Metastatic Merkel Cell Carcinoma in a kidney transplant patient: Experiences from treatment with a checkpoint inhibitor (avelumab) - A Case Report

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Abstract

Merkel Cell Carcinoma (MCC) is a rare, highly aggressive neuroendocrine skin cancer. Risk factors for MCC include age >65 years, immunosuppression, sun exposure and infection by polyomavirus. This neuroendocrine skin cancer is characterized by a high rate of recurrence and metastases, including regional nodal metastases. The use of checkpoint inhibitors (CPIs) has shown promising results in the treatment of metastatic MCC and, consequently, CPIs are emerging immunotherapeutic options for these patients. However, CPI treatment has not been recommended for patients with organ transplant due to increased risk for acute allograft rejection/failure possibly caused by such treatment. Limited data exist on safety and efficacy on use of CPIs among organ transplant recipients, since such recipients are routinely excluded from CPI cancer trials. In this case, we describe a 76 year old man, now deceased, who received a kidney transplant when he was 67 years old and started lifelong immunosuppressive therapy. After approximately five years, he presented with MCC and underwent complete surgery for his skin cancer. He progressed with metastases 16 months later and received initially radiotherapy and thereafter CPI treatment, with an anti-PD-L1 monoclonal antibody (avelumab).

Keywords: metastatic MCC, kidney transplant, immunosuppression, immunotherapy, check point inhibitor, avelumab

Introduction

Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine skin cancer often caused by either polyomavirus or ultraviolet exposure [1]. The 5-year overall survival rate is 14-27% for advanced or unresectable disease [2]. The in-cidence rate of patients with MCC increases (in US 0.7 cases per 100,000 person-years in 2013) [3]. Risk factors for MCC are poorly understood, but some evidence suggests that MCC is more common in individuals with abnormal immune function resulting from viral infection, autoimmune disease or immunosuppressive treatment after organ transplantation [4].

Solid organ transplant recipients have increased rates of cancer, which is the second lead cause of death in this population due to long-term use of antirejection immunosuppressants [4,5]. Solid organ transplantation carries a general 4.95-fold increase for MCC [5-7]. In this respect, MCC represents a serious complication among immunocompromised patients, as the risk of MCC increases 15-fold over the general population [8]. Kidney transplantation is a life-saving therapy for patients with end-stage kidney disease with overall improved survival and quality of life. All kidney transplant patients routinely receive lifelong immunosuppressive therapy.

Until recently, cytotoxic chemotherapy was the only systemic treatment option for metastatic MCC (mMCC), [9] Re-cent clinical trials of programmed cell death-1 (PD-1) pathway inhibitors in patients with mMCC, as first-line or later therapy, have demonstrated increased PFS and overall survival (OS) compared with historical data from patients receiving chemotherapy. In 2017, avelumab (anti–programmed death ligand-1 [PDL1]) became the first drug to receive FDA and EMA marketing authorisation for the treatment of mMCC. However, this treatment was not authorized for kidney transplanted patients. The purpose of this case report is to elucidate the experiences made by treating a kidney transplant patient on immuno-suppressive therapy and mMCC with a checkpoint inhibitor (avelumab).

Case Report

Patient and past medical history

This case describes a healthy 76 year old man, now deceased, who at age 67, was kidney, transplanted (with organs from deceased donor) due to hypertensive nephrosclerosis, and started lifelong immunosuppressive therapy with mycophenolate mofetil (CellCept), cyclosporine (Sandimmun) and prednisolone. The patient was on hemodialysis for about a year before transplantation. The first basal cell carcinoma was already detected and removed four months after the patient had kidney transplant. Five years after transplantation, in 2016 he presented with mMCC and initially treated with surgical resection with wide margins.

Treatments after recurrence with metastatic MCC

In March 2018, he presented with mMCC and diagnostic PET-CT confirmed metastases to the right axilla, liver and bone (stage IV disease). Otherwise, the patient was in good general condition (ECOG 0). In May 2018, due to threaten-ing compression of the medulla at level C2, the patient received a rigid neck collar, started dexamethasone and pallia-tive radiotherapy (RT) to the right axilla (3 Gy × 12) and several skeletal lesions including C2 (3 Gy × 10). Systemic treatment with platinum-containing chemotherapy was discussed but not recommended due to kidney transplant. The course of RT was complicated by perforation of the colon sigmoideum, most likely due to dexamethasone treatment, and was conservatively treated with antibiotics and systemic antifungal therapy (piperacillin-tazobactam (Tazocin) and fluconazole (Diflucan). The patient completed 10 RT treatments and end of treatment CT (June 2018) confirmed good response in the axillary lymph node. Otherwise he had stable disease in the liver and bone metastases. No renal complications were reported during the RT period.

A CT scan in July 2018 indicated progression in liver metastases. The patient was offered treatment with chemotherapy but wanted to try a check point inhibitor (CPI) as first line systemic treatment (Figure 1). Since avelumab was the only approved CPI for use in patients with mMCC, this treatment was selected, although not

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tested in kidney transplant patients. Avelumab is a programmed death-ligand 1 (PD-L1) blocking human IgG1 lambda monoclonal antibody.

Prior to initiation of CPI, the status of the patient was discussed in detail with his nephrologists and the transplant team. All, including the patient and his family, were made aware of risk of complications such as renal transplant rejection, and the risk of graftectomy and dialysis for the rest of the patient's life. Graftectomy prior start of CPI was also dis-cussed but nevertheless the patient wanted to start immunotherapy, which was supported by the physicians

The immune suppression medication was changed from the combination of cyclosporine (Sandimmun 75 mg × 1), mycophenolate mofetil (CellCept 1000 mg × 2) and prednisolone (5 mg × 1) to everolimus ((a kinase inhibitor targeting mTOR) 1,5 mg × 2) and prednisolone (5 mg × 1).

Treatment with checkpoint inhibitor, avelumab

Avelumab (Bavencio, Merck Europe B.V.) was given according to the Summary of Product Characteristics once every 2 weeks.. Response evaluation was performed every 3 months (Table 1).

The first treatment was given in August 2018. Blood sample was taken before dosing (nothing significant to note on the blood test result). No adverse event was reported, the general condition was good, weight stable and the 2nd dose was given 14 days after the 1st administration.

After 2nd dose the patient experienced some itchy skin without visible skin changes. It was also reported that the patient had mild sore throat, however without fever. No antibiotic was given.

The third and the fourth dose were given without any new reporting of side effects. Still some itchy skin (grade 2) (Ref; CTCAE version 4.0), which was successfully treated with hydroxyzine. Small papular changes were seen on the back. No renal complications were reported and there was nothing significant noted on the blood test result.

Prior to the 5th dose the patient was hospitalized due to fever and increased C-reactive protein (CRP), an autoimmune reaction was suspected, but pneumocystis infection was diagnosed and the patient was treated with (trimethoprim, sul-famethoxazole (Bactrim). The avelumab treatment was one week delayed. Low haemoglobin (Hb) was recorded (8.8 g/dl).

The patient received the 5th and 6th dose of avelumab without any significant events and 3 months response assessment was performed. CT showed shrinking of previously detected liver metastases and lesions in the peritoneum, but unfortunately multiple new lesions had appeared in the same areas. This could be related to pseudo-progression (Table 1).

Blood tests showed stable Neuron-specific Enolase (NSE), decreasing Lactate Dehydrogenase (LD) and Hb and unaf-fected kidney function (Figures 2 and 3). The patient was in good general condition and additional three months of treatment with avelumab was recommended.

The next four doses with avelumab went well and no significant side effects were reported. Grad 2 skin toxicity was persistent and treated with momethasone furoate cream on affected areas. Before the 10th dose the patient self-reported palpable new lesions in the thoracic wall and also increased size of the lymph node metastasis in the right axilla that was previously irradiated. It was decided to finalize the 12 administrations with avelumab and then, based on the 6 months response assessment, consider further treatment. The patient had been in good and stable general condition and did not experience any significant problems with the last two doses of avelumab. Nothing significant was noted on the blood test results but the patient felt he had become weaker in the left leg and had some pain.

The 6 months response assessment was performed and CT showed increased tumour burden in the peritoneal region even though a few lesions had decreased in size. Some liver lesion had decreased in size but the new lesion seen on previous scan had increased (Figure 2). Additional periosteal reactions in skeletal metastasis were detected, and NSE and LD increased progressively over the last 3 months of treatment. Avelumab treatment was therefore terminated. The patient felt better despite progressive disease and he tolerated the immunotherapy well and the kidney function had been unaffected (Figure 3). Besides low grad skin toxicity, the patient reported few side effects.

Treatment after immunotherapy

One month after stopping treatment with avelumab, it was decided to give the patient radiotherapy (4 Gy × 5) towards metastases in the right costa and the right flank and thereafter 6 cycles with chemotherapy. ACO chemotherapy, a combination of cyclophosphamide 1000 mg/m^2, vincristine 2 mg and doxorubicin 50 mg/m^2 at 3-weekly intervals, was chosen since the patient was a kidney transplant recipient. He started full dosing regimen, which was reduced to 75% after the first two cycles, since the patient experienced febrile neutropenia after the 2nd and 3rd cycle. He was also af-fected with constipation, weight loss and alopecia. The treatment was continued but the interval of treatment was increased to 4 weeks. The patient was hospitalized with neutropenia after the fourth and fifth cycle, after the 5th also with suspected pulmonary infection, which was treated with antibiotics.

After 6 cycles with chemotherapy, it was decided, due to the patient's reduced general condition that the patient should have a

Table 1. Patient characteristics before CPI (avelumab) administration (at baseline (before 1st avelumab administration) and after 3 months treatment (6 administrations) and end of treatment (6 months - 12 administrations).

Parameters	Baseline	After 3 months	End of treatment
Weight	77 kg	80 kg	82 kg
ECOG	2-3	1	2
Hemoglobin Ref. value 13.4-17.0 g/dl	10.0 g/dl	9.9 g/dl	11.7 g/dl
LD Ref. value <255 U/L	311 U/L	344 U/L	565 U/L
Serum creatinine Ref. value 60-105 mg/dl	78 mg/dl	91 mg/dl *	101 mg/dl
CRP Ref. value <5 mg/L	4 mg/L	9 mg/L	2 mg/L
NSE Ref. value: <12 ng/mL	16**	42 ng/mL	79 ng/mL
Disease response	-	Stable disease (^{W}/pseudo-progression)	Progressive disease

*Sample taken 2 weeks after 6th administration,
**measured ~1 months before the baseline assessment
NSE: Neuron-Specific Enolase, LD: Lactate Dehydrogenase, CRP: C-Reactive Protein

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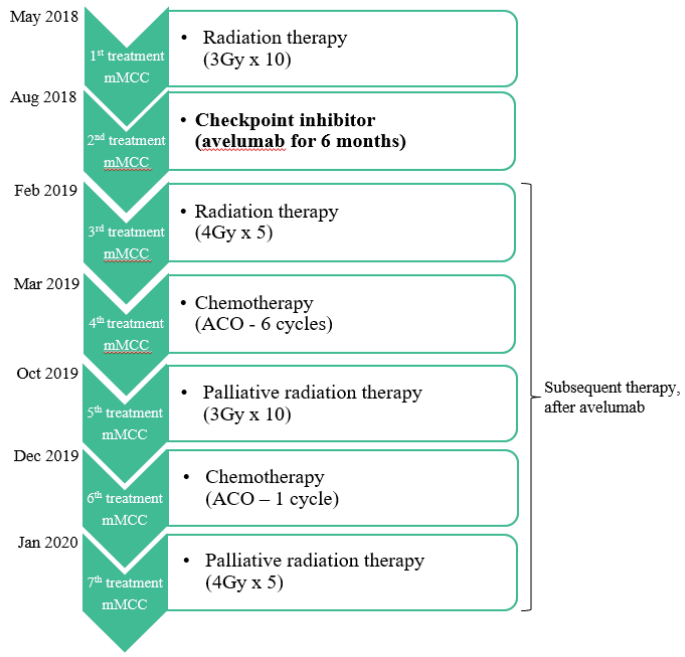

Figure 1. Cancer therapies in chronological order given to the patient over the 24 months he survived with metastatic MCC disease. Avelumab was initiated approximately 6 months after the patient presented with metastases and after initial radiotherapy. ACO chemotherapy; a combination of cyclophosphamide, vincristine and doxorubicin.

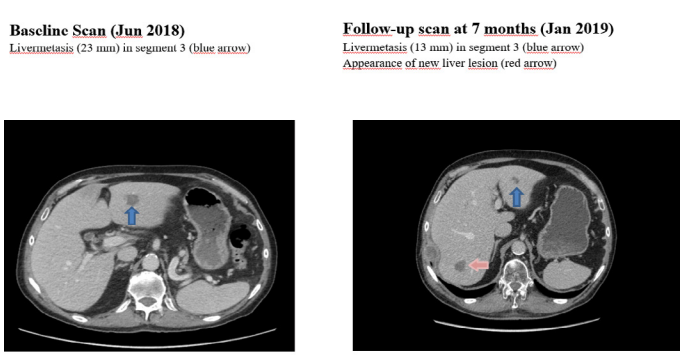

Figure 2. CT images of liver metastases at baseline and at 7 months (1 month after ended avelumab treatment). There is a significant reduction of in size of the liver metastases in segment 3 (blue arrows), but appearance of a new liver lesion (red arrow) indicate progression of disease at 7 months.

treatment break for two months. Disease evaluation (CT) done after radiotherapy/chemotherapy showed stabilization of the disease, with a small shrinkage in known metastases but still with residual disease. Some spreads scattered seals in the lungs that may be caused by infection and some pleura fluid of unknown cause was reported.

A year after the patient started immunotherapy with avelumab he was doing well (ECOG 1), without weight loss, with an active daily life and a good quality of life. Blood tests showed low haemoglobin (8.0 g/dl), platelets count (55 × 109/L) and leukocytes count (2 × 10^9/L).

The patient came back for control after treatment break, with increasing lower back pain with protrusion to the right thigh. He was re-evaluated to receive radiation therapy (3 Gy × 10) to the metastases in L2, L4 and proximal right fe-mur/collum femoris. The patient appeared with somewhat reduced general condition (ECOG 2) and needed walking support. He got opiates for pain relief. After completing radiotherapy, the patient had still pain and decreased power in the right leg.

The patient started chemotherapy a month after ended radiotherapy and tolerated only one cycle of chemotherapy ACO (75% dose). A new round of radiotherapy was requested, due to persistent pain in the right leg. During CT dose planning for radiotherapy, a fracture of the right femur was found and the patient was successfully operated two days later with hemiprosthesis for right femoral neck. He received postoperative radiotherapy (4 Gy × 5) one month after surgery. His general condition deteriorated and no further cancer directed treatment was considered. He died a few weeks later. Overall survival for the patient, after he was diagnosed with metastatic Merkel Cell Carcinoma was thus approximately 24 months.

A written informed consent was obtained from the patient's next-of-kin for publication of this case report, since the patient deceased.

Results and Discussion

Avelumab (CPI) in combination with everolimus (a kinase inhibitor targeting mTOR) and prednisolone was safe and well tolerated as treatment of mMCC in a kidney transplant patient. The kidney function was unaffected during the avelumab treatment and also during subsequent therapy in the follow-up period. Additionally, the patient did not experience any other dose limiting toxicities. He was in a general good health condition during the CPI treatment as showed in Figure 3.

In Norway, when this patient started treatment for his mMCC, standard of care was considered to be surgery, radiation and/or chemotherapy. Etoposide (VP-16) combined with cisplatin (or carboplatin) has been the most commonly used combination therapy for Merkel cell carcinoma in its advanced stages. 9 However, nephrotoxicity is a well-known side effect of cisplatin and therefore not recommended for transplant patients. Another option is ACO (cyclophosphamide, vincristine and doxorubicin) or ECO (epirubicin, cyclophosphamide and vincristine), but these combination chemother-apies are less effective and also have a risk of renal toxicity and other side effects. The use of CPI for treatment of advanced mMCC have shown compelling results and are consequently considered emerging therapeutic options for these patients today. 1 The core principle of CPI is to stimulate the immune system to destroy cancer cells, which contradicts a transplant recipient's need to suppress the immune system to prevent allograft rejection. Therefore, CPI treatment has not been recommended for organ transplant patients due to increased risk for acute allograft rejection after such treatment [10,11]. Recent analyses on pooled literature data indicated high rates of (~40%) of allograft rejection in such patients when treated with a checkpoint inhibitor [12,13].

This case report showed that treatment with Aavelumab was well tolerated. Careful and considered management of the immunosuppression around the time of CPI start up and choice of CPI might have been crucial. The immunosuppressive therapy was carefully addressed and adjusted before CPI treatment by a close collaboration with the treating oncologist, nephrologists and the transplant team. The goal was to devise a safe and effective immunotherapy regimen against the cancer while maintaining a good general condition for the patient with few side effects.

For this patient, before starting the treatment with avelumab (an anti–programmed death ligand-1 [PDL1]), the immu-nosuppressive triple regimen of cyclosporine (Sandimmun), mycophenolate mofetil (CellCept) and prednisolone was changed to everolimus (a kinase inhibitor targeting the mammalian target of rapamycin (mTOR)) and prednisolone. The use of mTOR inhibitors (everolimus, temsirolimus, and sirolimus) has been well studied in many cancers [14]. The effectiveness of using mTOR inhibitors in preventing immune-related adverse events associated with check point inhib-itors is not known [15] but in this patient a regimen including an mTOR inhibitor may have prevented adverse immune responses of avelumab. It could be speculated that one reason why this patient had a better outcome than projected during CPI treatment might have been the careful consideration of the underlying immunosuppressive regimen and the choice of CPI.

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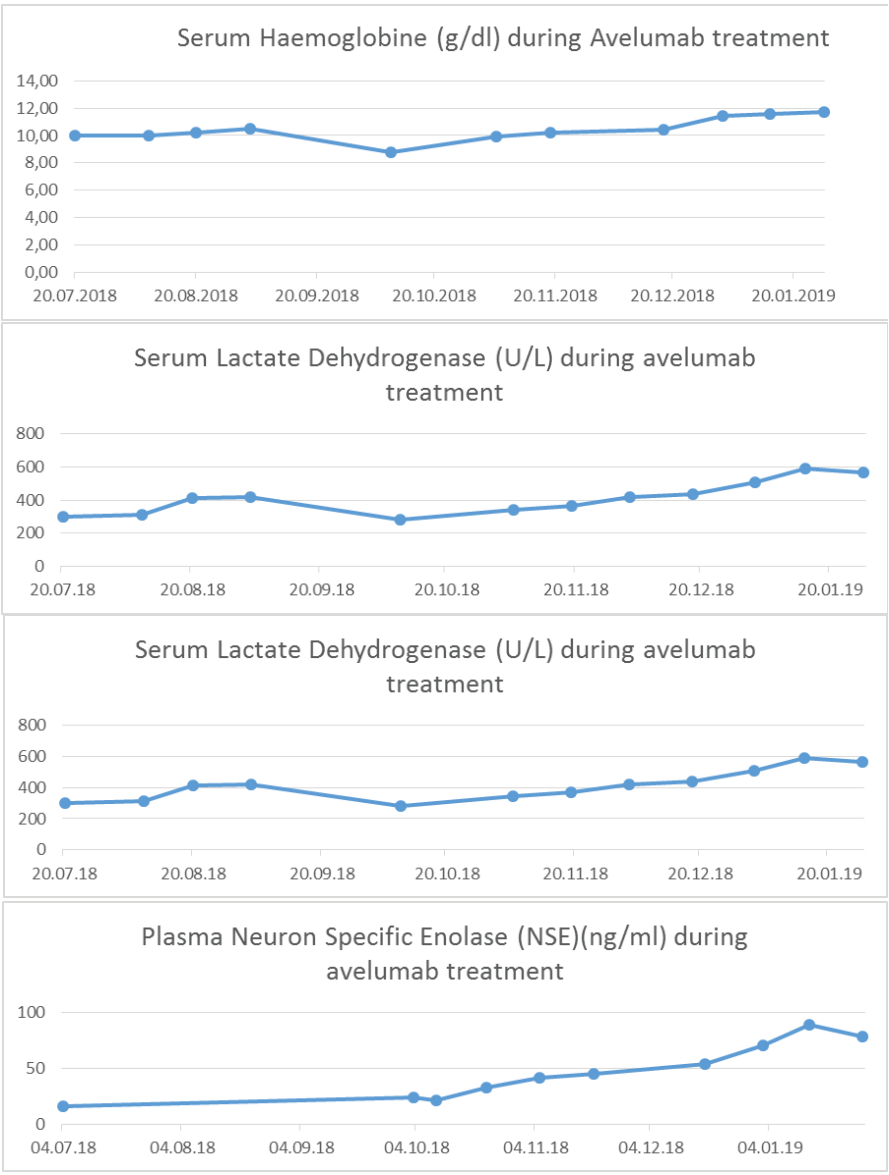

Figure 3. Changes in blood parameters (hemoglobine, lactate dehydrogenases, creatinine, and NSE) during CPI (avelumab) treatment; 12 administrations over 6 months, first dosing date 08.08.2018 and last dosing date 16.01.2019.

In the pivotal Javelin Merkel 200 phase 2 studies, 88 patients with metastatic MCC were included. In this study patients on average received a median of seven cycles of avelumab, and the median duration of treatment was 17 weeks [16]. Median progression free survival was 2.7 months and median overall survival was 12.9 months [16,17]. In comparison, this patient tolerated 12 cycles of avelumab over a 6 months period and lived for 18 months after start of CPI treatment. During this period the kidney function was unaffected and no serious side effects were reported.

During the 1 year follow-up period, after avelumab treatment, the patient was given both palliative radiation therapy and chemotherapy. In total he received 7 cycles of ACO (6 cycles with 25% dose reduction). He had symptomatic and objective response on the chemotherapy given. The patient tolerated chemotherapy for a period of almost 10 months despite toxicities and reduced general condition. A systemic tumor progression was observed during the RT courses and the treatment breaks. The response and the sustained effect of the chemotherapy after exposure to CPI in this case were surprising due to the aggressive nature of MCC and that the patient was immunosuppressed. There have been reports suggesting that CPI gives an immunotherapy-induced chemo sensitization effect [18-20]. The patient received avelumab for 6 months – 12 administrations– which stabilized the disease for approximately 3 months; and the patients lived for almost 18 months after start of CPI treatment.

Conclusion

Avelumab was well tolerated as treatment of mMCC in this patient on lifelong immunosuppressive therapy after kidney transplant. The patient had a transient response to CPI treatment and his general condition, including his renal function, was good. He responded also well to subsequent therapy after avelumab. The patient lived for about 2 years after he presented with metastatic MCC, despite being immunosuppressed. Avelumab was well tolerated as treatment of mMCC in this patient on lifelong immunosuppressive therapy after kidney transplant, and no allograft rejection was experienced.

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Disclosure

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References

1. Villani A, et al. "Merkel Cell Carcinoma: Therapeutic update and emerging therapies". *Dermatol Ther (Heidelb). 9 (*2019): 209-222.
2. Harms KL, et al."Analysis of prognostic factors from 9387 Merkel cell carcinoma cases forms the basis for the new 8th Edition AJCC Staging System". *Ann Surg Oncol.* 23 (2016):3564-3571.
3. Paulson KG, et al. "Merkel cell carcinoma: Current US incidence and projected increases based on changing demographics". *J Am Acad Dermatol.* 78.3(2018): 457-463.
4. Koljonen V, et al. "Incidence of Merkel cell carcinoma in renal transplant recipients". *Nephrol Dial Transplant.* 24.10(2009): 3231–3235.
5. Koljonen V, et al. "Post-transplant Merkel Cell Carcinoma". *Acta Derm Venereol.* 96 (2016): 442-447.
6. Krynitz B, et al. "Risk of skin cancer and other malignancies in kidney, liver, heart and lung transplant recipients 1970 to 2008 – a Swedish population-based study". *Int J Cancer.* 132.6 (2013):1429–1438.
7. Na R, et al. "Comparison of de novo cancer incidence in Australian liver, heart and lung transplant recipients". *Am J Transplant.* 13 (2013):174–183.
8. Heath M, et al. "Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features". *J Am Acad Dermatol.* 58.3 (2008):375–381.
9. Lebbe C, et al. "Diagnosis and treatment of MCC. European consensus-based interdisciplinary guideline". *Eur J Cancer.* 51.16 (2015): 2396-2403.
10. Smedman TM, et al. "Graft rejection after immune checkpoint inhibitor therapy in solid organ transplant recipients". *Acta Oncologica.* 57.10 (2018): 1414-1418.
11. Manohar S, et al. "Systematic review of the safety of immune checkpoint inhibitors among kidney transplant patients". *Kidney Int Rep.* 5.2(2020): 149-158.
12. Fisher J, et al. "Immune checkpoint inhibitor therapy in solid organ transplant recipients: A patient-centered systematic review". *JADD.* 82.6 (2020): 1490-1500.
13. Kumar V, et al. "The safety and efficacy of checkpoint inhibitors in transplant recipients: A case series and systematic review of literature". *The Oncologist.* 25.6 (2020):1-10.
14. Law BK. Rapamycin: an anti-cancer immunosuppressant? *Crit Rev Oncol Hematol.* 56.1(2005):47-60.
15. Barnett R,et al. "Preserved Renal-Allograft Function and the PD-1 Pathway Inhibitor Nivolumab". *N Engl J Med.* 376.2 (2017): 191-192.
16. Kaufman HI, et al. "Updated efficacy of avelumab in patients with previously treated metastatic Merkel cell carcinoma after ≥1 year of follow-up: JAVELIN Merkel 200, a phase 2 clinical trial". *J Immunother Cancer.* 19 (2018): 6-7 DOI 10.1186/s40425-017-0310.
17. Gaiser MR, et al. PD-L1 Inhibition with Avelumab for metastatic Merkel Cell Carcinoma. *Expert Rev Clin Pharmacol.* 11.4 (2018):345-359.
18. Hadash-Bengad R, et al. "Immunotherapy Potentiates the Effect of Chemotherapy in Metastatic Melanoma - A Retrospective Study". *Front Oncol.* 10.70 (2020) DOI 10.3389/fonc.2020.00070.
19. Saleh K, et al. "Response to salvage chemotherapy after progression on immune checkpoint inhibitors in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck". *Eur J Cancer.* 121 (2019):123-129.
20. Schvartsman G, et al. "Response Rates to Single-Agent Chemotherapy after Exposure to Immune Checkpoint Inhibitors in Advanced Non-Small Cell Lung Cancer". *Lung Cancer.* 112 (2017):90-95.

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