A Phase II Study of Palliative Radiation Therapy and Anti-PD-1/PD-L1 Checkpoint Blockade in Patients with Metastatic Merkel Cell Carcinoma

NCT03988647

Coordinating Center
Stanford Cancer Institute
875 Blake Wilbur Drive
Stanford, CA 94305

Protocol Director
Susan Jane Knox, PhD, MD
Department of Radiation Oncology
Stanford Cancer Center
875 Blake Wilbur Dr., MC5847
Stanford, CA 94305-5847
Phone: 1-650-725-2720
Fax: 1-650-723-7254
Email: sknox@stanford.edu

Co-Investigators
Harlan Pinto, MD
Department of Medical Oncology
Stanford Cancer Center
875 Blake Wilbur Dr., MC5820
Stanford, CA 94305-5820
Phone: 1-[redacted]
Fax: 1-[redacted]

Email: harlan@stanford.edu

Susan Swetter, MD
Department of Dermatology
450 Broadway St., Pavilion C, 2nd Floor
Redwood City, CA 94063-5334
Phone: 1-[redacted]
Fax: 1-[redacted]
Email: [redacted]

Sunil Arani Reddy, MD
Department of Medical Oncology
875 Blake Wilbur Dr., CC2232
Stanford, CA 94305-582
Phone: 1-[redacted]

Fax: 1- [redacted]

Email: sreddy@stanford.edu

Lisa Zaba, MD
Stanford Cancer Center South Bay
2589 Samaritan Dr.
San Jose, CA 95124
Phone: [redacted]
Fax: xxx-xxx-xxxx
Email: [redacted]

Biostatistician
Rie von Eyben, M.S.
Biostatistics, Radiation Oncology
875 Blake Wilbur Drive
Stanford, CA 94305
Phone: 1- [redacted]
Fax: 1- [redacted]
Email: [redacted]

Study Coordinator
Leanne Stamps-Deanda
Cancer Clinical Trials Office
800 Welch Road, FC3C67
Stanford, CA 94304
[redacted]
[redacted]
Email: [redacted]

Version # 1 / Version Date: (03-28-2019)
Amendment 1 / Amendment Date: (07-26-2019)
- Clarification of inclusion/exclusion criteria (3.1.5, 3.1.8, 3.2.4, 3.2.23)

Amendment 2 / Amendment Date: (09/10/2019)
- Weight based dosing (2.4)
- Update inclusion/exclusion criteria (3.1)
- Clarify TSH w/Reflex FT4 and pregnancy test requirements (4.)
- SAE reporting time frame (4. And 7.2)
- Prior therapy clarification (4.1.1)
- Dose limiting toxicity defined (6.)

- Study calendar updates, end of treatment visit window (9.)
- Update tumor measurement windows (10.1)
- Redesigned Eligibility Checklist (Appendix 2)

Amendment 3 / Amendment Date: (11/11/2020)

- The dose change to fixed dose of 200 kg
- In dose modification section, CTCAE version 4.0 changed to 5.0
- UA removed from treatment and follow-up schedule in study calendar and treatment and follow-up section in protocol. UA is required only at baseline screening.

SRC Approval Date: 04-04-2019

TABLE OF CONTENTS

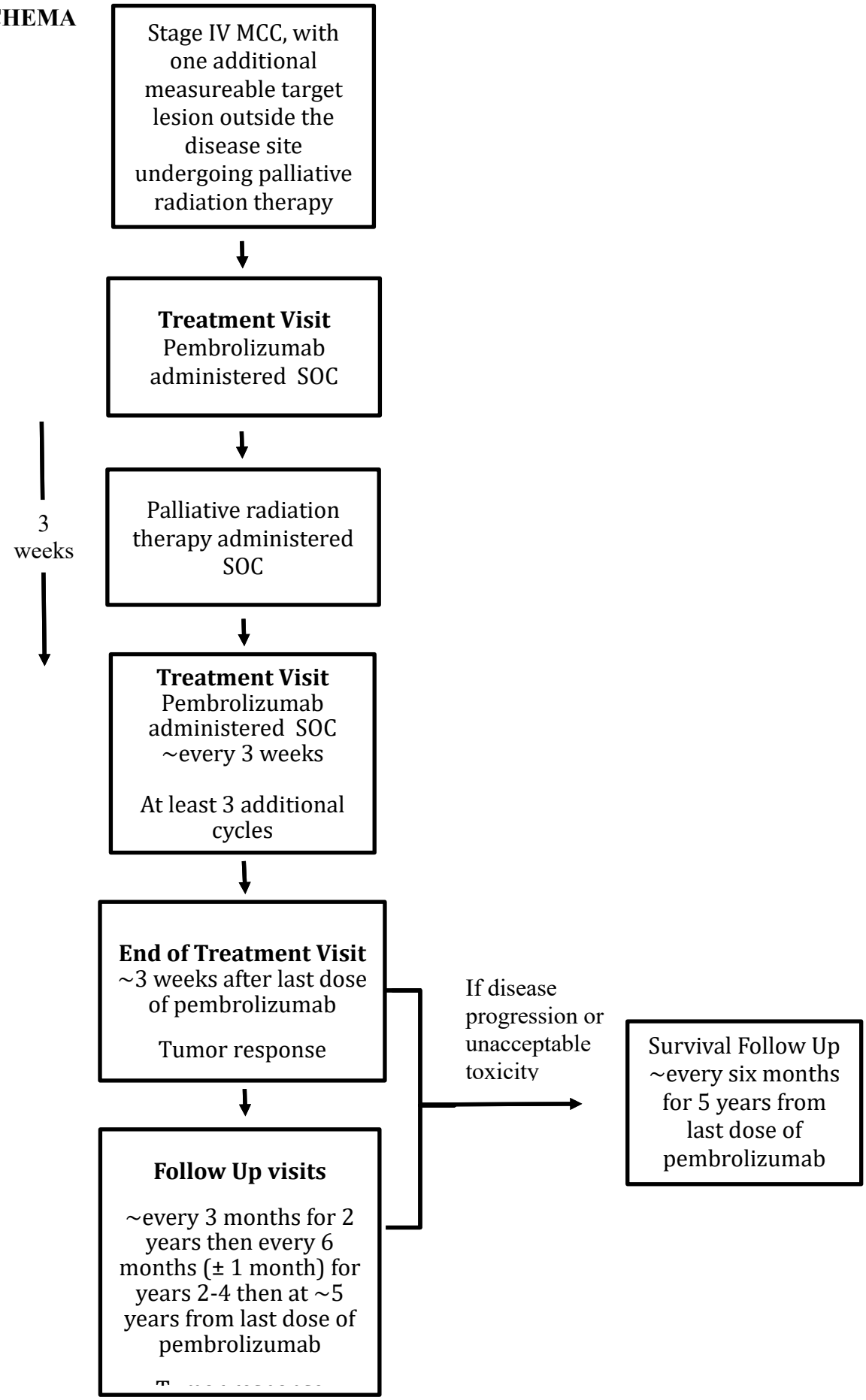
PROTOCOL SYNOPSIS

In the table below summarize the basic aspects of this research. This is to be used as a quick reference guide. Remove any section that is not relevant to the research.

TITLE	A Phase II Study of Palliative Radiation Therapy and Anti-PD-1/PD-L1 Blockade in Patients with Metastatic Merkel Cell Carcinoma (MCC)
STUDY PHASE	2
INDICATION	Metastatic Merkel Cell Carcinoma (stage IV)
INVESTIGATIONAL PRODUCT OR PROCEDURE	Pembrolizumab will be administered at a fixed dose of 200 kg iv per standard of care (SOC) every 3 weeks for 4 cycles or until disease progression or unacceptable toxicity occurs. Palliative radiation therapy to 1-2 sites of disease will occur between the first and second treatment with pembrolizumab.
PRIMARY OBJECTIVE(S)	The primary objectives of this study are to assess 1) the safety and 2) efficacy of combining Anti-PD-1/PD-L1 blockade with palliative radiation therapy in patients with Stage IV Merkel Cell Carcinoma. Efficacy for the primary objective will be tumor response rates (CR, PR, SD, irCR, irPR, irSD) at both irradiated and unirradiated sites.
SECONDARY OBJECTIVE(S)	Assessment of Overall Survival and disease control rate/duration of response (CR, PR, SD, irCR, irPR, irSD).
EXPLORATORY OBJECTIVE(S)	Optional exploratory objectives (dependent upon funding) will include mutational burden/MSI analysis, measurement of polyomavirus in the blood, immune response assays at baseline, 2 weeks (±1 weeks) and 8 weeks (±1 weeks) after radiation therapy, and possible tumor biopsy studies.
TREATMENT SUMMARY	Pembrolizumab will be administered ~every 3 weeks for at least 4 cycles with palliative radiation administered between cycle 1 and cycle 2. Subjects will participate until disease progression or unacceptable toxicity. Participants will have an end of treatment visit 3 weeks (±1 week) after the last dose of pembrolizumab and then follow up visits every 3 months (±1 month) for two years and then every 6 months (±1 month) for years 3-4, then again at year 5 (±1 month) from the last dose of pembrolizumab or until disease progression. Follow Up visits will then become optional and SOC. After

	discontinuation of treatment, subjects will enter survival follow up conducted every 6 months (±2 weeks) for 5 years from last dose of pembrolizumab.
SAMPLE SIZE	30 participants over 36 months
STATISTICAL CONSIDERATIONS	Data will be summarized using appropriate descriptive statistics: proportions with 95% confidence intervals, means, standard deviations, and ranges.

SCHEMA


Stage IV MCC, with one additional measureable target lesion outside the disease site undergoing palliative radiation therapy
Treatment Visit
Pembrolizumab administered SOC
3 weeks
Palliative radiation therapy administered SOC
Treatment Visit
Pembrolizumab administered SOC
~every 3 weeks
At least 3 additional cycles
End of Treatment Visit
~3 weeks after last dose of pembrolizumab
Tumor response
If disease progression or unacceptable toxicity
Survival Follow Up
~every six months for 5 years from last dose of pembrolizumab
Follow Up visits
~every 3 months for 2 years then every 6 months (± 1 month) for years 2-4 then at ~5 years from last dose of pembrolizumab

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
APC	Antigen presenting cell
CBC	Complete blood count
CI	Confidence interval
CMAX	Maximum concentration of drug
CNS	Central nervous system
CRF	Case report/Record form
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DOR	Duration of response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
FSH	Follicle stimulating hormone
GI	Gastrointestinal
Gy	Gray
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HPF	High-power field
HRT	Hormone replacement therapy
HTN	Hypertensions
IMRT	Intensity-modulated radiation therapy
IRB	Institutional Review Board
irRECIST	Immune-related response evaluation criteria in solid tumors
IV	Intravenous
LLN	Lower limit of normal
MCPyV	Merkel cell polyomavirus
OS	Overall survival
PLT	Platelet
PD	Progressive diseased
PFS	Progression free survival
PR	Partial response
RECIST	Response evaluation criteria in solid tumors
RR	Response rate
SAE	Serious adverse event
SBRT	Stereotactic body radiation therapy
SD	Stable disease
SOC	Standard of Care
TTP	Time to progression
ULN	Upper limit of normal
UNK	Unknown
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of childbearing potential

1. OBJECTIVES

1.1. Primary Objective

The primary objectives of this study are to assess 1) the safety and 2) efficacy of combining Anti-PD-1/PD-L1 blockade with palliative radiation therapy in patients with Stage IV Merkel Cell Carcinoma. Efficacy for the primary objective will be tumor response rates (CR, PR, SD, irCR, irPR, irSD) at both irradiated and unirradiated sites.

1.2. Secondary Objectives

Assessment of Overall Survival and disease control rate/duration of response (CR, PR, SD, irCR, irPR, irSD)

1.3. Exploratory Objective

Optional exploratory objectives (dependent upon funding) will include mutational burden/MSI analysis, measurement of polyomavirus in the blood, immune response assays at baseline, 2 weeks (±1 weeks) and 8 weeks (±1 weeks) after radiation therapy, and possible tumor biopsy studies.

2. BACKGROUND

2.1 Merkel Cell Carcinoma and Immunotherapy

Merkel Cell Carcinoma is a rare and aggressive skin cancer for which much is written although rigorous trials are lacking (1). In general, many patients still die of advanced stage IV disease having a 5 year survival of 13.5%. (2) Recent approval of the checkpoint inhibitor, avelumab, likely improves this dismal outcome, but to some extent increasing awareness and diagnosis of this entity may also be contributing to improved outcomes. Swedish Cancer Registry incidence shows a doubling in close to 20 years. (3) Besides, avelumab other recent breakthroughs in knowledge include the association in some cases of the DNA virus, known as Merkel Cell Polyomavirus with the disease. (4) Historically, patients with localized disease are treated with surgery with or without radiation. Although these treatments can be associated with good outcomes, the strength of data for the exact delivery of such treatments is still weak due to the lack of good controlled studies. In addition, many patients develop metastatic disease with chemotherapy being the major treatment option in previous decades. Again, the data is of low quality, but the lack of long-term responders suggests only minor benefit. Further improvements are clearly needed, including controlled studies and increased research on new ideas to improve upon current therapy.

Immunological aspects of Merkel Cell include, in some patients, viral association, and increasing incidence in the setting of immune suppression such as with transplant (5). Regardless of immunological profile, the recent approval of avelumab, an anti-PDL-1 monoclonal antibody (6) has led to much renewed interest in systemic therapy in general and immunotherapy specifically. Although the trial was not randomized, it did suggest benefit and showed long term efficacy in some patients. Further strengthening the efficacy of avelumab was its use after chemotherapy. Pembrolizumab (Keytruda), an anti-PD1 antibody, has also been studied with evidence of long-term clinical benefit. (7), and was approved by the FDA in December 2018.

Given our knowledge of efficacy of radiation (8) for local control and smaller benefits of chemotherapy for the treatment of Merkel cell carcinoma, combination therapy with checkpoint inhibitors and radiation therapy makes sense. The immunological nature and

radiosensitivity of Merkel cell carcinoma and encouraging results to date with PD-1/PD-L1 axis inhibition, provide a compelling rationale for the study of the combination of checkpoint inhibition and radiation therapy as a means of inducing a clinically meaningful anti-Merkel cell carcinoma immune response. We and others have studied this approach in melanoma (9, 10) and other diseases, with impressive results in a subset of patients. This continues to be a very active and promising area of clinical investigation. Given the features of Merkel cell carcinoma discussed above, we hypothesize that it is likely that this approach will be beneficial in Merkel cell carcinoma as well.

2.2 Anti-PD-L1/PD-1 Inhibition in Merkel Cell Carcinoma

Avelumab (Bavencio) is a programmed death ligand-1 (PD-L1) blocking antibody approved for 1) metastatic Merkel Cell Carcinoma (MCC) and 2) locally advanced and metastatic urothelial cancer. It is dosed at 800 mg IV every 2 weeks. Until progression of disease or unacceptable toxicity. The most common AEs (20% and above) in MCC patients were fatigue, musculoskeletal pain, diarrhea, nausea, infusion-related reactions, rash, decreased appetite and peripheral edema. The most common AEs in urothelial carcinoma patients were fatigue, infusion reactions, musculoskeletal pain, nausea, decreased appetite and urinary tract infections. In a study of 88 MCC patients, the overall response rate was 33 % with 11.4% complete responses, and duration of response ranging from 2.8-23.3+ months.

Pembrolizumab (Keytruda) is a PD-1 blocking antibody, approved for multiple indications, and most recently in December 2018, approved for recurrent locally advanced or metastatic MCC. The approval was based on the Phase II CITN-09/KEYNOTE-017 trial in which pembrolizumab resulted in an Overall Response Rate (ORR) of 56%, PR rate of 32% and CR rate of 24% in patients who had not previously received systemic therapy for their advanced disease. An additional 10% had stable disease. In this multicenter, single arm trial, 50 treatment naïve patients were treated with pembrolizumab at 2 mg/kg every 3 weeks. 86% of patients had metastatic disease and 64% were positive for Merkel cell polyomavirus (MCPyV). At a median follow up of 14.9 months the median duration of response (DOR) was not reached. Among the 28 patients with response, 96% had a DOR of at least 6 months, and 54% had a DOR of 12 months or more. Both Progression Free Survival (PFS) and median Overall Survival (OS) with pembrolizumab were higher than historical data for chemotherapy controls. The median time to response was 2.8 months, with most responses occurring by 12 weeks. Responses were observed regardless of Merkel cell polyomavirus (MCPyV) status, with an ORR of 59% in MCPyV-positive patients and 53% among MCPyV-negative patients. The most common AEs of pembrolizumab reported in at least 20% of patients who received single-agent pembrolizumab were fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain and abdominal pain. Overall, 96% of patients experienced all-grade treatment-related AEs, with 14% of patients discontinuing treatment dues to treatment-related AEs. Grade 3 and above treatment-related AEs were reported for 28%, and there was one treatment-related death in this study.

Additional information regarding pembrolizumab (e.g. PK, route of elimination, metabolism, etc.) can be found in the package insert.

2.3 Rationale

The underlying hypothesis for this study is that local radiation therapy (RT) can be safely used in combination with PD-1/PD-L1 blockade. This combination therapy may have the potential

to enhance the induction of systemic anti-Merkel cell carcinoma immune responses, which will inhibit growth and kill Merkel cell tumor cells in sites of established metastases outside of the local radiation therapy field.

This is a single institution study of pembrolizumab combined with palliative radiation therapy in patients with metastatic Merkel cell carcinoma. Palliative treatment means treatment to shrink a tumor, slow its growth or control symptoms. Patients must require radiation therapy for palliation of symptoms or to prevent local progression of disease and associated complications and/or symptoms from metastases.

Radiation therapy (RT) is commonly used to palliate sites of metastatic disease. Radiation can locally kill Merkel carcinoma cells and result in the release of tumor antigens in close proximity to antigen presenting cells (APC) in tumors, which could help to initiate an anti-tumor immune response. The combination of RT with PD-1/PD-L1 blockade, which inhibits co- inhibitory signaling in between T cells and tumor, may result in enhanced anti-tumor responses that result in greater tumor burden reduction systemically.

2.4 Study Design and Duration

This is a single institution, single arm, open-label, Phase II treatment study to evaluate the safety and efficacy of palliative radiation therapy combined with pembrolizumab as a means of providing for PD-1/PD-L1 checkpoint blockade in patients with metastatic Merkel Cell Carcinoma as either first line therapy or upon progression on prior therapy.

In this study, pembrolizumab will be administered at 200 kg IV every 3 weeks as standard of care as approved by the FDA. Palliative radiation therapy will be given between the first and second cycles of immunotherapy.

Subject participation in this study comprises the following time periods:

- Screening
  -Screening assesses the subject's eligibility to participate as determined by the inclusion/exclusion criteria.
  - Screening labs and ECOG Performance Status must be completed within 4 weeks of confirmation of eligibility. Imaging must be completed within 4 weeks of confirmation of eligibility and within 6 weeks of starting pembrolizumab therapy.
  -Eligibility must be confirmed within 28 days of signing the informed consent form.

- Pembrolizumab
  - Patients will receive pembrolizumab as a single agent administered 200 kg as standard of care intravenously every 3 weeks until progression or unacceptable toxicity.
  - Laboratory evaluations must be performed and the results examined before administration of each dose.
  - As durable disease stabilization and/or objective tumor response can be seen after early progression before Week 12, it is recommended that, in the absence of dose-limiting toxicities (e.g., serious AEs), immunotherapy be administered over

the initial 12 weeks even in the setting of apparent clinical progression, providing the subject's performance status remains stable.
- All subjects, including those who may have discontinued treatment for drug-related AEs and/or who have evidence of clinical progression, should obtain a tumor assessment 3weeks (±1 week) after the last dose of pembrolizumab.
- Based on clinical experience in ongoing and completed immunotherapy studies, the following recommendations apply for subject management in light of the tumor assessment taken 3 weeks (±1 week) after the last dose of pembrolizumab:
  - The appearance of new lesions in subjects with other stable or shrinking baseline tumor burden may be experiencing clinical benefit and should continue on treatment before alternative anti-cancer agents are considered. These subjects can be seen to have continued tumor shrinkage in subsequent imaging.
  - As long as overall tumor burden is stable or decreasing, subjects can remain in treatment, even in the presence of new lesions, at the discretion of the treating physician.
  - Clinical progression warranting alternative anti-cancer treatment should be considered in subjects whose overall tumor burden appears to be substantially increased and/or in subjects whose performance status is decreased.

- Follow-Up

  - Subjects with SD, PR or CR will continue receiving pembrolizumab every 3 weeks per standard of care. After the last dose of pembrolizumab, subjects will enter Follow-Up. Efficacy assessments for these subjects are per standard of care.

- Survival Follow-Up (Post Study Follow-Up)

  - Subjects who are no longer receiving pembrolizumab due to unacceptable toxicity (e.g., refractory Grade > 3 AEs), disease progression, investigator judgment, or study closure are managed in survival follow-up.
  - If possible, subjects will be contacted or medical records reviewed every 6 months (±2 weeks) for 5 years after the last dose of pembrolizumab to evaluate survival status.

2.5 Correlative Studies Background

Correlative studies will be performed if/when funding for them becomes available.

- Mutational burden/MSI - has been associated with response to checkpoint inhibitors in other solid tumor types (e.g. melanoma), and we would look at this to see if there is an association between this endpoint and response in MCC in our study
- Measurement of MC polyomavirus - to look for an association between this endpoint and response
- Immune Response Assays - to look for potential immune response biomarkers associated with response - e.g. may include Luminex for 51 cytokines testing in serum or plasma, ELISA for MHC class 1 polypeptide-related sequence A (MYCA) and MHC class 1 polypeptide-related sequence B (MYCB) in serum or plasma, immunophenotyping including myeloid-derived suppressor cells (MDSC) and gamma/delta T cells, mass cytometry or CyTOF ICS with phorbol 12-myristate 13-acetate (PMA) + ionomycin stimulation (global immunocompetence assay)

Because of relatively small patient numbers we will be looking for trends/correlations with response.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

3.1 Inclusion Criteria

3.1.1 Histologically confirmed metastatic or locally advanced Merkel Cell Carcinoma (includes in-transit or bilateral bulky disease) with at least two distinct sites of disease.

3.1.2 Subjects with brain metastases and/or carcinomatous meningitis are eligible providing they are neurologically stable (if systemic steroids are required, subjects should be stable on the lowest clinically effective dose, as steroids may interfere with the activity of immunotherapy if administered at the time of the first Anti-PD-1/PD-L1 dose.)

3.1.3 Must be at least 14 days since treatment for MCC, and recovered (baseline or residual non ir Grade 1 toxicity or ir Grade 2 toxicity at the investigator's discretion, see section 4.1.1) from any clinically significant toxicity experienced during treatment before the first dose of on study pembrolizumab therapy.

3.1.4 Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.

3.1.5 Life expectancy of ≥ 16 weeks.

3.1.6 Subjects must have measurable disease according to RECIST v1.1, and have baseline (screening/baseline) radiographic images, (e.g. CT, PET CT or MRI brain, chest, abdomen, pelvis, to be determined by the attending physician) within 4 weeks of confirmation of eligibility and within 6 weeks before the initiation of on study pembrolizumab therapy.

3.1.7 Required values for initial laboratory tests:

-WBC: ≥ 2000/μL (~ 2 x 10^9/L)
-ANC: ≥ 1000/μL (~ 1 x 10^9/L)
-Platelets: ≥ 50 x 10^3/μL (~ 50 x 10^9/L)
-Hemoglobin: ≥ 8 g/dL
-Calculated creatinine clearance (eGFR) greater than 30mL/min
-AST/ALT: Less than 2.5 x ULN for subjects without liver metastasis, less than 5 times ULN for liver metastases
-Bilirubin: less than 3.0 x ULN (except for subjects with Gilbert's Syndrome, who must have a total bilirubin of less than 3.0 mg/dL)
-Non-clinically significant laboratory abnormalities such as lipase elevation would not be an exclusion.

3.1.8 No known active or chronic infection with HIV, Hepatitis B, or Hepatitis C, or active infection requiring systemic antibiotics. Testing for the above is not required unless clinically suspected.

3.1.9 At least one measurable site of disease (≥ 10 mm as per RECIST v1.1 except for lymph nodes that must be 15 mm or greater on the short axis) outside of the planned palliative radiation therapy field.

3.1.10 Require radiation therapy for palliation of symptoms or to prevent local progression of disease and associated complications and/or symptoms from metastases.

3.1.11 Men and women, at least 18 years of age.

3.1.12 Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study [and for up to 26 weeks after the last dose of investigational product] in such a manner that the risk of pregnancy is minimized.

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Post-menopausal is defined as:

- Amenorrhea ≥ 12 consecutive months without another cause, or
- For women with irregular menstrual periods and on hormone replacement therapy (HRT), a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL

Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (e.g., vasectomy) should be considered to be of childbearing potential. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 1 week prior to the start of investigational product.

3.1.13 Men of fathering potential must be using an adequate method of contraception to avoid conception throughout the study [and for up to 26 weeks after the last dose of investigational product] in such a manner that the risk of pregnancy is minimized.

3.2 Exclusion Criteria

3.2.1 WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study and for up to 26 weeks after the last dose of investigational product.

3.2.2 Women who are breastfeeding.

3.2.3 WOCBP with a positive pregnancy test within 6 weeks before enrollment.

3.2.4 Autoimmune disease: Poorly controlled autoimmune disease is excluded. Well controlled autoimmune disease (e.g. well controlled RA) will be assessed by the study team and a decision made regarding eligibility based on the degree of immunosuppression and severity of symptoms.

3.2.5 Any subject who has a life-threatening condition that requires high-dose immunosuppressant(s). Steroid doses greater than 20 mg/day will exclude the patient from participation in the trial.

3.2.6 Presence of known hepatitis B or hepatitis C infection, regardless of control on antiviral therapy.

3.2.7 Subjects who have another active, concurrent, malignant disease are not eligible, with the exception of subjects with adequately treated basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix, or other cancers that are in remission/not measurable. Patients will be excluded if they have any known additional malignancy that requires active treatment while on treatment for Merkel Cell Carcinoma.

3.2.8 Evidence of symptomatic interstitial lung disease or symptomatic active, noninfectious pneumonitis.

3.2.9 Participants with impaired cardiac function or clinically significant cardiac disease such as unstable angina/uncompensated heart failure, uncontrolled symptomatic arrhythmia.

3.2.10 Chronic or current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment. This exclusion does not include prophylactic antibiotics or topical antibiotics.

3.2.11 Known hypersensitivity to another monoclonal antibody, which cannot be controlled with standard measures (e.g. antihistamines and corticosteroids).

3.2.12 Any condition that would, in the investigator's judgment, interfere with full participation in the study.

3.2.13 Prisoners or subjects who are involuntarily incarcerated.

3.2.14 Subjects with acute or poorly controlled psychiatric illness or subjects who are compulsorily detained for physical (e.g., infectious disease) illness, with the exception of patients that are well supported and able to participate (e.g. paraplegia from a motor vehicle accident).

3.2.15 Any underlying medical or psychiatric condition that, in the opinion of the investigator, could make the administration of anti-PD-1/PD-L1 hazardous or could obscure the interpretation of adverse events.

3.2.16 Any live vaccine therapy for up to 4 weeks before or after any dose of immunotherapy on this trial.

3.3 Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation.

Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

3.4 Randomization Procedures

Randomization is not used for this open label single arm study.

3.5 Study Timeline

Primary Completion:

The study will reach primary completion 7 ½ years from the time the study opens to accrual.

Study Completion:

The study will reach study completion 7 ½ years from the time the study opens to accrual.

4. TREATMENT PLAN

Screening/Baseline Visit

The following tests and examinations must be performed and the eligibility criteria satisfied before treatment may begin:

- Histologic diagnosis of Merkel Cell Carcinoma
- Demographics and medical history
- Measurements of weight, height, temperature, pulse, respiratory rate, and resting systolic and diastolic blood pressure
- Complete physical examination
- ECOG Performance Status
- Clinical laboratory tests:

  - Hematology: hemoglobin, hematocrit, CBC counts with differential (including absolute lymphocyte count) and direct platelet count

  - Serum Chemistry: albumin, serum alkaline phosphatase, SGOT (AST)/SGPT (ALT), total bilirubin, calcium, creatinine, glucose, lactate dehydrogenase (LDH), total protein, urea nitrogen (BUN), electrolytes (including sodium, potassium, chloride, and bicarbonate), TSH w/Reflex FT4

  - Urinalysis:
    - Gross examination including specific gravity, protein, glucose, and blood
    - Optional microscopic examination including WBC/HPF, RBC/HPF and any additional findings
- Optional Blood sample obtained for investigational immune response assays
- Chest radiography unless baseline CT scan was performed
- Electrocardiogram
- Relevant baseline radiographic images (e.g. brain, chest, abdomen, pelvis, and bone scans with the exact imaging studies utilized determined by the attending physician) within 6 weeks of initiation of anti-PD-1/PD-L1

- Current medications
- Baseline review of symptoms
- Pregnancy test
- Optional Tumor biopsy

Treatment Visits

The day subjects receive the first dose of pembrolizumab therapy will define Day 1. Subjects are required to have blood collected and chemistry labs analyzed up to 1 week prior to each dose of pembrolizumab. Investigators or an assigned medical professional must review liver function tests from the predosing labs and ensure the results meet dosing requirements prior to authorizing administration of each dose of pembrolizumab.

Subjects will receive a single dose of pembrolizumab as standard of care with 200kg IV every 3 weeks (with a -3 and +7-days window) until disease progression or unacceptable toxicity occurs.

During this treatment phase, the following procedures will be performed within 1 week of each scheduled visit:

- Pregnancy test for WOCBP, required within 6 weeks before first dose of pembrolizumab, then optional as clinically indicated for ongoing doses
- Vital sign measurements will include weight, temperature, pulse, and resting systolic and diastolic blood pressure. Vital sign measurements of pulse, and systolic and diastolic blood pressure will be collected prior to the infusion of anti-PD-1/PD-L1.
- Physical examination
- ECOG Performance Status
- Clinical laboratory tests (as outlined in the screening phase) (taken and results reviewed prior to study drug administration):
  - Hematology
  - Serum chemistry
  - TSH w/Reflex FT4- week 13 only (for patients who continue pembrolizumab past week 10)
- Blood (optional) for investigational immune response assays at 2 weeks (±1 weeks) and 8 weeks (±1 weeks) after completion of radiation therapy.
- Concomitant medications
- Adverse event assessment
- Optional Tumor biopsy

Follow-up

Patients will be seen for an end of treatment visit 3 weeks (±1 week) after the last pembrolizumab dose and again for follow up visits every 3 months (±1 month) for 2 years and then every 6 months (± 1 month) for years 3-4 and again at year 5 (±1 month) per SOC thereafter until progression of disease by imaging criteria or increased symptomatology that requires another therapy. Follow up visits will be performed until 5 years from the last dose of pembrolizumab and will then become optional and SOC.

The following procedures will be performed at each scheduled follow-up visit ±1 month during the first 2 years. During years 3-5 the clinical laboratory tests will be performed only once per year.

- Measurements of vital signs (resting systolic and diastolic blood pressure, pulse, respiratory rate, and temperature) and weight
- Physical examination
- ECOG Performance Status
- Clinical laboratory tests
  - Hematology
  - Serum chemistry
  - TSH w/Reflex FT4
- Concomitant medications (for the first 2 years)
- Adverse event assessment (for the first 2 years)
- Status of new and continuing AEs and SAEs (at minimum, collected up to 60 days following last dose of pembrolizumab, 6 months for irSAEs definitely related)
- Relevant imaging studies for tumor measurements
- Optional Tumor biopsy

Survival Follow-Up Assessment for all Subjects

After a subject progresses or changes therapy due to symptomatology, they will enter survival follow-up. In the event a subject withdraws from the treatment phase of the study or discontinues from all other study procedures, the investigators may continue to contact the subject (with his/her agreement) for the collection of survival follow-up data. The subject's decision should be documented in the source records. If possible, contact will be made for all subjects enrolled in the study, regardless of enrollment date. If possible subjects or their caregivers will be contacted every 6 months (±2 weeks) for 5 years from the last dose of pembrolizumab and inquiries will be made about survival data and/or death date.

4.1 General Concomitant Medication and Supportive Care Guidelines

Concomitant medications/supportive care will be administered per SOC.

4.1.1 Prohibited and/or Restricted Treatments

Subjects in this study may not use live vaccines for the treatment of cancer or prevention of disease (including those for common medical conditions) for up to 4 weeks before and after dosing with Anti-PD-1/PD-L1. Concomitant anti-cancer medications or treatments are prohibited in this study while subjects are receiving Anti-PD-1/PD-L1.

Subjects may not use any of the following therapies during the study:

- Any non-study anti-cancer agent (investigational or non-investigational)
- Any other investigational agents
- Immunosuppressive agents (unless required for treating potential AEs)

- Chronic systemic corticosteroids greater than 20 mg/day (unless required for treating treatment emergent AEs or required for management of signs or symptoms due to brain metastases)
- Any non-oncology live vaccine therapies used for the prevention of infectious diseases (for up to 4 weeks before or after any dose of study drug).

Subjects may be allowed with the following prior therapies:

- Prior treatment with an anti-PD-1/PD-L1 antibody does not exclude patients from this study. Each case will be considered individually and a decision made by the study team. The team will consider if a subject was discontinued from the prior anti-PD-1/PD-L1 treatment due to an AE or SAE. For example, non-clinically significant immune-related laboratory abnormalities – may not automatically exclude patients from participating in this study – e.g. asymptomatic elevated amylase; responsiveness to steroids.

- A history of AEs with prior IL-2 or Interferon will not preclude subjects from entering the current study.

4.2 Criteria for Removal from Study

Subjects MUST discontinue study treatment for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Any clinical AE, laboratory abnormality, or intercurrent illness that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Progressive disease, based on the investigator's judgment, at or after the end of treatment visit. Progression before the end of treatment visit can be followed by objective response and does not require discontinuation. Small new lesions, by themselves, are not defined as progression.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

All subjects who discontinue study treatment should comply with protocol-specified follow-up procedures as outlined in Section 4. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

4.3 Alternatives

Alternatives to participation in this study include:

- Getting treatment without being in a study which may include other Merkel cell carcinoma therapy such as:
  - Immunotherapy without radiotherapy

- Chemotherapy
- Targeted therapy
- Radiotherapy alone without immunotherapy

- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the Merkel cell carcinoma. It does not treat the cancer directly but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

5. INVESTIGATIONAL AGENT/DEVICE/PROCEDURE INFORMATION

5.1 Investigational Agent/Device/Procedure

5.1.1 Pembrolizumab

Unit: Pembrolizumab 200 kg; comes in 100 mg/4mL solution vials
Route: Intravenous infusion
Source: Stanford Hospital Pharmacy

5.1.1.1 Handling and Dispensing

Pembrolizumab must be stored refrigerated (2ºC - 8ºC) with protection from light. In preparation of infusion, pembrolizumab may be stored in IV infusion bags (PVC, non-PVC/non-DEHP) or glass infusion containers at room temperature for up to 6 hours or refrigerated (2ºC - 8ºC) for up to 24 hours. Drug must be completely delivered to the subject within 24 hours of preparation. This includes any time in transit plus the total time for the infusion.

As with all injectable drugs, care should be taken when handling and preparing pembrolizumab. Whenever possible, it should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents, applying aseptic technique. Latex gloves are required. If pembrolizumab concentrate or solution comes in contact with skin or mucosa, immediately and thoroughly wash with soap and water.

5.1.1.2 Preparation and Administration of Pembrolizumab

Pembrolizumab will be prepared according to standard of care and administered intravenous at a dose of 200 /kg according to standard of care. See the current package insert for additional details.

Pembrolizumab should be administered under the supervision of a physician experienced in the use of intravenous agents. Pembrolizumab is administered as an intravenous infusion only. Patients may be premedicated as per standard of care as needed. Infusions will be interrupted, or the rate slowed as needed for mild or moderate (grade 1 or 2) infusion-related reactions. Infusions will be permanently stopped for severe or life-threatening (grade 3 or 4) infusion reactions.

5.1.1.3 Criteria that Require Permanent Discontinuation of Pembrolizumab

Subjects MUST discontinue study treatment for any of the following reasons that are not related to a related adverse event:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Pregnancy
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

Exceptions to Permanent Discontinuation of pembrolizumab dosing under the following situations:

- Potentially reversible inflammation (< Grade 4), attributable to a local antitumor reaction and a potential therapeutic response. This includes inflammatory reactions at sites of tumor resections or in draining lymph nodes, or at sites suspicious for, but not diagnostic of metastasis.
- Hospitalization for < Grade 2 adverse events where the primary reason for hospitalization is to expedite the clinical work-up.
- Subjects with the following conditions where in the investigator's opinion continuing study drug administration is justified:
  - Ocular toxicity that has responded to topical therapy
  - Endocrinopathies where clinical symptoms are controlled with appropriate hormone replacement therapy.

Note: Pembrolizumab may not be restarted while the subject is being treated with systemic corticosteroids except for subjects on stable doses of hormone replacement therapy such as hydrocortisone.

All subjects who discontinue treatment prematurely due to a drug-related AE or symptomatic progression prior to disease assessment at the end of treatment visit are required to return for the 3 weeks (±1 week) after the last dose of pembrolizumab visit, unless they are switched to an alternate anti-neoplastic medication.

5.1.2 Radiation Therapy

Patients will receive palliative radiation therapy to 1-2 sites of disease. Radiation therapy will be delivered between the first and second cycles of anti-PD-1/PD-L1 therapy. The total dose and fractionation regimen of radiation will be determined by the attending physician by such factors as the location and size of the lesion that requires radiation, volume of radiosensitive normal tissue in the field, and clinical status of the patient. Patients will be treated with either 9 Gy X 3 (27 Gy in 3 fractions), or 4-6 Gy X 5 (20-30 Gy in 5 fractions). Radiation therapy will be planned in 3 or 4 D, and may be delivered using conventional, IMRT/ rapid arc or SBRT. Portal imaging for QC will occur according to SOC. All patients will be seen at least weekly by the attending physician while on treatment.

5.2 Availability

Both pembrolizumab and palliative radiation therapy are SOC.

5.3 Agent Ordering

Pembrolizumab will be obtained through the Stanford Hospital Pharmacy as SOC.

5.4 Agent Accountability

Pembrolizumab is FDA approved SOC therapy for Merkel cell carcinoma being dispensed from the Stanford Hospital Pharmacy and will not require accountability tracking.

6. DOSE MODIFICATIONS

Decisions to skip or modify a pembrolizumab dose will be made based on specified safety criteria as shown in the table below.

Recommended Dose Modifications of Pembrolizumab for Adverse Reactions

Treatment-Related Adverse Reaction	**Severity of Adverse Reactions***	**Dose Modification**
Immune-Mediated Pneumonitis	Grade 2 pneumonitis	Withhold (a)
	Grade 3 or 4 pneumonitis or recurrent Grade 2 pneumonitis	Permanently discontinue.
Immune-Mediated Hepatitis	Aspartate aminotransferase (AST)/or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal	Withhold Pembrolizumab. Resume Pembrolizumab in patients with complete or partial resolution (Grade 0 to 1) of hepatitis after corticosteroid taper.
	If no liver mets, AST or ALT more than 5 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal; if liver mets and grade 2 AST or ALT at baseline with at least 50% increase that persist for one week or more	Permanently discontinue.
Immune-Mediated Colitis	Grade 2 or 3 diarrhea or colitis	Withhold. Resume in patients with complete or partial resolution (Grade 0 to 1)

		of colitis or diarrhea after corticosteroid taper.
	. Grade 4 diarrhea or colitis or recurrent Grade 3 diarrhea or colitis	Permanently discontinue.
Immune-Mediated Endocrinopathies (including but not limited to hypothyroidism, hyperthyroidism, adrenal insufficiency, hyperglycemia)	Grade 3 or 4	Withhold until clinically stable.
Immune-Mediated Nephritis and Renal Dysfunction	Grade 2	Withhold. Resume in patients with complete or partial resolution (Grade 0 to 1) of nephritis and renal dysfunction after corticosteroid taper.
	Grade 3 or 4	Permanently discontinue.
Other immune-mediated adverse reactions (including but not limited to myocarditis, myositis, psoriasis, arthritis, hypopituitarism, uveitis, Guillain-Barré syndrome, pancreatitis, rhabdomyolysis, myasthenia gravis, histiocytic necrotizing lymphadenitis, demyelination, vasculitis, hemolytic anemia, hypophysitis, iritis, and encephalitis) *For Immune-mediated*	For any of the following: Grade 2 or 3 based on severity and type Grade 3 based on severity and type or grade 4 Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis	 Withhold (a) Permanently discontinue. Withhold

skin AEs	(TEN) Grade 4 or confirmed SJS or TEN	Permanently discontinue.
	For any of the following: Life-threatening adverse reaction (excluding endocrinopathies) Recurrent severe immune-mediated adverse reaction Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks Persistent Grade 2 or 3 immune-mediate adverse reactions lasting 12 weeks or longer	Permanently discontinue.
Infusion-related reaction	Grade 1 or 2	Interrupt or slow the rate of infusion.
	Grade 3 or 4	Permanently discontinue.

*Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 5.0 (NCI CTCAE V5)

(a) Resume if complete or partial resolution (Grade 0, 1) after corticosteroid taper.

Dose Limiting Toxicity (DLT) Definition:

Dose limiting toxicity is when therapy is permanently discontinued due to toxicity as defined in the dose modification table above or when the patient withdraws from treatment due to toxicity that the patient finds unacceptable.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Potential Adverse Events

7.1.1 Pembrolizumab alone:

Pembrolizumab may cause one or more of the side effects listed below. This information is

based on data from cancer subjects in other clinical trials with pembrolizumab.

The most common side effects (greater than 5% chance of happening) of pembrolizumab are:
•Fatigue
•Skin reactions: including rash, itching, hives, redness, blisters, and dry skin. Stevens Johnson Syndrome and toxic epidermal necrolysis, are rare and potentially life threatening diseases characterized by blistering and peeling of the top layer of skin resembling that of a severe burn.
•Diarrhea
•Nausea
•Abdominal pain
•Decreased appetite
•Joint pain or stiffness
•Thyroid gland abnormalities
•Dehydration

Less common side effects of pembrolizumab (between 2-5% chance of happening) include:
•Liver function blood test abnormalities
•Dry mouth
•Vomiting
•Low electrolyte counts in your blood, for example sodium
•Lung inflammation (pneumonitis - see details below)
•Cough
•Headache
•Fever
•Muscle soreness, weakness, stiffness spasms or paralysis
•Pain in back, arms or legs
•Shortness of breath
•Constipation
•Swelling of the face, arms, or legs
• Increase in inflammatory blood proteins (e.g., lipase)
•Liver injury

Rare but potentially serious side effects (less than 2% chance of this happening but potentially serious) of pembrolizumab include:
•Low blood oxygen level
•Acute lung injury or failure
•Collection of fluid around the lungs
•Adrenal gland abnormalities
•Pituitary gland inflammation
•Changes in vision (including decreased or blurry vision), dry eye, inflammation of the eye, or bleeding into the eye
•Tingling, burning, or numbness in hands and feet
•Hepatitis
•Changes in kidney function tests and acute kidney injury or failure
•Inflammation of the mouth and lining of the digestive tract
•Inflammation of the pancreas
•Autoimmune disorders, including Guillain-Barre syndrome (associated with progressive muscle weakness or paralysis)

•Chest discomfort
•Heart palpitations
•Inflammation of the heart or its lining or blood vessels
•Chills
•Dry skin
•Diabetes
•Increased level of blood acid called ketones
•Dizziness
•Infections: including sepsis, lung infections, and skin infections.
•Hair loss
•Changes in blood pressure
•Inflammation or loss of brain nerves supplying vision and spinal cord, abnormal brain function
•Drug reaction with rash, blood cell abnormalities, enlarged lymph nodes, and internal organ involvement (including liver, kidney, and lung); known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
•Myasthenia gravis, a nerve disease that may cause weakness of eye, face, breathing, and swallowing muscles. One death in a patient who received nivolumab combined with ipilimumab was considered due to myasthenia gravis and severe infection (sepsis).
•Rhabdomyolysis (muscle fiber released into the blood stream which could damage your kidney) and polymyositis (chronic muscle inflammation with muscle weakness)
•Colitis: Inflammation of intestine. It may cause abdominal pain and diarrhea with or without blood. Fever may be present. It may require you to receive additional fluids. If left untreated, this may lead to a tear in the wall of the intestine which can be serious and life threatening. Tell your study doctor right away if you have any of these symptoms.
•Guillain-Barre syndrome: A disorder characterized by progressive symmetrical paralysis and loss of reflexes, usually beginning in the legs. The paralysis characteristically involves more than one limb (most commonly the legs), is progressive, and usually proceeds from the end of an extremity toward the torso.
•Sarcoidosis: growth of tiny collections of inflammatory cells (granulomas) in different parts of your body — most commonly the lungs, lymph nodes, eyes and skin.
•Loss of color (pigment) from areas of skin
•Allergic reaction
•Rejection of organ or tissue transplant
•Graft versus host disease (GVHD): In patients who have received a transplant containing blood cells from another person (allogenic transplant), the donor's immune cells attack the normal cells. Symptoms can be rapid and severe and can occur in any organ of the body. This has resulted in death when nivolumab, an antibody similar to pembrolizumab, or nivolumab and ipilimumab were given after allogenic transplant.

Lung Inflammation (pneumonitis): It is possible that pembrolizumab may cause inflammation of the tissues of the lung. This adverse effect has been reported infrequently in patients treated with pembrolizumab. While many patients with x-ray or CT abnormalities have not developed any symptoms, some patients have developed mild to severe symptoms and in rare cases, death has occurred as a result of their lung inflammation. Signs and symptoms of lung inflammation may include difficulty breathing, pain or discomfort while breathing, chest pain, cough, shortness of breath, increased rate of breathing, fever, low blood oxygen levels, or fatigue.

Your study doctor and nurse will watch you closely for changes in your ability to breathe and

for other signs or symptoms that might show you are developing this type of lung inflammation and will perform regular tests including physical exams, measurement of oxygen levels through non-invasive testing (i.e., pulse oximeter), blood tests, chest x-rays and/or CT scans.

Please inform your study doctor or nurse AT ONCE if you experience any of the following:
•Any new or increased shortness of breath;
•Any new or increased chest pain;
•Any new or increased pain/difficulty while breathing;
•Any new or increased cough or any significant change in your type of cough; for example any new or increased mucous or blood in your cough;
•Any change in the amount of oxygen you require;
•Any fever, fatigue, or other symptoms that occur at the same time as any changes to your breathing or other lung symptoms.

If you start to develop symptoms, your study doctor will ask you to return to the clinic for additional tests, which could include a physical exam, measurement of oxygen levels, blood tests, chest x-rays, and/or CT scans. You will be monitored very closely for changes in your overall lung symptoms, monitoring may require hospitalization. You may require specific treatment in order to control pneumonitis. You may also be seen by a special doctor called a pulmonologist, who has special training to be an expert in how your lungs work.

Prolonged treatment with medicines that suppress inflammation, sometimes needed to manage the side effects of pembrolizumab treatment, may lower your body's ability to fight off certain infections (i.e., opportunistic infections). These infections may require treatment with antibiotic or antifungal medications and may be fatal.

7.1.2 Radiotherapy alone:

Radiotherapy will be delivered by standard of care palliative radiotherapy.
Radiotherapy will be administered in 3-5 treatments to 1-2 sites of disease. This will occur between the first and second dose of pembrolizumab.

Side Effects Related to Radiotherapy:
Side effects of radiation therapy are determined by the site irradiated, normal tissues in the field, and the total dose and number of treatments given. Your radiation oncologist will discuss this in detail with you and you will be asked to sign a separate consent form for the radiation therapy. In general, side effects from radiation therapy are described below.
Likely:
•Rash
•Skin irritation

Less Likely:

•Feeling tired
•Lowering of blood counts which may make infection and bleeding more likely
•Nausea

Rare, but serious:

•Development of a second cancer
•Increase in pressure in an arm or leg from inflammation that requires surgical intervention

7.2 Adverse Event Reporting

Adverse events will be graded according to CTCAE v5.0. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study specific Case Report Forms (CRFs). The Protocol Director or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, or Investigator's Brochure, and related to the investigation. All Serious Adverse Events (SAEs) will be tracked until resolution or until 60 days after the last dose of the study treatment. Immune related serious adverse events (irSAEs) definitely related to study treatment will be captured for 6 months after the last dose of study treatment.

SAEs CTCAE Grade 3 and above, and all subsequent follow-up reports will be reported to the Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) using the study specific CRF regardless of the event's relatedness to the investigation. Following review by the DSMC, events meeting the IRB definition of 'Unanticipated Problem' will be reported to the IRB using eProtocol within 10 working days of DSMC review, or within 5 working days for deaths or life-threatening experiences.

8. CORRELATIVE/SPECIAL STUDIES

8.1 Laboratory Correlative Studies

- Optional biopsies will be frozen and fixed as per SOC protocols in the pathology lab
- Immune response assays
    - - blood collection, processing and assays will be performed as per the protocols in the Stanford Biobank and Human Immune Monitoring Center where the samples will be stored and assays performed, respectively.
- Others will be sent to relevant reference laboratories

9. STUDY CALENDAR

Visits	Pre Study Visit	Treatment Visits					End of Treatment Visit	Follow Up Visit	Post Study Follow Up
Weeks/Months	Wk 0	Wk 1[h]	Btw Wk 1-3	Wk 4	Wk 7	Wk 10	3 Wks after last dose of Pembrolizumab	Every 3, 6M, or at yr 5 from last dose of Pembrolizumab	Upon progression or unacceptable symptomatology
Investigational Agent[a]		X		X	X	X			
Radiation Therapy[b]			X						
Informed consent	X								
Inclusion/Exclusion Criteria	X								

Demographics	X								
Medical history	X								
Physical Exam	X	X		X	X	X	X	X	
Concurrent meds[c]	X	X		X	X	X	X	X	
Vital signs	X	X		X	X	X	X	X	
ECOG Performance status	X	X		X	X	X	X	X	
ECG	X								
Chest Radiography	X								
Adverse event evaluation		X		X	X	X	X	X	
Tumor measurements	X						X	X	
CBC w/diff	X	X		X	X	X	X	X	
Pregnancy Test[d] (Urine or Serum)	X	X		X	X	X			
Hemoglobin	X	X		X	X	X	X	X	
Hematocrit	X	X		X	X	X	X	X	
Metabolic panel, comp	X	X		X	X	X	X	X	
LDH total serum plasma	X	X		X	X	X	X	X	
Urinalysis Macro (Opt Micro)	X								
TSH w/Reflex FT4[e]	X						X	X	
Optional Immune Response and Polyomavirus Tests[f]	X		X	X		X	X		
Optional Tumor Biopsy[f]	X		X	X	X	X	X	X	
Survival Follow Up[g]									X

a: Investigational Agent- pembrolizumab 200 kg infused SOC every 3 weeks

b: Radiation Therapy- 1-2 sites of disease, delivered between the first and second cycles of pembrolizumab, 9 Gy X 3 (27 Gy in 3 fractions), or 4-6 Gy X 5 (20-30 Gy in 5 fractions)

c: Concurrent meds will be collected until the patient goes off study due to disease progression or change in therapy for Merkel cell carcinoma or for 2 years of continuing response

d: Pregnancy test conducted and negative result confirmed before administration of pembrolizumab in women with the potential to become pregnant, pregnancy test is required ≤ 6 weeks before first dose of pembrolizumab and optional as clinically indicated for ongoing doses

e: Assessed at week 13 for patients who continue pembrolizumab past week 10

f: If funding is available, a variety of optional immune response assays will be performed that may include Luminex for 51 cytokines testing in serum or plasma, ELISA for MHC class 1 polypeptide-related sequence A (MYCA) and MHC class 1 polypeptide-related sequence B (MYCB) in serum or plasma, immunophenotyping including myeloid-derived suppressor cells (MDSC) and gamma/delta T cells, mass cytometry or CyTOF ICS with phorbol 12-myristate 13-acetate (PMA) + ionomycin stimulation (global immunocompetence assay). These assays will be performed at baseline, 2 weeks (±1 weeks) and 8 weeks (±1 weeks) after radiation therapy. Possible tumor biopsies (optional) may be performed before, during/after treatment to assess response to therapy and changes in immune cell subsets. Optional tests to assess polyomavirus in the blood may be performed at baseline and 3 months ± 1 month.

g: Applicable to all subjects who discontinued, regardless of enrollment date. During the Survival Follow-Up Phase, telephon contact will be made every 6 months (±2 weeks) for 5 years from the last dose of pembrolizumab. The site will inquire about overall subject survival status. Subjects that withdraw from the treatment phase of the study but do not return to the site for any further assessment will be contacted by the site to inquire about AEs and SAEs up to at least 60 days from the last dose of pembrolizumab. Definitely related immune related serious adverse events (irSAEs) will be captured for 6 months after the last dose of study treatment.

h: Required before first dose of pembrolizumab

1. If systemic steroids are required, subjects should be stable on the lowest clinically effective dose (≤ 20 mg/day)

2. Must be at least 14 days since treatment for MCC, and recovered (baseline or residual non ir Grade 1 toxicity or ir Grade 2 toxicity at the investigator's discretion, see section 4.1.1) from any clinically significant toxicity experienced during treatment before the first dose of on study pembrolizumab therapy.
3. ≤ 6 weeks demonstrate measurable disease according to RECIST v1.1, and have baseline (screening/baseline) radiographic images, (e.g. CT, PET CT or MRI brain, chest, abdomen, pelvis, to be determined by the attending physician)
4. ≤ 6 weeks pregnancy test for WOCBP
5. ≤ 1 week labs and liver function tests performed and results evaluated

10. MEASUREMENTS

Title: Tumor response rates (CR, PR, SD, irCR, irPR, irSD) as accessed by RECIST v1.1/irRECIST at both irradiated and unirradiated sites

Time Frame: Response will be accessed at the end of treatment visit and follow up visits

Safety Issue: This outcome is not measuring a safety issue. Safety will be monitored using AE assessment during the trial using the CTCAE v5.0 criteria.

10.1 Primary and Secondary Outcome measures

The primary and secondary outcomes will be assessed by obtaining relevant tumor images at baseline line, end of treatment visit, and then at least every 3 months (±1 month) for two years and then every 6 months (±1 month) for years 3-4, then again at year 5 (±1 month) from the last dose of pembrolizumab or until disease progression. Response and progression will be evaluated using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)[11] as well as the Immune-related RECIST (irRECIST).[12] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria. RECIST/irRECIST criteria will be used to score response of both the irradiated and unirradiated disease sites.

10.1.1 Relevant Subset

All patients are in a single arm.

10.1.2 RECIST v1.1

10.1.2.1 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters.

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless progression is documented, or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. ‘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.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any non-measureable as well as measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

10.1.2.2 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 6 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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 is preferable.

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. MRI is also acceptable in certain situations (e.g. for body scans), but NOT lung.

FDG-PET: It is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible

'new' disease). 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: If the positive FDG- PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG- PET scan). 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, this is not PD.

10.1.2.3 Response Criteria

Determination of response should take into consideration all target and non-target lesions.

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes
(whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest mm diameters while on study.

Not Evaluable (NE): When at least one target lesion is not evaluated at a particular time point.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of excising non-target lesions. Unequivocal progression should normally trump target lesions status. It must be representative of overall disease status change, not a single lesion increase.

Not Evaluable (NE): When at least one non-target lesion is not evaluated at a particular time point.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances.

10.1.2.4 Evaluation of Best Overall (unconfirmed) Response

The best overall response is the best time point response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest sum recorded since baseline). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria in some circumstances.

10.1.2.5 Best Overall Confirmed Response

Confirmation of CR and PR for determination of best overall response is required for studies with a primary endpoint that includes response.

Time Point Response First time	**Time Point Response Subsequent time point** ≥4 weeks from first time point	**BEST overall confirmed response**
C	CR	CR
C	PR	SD, PD or PR*
C R	SD	SD provided minimum criteria for SD duration met, otherwise, PD
C R	PD	SD provided minimum criteria for SD duration met, otherwise, PD
C R	NE	SD provided minimum criteria for SD duration met, otherwise, PD
P	CR	PR
P	PR	PR
P	SD	SD
P R	PD	SD provided minimum criteria for SD duration met, otherwise, PD
P R	NE	SD provided minimum criteria for SD duration met, otherwise, NE
N	NE	NE

*If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR or SD, not CR at the first time point. Under these circumstances, the original CR should be changed to PR or SD and the best response is PR or SD. PR as best overall response requires ≥4 weeks confirmation.

Patients with a global deterioration of health status requiring discontinuation of treatment or die without objective evidence of disease progression at that time should be reported to be off study treatment due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of

treatment.

10.1.2.6 Duration of Response:

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

10.1.2.7 Recurrence:

Recurrence is defined as newly evident disease for patients who have no evidence of disease at baseline or progressive disease for patients who have strictly non-measurable disease at baseline.

10.1.2.8 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from study entry to time of progression or death, whichever occurs first.

10.1.2.9 Survival

Survival is defined as the duration of time from study entry to time of death or the date of last contact.

10.1.3 irRECIST

10.1.3.1 Baseline Assessments in irRECIST

In irRECIST, baseline assessment and measurement of measurable/non-measurable and target/non-target lesions and lymph nodes are in line with RECIST 1.1

10.1.3.2 Follow-up Assessments in irRECIST

A. Follow-up recording of target and new measurable lesions

A key difference in irRECIST is that the appearance new lesions does not automatically indicate progression. Instead, all measured lesions (baseline-selected target lesions and new measurable lesions) are combined into the total measured tumor burden (TMTB) at follow up. Baseline-selected target lesions and new measurable lesions are NOT assessed separately. Measurements of those lesions are combined into the TMTB, and one combined assessment provided.

In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total,

per time point), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions should be prioritized according to size, and the largest lesions elected as new measured lesions.

B. Follow-up non-target assessment

RECIST 1.1 definitions for assessment of non-target lesions apply. The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD. In alignment with RECIST 1.1, baseline selected non-target lesions can never convert to measurable lesions, not even if they increase in size at subsequent time points and become measurable. Only true new lesions can be measured and contribute to the TMTB.

C. Follow-up for New Non-Measurable Lesions

All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the time point. Persisting new non-measurable lesions prevent irCR.

10.1.3.3 Overall Assessments for irRECIST

The irRECIST overall tumor assessment is based on TMTB of measured target and new lesions, non-target lesion assessment and new non-measurable lesions.
At baseline, the sum of the longest diameters (SumD) of all target lesions (up to 2 lesions per organ, up to total 5 lesions) is measured. At each subsequent tumor assessment (TA), the SumD of the target lesions and of new, measurable lesions (up to 2 new lesions per organ, total 5 new lesions) are added together to provide the total measurable tumor burden (TMTB).

Overall Assessments by irRECIST	
Complete Response (irCR)	Complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis.
Partial Response (irPR)	Decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions • If new measurable lesions appear in subjects with no target lesions at baseline, irPD will be assessed. That irPD time point will be considered a new

	baseline, and all subsequent time points will be compared to it for response assessment. irPR is possible if the TMTB of new measurable lesions decreases by ≥ 30% compared to the first irPD documentation • irRECIST can be used in the adjuvant setting, in subjects with no visible disease on CT/MRI scans. The appearance of new measurable lesion(s) automatically leads to an increase in TMTB by 100% and leads to irPD. These subjects can achieve a response if the TMTB decreases at follow-up, as a sign of delayed response. • Based on the above, sponsors may consider enrolling subjects with no measurable disease and/or no visible disease in studies with response related endpoints.
Stable Disease (irSD)	Failure to meet criteria for irCR or irPR in the absence of irPD
Progressive Disease (irPD)	Minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment. An irPD confirmation scan may be recommended for subjects with a minimal TMTB %-increase over 20% and especially during the flare time-window of the first 12 weeks of treatment, depending on the compound efficacy expectations, to account for expected delayed response. • In irRECIST a substantial and unequivocal increase of non-target lesions is indicative of progression. • IrPD may be assigned for a subject with multiple new non-measurable lesions if they are considered to be a sign of unequivocal massive worsening
Other	irNE: used in exceptional cases where insufficient data exist. irND: in adjuvant setting when no disease is detected irNN: no target disease was identified at baseline, and at follow-up the subject

	fails to meet criteria for irCR or irPD

10.1.4 Measurement Time Points

Tumor measurements will be taken and RECIST v1.1/irRECIST will be calculated from the scans (CT, PET CT or MRI brain, chest, abdomen, pelvis, to be determined by the attending physician) performed at baseline, end of treatment visit, and follow up visits.

10.2 Exploratory Outcome

10.2.1 Relevant Subset

All patients are in a single arm.

10.2.2 Measurement Definition

If funding is available, the exploratory outcomes will be assessed. A variety of optional immune response assays will be performed that include Luminex for 51 cytokines testing in serum or plasma, ELISA for MHC class 1 polypeptide-related sequence A (MYCA) and MHC class 1 polypeptide-related sequence B (MYCB) in serum or plasma, immunophenotyping including myeloid-derived suppressor cells (MDSC) and gamma/delta T cells, mass cytometry or CyTOF ICS with phorbol 12-myristate 13-acetate (PMA) + ionomycin stimulation (global immunocompetence assay). Optional tumor biopsies may also be collected to assess response to therapy and changes in immune cell subsets. Optional assays to access mutational burden/MSI and to measure polyomavirus in the blood may be performed dependent upon funding.

10.2.3 Measurement Methods

At each blood collection, 3 or 4 of 10cc heparin (green-top) tubes for PBMC will be used for intracellular cytokine staining (ICS), immunophenotyping and CyTOF assays, and 1 of 5cc SST (red-top) tube for serum will be used for Luminex and MYCA/MYCB assays. A minimum blood volume of 5ml per tube for the 10cc heparin tubes and 2.5ml per tube for the 5cc SST tube are acceptable for assays.

10.2.4 Measurement Time Points

The optional immune response testing will be performed at baseline, 2 weeks (±1 weeks) and 8 weeks (±1 weeks) after radiation therapy. Possible tumor biopsies (optional) may be performed before, during/after treatment to assess response to therapy and changes in immune cell subsets. Optional tests to assess polyomavirus in the blood may be performed at baseline and 3 months ± 1 month.

11. REGULATORY CONSIDERATIONS

11.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information

to all participating investigators.

11.2 Data and Safety Monitoring Plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

11.3 Data Management Plan

The Protocol Director, or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document treatment outcomes for data analysis. Case report forms will be developed using the OnCore database system and will be maintained by the CCTO OnCore team. CRFs will be kept in a locked office, only accessible to the research team."

12. STATISTICAL CONSIDERATIONS

12.1 Statistical Design

This is a single arm non-randomized open trial to determine the response rate for patients who are treated with both pembrolizumab and palliative radiation therapy.

12.1.1 Randomization

There is no randomization, as all patients are in a single arm.

12.2 Interim Analyses

An interim analysis for futility will be performed after 15 patients have completed the treatment phase. A response rate of 20% is expected, so if one or fewer of 15 patients have demonstrated a PR or CR, the study will be stopped for futility.12.3 Primary Analysis

Primary Endpoint: The determination of the complete response rate and the 95%CI using Wilson's method

12.3.1 Analysis Population

All Treated Subjects: All subjects who received at least
one dose of pembrolizumab and completed the prescribed course of palliative radiation therapy.

12.3.2 Analysis Plan

Data will be summarized using appropriate descriptive statistics: proportions with Wilson's 95% confidence intervals, means, standard deviations, ranges, and Kaplan-Meier estimates for time to event data. The toxicity rates will be monitored continuously and a final count of toxicities will be performed.

12.4 Secondary Analysis

Secondary endpoints: Response rate, overall survival, and duration of response (please see section 10.1).

12.4.1 Analysis Population

All Treated Subjects: All subjects who received at least one dose of pembrolizumab and completed the prescribed course of palliative radiation therapy.

12.4.2 Analysis Plan

Data will be summarized using appropriate descriptive statistics: proportions with Wilson's 95% confidence intervals, means, standard deviations, ranges, and Kaplan-Meier estimates for time to event data. The toxicity rates will be monitored continuously and a final count of toxicities will be performed.

12.5 Sample Size

A sample of 30 patients would provide 87% power to ensure a half-width of 15.5% of the 95% confidence interval using Wilson's method assuming that the observed rate is 20%. If the observed rate is exactly 20% then the 95%CI using Wilson's method will be [9.5%, 37.3%].

13. REFERENCES

1. Alam M, Bordeaux JS, Yu SS (Eds.). (2013). Merkel Cell Carcinoma. Springer Press.
2. Amin MB, et. Al. (Eds.). (2017). AJCC Cancer Staging Manual, Eight Edition. Springer Press.
3. Zaar O, Gillstedt M, Lindelöf B, Wennberg-LarköAM, Paoli J. J Eur Acad Dermatol Venereol. 2016;30(10):1708.
4. MacDonald M, You J. Merkel Cell Polyomavirus: A New DNA Virus Associated with Human Cancer. Adv Exp Med Biol. 2017;1018:35-56.
5. Clarke CA, Robbins HA, Tatalovich Z, Lynch CF, Pawlish KS, Finch JL, Hernandez BY, Fraumeni JF Jr, Madeleine MM, Engels EA. Risk of merkel cell carcinoma after solid organ transplantation. J Natl Cancer Inst. 2015;107(2) Epub 2015 Jan 8.
6. Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, Shih KC, Lebbé C, Linette GP, Milella M, Brownell I, Lewis KD, Lorch JH, Chin K, Mahnke L, von Heydebreck A, Cuillerot JM, Nghiem P. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol. 2016 Oct;17(10):1374-1385. doi: 10.1016/S1470-2045(16)30364-3. Epub 2016 Sep 1.
7. Nghiem PT, Bhatia S, Lipson EJ, Kudchadkar RR, Miller NJ, Annamalai L, Berry S, Chartash EK, Daud A, Fling SP, Friedlander PA, Kluger HM, Kohrt HE, Lundgren L, Margolin K, Mitchell A, Olencki T, Pardoll DM, Reddy SA, Shantha EM, Sharfman WH, Sharon E, Shemanski LR, Shinohara MM, Sunshine JC, Taube JM, Thompson JA, Townson SM, Yearley JH, Topalian SL, Cheever MA. Durable tumor regression and overall survival (OS) in patients with advanced Merkel cell carcinoma receiving pembrolizumab as first-line therapy. J. Clin Oncol 2018:36 (suppl. Abstr 9506).
8. Green MD, Hayman JA. Radiotherapy in the Multidisciplinary Management of Merkel Cell Carcinoma. J Natl Compr Canc Netw. 2018 Jun;16(6):776-781. doi: 10.6004/jnccn.2018.7045.
9. Hiniker SM, Chen DS, Knox SJ. Abscopal effect in a patient with melanoma. N Engl J Med. 2012 May 24;366(21):2035; author reply 2035-6. doi: 10.1056/NEJMc1203984.
10. Barker CA, Postow M, Goldman DA, Panageas KS, Halpenny D, McCabe D, Macri M, Schwarzenburger P, Ricciardi R, Ryan A, Venhaus R, Knox SJ. A Phase I Clinical Trial of Ipilimumab, Nivolumab and Radiotherapy for Patients with Metastatic Melanoma. 2018. ASTRO, San Antonio, TX.
11. Eisenhauer, E.A., et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Ca 2009;45: 228-247.
12. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009;15(23):7412-20.

APPENDICES:

APPENDIX 1**: ECOG PERFORMANCE STATUS**

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

* Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649-655.

APPENDIX 2: **PARTICIPANT ELIGIBILITY CHECKLIST**

A Participant Eligibility Checklist must be completed in its entirety for each subject prior to registration. The completed, signed, and dated checklist must be retained in the patient's study file.

The study coordinator, treating physician and an independent reviewer must verify that the participant's eligibility is accurate, complete, and legible in source records. A description of the eligibility verification process should be included in the EPIC or other Electronic Medical Record progress note.**I. Protocol Information:**

Protocol Title:	A Phase II Study of Palliative Radiation Therapy and Anti-PD-1/PD-L1 Checkpoint Blockade in Patients with Metastatic Merkel Cell Carcinoma**,** Amendment 2, September 10, 2019
Protocol Number:	OnCore: SKIN0047 IRB: 50888
Principal Investigator:	Susan J Knox, PhD, MD

II. Subject Information:

Subject ID/Initial:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC Approved ☐ IRB Approved ☐

IV. Inclusion/Exclusion Criteria

	Patient Selection	**Window**	**Last Date to Register**	**Supporting Documentation**	**Location of Document**	**Yes**	**No**
	Signed and Dated Informed Consent Form	NA		Signed ICF date:		☐	☐
3.1.1	Histologically confirmed metastatic or locally advanced Merkel Cell Carcinoma (includes in-transit or bilateral bulky disease) with at least two distinct sites of disease.	NA		Bx Date:		☐	☐
3.1.2	Subjects with brain metastases and/or carcinomatous meningitis are eligible providing they are neurologically	NA				☐	☐

	stable (if systemic steroids are required, subjects should be stable on the lowest clinically effective dose, as steroids may interfere with the activity of immunotherapy if administered at the time of the first Anti-PD-1/PD-L1 dose.)						
3.1.3	Must be at least 14 days since treatment for MCC, and recovered (baseline or residual non ir Grade 1 toxicity or ir Grade 2 toxicity at the investigator's discretion, see section 4.1.1) from any clinically significant toxicity experienced during treatment before the first dose of on study pembrolizumab therapy.	NA				☐	☐
3.1.4	Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2	28 days		ECOG Date:		☐	☐
3.1.5	Life expectancy of ≥ 16 weeks.	NA				☐	☐
3.1.6	Subjects must have measurable disease according to RECIST v1.1, and have baseline (screening/baseline) radiographic images, (e.g. CT, PET CT or MRI brain, chest, abdomen, pelvis, to be determined by the attending physician) within 4 weeks of confirmation of eligibility and within 6	4 weeks		Imaging Type: Imaging Date:		☐	☐

	weeks before the initiation of on study pembrolizumab therapy.						
3.1.7	Required values for initial laboratory tests: -WBC: ≥ 2000/µL (~ 2 x 10^9/L) -ANC: ≥ 1000/µL (~ 1 x 10^9/L) -Platelets: ≥ 50 x 10^3/µL (~ 50 x 10^9/L) -Hemoglobin: ≥ 8 g/dL -Calculated creatinine clearance (eGFR) greater than 30mL/min -AST/ALT: Less than 2.5 x ULN for subjects without liver metastasis, less than 5 times ULN for liver metastases -Bilirubin: less than 3.0 x ULN (except for subjects with Gilbert's Syndrome, who must have a total bilirubin of less than 3.0 mg/dL) -Non-clinically significant laboratory abnormalities such as lipase elevation would not be an exclusion.	4 weeks		Lab Date: WBC: ANC: Platelets: Hemoglobin Creatinine clearance: AST: ALT: Bilirubin:		☐	☐
3.1.8	No known active or chronic infection with HIV, Hepatitis B, or Hepatitis C, or active infection requiring systemic antibiotics. Testing for the above is not required unless clinically suspected.	NA				☐	☐
3.1.9	At least one measurable site of disease (≥ 10 mm as per RECIST v1.1 except for lymph nodes	4 weeks				☐	☐

	that must be 15 mm or greater on the short axis) outside of the planned palliative radiation therapy field.						
3.1.10	Require radiation therapy for palliation of symptoms or to prevent local progression of disease and associated complications and/or symptoms from metastases.	4 weeks				☐	☐
3.1.11	Men and women, at least 18 years of age.	NA				☐	☐
3.1.12	Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study [and for up to 26 weeks after the last dose of investigational product] in such a manner that the risk of pregnancy is minimized. WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Post-menopausal is defined as: • Amenorrhea ≥ 12 consecutive months without another cause, or	6 week before therapy		Preg. Test Date:		☐	☐

	• For women with irregular menstrual periods and on hormone replacement therapy (HRT), a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (e.g., vasectomy) should be considered to be of childbearing potential. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 6 week prior to the start of investigational product.						
3.1.13	Men of fathering potential must be using an adequate method of contraception to avoid conception throughout the study [and for up to 26 weeks after the last dose of investigational product] in such a manner that the risk of pregnancy is minimized.	NA				☐	☐

	Conditions for Patient Ineligibility						
3.2.1	WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study and for up to 26 weeks after the last dose of investigational product.	NA				☐	☐
3.2.2	Women who are breastfeeding.	NA				☐	☐
3.2.3	WOCBP with a positive pregnancy test within 6 weeks before enrollment.	6 week before therapy		Preg. Test Date:		☐	☐
3.2.4	Autoimmune disease: Poorly controlled autoimmune disease is excluded. Well controlled autoimmune disease (e.g. well controlled RA) will be assessed by the study team and a decision made regarding eligibility based on the degree of immunosuppression and severity of symptoms.	NA				☐	☐
3.2.5	Any subject who has a life-threatening condition that requires high-dose immunosuppressant(s). Steroid doses greater than 20 mg/day will exclude the patient from participation in the trial.	NA				☐	☐
3.2.6	Presence of known hepatitis B or hepatitis C infection, regardless of control on antiviral	NA				☐	☐

	therapy.						
3.2.7	Subjects who have another active, concurrent, malignant disease are not eligible, with the exception of subjects with adequately treated basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix, or other cancers that are in remission/not measurable. Patients will be excluded if they have any known additional malignancy that requires active treatment while on treatment for Merkel Cell Carcinoma.	NA				☐	☐
3.2.8	Evidence of symptomatic interstitial lung disease or symptomatic active, noninfectious pneumonitis.	NA				☐	☐
3.2.9	Participants with impaired cardiac function or clinically significant cardiac disease such as unstable angina/uncompensated heart failure, uncontrolled symptomatic arrhythmia.	NA				☐	☐
3.2.10	Chronic or current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment. This exclusion does not include prophylactic antibiotics or topical antibiotics.					☐	☐
3.2.	Known hypersensitivity to another monoclonal	NA				☐	☐

11	antibody, which cannot be controlled with standard measures (e.g. antihistamines and corticosteroids).						
3.2.12	Any condition that would, in the investigator's judgment, interfere with full participation in the study.	NA				☐	☐
3.2.13	Prisoners or subjects who are involuntarily incarcerated.	NA				☐	☐
3.2.14	Subjects with acute or poorly controlled psychiatric illness or subjects who are compulsorily detained for physical (e.g., infectious disease) illness, with the exception of patients that are well supported and able to participate (e.g. paraplegia from a motor vehicle accident).	NA				☐	☐
3.2.15	Any underlying medical or psychiatric condition that, in the opinion of the investigator, could make the administration of anti-PD-1/PD-L1 hazardous or could obscure the interpretation of adverse events.	NA				☐	☐
3.2.16	Any live vaccine therapy for up to 4 weeks before or after any dose of immunotherapy on this trial.	NA				☐	☐

*All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

IV. Statement of Eligibility

This subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. By signing this form, I verify the subject's eligibility. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	