A RANDOMIZED PHASE II STUDY OF ANTI-PD1 ANTIBODY [MK-3475 (PEMBROLIZUMAB)] ALONE VERSUS ANTI-PD1 ANTIBODY PLUS STEREOTACTIC BODY RADIATION THERAPY IN ADVANCED MERKEL CELL CARCINOMA

Registration Eligibility Criteria (See Section 3.2)

Pathologically (histologically or cytologically) proven diagnosis of MCC by local pathology review.

Have measurable disease based on RECIST 1.1 with at least two cancerous deposits. At least one deposit must be RECIST measurable while at least ***one deposit*** must meet criteria for SBRT (See Section 7.1)

Advanced or metastatic MCC defined as evidence of distant metastasis(es) on imaging.

No prior immunotherapy for advanced/metastatic MCC (prior palliative RT is allowed as long as there are two unirradiated measurable cancerous deposits

No History of the following:

- Autoimmunity requiring systemic immunosuppression within 2 years
- Patients known to be HIV positive are eligible if they meet the following criteria within 30 days prior to registration: stable and adequate CD4 counts (≥ 350 mm^3), and serum HIV viral load of < 25,000 IU/ml. Patients may be on or off antiviral therapy so long as they meet the CD4 count criteria.

No other active malignancy that the investigator determines would interfere with treatment and safety analysis.

Not pregnant and not nursing (See Section 3.2)

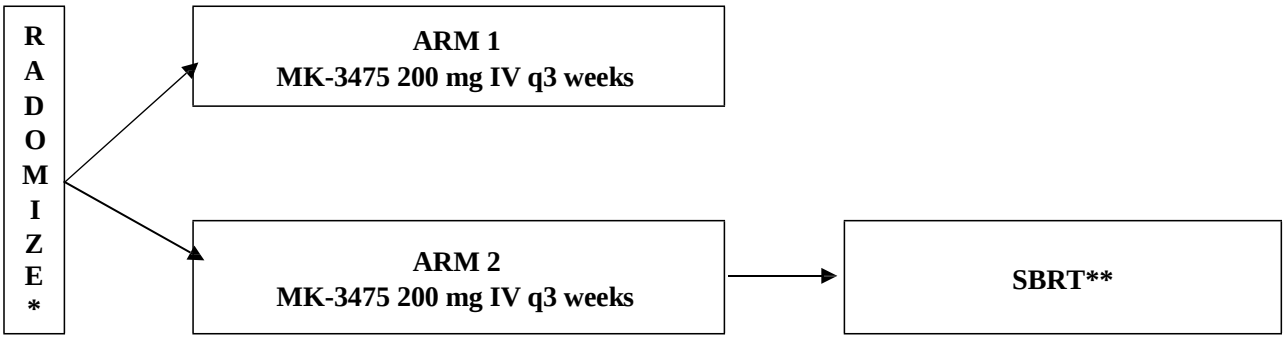
Age ≥ 18

ECOG performance status 0 - 2

Required Initial Laboratory Values	
Absolute neutrophil count (ANC)	≥ 1500/mm^3
Platelet Count	≥ 100,000/mm^3
Hemoglobin	≥ 9.0g/dl
Total Bilirubin	≤ 2.0 mg/dl
AST / ALT	≤ 3.0 x ULN WNL*
Systolic BP	≤150 mg HG
Diastolic BP	≤ 90 mg HG
Albumin	>3mg/dl
BUN	≤30 mg/dl
Creatinine	≤1.7 mg/dl
* Supplementation acceptable	

Schema

1 Cycle = 21 Days



* All sites have identified the metastasis to be irradiated in the event their patient is randomized to arm 2.

** Radiation therapy will be administered to 1 cancer deposit concurrent with the first dose or started within the first cycle of MK-3475 administration. This cancer deposit to be irradiated will be defined prior to randomization and treatment per the guidelines in Section 7.1.

Treatment is to continue until disease progression or unacceptable adverse event for a maximum period of two years. Patients will be followed for 5 years or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Include as applicable: Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.2 Eligibility Criteria

___ 3.2.1 Documentation of Disease:

Patients must have pathologically (histologically or cytologically) proven diagnosis of MCC by local pathology review.

___ 3.2.2 Measurable disease and/or non-measurable disease as defined in Section 11.0.

Have measurable disease based on RECIST 1.1 including at least two cancerous deposits. At least one deposit must be RECIST measurable while at least ***one deposit*** must meet criteria for SBRT (See Section 7.1). Non-radiated tumor will be identified prior to randomization on the protocol.

___ **3.2.3 Patients must have advanced or metastatic MCC defined as evidence of distant metastasis(es) on imaging.**

- Patients with locoregionally confined disease are not eligible.

___ **3.2.4 Prior Treatment**

- No prior immunotherapy for advanced/metastatic MCC
- Patients with known or suspected CNS metastases, untreated CNS metastases, or with the CNS as the only site of disease are excluded. However, subjects with controlled brain metastases will be allowed to enroll. Controlled brain metastases are defined as no radiographic progression for at least 4 weeks following radiation and/or surgical treatment (or 4 weeks of observation if no intervention is clinically indicated), and off of steroids for at least 2 weeks, and no new or progressive neurological signs and symptoms
- Patients having received palliative radiotherapy for extracranial metastasis(es) are eligible as long as there are 2 cancerous deposits that have not received prior RT and they meet the following criteria.
    - No prior radiation therapy (>5 Gy) to the metastasis intended to be treated with SBRT

___ **3.2.5 No History of the following:**

- Autoimmunity requiring systemic immunosuppression within 2 years
- Patients known to be HIV positive are eligible if they meet the following:
    - CD4 counts $\geq$ 350 mm^3
    - Serum HIV viral load of <25,000 IU/ml.

___ **3.2.6 No other active malignancy that the investigator determines would interfere with the treatment and safety analysis.**

___ **3.2.7 Not pregnant and not nursing,** because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.

Therefore, for women of childbearing potential only, a negative (if your test schedule specifically indicates a urine or serum pregnancy test, add that information at this point) pregnancy test done $\leq$ 28 days prior to registration is required.

___ **3.2.8 Age $\geq$ 18 years**

___ **3.2.9 ECOG Performance Status 0-2**

___ **3.2.10 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC)	$\geq$ 1,500/mm^3
Platelet Count	$\geq$ 100,000/mm^3
Hemoglobin	$\geq$ 9.0g/dl
Total Bilirubin	$\leq$ 2.0 mg/dl
AST / ALT	$\leq$ 3.0 x ULN
Systolic BP	$\leq$150 mg HG
Diastolic BP	$\leq$ 90 mg HG
Albumin	>3mg/dl
BUN	$\leq$30 mg/dl
Creatinine	$\leq$1.7 mg/dl