Journal of Nuclear Medicine, published on September 2, 2021 as doi:10.2967/jnumed.121.262344

Response to combined peptide receptor radionuclide therapy and checkpoint immunotherapy with ipilimumab plus nivolumab in metastatic Merkel cell carcinoma

Running title: Immunotherapy and PRRT in MCC

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Word count: 2498

Keywords: immunotherapy, PRRT, SSTR, Merkel cell carcinoma, PD-L1

Abstract

For patients with Merkel cell carcinoma (MCC) who are refractory to immune checkpoint inhibition (ICI), treatment options are limited. Few cases of MCCs were reported to show responses upon peptide receptor radionuclide therapy (PRRT). A combination of PRRT and ICI has not been reported in MCC to date.

A patient with metastatic MCC, who was resistant to first-line avelumab and acquired resistance to ipilimumab/nivolumab (IPI/NIVO) with additional RT, presented with multiple distant metastases. After confirmation of SSTR expression, treatment was continued with additional four doses of IPI/NIVO combined with two cycles of PRRT. Treatment was well tolerated with transient hematoxicity and mild nausea. Re-staging after three months demonstrated an exceptional response.

This case demonstrates the feasibility of combined treatment with IPI/NIVO and PRRT as an option for MCC patients progressing under ICI. Prospective evidence confirming additive value of combining ICI and radionuclide therapy in a larger cohort is needed.

INTRODUCTION

Merkel cell carcinoma (MCC) is an aggressive form of neuroendocrine skin cancer. In the United States, the incidence of MCC is around 0.8 per 100,000 and the numbers continue to rise. Metastatic MCC (mMCC) is characterized by a particularly poor prognosis, with a 5-year overall survival rate of approximately 30%. (*1*)

Based on the high immunogenicity of MCC and the need for more effective therapies immune checkpoint inhibitors (ICI) were successfully introduced for first- and second-line treatment of mMCC. (*2*) Similar to many other neuroendocrine malignancies, MCC expresses somatostatin receptors (SSTR) enabling receptor-targeted positron emission tomography (SSTR-PET) and peptide receptor radionuclide therapy (PRRT). (*3*)

PRRT led to significantly prolonged survival compared to treatment with somatostatin analogues in patients with neuroendocrine tumors of the midgut. (*4*) PRRT for mMCC exhibited promising response in few case reports. (*5-7*) Here, we report the case of a patient with mMCC who progressed upon multiple lines of ICI and subsequently responded well to a combined therapy of ipilimumab plus nivolumab ICI and somatostatin PRRT.

MATERIALS AND METHODS

A 60-year old, immune competent man presented with a red lump on his right upper thigh. Surgical excision and histopathology revealed a high-grade MCC with positive margins. Sentinel lymph node biopsy confirmed nodal involvement. The tumor was MCPyV-positive with low tumor mutational burden but lacked significant PD-L1 expression.

Initial TNM stage was pT2 pN1b cM0. Subsequently, the patient received adjuvant radiotherapy to the tumor bed (60 Gy) and the draining lymph node region (50 Gy). Follow-up CT staging demonstrated multiple enlarged retroperitoneal lymph nodes, indicative of metastases

(Figure 1). Systemic treatment with avelumab 800 mg q2w was initiated and tolerated well but imaging after four doses of avelumab revealed progressive disease (Figure 1). The immunotherapeutic regimen was switched to ipilimumab 3 mg/kg and nivolumab 1 mg/kg q3w (IPI/NIVO) which was accompanied by severe diarrhoea requiring treatment interruption. Additionally, radiotherapy (50.4 Gy) of the retroperitoneal lymph nodes was performed and resulted in a partial response (Figure 1). At the same time, the patient took artesunate supplements (*8*) and received multiple administrations of Newcastle disease virus – both treatments were given on the patient's own initiative outside of our center. (*9*)

Shortly after pausing immunotherapy, the patient developed oligoprogression with new bone metastases and started supportive treatment with denosumab and palliative radiation therapy delivered to selected bone metastases of the spine. After recovering from the previous immune-related toxicity, the patient started on nivolumab 480 mg q4w maintenance therapy but again progressed dramatically within 30 days with several new skeletal lesions.

Re-staging with SSTR-PET confirmed high levels of SSTR-expression at all sites of disease (bone and lymph nodes). We therefore decided to re-challenge the patient with IPI/NIVO together with PRRT. Written informed consent for publication was obtained from the patient.

RESULTS

The patient received a cumulative activity of 14.8 GBq ^{177}Lu-DOTATOC over two cycles of PRRT. (*4*). Post-treatment scintigraphy was performed to verify retention of the radionuclide in tumor lesions (Figure 2**).** IPI/NIVO was given as ipilimumab 3 mg/kg and nivolumab 1 mg/kg q3w. The treatment was well tolerated with transient grade 3 leukopenia, mild nausea (grade 2), and auto-immune related thyroiditis (CTCAE grade 1). After two cycles of PRRT and 4 doses of IPI/NIVO, we performed re-staging with SSTR-PET . Here, we noted a marked response of

multiple skeletal lesions (Figure 2). However, we found one new lymph node metastasis on the left side of the neck, which was excised and histologically confirmed as MCC. Increased SSTR-PET uptake in the thyroid was rated as thyroiditis. Due to good treatment response in the imaging and his good clinical condition, the patient currently continues PRRT with a 50% reduced dose (3.8 GBq/cycle) together with maintenance nivolumab 480 mg q4w. At time of submission, the patient had ongoing response for five months.

DISCUSSION

Introduction of ICI greatly improved patient outcomes in advanced MCC. (*10*) However, half of patients either primarily do not respond or exhibit acquired resistance. Our patient eventually progressed during all immunotherapeutic regimens but initially responded well to a combination ICI with IPI/NIVO. We therefore decided on an individual salvage regimen with re-induction of IPI/NIVO and addition of PRRT.

Radiation leads to immunogenic cell death and activation of immune effector cells, which could enhance efficacy of ICI therapy. (*11*) Further, radiation alters the microenvironment of tumors via the expression of chemokines and release of (neo-)antigens, allowing for immune cell infiltration of irradiated tissue. (*12*) Conversely, ICI therapy may enhance the therapeutic effects of radiation by counteracting tumor hypoxia and influx of myeloid-derived suppressor cells, which are known mechanisms of radioresistance. (*13*)

In contrast to external beam radiation therapy, PRRT delivers radiation to every metastatic lesion with target expression. In the phase III NETTER-1 trial PRRT led to prolonged progression-free survival and improved quality of life in patients with midgut neuroendocrine tumors (NETs) compared to therapy with somatostatin analogues. (*4*) Generally, PRRT is well tolerated with lymphopenia, nausea and fatigue as most frequent but often mild adverse effects. (*4*) MCCs often

express SSTR at moderate to high levels and are thus amenable to PRRT. (*14*) In our patient, SSTR-PET prior to treatment initiation revealed high and homogenous expression of SSTR.

There is increasing interest in combining radionuclide therapy and ICI therapy. Promising preclinical data shows that ICI enhances radionuclide therapy in prostate cancer (*15*) and two clinical trials are underway (NCT03658447 & NCT03805594). In a recent phase Ib trial in patients with NET of the lung, combined PRRT and nivolumab was well tolerated and showed signs of antitumor activity. (*16*) Disease control was achieved in 3/9 (33%) patients.

The National Comprehensive Cancer Network (NCCN) guidelines have implemented the use of PRRT for several NET, but not yet for MCC. (*17*) To date, there have only been few reported cases of successful PRRT in mMCC (*5*-*7*) and no cases of combined PRRT and immunotherapy. Recently, the GoTHAM trial (NCT04261855) was launched and investigates the efficacy of first-line avelumab plus PRRT for the treatment of mMCC. The three-armed design compares avelumab, avelumab plus radiotherapy, or avelumab plus PRRT, and stratifies patients by SSTR-expression level. Results of this trial will shed light on the added value of radiation to ICI therapy. However, survival data is not expected before 2024. Trials evaluating PRRT as monotherapy in MCC are also urgently needed, ideally comparing PRRT to PRRT + ICI. Meanwhile, PRRT alone or in combination with ICI therapy will be reserved for individuals who failed other therapeutic regimens. Our case underlines the intriguing promise of radionuclide therapy potentially turning immunotherapy-unresponsive into immunotherapy-responsive tumors.

CONCLUSION

We report response to combined IPI/NIVO plus PRRT in a patient with mMCC refractory to multiple previous ICI regimens. While a prospective clinical trial is underway, our case

highlights the need for rapid clinical development of combination strategies for patients with no response to immunotherapy alone.

ACKNOWLEDGMENTS

Funding: none.

Competing interests:

WPF is a consultant for BTG and Parexel/Calyx, and he received fees from RadioMedix, Bayer, and Parexel outside of the submitted work. LZ reports honoraria from Roche, Bristol Myers Squibb, MSD, Novartis, Pierre Fabre; consultancy or advisory role from Bristol Myers Squibb, Novartis, Pierre Fabre, Sun Pharma, Sanofi, MSD; research funding from Novartis; travel support from Bristol Myers Squibb, Pierre Fabre, Sanofi, Amgen, Novartis, Sun Pharma. EL served as consultant and/or has received honoraria from Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Janssen, Medac, Sanofi, Sunpharma and travel support from Amgen, Merck Sharp & Dohme, Bristol-Myers Squibb, Pierre Fabre, Sunpharma and Novartis, outside the submitted work. DS acted as a speaker for, participated in an advisory board for, received research funding, and/or received honoraria from 4SC Amgen; Array BioPharma; Bristol-Myers Squibb; Immunocore; Incyte; InFlarX; Helsinn; Merck Serono; Merck Sharp & Dohme; Nektar, Neracare; Novartis; OncoSec, Pfizer; Philogen; Pierre Fabre; Regeneron Pharmaceuticals; Replimune, Roche; Sandoz-Hexal; Sanofi, Sun Pharma, and Ultimovacs. His group receives research grants from Bristol-Myers Squibb, Roche, Novartis and Amgen. None of the other authors declared any potential conflict of interest. KH reports personal fees from Bayer, personal fees and other from Sofie Biosciences, personal fees from SIRTEX, non-financial support from ABX, personal fees from Adacap, personal fees from Curium, personal fees from Endocyte, grants and personal fees from BTG, personal fees from IPSEN, personal fees from Siemens Healthineers, personal fees

from GE Healthcare, personal fees from Amgen, personal fees from Novartis, personal fees from ymabs, personal fees from HotKnot Therapeutics, personal fees from Theragnostics, personal fees from Pharma15, outside the submitted work. JCB is receiving speaker's bureau honoraria from Amgen, Pfizer, MerckSerono, Recordati and Sanofi, is a paid consultant/advisory board member/DSMB member for Boehringer Ingelheim, eTheRNA, InProTher, MerckSerono, Pfizer, 4SC, and Sanofi/Regeneron. His group receives research grants from Bristol-Myers Squibb, Merck Serono, HTG, IQVIA, and Alcedis. SU declares research support from Bristol Myers Squibb and Merck Serono; speakers and advisory board honoraria from Bristol Myers Squibb, Merck Sharp & Dohme, Merck Serono, Novartis and Roche, and travel support from Bristol Myers Squibb, and Merck Sharp & Dohme.

KEY POINTS

Question: Can immunotherapy and PRRT be combined to achieve response in patients with metastatic MCC who progressed under immunotherapy?

Pertinent Findings: Our case shows that combined immunotherapy and PRRT resulted in acceptable toxicity and exceptional response.

Implications for Patient Care: Combining immunotherapy and PRRT should be explored in prospective clinical trials; until then it is a feasible option for patients who have exhausted all other options.

REFERENCES

1. Becker JC, Stang A, DeCaprio JA, et al. Merkel cell carcinoma. *Nat Rev Dis Primers.* 2017;3:17077.

2. Nghiem P, Bhatia S, Lipson EJ, et al. Durable Tumor Regression and Overall Survival in Patients With Advanced Merkel Cell Carcinoma Receiving Pembrolizumab as First-Line Therapy. *J Clin Oncol.* 2019;37:693-702.

3. Buder K, Lapa C, Kreissl MC, et al. Somatostatin receptor expression in Merkel cell carcinoma as target for molecular imaging. *BMC Cancer.* 2014;14:268.

4. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of (177)Lu-Dotatate for Midgut neuroendocrine Tumors. *N Engl J Med.* 2017;376:125-135.

5. Meier G, Waldherr C, Herrmann R, Maecke H, Mueller-Brand J, Pless M. Successful targeted radiotherapy with 90Y-DOTATOC in a patient with Merkel cell carcinoma. A Case Report. *Oncology.* 2004;66:160-163.

6. Kasi PM, Sharma A, Jain MK. Expanding the indication for novel theranostic 177Lu-Dotatate Peptide Receptor Radionuclide Therapy: Proof-of-Concept of PRRT in Merkel Cell Cancer. *Case Rep Oncol.* 2019;12:98-103.

7. Moghadam SZ, Divband G, Shakeri S, Aryana K. Favorable Response after only one Cycle of Peptide Receptor Radionuclide Therapy with 177Lu-DOTATATE in a Patient With Metastatic Merkel Cell Carcinoma. *Clin Nucl Med.* 2019;44:650-652.

8. Sarma B, Willmes C, Angerer L, et al. Artesunate affects T Antigen Expression and Survival of Virus-Positive Merkel Cell Carcinoma. *Cancers (Basel).* 2020;12:919.

9. Vasaturo A, Di Blasio S, Peeters DG, et al. Clinical Implications of co-inhibitory Molecule Expression in the Tumor Microenvironment for DC Vaccination: A Game of Stop and Go. *Front Immunol.* 2013;4:417.

10. D'Angelo SP, Russell J, Lebbe C, et al. Efficacy and Safety of first-line Avelumab Treatment in Patients with Stage IV Metastatic Merkel Cell Carcinoma: A Preplanned Interim Analysis of a Clinical Trial. *JAMA Oncol.* 2018;4:e180077.

11. Twyman-Saint Victor C, Rech AJ, Maity A, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. *Nature.* 2015;520:373-377.

12. Weichselbaum RR, Liang H, Deng L, Fu YX. Radiotherapy and immunotherapy: a beneficial liaison? *Nat Rev Clin Oncol.* 2017;14:365-379.

13. Wang Y, Liu ZG, Yuan H, et al. The Reciprocity between Radiotherapy and Cancer Immunotherapy. *Clin Cancer Res.* 2019;25:1709-1717.

14. Akaike T, Qazi J, Anderson A, et al. High somatostatin receptor expression and efficacy of somatostatin analogues in patients with metastatic Merkel cell carcinoma. *Br J Dermatol.* 2021;184:319-327.

15. Czernin J, Current K, Mona CE, et al. Immune-Checkpoint Blockade enhances (225)Ac-PSMA617 Efficacy in a Mouse Model of Prostate Cancer. *J Nucl Med.* 2021;62:228-231.

16. Kim C, Liu SV, Subramaniam DS, et al. Phase I study of the (177)Lu-DOTA(0)-Tyr(3)-Octreotate (lutathera) in combination with nivolumab in patients with neuroendocrine tumors of the lung. *J Immunother Cancer.* 2020;8:e000980.

17. Shah MH, Goldner WS, Halfdanarson TR, et al. NCCN Guidelines Insights: Neuroendocrine and Adrenal Tumors, Version 2.2018. *J Natl Compr Canc Netw.* 2018;16:693-702.

Figure 1: Retroperitoneal lymph node metastasis

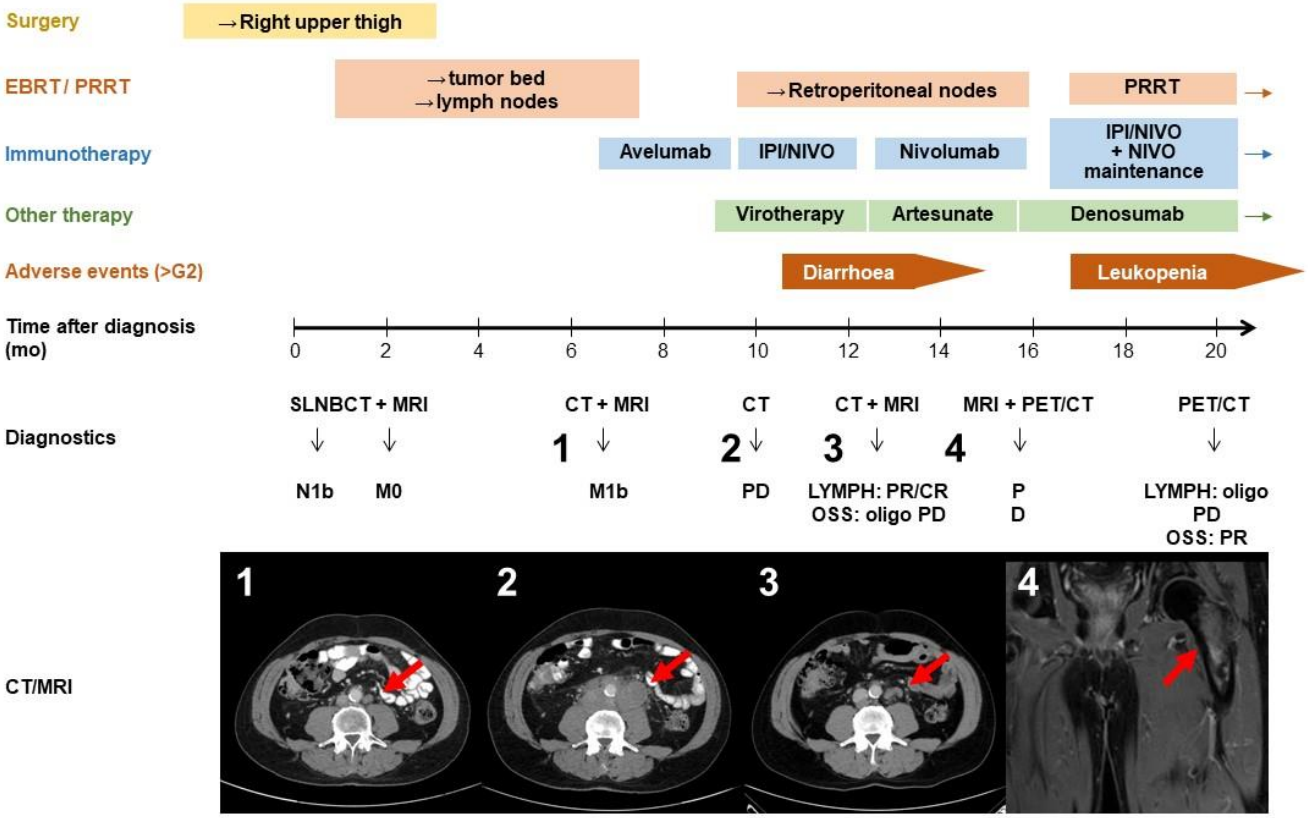

Figure 1. Flow chart of important events since initial diagnosis and CT and MRI images of retroperitoneal lymph node metastases (**1-3**; red arrows). After detection of lymph node metastasis (***1***), immunotherapy with avelumab was initiated. After one month, rapid increase of lactate dehydrogenase serum levels was noted, and re-staging revealed progressive disease (***2***). Treatment was switched to ipilimumab plus nivolumab (IPI/NIVO) plus radiotherapy to the retroperitoneal lymph nodes. While the lymph node metastases showed a strong response to IPI/NIVO (**3**), new bone metastases were detected (**4;** red arrow). EBRT = external beam radiation therapy, PRRT = peptide radio receptor therapy, IPI/NIVO = ipilimumab/nivolumab, PD = Progressive disease, PR = partial response, CR = complete response,

Figure 2: Response after IPI/NIVO + PRRT

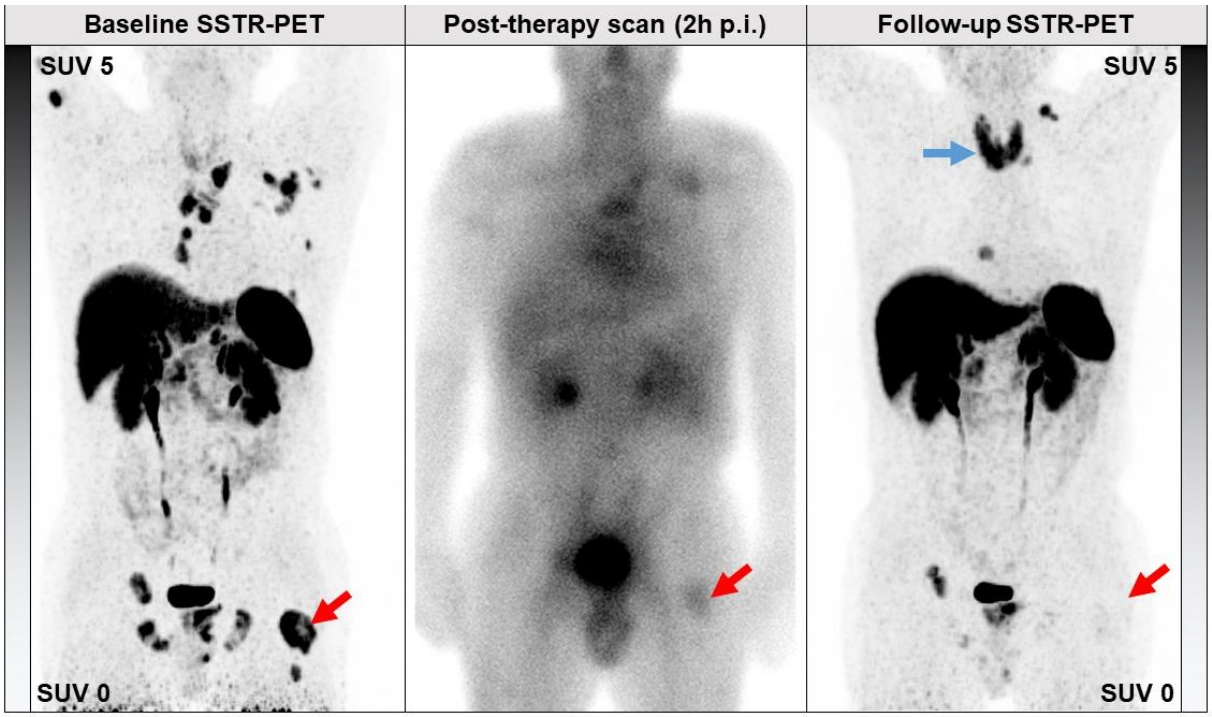

Figure 2. Maximum intensity projections of baseline (left) and follow-up (right) ^{68}Ga-DOTATOC positron emission tomography scans (SSTR-PET) indicating a favourable response of bone metastases (red arrows) to PRRT plus IPI/NIVO therapy. Physiologic uptake can be seen in liver, spleen and urinary tract. Post therapy scan after the first PRRT cycle (center) confirmed retention of ^{177}Lu-DOTATOC in tumor sites. Follow-up SSTR-PET (right) 13 weeks after the first cycle revealed a new uptake in the thyroid gland (blue arrow). The patient was diagnosed with autoimmune thyroiditis as a side-effect of ICI therapy with IPI/NIVO.

Graphical Abstract