS metastasis are present. Use same imaging throughout the study.
4. At the completion of cycle 4 (approximately week 12) and then at completion of every 4th cycle (approximately every 12 weeks) thereafter (±7days) until PD.
5. Tissue specimens must be collected and submitted after registration but prior to the start of treatment, at completion of cycles 2 and 4 (approximately weeks 6 and 12).
6. For women of childbearing potential only. Must be done ≤ 72 hours prior to start of treatment. Must be repeated if pre-registration test is > 72 hours prior to the start of treatment.

R Research funded (see Section 19.0)

4.1 Event Monitoring/Survival Follow-up

	Event Monitoring Phase[1]				
	q. 6 months until PD	At PD	After PD q. 6 months	Death	New Primary
Event Monitoring	X	X	X	X	At each occurrence

1. If a patient is still alive 3 years after registration, no further follow-up is required.

5.0 Stratification Factors OR Grouping Factor:

None

6.0 Registration/Randomization Procedures

6.1 To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [redacted] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted] If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.2 Correlative Research.

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19c and 17.1*)*.

6.3 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office [redacted] If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.4 Prior to accepting the registration, registration application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.5 At the time of registration, the following will be recorded:
- Patient has/has not given permission to store and use his/her sample(s) for future research of melanoma at Mayo Clinic.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.

6.6 Treatment cannot begin prior to registration and must begin ≤ 14 days after registration.

6.7 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.8 All required baseline symptoms (see Section 10.6) must be documented and graded.

6.9a Treatment on this protocol must commence at Mayo Clinic Florida under the supervision of a medical oncologist.

6.9b Study drug is available on site.

7.0 Protocol Treatment

7.1 Treatment Schedule - Use actual weight or estimated dry weight if fluid retention

Agent	Dose	Route	Day	ReRx
Pembrolizumab	200 mg	IV	Day 1	every 21 (+/- 3) days for a maximum of 2 years (approximately 35 cycles)
Imiquimod	5%	Cutaneous	M-F[a,b]	

a Regardless of what day of the week the cycle starts, imiquimod is to be administered daily for the remaining weekdays up to and including Friday.

b. At the completion of cycle 2 and cycle 4, a biopsy of the treated lesion will be performed (and if appropriate, a biopsy of an untreated lesion). Imiquimod is not to be administered the day of the biopsy or for six days following the biopsy. If the biopsy is performed on Monday, Imiquimod treatment should be given the following M-F. If the biopsy is performed on Tuesday, Imiquimod treatment should be given the next Tuesday-Friday and then M-F for the remainder of the cycle. If the biopsy is performed on Wednesday, Imiquimod treatment should be given the next Wednesday-Friday and then M-F for the remainder of the cycle. If the biopsy is performed on Thursday, Imiquimod treatment should be given the next Thursday-Friday and then M-F for the remainder of the cycle. If the biopsy is performed on Friday, Imiquimod treatment should be given the next Friday and then M-F for the remainder of the cycle.

7.2 Patients can be instructed in administration techniques of imiquimod and granted treatment independence.This training must be documented in medical record. Imiquimod is a commercial product dispensed from the pharmacy and is the same drug that would be prescribed to any other patient not on trial.

7.3 Imiquimod will be held for one week after biopsy to allow for proper wound healing.

7.4 If more than 1 cutaneous lesion is present, at least one lesion will not be treated with imiquimod to serve as a control for the effect of just pembrolizumab. The untreated lesion must be at least 2 cm from the treated lesion to account for possible treatment effect from the imiquimod on the primary.

7.5 Treatment by a local medical doctor (LMD) is not allowed.

8.0 Dosage Modification Based on Adverse Events

8.1 Dose-Modification Guidelines for Drug Related Adverse Events for Pembrolizumab

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	Hold Treatment for Grade	Timing for Restarting Treatment	Discontinue Subject
Gastrointestinal disorders	Diarrhea/Colitis	2-3	AE resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10mg or less of prednisone or equivalent per day within 12 weeks.
		4	Permanently discontinue	Permanently discontinue
Investigations	AST, ALT, or Blood bilirubin	2	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose
		3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Metabolism and nutrition disorders	Glucose intolerance (Type 1 diabetes mellitus [if new onset] or Hyperglycemia	Type 1 diabetes mellitus or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Endocrine disorders	Hypophysitis	2-3	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10mg or less of prednisone or equivalent per day within 12 weeks
		4	Permanently discontinue	Permanently discontinue
Endocrine disorders	Hyperthyroidism	3	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
		4	Permanently discontinue	Permanently discontinue

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	Hold Treatment for Grade	Timing for Restarting Treatment	Discontinue Subject
Endocrine disorders	Hypothyroidism	2-4	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
General disorders and administration site conditions	Infusion reaction	3-4	Permanently discontinue	Permanently discontinue
Respiratory, thoracic and mediastinal disorders	Pneumonitis	2	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10mg or less of prednisone or equivalent per day within 12 weeks.
		3-4	Permanently discontinue	Permanently discontinue
Renal and urinary disorder	Acute kidney injury or Chronic kidney disease (e.g. Renal failure or Nephritis)	2	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
		3-4	Permanently discontinue	Permanently discontinue
	All Other Drug Related Adverse Events[2]	2	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		3-4	Permanently discontinue	Permanently discontinue

* Located at [redacted]

NOTE: Permanently discontinue Treatment for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[a]For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.
[b]Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

8.2 Dose-Modification Guidelines for Drug Related Adverse Events for Imiquimod

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	Hold Treatment for Grade	ACTION
General Disorders and administration site conditions	Local skin reaction	3	Temporarily interrupt treatment for up to several days for severe or intolerable reactions; may consider resuming therapy once reaction subsides.
	Flu-like symptoms	3	Temporary disruption of therapy

9.0 Ancillary Treatment/Supportive Care

9.1 Full supportive care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.2 Hypersensitivity reactions

Patients do not require premedication prior to pembrolizumab treatment, as hypersensitivity reactions is not expected. In the unlikely event of a hypersensitivity reaction, treatment with antihistamines, H2 blockers, and corticosteroids is recommended. Patients should be pre-medicated with the typical regimen for subsequent cycles.

9.3 Patients may not enroll in a different clinical study, including Cancer Control studies, in which investigational procedures or agents are being used, while participating in this study.

9.4 Patients must terminate study treatment if they are to receive radiation therapy for palliative reasons as it impacts upon assessing response.

9.5 General patient monitoring and supportive care guidelines

9.51 Patients should be carefully monitored during the treatment phase and then followed appropriately. Decisions for retreatment or dose modifications/interruption should follow the guidelines in Sections 8.2.

9.52 Patients who have an ongoing study agent-related serious adverse event upon study completion or at discontinuation from the study will be contacted by the treating physician or his/her designee at least every 2 weeks until the event is resolved or determined to be irreversible.

9.6 Side effect management for **PEMBROLIZUMAB** toxicities- these are to be regarded as guidelines for managing toxicity that occurs with pembrolizumab therapy and should not replace clinical judgement (i.e. - patients with grade 1 rash may require systemic steroids).

9.61 Diarrhea

9.611 Grade 1- without abdominal pain/or blood in stool and symptoms, may be caused either by pembrolizumab. Infectious etiologies should be ruled out. Patients may be managed symptomatically, including the use of loperamide.Instruct patients to report any increase in stools.

9.612 Grade 2- without abdominal pain/or blood in stool and symptoms **< 1 week**, and resolve to grade 0 or 1- continue to monitor. Infectious etiologies should be ruled out.

9.613 Grade 2- symptoms **>1 week**, should be started on systemic steroid therapy. Infectious etiologies should be ruled out.

9.614 Grade 3 or greater- **who have other etiologies ruled out** should be started on systemic steroids Assess for dehydration. Patients may require hospitalization for IV steroids followed by oral steroids.

** Once patients have improvement of symptoms to grade 0 or 1 taper of steroids should occur over at least 1 month- if patients have been started on budesonide in addition to systemic steroids, start tapering the prednisone **FIRST**.

Do NOT administer loperamide in patients with ≥ Grade 2 diarrhea as this may cause toxic megacolon and/or perforation.

If at any time patients experience diarrhea with the following symptoms: fever or abdominal pain patients should have a CT scan of the abdomen to rule out perforation. Emergent surgical evaluation should be performed if perforation is found. If a patient has bloody diarrhea, a Gastroenterology consult should be obtained. A Gastroenterology consult should be obtained if provider is considering infliximab for treatment of colitis.

For all patients- assess hydration status and monitor electrolytes, including magnesium.

9.62 Rash

9.621 Grade 2- Initiate therapy with topical or systemic steroids at 0.5-1mg/kg/day of prednisone or equivalent.

9.622 Grade 3 or greater. Initiate systemic steroid therapy at 1-2 mg/kg/day of prednisone or equivalent.

9.63 Hyperthyroidism

9.631 Grade 3- Initiate systemic steroid treatment at 1-2 mg/kg/day of prednisone or equivalent.

9.632 Grade 4 - Initiate systemic steroid therapy at 1-2 mg/kg/day of prednisone or equivalent.

9.64 Immune-Mediated Hypophysitis

9.641 Grade 2 and 3 – Initiate systemic steroid at 0.5-1mg/kg/day of prednisone or equivalent and physiologic replacement dose.

9.642 Grade 4 – Initiate systemic steroid at 1-2 mg/kg/day of prednisone or equivalent and physiologic replacement dose.

9.65 Pneumonitis

9.651 Grade 1- No change in treatment

9.652 Grade 2- Initiate steroids at 0.5-1mg/kg/day of prednisone or equivalent.

9.653 Grade 3 or greater- Consider hospitalization, and initiate systemic steroids

9.66 Liver Dysfunction (AST or ALT)

9.661 AST or ALT ≤ 3 ULN- No change in treatment

9.662 AST or ALT >3 but <5 ULN or Grade 2- Consider initiating systemic steroids at 0.5-1mg/kg/day of prednisone or equivalent.

9.663 AST or ALT ≥ Grade 3- Discontinue pembrolizumab. Initiate systemic steroid therapy.

9.67 Liver Dysfunction (Bilirubin)

9.671 Grade 1- No change in treatment

9.672 Grade 2- Consider initiating systemic steroids at 0.5-1mg/kg/day of prednisone or equivalent.

9.673 Grade 3 or greater- Monitor levels until resolved to ≤ Grade 1. Initiate therapy with steroids at 1-2 mg/kg/day of prednisone or equivalent.

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).
- Any outcomes related to pregnancy while on study.

- Summary of SAE Reporting for this study

(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
All sites	Pregnancy Reporting [redacted]	Mayo Sites – attach to MCCC Electronic SAE Reporting Form Non Mayo sites – complete and forward to [redacted]
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form: [redacted]	Will automatically be sent to [redacted]

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

Unanticipated Adverse Device Event (UADE)
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:
([redacted])

a. Identify the grade and severity of the event using the CTCAE version 4.0.

b. Determine whether the event is expected or unexpected (see Section 10.2).

c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).

e. Determine if other reporting is required (see Section 10.5).

f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general

investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

Definite - The AE *is clearly related* to the agent(s)/procedure.
Probable - The AE *is likely related* to the agent(s)/procedure.
Possible - The AE *may be related* to the agent(s)/procedure.
Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

10.31 AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME (Combination) Arm

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the **entire combination (arm) is then considered an investigational intervention for reporting.**

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for **investigational** agents/interventions.
- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report, unless hospitalization is required. Refer to Section 10.4 for specific AE reporting requirements or exceptions.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent)

occurs with a higher degree of severity or specificity, expedited reporting is required.

- An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.

- Commercial agent expedited reports must be submitted to the FDA via MedWatch 3500A for Health Professionals (complete all three pages of the form).

[redacted]

Instructions for completing the MedWatch 3500A:

[redacted]

10.32 **EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting**

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6). *

*Report any clinically important increase in the rate of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event.

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported.[1]
General disorders and administration site conditions	Fatigue	≤Grade 3
	Malaise	≤Grade 3
	Cutaneous irritation from imiquimod	≤Grade 3

[1]These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

Specific protocol exceptions to expedited reporting should be reported expeditiously be investigators **ONLY** if they exceed the expected grade of the event.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:
● Hospitalizations for respite care
● Planned hospitalizations required by the protocol
● Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
● Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
● Hospitalization for administration of study drug or insertion of access for administration of study drug
● Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
● Hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer.]

10.4 Expedited Reporting Requirements for IND/IDE Agents

10.41 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:
1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥24 hrs	7 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

NOTE: Refer to Section 10.32 for exceptions to Expedited Reporting

10.42 General reporting instructions

Use Mayo Expedited Event Report form [redacted] for investigational agents or commercial/investigational agents on the same arm.

Submit to: [redacted]

For commercial agents:

Submit form [redacted]

10.43 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. 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;
2. Related or possibly related to participation in the research (in this guidance document, 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

3. 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.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

Mayo Clinic Cancer Center (MCCC) Institutions:

If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO, provide the Reportable Event coversheet and appropriate documentation to [redacted] The Mayo Regulatory Affairs Office will review and process the submission to the Mayo Clinic IRB.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and**

polyps) – Other (Progressive Disease)" under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE will be reported. Three options are available to describe the event:
    - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
    - Myelodysplastic syndrome (MDS)
    - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

10.55 Pregnancy, Fetal Death, and Death Neonatal

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician. If the baby is born with a birth defect or anomaly, a second expedited report is required.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation. Include this form:

[redacted]

10.541 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.542 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)"** under the Pregnancy, puerperium and perinatal conditions SOC.

10.543 Death Neonatal

Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration - Other (neonatal loss)"** under the General disorders and administration SOC.

10.6 Required Routine Reporting

10.61 Baseline and Adverse Events Evaluations

Pretreatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation per CTCAE v4.0 grading **unless** otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Blood and lymphatic system disorders	Anemia	X	X
	Febrile Neutropenia		X
Cardiac Disorders	Myocardial infarction		X
Gastrointestinal disorders	Nausea	X	X
	Vomiting	X	X
	Abdominal pain	X	X
	Baseline # of stools	X	

	Diarrhea		X
General disorders and administration site conditions	Fatigue	X	X
	Fever		X
Immune system disorders	Allergic reaction		X
	Anaphylaxis		X
Investigations	Neutrophil count decreased		X
	Platelet count decreased		X
	White blood cell decreased		X
	Aspartate aminotransferase increased	X	X
	Alkaline phosphatase increased	X	X
	Blood bilirubin increased	X	X
Musculoskeletal and connective tissue disorders	Arthralgia	X	X
	Myalgia	X	X
Nervous system disorders	Peripheral sensory neuropathy	X	X

10.62 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.621 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.622 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.623 Grade 5 AEs (Deaths)

10.6231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.7 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation Using RECIST 1.1 Guideline

11.1 The first scan after treatment initiation will be performed after the completion of cycle 4 (approximately week 12) and will be then performed every 12 weeks until disease progression is confirmed

Disease progression for this protocol is defined as meeting the RECIST criteria for disease progression on two consecutive evaluations at least 6 weeks apart (see Section 13.2).

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

NOTE: *Tumor lesions in a previously irradiated area are not considered measurable disease.*

11.22 Non-Measurable Disease

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

NOTE: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lymph nodes that have a short axis <1.0 cm are considered non- pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

- Chest X-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scans are preferable.

- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A ‘positive’ FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered ‘negative.’ New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

  a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

  b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

     i. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

     ii. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.

     iii If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.33 Measurement at Follow-up Evaluation:

- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in 11.21), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target

lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

11.431 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

- Complete Response (CR): All of the following must be true:
  a. Disappearance of all target lesions.
  b. Each target lymph node must have reduction in short axis to <1.0 cm.
- Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).
- Progression (PD): At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR): All of the following must be true:

a. Disappearance of all non-target lesions.

b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.

- Progression (PD): At least one of the following must be true:

a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.431

11.45 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Weight loss >10% of body weight.
- Worsening of tumor-related symptoms.
- Decline in performance status of >1 level on ECOG scale.

12.0 Descriptive Factors

None

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who have not had disease progression and have experienced acceptable toxicity are to continue treatment per protocol or a maximum of 2 years (approximately 35cycles) or until confirmed PD, unacceptable toxicity or refusal.

13.2 The first instance in which a patient's disease status meets the RECIST criteria for PD will continue for two additional cycles of treatment per protocol (approximately 6 weeks) and then undergo a disease evaluation.If the initial documented progression is not confirmed by this scan, patients will continue treatment per protocol.If the initial documented progression is confirmed by this scan, patients will go to the event-monitoring phase until death or a maximum of years post-registration.

Exception: Patients who develop PD in the CNS only should discontinue study treatment and go to Event Monitoring.

13.3 Criteria for discontinuation of protocol therapy include:

- Disease progression where disease progression is: the development of a new metastatic lesion or an objective status of disease progression (as defined by RECIST criteria) on two consecutive evaluations at least 6 weeks apart (section 13.2). ***Exception: Patients who develop PD in the CNS only should discontinue study treatment and go to Event Monitoring.***

  - Request by patient to discontinue study treatment
  - Unacceptable toxicity
  - Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree or require discontinuation of drug
  - Administration of radiotherapy, non-protocol chemotherapy, immunotherapy, biological agents, or an experimental drug during the trial
  - Development of new primary cancer
  - Ineligibility

  Patients who discontinue treatment due to intolerability, patient request, physician decision, or inter-current illness preventing further administration of protocol treatment will proceed to event monitoring phase of the trial where patient and disease status until death or a maximum of 3 years post-registration

13.4 Patients who complete 2 years of protocol treatment (approximately 35 cycles) without (confirmed) disease progression will proceed to the Observation phase until confirmed disease progression or a maximum of 3 years post registration. If the patient has a documented confirmed disease progression during observation, the patient will continue on to the event monitoring phase for a maximum of 3 years post registration.

13.5 A patient is deemed ineligible if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry.

- If the patient received any protocol treatment, all data (except biospecimens) up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

- If the patient never received any protocol treatment, on-study material (except biospecimens) and the End of Active Treatment/Cancel Notification Form must be submitted. No further No further data submission is necessary.

13.6 A patient who withdraws consent before any study treatment is given. On-study material (except biospecimens) and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Specimens

None

15.0 Drug Information

15.1 Pembrolizumab (MK-3475, SCH 900475, Keytruda®)

15.11 **Background**: Pembrolizumab is a potent humanized IgG4 monoclonal antibody with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1.

15.12 **Formulation**

Pembrolizumab is available as a liquid 25 mg/mL, 100 mg/vial.

15.13 **Preparation and storage**:

Vials should be stored in the refrigerator at temperatures between 2-8°C. Drug concentrate is further diluted with normal saline (or 5% dextrose in the concentration range of 1 to 10 mg/mL) in IV containers made of polyvinyl chloride (PVC) or non-PVC material. The infusion solution in the IV bag should be immediately administered. Pembrolizumab solutions may be stored at room temperature for a cumulative period of up to 4 hours. This includes room temperature storage of reconstituted solution in vials, room temperature storage of infusion solution in the IV bag and the duration of infusion.

In addition,IV bags may be stored at 2-8 °C for up to a cumulative time of 20 hours. If refrigerated, the vials and/or IV bags should be allowed to equilibrate to room temperature prior to subsequent use.

15.14 **Administration:** Pembrolizumab is administered by intravenous infusion over 30 minutes via a 0.22 micron in-line filter. The final infusion volume must be between 1 and 10 mg/mL. Maximum rate of infusion should not exceed 6.7 mL/minute through a peripheral or indwelling catheter. Flush the line with 0.9% NaCL following the completion of the infusion.

15.15 **Pharmacokinetic information**:
a) Absorption – during repeated dosing of MK-3475 every two weeks, steady state conditions were reached within 16 weeks of treatment. Steady state trough concentrations obtained at 24, 36 and 48-weeks of treatment

with 10 mg/kg Q2W were on average 20% percent higher compared to 10 mg/kg Q3W treatment.
b) Distribution – pembrolizumab has a limited volume of distribution.
c) Excretion – mean estimated $t_{1/2}$ values from the 28-day single dose profiles ranged from 14.1 to 21.6 days. Clearance is nonlinear and saturable.

15.16 **Potential Drug Interactions**: There are no known significant drug interactions.

15.17 **Known potential toxicities**:
Common known potential toxicities, >10%:
Cardiovascular: Peripheral edema
Central nervous system: Fatigue, headache, chills, insomnia, dizziness
Dermatologic: Pruritus, skin rash, vitiligo
Endocrine & metabolic: Hyperglycemia, hyponatremia, hypoalbuminemia, hypertriglyceridemia, hypocalcemia
Gastrointestinal: Nausea, decreased appetite, constipation, diarrhea, vomiting, abdominal pain
Hematologic & oncologic: Anemia
Hepatic: Increased serum AST
Neuromuscular & skeletal: Arthralgia, limb pain, myalgia, back pain
Respiratory: Cough, dyspnea, upper respiratory tract infection
Miscellaneous: Fever

Less common known potential toxicities, 1% - 10%:
Dermatologic: Cellulitis
Endocrine & metabolic: Hypothyroidism, hyperthyroidism
Gastrointestinal: Colitis
Infection: Sepsis
Renal: Renal Failure
Respiratory: Pneumonitis, pneumonia

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Adrenocortical insufficiency (immune-mediated), arthritis (immune-mediated), exfoliative dermatitis (immune-mediated), hemolytic anemia (immune-mediated), hepatitis (including autoimmune hepatitis; grade 4: <1%), hypophysitis (grade 2: <1%; grade 4: <1%), interstitial nephritis (with renal failure; grade 3: <1%; grade 4: <1%), Lambert-Eaton syndrome (immune-mediated), myositis (immune-mediated), nephritis (grade 2 autoimmune: <1%), optic neuritis (immune-mediated), pancreatitis (immune-mediated), partial epilepsy (immune-mediated; in a patient with inflammatory foci in brain parenchyma), rhabdomyolysis (immune-mediated), uveitis (immune-mediated)

15.18 **Drug procurement:** Pembrolizumab will be provided free of charge to study participants by Merck.

15.19 **Nursing Guidelines:**

15.191 Pembrolizumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening.

Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids.

15.192 Diarrhea can be seen however, is less common than that seen with anti-CTLA-4 agents. However it can be severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.

15.193 Rash/pruirits/dermatitis is seen. Patients should report any rash to the study team. Treat per Section 9.0 and monitor for effectiveness.

15.194 Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.

15.195 Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.

15.196 Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysistis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and "not feeling well." Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.

15.197 Patients who are started on steroid therapy for any side effects of pembrolizimab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.

15.198 Fatigue is common and may or may not be associated with immune related side effects. Assess patient's fatigue level prior to each cycle of therapy and report any changes to the study team.

15.199 Patients should avoid receiving live vaccines within 30 days of study drug administration or per other study guidelines.

15.200 Patients who have undergone an allogenic bone marrow transplant, have an increased risk of severe complications including early GVHD, and venoocclusive disease, if they have previously been treated with pembrolizumab.

15.201 Myocarditis has been reported and associated with pembrolizumab. Instruct patients to report chest pain, SOB, or dyspnea to study team immediately and/or seek emergency medical attention.

15.202 Autoimmune hematologic disorders including ITP and hemolytic anemia have been reported. Monitor blood counts closely and report any abnormalities to the study team.

15.203 Rare neurologic disorders including Guillian-Barre syndrome and myasthenia gravis have been reported. Instruct patients to report any neurologic symptoms including weakness, parasthesias, or numbness, tingling to the study team immediately.

15.2 Imiquimod

15.21 **Preparation and Storage:**
Single-use, 0.25 gm packets, containing 5% imiquimod. This is a commercial product that will be dispensed from the pharmacy. One or two packets will be used for each application.

15.22 **Known Potential Toxicities:**

Local Reactions:

Local skin reactions have been reported with imiquimod as used for genital warts. Erythema, excoriation/flaking, and edema are described as "common" in the package insert. Itching, burning, pain, and soreness occur at the treatment site. Remote skin reactions can occur in less than 5% of patients. Ulceration, scabbing, and vesicles occur in 3 to 5%. Fungal infections are reported in 11% of women using imiquimod. The vaginal and cervical tissues are likely to be at least as sensitive to the inflammatory effects as the vulvar tissues. Examination prior to each application will be the primary means of protecting patients from cumulative local toxicities.

Systemic Reactions:

Systemic reactions have not been a major problem with topical use of imiquimod. When systemic symptoms are reported, they are suggestive of a viral syndrome. Headaches, myalgias, and flu-like symptoms have been reported. The frequency of these symptoms with vulvar application appears to be elevated no more than 1% over the frequency in the placebo group. The frequency of systemic symptoms with repeated application will be monitored in this trial.

15.23 **Nursing guidelines:**

15.231 Patients should wear gloves (if possible) while applying imiquimod. Instruct patient to wash hands carefully when done.

15.232 Avoid contact with eyes and mucous membranes.

15.233 A certain amount of redness, irritation, and/or burning is expected at the site of administration. Patients experiencing large areas of erythema or significant pain with administration should be instructed to call the study team immediately.

15.234 Rarely if patients are applying to large surface areas, they can experience mild flu-like symptoms (i.e myalgias, fatigue, etc). Instruct patient to report these to the study team. Treat symptomatically and monitor for effectiveness.

15.24 **Drug Procurement**

The research base pharmacy will obtain the drug from 3M Pharmaceuticals. Each institution will order the drug from the research base pharmacy. Submit the drug order form to:

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

16.0 Statistical Considerations and Methodology

16.1 This pilot study will enroll 10 patients to gain preliminary data on the anti-tumor activity and safety profile of the combination of imiquimod and pembrolizumab in patients with unresectable cutaneous melanoma.

If there are no tumor responses documented among these 10 patients, then upper bound of a one-sided 95% confidence interval for the tumor response rate would be 25.9%.

All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for assessment of all of the clinical endpoints.

16.2 Tumor response rate and duration of response

16.21 Tumor response rate is defined as percentage of patients whose objective disease status meets the criteria for RECIST criteria for partial or complete response on two consecutive disease evaluations at least 12 weeks apart.

16.22 For those patients who disease had a partial or complete response to treatment on two consecutive disease evaluations at least 12 weeks apart, the duration of treatment response is defined as the time from registration to disease progression.

16.3 Safety Profile

16.31 Adverse events will be graded and attribution assigned using CTC CAE version 4.0. For each type of toxicity reported, the proportion of patients experiencing a severe level of that toxicity will be determined.

16.4 Progression-free and overall survival

16.41 Progression-free survival time is defined as the time from registration to documentation of first disease progression or death due to any cause. Survival time is defined as the time from registration to death due to any cause.

16.42 The duration of response and the distributions of OS times and PFS times will be estimated using the Kaplan-Meier method.

16.5 Biomarker changes during treatment

16.51 Biomarkers will be assessed prior to treatment and 6 and 12 weeks following the start of treatment. For each patient and each biomarker, a times-series plot of biomarker value will be constructed. These graphs will be visually examined for trends within and between the group of patients whose tumor responded to treatment and the group of patients whose tumor did not respond to treatment.

16.52 Plots of the percent change in biomarker level at 6 weeks versus response (yes vs. no) to visually assess whether the percent change in biomarker level at 6 weeks tends to be greater for one group versus the other. This will be repeated for the value of the biomarker at 6 weeks to gain insight into whether it is the amount of the change or where the biomarker lands after 6 weeks of treatment that separates the two groups.

16.6 Monitoring of the trial

This clinical trial will be monitored by the Mayo Clinic Cancer Center Data and Safety Monitoring Board (MCCC DSMB). The study statistician will prepare a report containing accrual and adverse event that will be submitted to MCCC DSMB every 6 months.

16.61 Safety Stopping rules

After every 5th patient has been enrolled, the tolerability of the regimen will be examined. If 2 out of the first 5 patients enrolled or more than 25% of the patients thereafter develop a grade 4 adverse event anything during the course of treatment that is considered possibly, probably, or definitely related to treatment,

enrollment will temporarily close. The study team will review all adverse event data. A trial recommendation will be formulated and presented to the MCCC DSMB – the study may permanently close or may re-open to accrual after MCCC DSMB review and IRB approval of protocol/consent form modifications.

16.7 Inclusion of Women and Minorities

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	0	0
Not Hispanic or Latino	4	6	10
Ethnic Category: Total of all subjects*			
Racial Category			
American Indian or Alaskan Native			
Asian			
Black or African American			
Native Hawaiian or other Pacific Islander			
White	4	6	10
Racial Category: Total of all subjects*	4	6	10

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

Core tissue biopsies will be performed at baseline, 6 weeks, and 12 weeks. Core biopsies with 16 gauge needles will be taken from at least one lesion treated with imiquimod and if present one untreated. Cores will be formalin fixed paraffin embedded and stored until the end of the study when correlative research will be performed.

17.1 Summary Table of Research Tissue Specimens to be Collected for this Protocol

Correlative Study (Section for more information)	**Mandatory or Optional**	**Type of Tissue to Collect**	**Block, Slides, Core, etc. (# of each to submit)**	**Visit 1 (Baseline)**	**Visit 2 *(*6 weeks)**	**Visit 3 (12 weeks)**	**Process at site? (Yes or No)**	**Temperature Conditions for Storage /Shipping**
IHC PDL1	Mandatory	FFPE	1 slide	X	X	X	Yes	Ambient
IHC PD1	Mandatory	FFPE	1 slide	X	X	X	Yes	Ambient
IHC CD3	Mandatory	FFPE	1 slide	X	X	X	Yes	Ambient
IHC CD4	Mandatory	FFPE	1 slide	X	X	X	Yes	Ambient
IHC CD8	Mandatory	FFPE	1 slide	X	X	X	Yes	Ambient
RNA expression Nanostring immune panel	Mandatory	FFPE	5 slides	X	X	X	Yes	Ambient

17.2 Diagnostic Slides from Original and /or Recurrent Tissue

Hematoxylin and eosin stain, S100, and HMB-45 will be performed by dermatopathologist, [redacted]

Along with original diagnostic slides, include pathology reporting form, surgical pathology report and operative report.

17.3 Correlative Tissue Collection

17.31 FFPE tumor tissue blocks/slides (10 unstained slides) will be collected in order to assess correlation of tumor bound PD-L1 expression and level of tumor infiltrating T-cells (CD3, CD4, and CD8) in response to treatment. Both measurements will be semi-quantitatively assessed by established immunohistochemistry (IHC) methodology in our laboratory.

17.32 Definitive immunohistochemical analysis using tumor biopsies will be performed at the completion of the study, comparing pre-treatment measurements with changes at time of tumor progression on therapy.

17.33 RNA expression analysis of an immune panel from Nanostring of tumor biopsies will be performed at the completion of the study, comparing pre-treatment measurements with changes at time of tumor progression on therapy.

17.33 At the completion of the study, any unused/remaining material will be stored in the Biospecimens Accessioning and Processing (BAP) at Mayo Clinic Florida for future research according to the patient consent permission. Potential future research may include immunohistochemistry (IHC) analyses to analyze predictive biomarkers, changes in expression pattern with therapy, and correlation with response and/or adverse events. When a protocol is developed, it will be presented for IRB review and approval.

17.4 Background and Methodology

17.41 Immunohistochemistry will be performed to assess expression of PDL1, PD1, CD3, CD8, and CD4. These markers will be assessed both at baseline, 6 weeks, and 12 weeks in both the lesion treated with imiquimod and untreated lesion (when available). We will analyze the possible association of baseline expression as well as change in expression with response to treatment.

17.42 RNA expression of a panel of immune related genes will be assessed using Nanostring immune panel of 500+ immune related genes. We will analyze the possible associations of baseline and change in baseline immune genes with response to treatment in the lesion treated with imiquimod and untreated lesions (when available).

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18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Event monitoring

See Section 4.0 and data submission table for the event monitoring schedule.

18.3 CRF completion

This study will use Medidata Rave for remote data capture (rdc) of all study data.

18.4 Site responsibilities

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

This study requires supporting documentation for diagnosis and progression prior to study entry as well as for evidence of response to study therapy and progression after study therapy. Supporting documentation for diagnosis will include a copy of the imaging report demonstrating metastatic melanoma This report should be submitted within 14 days of registration.

For progression of disease prior to study entry, supporting documentation includes the evidence needed to determine the patient's progression prior to enrollment. These documents should be submitted within 14 days of registration.

For response to treatment, supporting documentation includes a copy of the imaging report.

For patients who progress after study therapy supporting documentation includes a copy of the imaging report.

18.6 Labelling of materials

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Incomplete materials

Any materials deemed incomplete by the MCCC Operations Office will be considered "not received" and will not be edited or otherwise processed until the missing

19.0 Budget

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded:
Correlatives per Section 17

19.3 Other budget concerns:

20.0 References

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Appendix I ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. 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. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

[redacted]