Alliance A091605: 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

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Rationale

Merkel cell carcinoma (MCC) is a rare but extremely aggressive cutaneous malignancy. Risk factors for developing MCC include chronic ultraviolet light exposure as well as immuno-suppression.[1,2] Approximately 80-90% of MCC are associated with infection by the Merkel cell polyomomavirus, which leads to oncogenic expression of viral proteins, including the large and small T antigens.[3,4] Approximately 40% of patients with MCC develop metastatic disease with a median overall survival of approximately 9.5 months.[5]

Standard treatment for metastatic MCC has historically included platinum-based chemotherapy with radiation therapy reserved for palliation in appropriate symptomatic patients.[6] However, given poor survival in metastatic MCC, novel treatment strategies are needed. One such strategy is using immune-based therapies to treat metastatic MCC. Blockade of the PD1/L1 axis particularly has been an attractive target given the known association of PD-L1 expression in virally infected cells. Despite the ability to get good responses with anti-PD1/L1 therapy, the median progression-free survival is only nine months indicating that while an important step forward, this treatment paradigm needs to be augmented to improve response rates and survival of metastatic MCC patients.

Radiation therapy has long been used to treat MCC. Newer radiation techniques, such as stereotactic body radiotherapy (SBRT) deliver single or few radiation treatments at doses 2-10 times that of conventional radiation treatments.[7] SBRT reduces the overall time of radiation treatment and offers a greater potential for cell kill compared to standard fractionation schemas. The combination of SBRT and anti-PD-1/PD-L1 treatment may not only have improved treated tumor control, but may also have improved overall progression-free survival if SBRT enhances the effect of systemic therapy.

1 - Prieto, I., et al., Merkel cell carcinoma: An algorithm for multidisciplinary management and decision-making. Crit Rev Oncol Hematol, 2016. 99: p. 170-9. 2 - Wong, S.Q., et al., UV-Associated Mutations Underlie the Etiology of MCV-Negative Merkel Cell Carcinomas. Cancer Res, 2015. 75(24): p. 5228-34. 3 - Goh, G., et al., Mutational landscape of MCPyV-positive and MCPyV-negative Merkel cell carcinomas with implications for immunotherapy. Oncotarget, 2016. 7(3): p. 3403-15. 4 - Feng, H., et al., Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science, 2008. 319(5866): p. 1096-100. 5 - Miller, N.J., et al., Emerging and mechanism-based therapies for recurrent or metastatic Merkel cell carcinoma.Curr Treat Options Oncol, 2013. 14(2): p. 249-63. 6 - Poulsen, M., et al., High-risk Merkel cell carcinoma of the skin treated with synchronous carboplatin/etoposide and radiation: a Trans-Tasman Radiation Oncology Group Study--TROG 96:07. J Clin Oncol, 2003. 21(23): p. 4371-6. 7 - Kirkpatrick, J.P., et al., Stereotactic body radiotherapy: A critical review for non-radiation oncologists. Cancer, 2013

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Objective

Primary

- To describe the PFS of SBRT + MK-3475compared to MK-3475 alone in advanced/metastatic MCC patients.

Secondary

- To describe the PFS of SBRT + MK-3475 compared to MK-3475 alone across RECIST measurable (including both radiated and non-radiated) cancer deposits.
- To describe the overall response rate of SBRT + MK-3475 compared to MK-3475 alone in both radiated and in non-radiated deposit(s).
- To determine the PFS at 6 months of SBRT + MK-3475 compared to MK-3475 alone across all cancerous deposits by RECIST.
- To determine the rate of grade >3-4 adverse events, by organ system, by CTCAEv4.0.
- To determine the local control of SBRT treated tumors.
- To calculate delivered radiation dose using cone-beam CT images collected on the radiation treatment table in the final treatment position.

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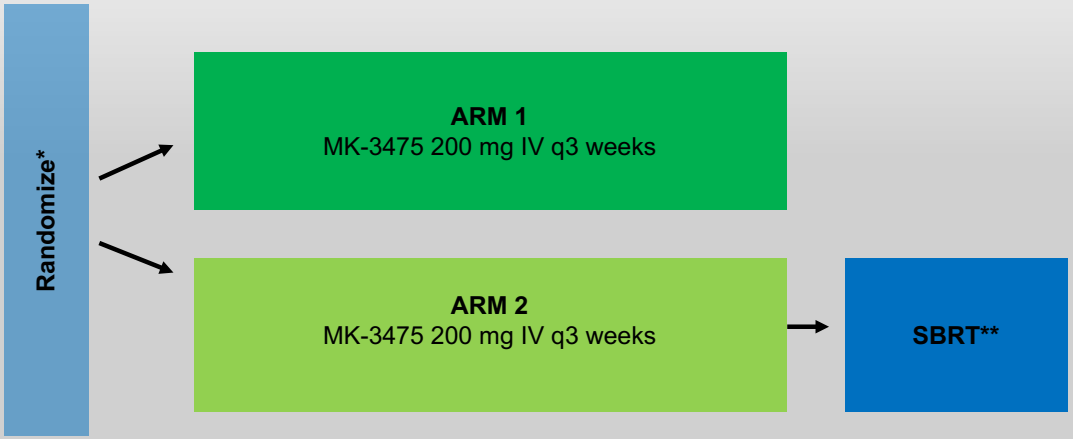
Study Schema



*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 protocol.

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.

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Correlative and Companion Studies

There is specimen biobanking for this study for future use and all patients are encouraged to participate.

Biobanking for Future Correlative Science

Blood, tissue, and stool specimens will be collected and stored for future translational research for patients who consent to participate. Testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies. Future studies may include the following aims:

Hypotheses/Aims

1. Gene expression profiling based on T cell based immune signatures may better predict response or lack of response to monotherapy anti-PD1 and may suggest expression phenotypes where the addition of radiation can facilitate response.*

a) Gene expression profiling assays have a robust capacity to capture the tumor-immune microenvironment with prior analysis from metastatic melanoma clearly correlating with treatment outcomes to immunotherapy.[1-3] Further in prior studies of MK-3475 in head and neck, gastric, urothelial cancers and melanoma, large datasets have supported gene expression as harboring a greater ability to stratify treatment response relative to PD-L1 immunohistochemistry.[4-7] Further, IHC for PD-L1 as well as Merkel-cell polyomavirus did not show statistically significant associations with treatment outcomes in the NEJM report of MK-3475, though sample sizes were small.[8]

2. The intensity and/or location of staining for CD8 and PD-L1 by immunohistochemistry may differentiate responding vs. non-responding patients to monotherapy anti-PD1 or radiation with immunotherapy.*

a) Though statistically significant associations have not been observed for PD-L1 and CD8 in MCC to date, the sample sizes investigated were small and such associations have been observed in other tumors[32].

3. Tumor intrinsic mutations or mutational load may predict resistance or response to anti-PD-1 and/or the combination of radiation and immunotherapy.*

a) Multiple papers have demonstrated associations between mutational load and treatment outcome to anti-PD1 immunotherapy. Further, a hypothesis in the field of MCC has been that non-Merkel-cell polyomavirus associated tumors may have a high response rate due to the presence of increase mutational load (and by extrapolation neoantigen burden).

b) Recent reports have suggested that de novo or acquired resistance to immuno-therapy can be mediated via mutation in JAK/STAT signaling or the antigen processing machinery.[9] Exploratory DNA based genomic analysis will thus be particularly of interest in any patients who have no clinical benefit to this approach of radiation with PD1 Ab.

4. Single nucleotide polymorphisms from the germline DNA may be identified that portend an improved response phenotype to immunotherapy.

a) The identification of SNPs in immune regulatory genes is an area of increasing interest in the field of immunotherapy. At the University of Chicago, we have identified multiple such targets (data unpublished) and several commercial entities are also moving forward in this space (personal communication Foundation Medicine and Nanostring technologies).

5. The composition of the fecal microbiota may predict the likelihood or response or toxicity to anti-PD1 or radiation with immunotherapy.

a) We and other groups have previously identified an important role for the gut microbiome in modulating both immunotherapy treatment response outcome as well as toxicity.[10-12]

6. Changes in MCPyV specific T lymphocytes and other circulating factors such as MCPyV small T-antigen oncoprotein antibody titers will associated with outcomes to immunotherapy.

1 - Harlin, H., et al., Chemokine expression in melanoma metastases associated with CD8+ T-cell recruitment. Cancer Res, 2009. 69(7): p. 3077-85 ; 2 - Ji, R.R., et al., An immune-active tumor microenvironment favors clinical response to ipilimumab. Cancer Immunol Immunother, 2011; 3 - Topalian, S.L., et al., Safety, activity, and immune correlates of anti-PD-1 antibody in cancer.N Engl J Med, 2012. 366(26): p. 2443-54; 4 - Ribas A, R.C., Hodi FS, Wolchok JD, Joshua AM, Hwu WJ, Weber JS, Zarour HM, Kefford R, Loboda A, Allnright A, Kang SP, Ebbinghaus S, Yearley J, Murphy E, Nebozhyn E, Lunceford JK, McClanahan T, Ayers M, Daud A, Association of response to programmed death receptor 1 (PD-1) blockade with pembrolizumab (MK-3475) with an interferon-inflammatory immune gene signature.J Clin Oncol 33, 2015 (suppl; abstr 3001); 5 - Sekwert, T.Y., et al., Inflamed-phenotype gene expression signatures to predict benefit from the anti-PD-1 antibody pembrolizumab in PD-L1+ head and neck cancer patients. J Clin Oncol 33, 2015 (suppl; abstr 6017); 6 - Shankaran, V., et al., Correlation of gene expression signatures and clinical outcomes in patients with advanced gastric cancer treated with pembrolizumab (MK-3475). J Clin Oncol 33, 2015 (suppl; abstr 3026); 7 - Plimack, E.R., et al., Pembrolizumab (MK-3475) for advanced urothelial cancer: Updated results and biomarker analysis from KEYNOTE-012. J Clin Oncol 33, 2015 (suppl; abstr 4502); 8 - Nghiem, P.T., et al., PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. N Engl J Med, 2016; 9 - Zaretsky, J.M., et al., Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma. N Engl J Med, 2016. 375(9): p. 819-29; 10 - Sivan, A., et al., Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science, 2015. 350(6264): p. 1084-9; 11 - Vétizou, M., et al., Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science, 2015. 350(6264): p. 1079-84; 12 - Dubin, K., et al., Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis. Nat Commun, 2016. 7: p. 10391.

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Key Eligibility Criteria

Inclusion Criteria

- Histologically or cytologically proven diagnosis of MCC by local pathology review
- Measurable disease based on RECIST 1.1 including at least 2 cancerous deposits; at least 1 deposit must be RECIST measurable while at least 1 deposit must meet criteria for SBRT; non-radiated tumor will be identified prior to randomization on the protocol
- Advanced or metastatic MCC defined as evidence of distant metastasis(es) on imaging; patients with locoregionally confined disease are not eligible
- No prior immunotherapy for advanced/metastatic MCC
- Patients with known or suspected central nervous system (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 radiation therapy (RT) and they meet the following criteria; no prior radiation therapy (> 5 Gy) to the metastasis intended to be treated with SBRT
- No history of the following:
  - Autoimmunity requiring systemic immunosuppression within 2 years
  - Patients known to be human immunodeficiency virus (HIV) positive are eligible if they meet the following: 1) CD4 counts >= 350 mm^3; 2) Serum HIV viral load of < 25,000 IU/ml

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