MEDICINE

Retrospective Multicenter Analysis of the Outcome of a Re-Induction with Immune Checkpoint Inhibitors in Advanced Merkel Cell Carcinoma

H. M. Stege [1,2] · F. Bradfisch [1,2] · M. I. Fleischer [1,2] · P. Mohr [2,3] · S. Ugurel [2,4] · P. Terheyden [2,5] · A. Thiem [2,6,7] · F. Kiecker [2,7] · U. Leiter [2,8] · J. C. Becker [2,4,9] · S. Grabbe [1,2] · C. Loquai [1,2]

Abstract

Significant progress has been made in the treatment of advanced Merkel cell carcinoma (MCC) by establishing immune checkpoint inhibitors (ICI). Tumor progression, durable response, or adverse events may lead to ICI discontinuation in MCC patients. If in these patients tumor progression occurs, the question remains if re-induction with ICI achieves renewed tumor response. This retrospective multicenter study evaluated patients in with re-induction of anti-PD-1/anti-PD-L1 therapy for advanced MCC. Clinical data were extracted at treatment initiation, tumor response, treatment cessation, and subsequent tumor response to re-induction. Eight patients from seven centers (mean age 67.8 years) were included. The median duration of initial therapy with anti-PD-1/anti-PD-L1 was 9.6 months (2–21 months). Two patients achieved complete response (CR), four patients partial response (PR), one patient stable disease (SD), while in one patient progressive disease (PD) occurred as best overall response (BOR) to ICI. Reason for discontinuation of ICI was PD in three patients and severe adverse events in five patients. Following a median anti-PD-1/anti-PD-L1 therapy-free interval of 9.5 months (3–18 months), re-induction with ICI therapy was initiated. Five of eight patients (62.5%) achieved an objective response upon re-induction, while in three patients, no response could be observed. Notably, adverse events, which had led to the discontinuation of the first ICI treatment line, were not observed upon re-induction. The initial response to immune checkpoint inhibitors seems to be an important marker for successful re-induction. Interestingly, adverse events leading to treatment discontinuation were not observed during re-induction.

This article is part of the Topical Collection on *Medicine*

✉ H. M. Stege
   Henner.Stege@unimedizin-mainz.de

1 Hautklinik und Poliklinik Universitätsmedizin Mainz, Langenbeckstraße 1, 55131 Mainz, Germany

2 Translational Skin Cancer Research, Deutsches Konsortium für translationale Onkologie (DKTK) Partner Site Essen, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany

3 Klinik für Dermatologie Elbe-Kliniken Buxtehude, Buxtehude, Germany

4 Klinik für Dermatologie Universitätsklinikum Essen, Essen, Germany

5 Klinik für Dermatologie der Universität zu Lübeck, Lübeck, Germany

6 Klinik für Dermatologie Universitätsklinikum Würzburg, Würzburg, Germany

7 Klinik für Dermatologie Universitätsklinikum Rostock, Rostock, Germany

8 Klinik für Dermatologie Charite Universitätsmedizin Berlin, Berlin, Germany

9 Zentrum für Dermatoonkologie, Universitäts-Hautklinik Tübingen, Tübingen, Germany

Introduction

The therapy of metastatic Merkel cell carcinoma (MCC) has undergone major changes in recent years. Before introducing immune checkpoint inhibitors, the only treatment option for metastatic MCC was chemotherapy. Typically, this treatment option showed good initial response, but did not result in significant increase in overall survival (OS) and progression-free survival (PFS). The remarkable success of ICI therapy for immunogenic tumor entities, such as malignant melanoma, encouraged clinical studies, in which ICI therapy was also used for the treatment of metastatic MCC. These studies illustrated that ICI therapy shows a good initial response, while also contributing to a significantly prolonged OS and PFS. These data were confirmed in the Checkmate 358 and Javelin Merkel 200 studies, so that both the FDA and the European Commission granted approval [1–3]. Despite good tolerability in general, in 10–20% of treated patients, immune-mediated side effects can lead to treatment discontinuation [4]. Cessation of treatment bears the risk of tumor progression. Two research questions guided this study: Can re-induction ICI lead to a renewed tumor response, and how is ICI re-induction therapy tolerated, especially in patients under re-challenge, who had to stop their first treatment due to immune related side effects? To investigate these questions, we initiated a retrospective study on the outcome of patients under re-induction treatment with ICI.

Patients and Methods

In a survey of 31 German, two Swiss and two Austrian Skin Cancer Centers, eight patients were identified who fulfilled the inclusion criteria for the study's objectives. Eligibility criteria were inoperable MCC and re-challenge of checkpoint inhibitor treatment with anti-PD1/anti-PD-L1 after interruption/termination of anti-PD1/anti-PD-L1 therapy for at least 3 months with subsequent re-induction for at least another 3 months.

The multicenter collection of patient data was approved by the Ethics Committee of Rheinland-Pfalz (2019-14436) and was conducted in accordance with the principles of the Helsinki Declaration in its current version.

The following demographic and disease-related data were collected and evaluated: age at the start of PD-1 treatment, sex, primary localization of the MCC, site of metastasis, ECOG performance status, immunosuppression due to drugs or underlining diseases, type of anti-PD1/anti-PD-L1 treatment (pembrolizumab or avelumab), duration of each treatment cycle, best overall response (BOR) to each treatment cycle (complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD)), reason for discontinuation, subsequent treatment after anti-PD1/anti-PD-L1, time to re-induction of anti-PD1/anti-PD-L1, and treatment outcome.

Results

A total of eight patients fulfilled the defined inclusion criteria. Two patients were female and six patients were male. All patients were diagnosed with an inoperable or metastatic MCC before onset of ICI. The median age at beginning of anti-PD1/anti-PD-L1 was 67.8 years (54–83 years) (Table 1). Six patients received pembrolizumab (anti-PD-1) as first-line treatment; two patients received avelumab (anti-PDL1).

The duration of the first cycle of anti-PD1/anti-PD-L1 therapy ranged from 2 to 21 months with a median of 9.6 months. Two patients experienced complete response as best response to initial PD- anti-PD1/anti-PD-L1 therapy, while four patients had partial response. In one patient, the disease stabilized, and in one patient, the disease progressed. In three patients, the first treatment cycle of anti-PD1/anti-PD-L1 therapy was discontinued due to progressive disease, while adverse side effects led to discontinuation in five patients.

For re-induction, six patients received avelumab, and two patients, pembrolizumab. A crossover from pembrolizumab to avelumab occurred in five patients, and in one patient, crossover from avelumab to pembrolizumab. Crossover was done in order to avoid the recurrence of the same side effect that led to the initial discontinuation of the ICI. Although up to now, there is no data supporting this theory.

The time from the start of the initial anti-PD1/anti-PD-L1 therapy to the most recent follow-up was defined as observation time, with a median of 20.8 months.

During interruption between the first cycle anti-PD1/anti-PD-L1 therapy and re-induction of anti-PD1/anti-PD-L1 therapy, another antitumor (2/8) or immunosuppressive therapy could be administered. The median interval between initial PD-1i/PD-L1i treatment and treatment re-induction was 8.3 months (range 3 to 18 months) (Table 1).

The median duration of the second anti-PD1/anti-PD-L1 therapy currently is 6.8 months (range 2 to 16 months; in four patients, the treatment is ongoing). An overview of the treatment cycles is summarized in Fig. 1. A renewed tumor response upon re-induction of anti-PD1/anti-PD-L1 therapy was overserved in 75% of patients, in which an initial response upon receiving anti-PD1/anti-PD-L1 therapy occurred.

Interestingly, recurrence of adverse events that lead to the initial discontinuation of anti-PD1/anti-PD-L1 therapy in the five patients was not observed during re-induction. Only minor adverse events such as fatigue or pruritus were monitored (Table 2).

Due to laboratory abnormalities or adverse events (CTCAE Grad 1–2), the recommended therapy intervals for pembrolizumab (every 3 weeks) and avelumab (every 2 weeks) could not always be applied with.

The treatment courses and outcomes of the 8 patients who received anti-PD-1/anti-PD-L1 rechallenge are described in detail below:

Table 1   Individual patient and tumor characteristics of patients with metastatic Merkel cell carcinoma

Patient	Age at start of PD-1 treatment	Sex	Primary localization	Site of metastasis	Eastern Cooperative Oncology Group
1	83	w	Femoral	Lymph nodes, cutaneous	1
2	54	m	Gluteal	Lymph nodes, muscular	0
3	65	w	Cancer of unknown primary	Lymph nodes, cutaneous	1
4	57	m	Cancer of unknown primary	Pulmonal, lymph nodes, adrenal gland	0
5	62	m	Cheek	Hepatic,	1
6	81	m	Pretibial	Lymph nodes	1
7	71	m	Upper arm	Osseous	0
8	70	m	Cancer of unknown primary	Lymph nodes, pancreatic	0

Baseline characteristics at start of anti-PD-1/anti-PD-L1 treatment

Patient 1 initially received pembrolizumab for 10 months (12 infusions of pembrolizumab 3 mg/kg body weight) and showed PR with regressing cutaneous metastasis. During treatment, the patient described increasing dyspnea, fatigue, and coughing. A CT scan revealed multifocal peripheral opacities and consolidations, confirming pneumonitis (CTCAE 2°) as adverse event. Therefore, treatment was discontinued for 8 months, without additional steroid treatment, until remission of pneumonitis. Subsequent clinical and radiological staging revealed PD and treatment with avelumab was started. Similar to first-line treatment a renewed tumor response was achieved upon re-induction of anti-PD-1/anti-PD-L1 treatment. Treatment is still ongoing (7+ months).

Patient 2 was treated with pembrolizumab for 21 months (21 infusions of pembrolizumab 3 mg/kg body weight) showing PR as BOR. However, staging revealed PD and therefore treatment regime was changed to mono-chemotherapy with doxorubicin. During treatment with doxorubicin, no response was observed. After 6 months re-induction of ICI occurred in a form of ant-PD-L1 treatment with avelumab. The treatment showed no response, and the patient died 5 months after re-induction of the second cycle of anti-PD-L1.

Patient 3 received pembrolizumab for 2 months, without any tumor response. After progressive disease was confirmed, mono-chemotherapy with doxorubicin was started. Doxorubicin was given for 6 months, without tumor response. Once more, the treatment regime was changed, and for 3 months, the patient was treated with avelumab. Continuous progressions of the MCC led to the patient's death.

Patient 4 responded to treatment with pembrolizumab with PR. Due to pneumonitis with severe symptoms such as dyspnea and fatigue, anti-PD-1 was discontinued. As clinical symptoms worsened, an immunosuppressive therapy with prednisolone was started. A response durability of 18 months
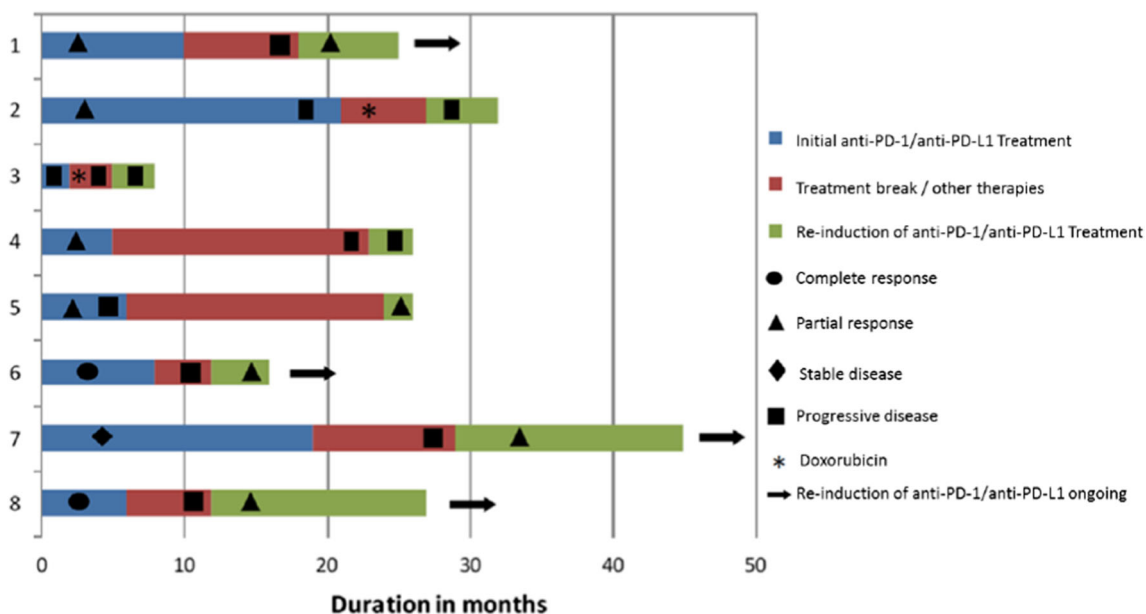
Fig. 1 Swimmer plot showing the best overall response to initial anti-PD-1/anti-PD-L1 treatment, subsequent treatment, and re-induction to anti-PD-1/anti-PD-L1 treatment in all eight patients

Table 2 Course, response, relapse, and response to re-induction to PD-1i/PD-L1i treatment. Best overall response to intimal anti-PD-1/anti-PD-L1 treatment, subsequent treatment, and re-induction to anti-PD-1/anti-PD-treatment

Patient	First anti-PD-1/anti-PD-L1 treatment	Duration (month)	Cycle	BOR	Reason for discontinuation	Subsequent treatment	Time to re-induction (months)	Re-induction of anti-PD-1/anti-PD-L1 treatment	Duration (months)	BOR	Adverse events upon re-induction	Treatment outcome
1	Pembrolizumab	10	12	PR	Pneumonitis CTCAE 2°	–	8	Avelumab	7 ongoing	PR	Pruritus CTCAE 1°	Alive
2	Pembrolizumab	21	21	PR	PD	Doxorubicin	6	Avelumab	5	*	–	Dead
3	Pembrolizumab	2	2	PD	PD	Doxorubicin	3	Avelumab	3	PD	–	Dead
4	Pembrolizumab	5	5	PR	Pneumonitis CTCAE 2°	Cortisone	18	Avelumab	3	PD	Fatigue CTCAE 1°	Alive
5	Avelumab	6	9	PR	PD	–	12	Pembrolizumab	2	clinical PR**	–	Alive
6	Avelumab	8	18	CR	ECOG worsening under treatment	–	4	Avelumab	4 ongoing	PR	Pruritus, exanthema CTCAE 1°	Alive
7	Pembrolizumab	19	19	SD	Pneumonitis/Colitis CTCAE 2°	Cortisone	10	Avelumab	16 ongoing	PR	–	Alive
8	Pembrolizumab	6	7	CR	Pancreatitis CTCAE 3°	–	6	Pembrolizumab	15 ongoing	PR	–	Alive

BOR, best overall response; *ICI*, immune checkpoint inhibitors; *CR*, complete response; *PR*, partial response; *SD*, stable disease; *PD*, progressive disease; *CTCAE*, Common Terminology Criteria for Adverse Events; *ECOG*, Eastern Cooperative Oncology Group;

*Death because of other disease

**Patient rejects further radiological staging

was observed. PD was confirmed through CT scans. Re-induction of anti-PD-L1 with avelumab did not result in a renewed tumor response. Treatment was stopped once staging revealed tumor progression.

Patient 5 received avelumab for 6 months (9 infusions) with PR as BOR. In subsequent staging, increase in hepatic and cutaneous metastasis confirmed PD. The patient declined second-line chemotherapy and opted for best supportive care only. Over the next 12 months, a slow progression of the disease was monitored. Re-induction of anti-PD-1 with pembrolizumab resulted in regression of the cutaneous metastasis. After 2 months, treatment was discontinued upon the patient's request. The cutaneous metastases showed an ongoing regression. The patient refused further radiological imaging.

Patient 6 was treated with avelumab for 8 months (16 infusions) which resulted in CR. Due to treatment-unrelated deterioration of his health, anti-PD-L1 therapy was discontinued. Four months later, radiological imaging showed PD, and avelumab was re-induced. Upon re-induction, a renewed tumor with PR was observed within the first 4 months. At data cutoff, anti-PD-L1 therapy is ongoing.

In patient 7, the first cycle of pembrolizumab led to a SD, which lasted for 19 months (19 infusions). Upon receiving anti-PD-1, the patient developed pneumonitis and colitis resulting in discontinuation of the treatment and initiation of immunosuppressive therapy with prednisone at 1 mg/kg body weight. Response durability was overserved for 10 months. PD resulted in re-induction of anti-PD-1/anti-PD-L1. Treatment and response is ongoing at the time of data cutoff (16 months) without reemergence of adverse events.

Patient 8 responded to pembrolizumab with CR. Pancreatitis with an increase in lipase and amylase levels (CTCAE 2°) caused discontinuation of pembrolizumab. Re-induction to pembrolizumab was administered 6 months later due to tumor progression. At time of re-induction, pancreas enzymes had returned to normal levels. Treatment with pembrolizumab is still ongoing and partial response is achieved without any severe adverse reactions, especially no signs of pancreatitis (follow-up time 16 months).

Discussion

Introduction of anti-PD-1/anti-PD-L1 revolutionized the treatment for metastatic MCC cumulating in a significant increase of overall and progression free survival. Currently, most guidelines recommend anti-PD-1/anti-PD-L1 as a first-line treatment of metastatic MCC. Even though treatment with anti-PD-1/anti-PD-L1 is generally tolerated, severe adverse events next to PD are the main reasons for discontinuation of therapy [4, 5]. In our patient cohort, discontinuation of anti-PD-1/anti-PD-L1 due to severe adverse events was associated with PD in five patients. This may differ from other

tumors like malignant melanoma, where development of severe adverse events upon ICI and subsequent discontinuation of treatment seemed to have no impact on the overall survival and progression-free survival [6]. However, 75% of the patients showed a therapeutic response after re-induction of anti-PD-1/anti-PD-L1. In contrast to our preliminary data, metastatic MCC continues CR durability upon receiving anti-PD-1/anti-PD-L1 for > 24 months and has been documented in metastatic melanoma. Compared with these data, the response durability in our cohort of metastatic MCC is significantly shorter (median 9.2 months).

Limitations of this study are the retrospective design and small sample size. Since MCC is a rare malignant disease, this study is underpowered and only descriptive analysis was applied. However, the clinical data of our patients regarding treatment duration and response durability are consistent with those of larger studies in metastatic MCC [7].

Severe adverse events were the reason for discontinuation of the first anti-PD-1/anti-PD-L1 therapy in five cases after median therapy duration of 9.6 months, while progressive disease caused discontinuation in three cases also after median therapy duration of 9.6 months. In the MK-3475 study, a similar duration of treatment with pembrolizumab was reported [8, 9].

Our patient cohort shows that re-induction to checkpoint inhibitor seems to be feasible and successful. One parameter predicting the response on re-induction may be the initial response on ICI treatment as 5 of 6 of our patients with an initial response showed a renewed response upon re-induction of anti-PD-1/anti-PD-L1 therapy. This seems to be different to other tumor entities like metastatic melanoma where only 30–50% of patients who initially responded to checkpoint inhibitor therapy also showed a positive response upon re-induction [6, 10, 11].

During the first treatment cycle, the majority of patients (n = 6) received pembrolizumab (anti-PD-1). In the case of re-induction, six patients were switched to avelumab (anti-PD-L1), mainly to avoid recurrence of the same adverse events that led to the initial discontinuation. Although up to now, there is no data supporting this theory. The sequence of therapy does not seem to have an influence on tumor response. This is consistent with data concerning patients with malignant melanoma undergoing re-induction [11, 12].

While adverse events of anti-PD-1/anti-PD-L1 therapy were the main reasons for discontinuation of the first treatment cycle, interestingly, adverse effects did not reoccur during the second treatment cycle. This finding is in accordance with re-induction of ICI in other tumor entities, where ICI induced adverse side effects did not recur during re-induction [13, 14].

In summary, our preliminary results support re-induction of PD-1i/PD-L1i therapy in patients with metastatic Merkel cell carcinoma as a potentially effective therapeutic option, especially after preceding discontinuation due to severe adverse events and in case of benefit of the patient in the first cycle of ICI.

Our initial data should be confirmed through further broad-based studies.

Authors' Contributions SHM worked on drafting the manuscript, interpretation of data, collection of patient data and visualized the results, and was the major contributor in writing the manuscript. SM, BF, and FMI collected patient data; BJC, US, TP, KF, and GS collected patient data and worked on review and editing the manuscript. CL had the project's administration and was responsible for conceptualization of the project. She also supported writing and editing the manuscript in a fundamental way. All authors read and approved the final manuscript.

Data Availability The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

Conflict of Interest Becker JC: speaker honoraria from Amgen, Merck Serono, Sanofi, and Pfizer, advisory board honoraria from 4SC, Amgen, CureVac, eTheRNA, Lytix, Merck Serono, Novartis, ReProTher, Rigontec, and Sanofi as well as research funding from Alcedis, Amgen, Bristol-Myers Squibb, IQVIA, and Merck Serono; he also received travel support from 4SC and Incyte. Ugurel S: research support from Bristol Myers Squibb and Merck Serono; speakers and advisory board honoraria from Bristol Myers Squibb, Merck Sharp and Dohme, Merck Serono, Novartis and Roche, and travel support from Bristol Myers Squibb, Merck Sharp and Dohme. Terheyden P: speaker's honoraria from BMS, Novartis, MSD, Pierre-Fabre, CureVac and Roche, consultant's honoraria from BMS, Novartis, Pierre-Fabre, Merck Serono, Sanofi und Roche and travel support from BMS, Pierre-Fabre and Roche. Kiecker F: AdBoards/travel support/Speakers fee from Amgen, Novartis, BMS, MSD, Roche, Sanofi. Grabbe S: honoraria for advisory boards, oral presentations and travel expenses from Roche, Novartis, MSD, and BMS. Loquai C: received honoraria for advisory boards and oral presentations from Amgen, MSD, Roche, BMS, Novartis, Leo, Pierre Fabre; consultant for Roche-Posay, Roche, BMS and Biontech; travel expenses from Roche, Amgen, BMS, MSD and Novartis. Stege HM, Bradfisch F, Mohr P, Thiem A, Leiter U, Fleischer MI, and Schultheis M declare no conflict of interest.

Ethics Approval and Consent to Participate The multicenter collection of patient data was approved by the Ethics Committee of Rheinland-Pfalz (2019-14436) and was conducted in accordance with the principles of the Helsinki Declaration in its current version.

Consent for Publication Not applicable.

References

1. Cowey CL, Mahnke L, Espirito J, Helwig C, Oksen D, Bharmal M. Real-world treatment outcomes in patients with metastatic Merkel cell carcinoma treated with chemotherapy in the USA. Future Oncol. 2017;13(19):1699–710.

2. D'Angelo SP, et al. Early objective response to avelumab treatment is associated with improved overall survival in patients with metastatic Merkel cell carcinoma. Cancer Immunol Immunother. 2019;68(4):609–18.

3. Becker JC, Stang A, DeCaprio JA, Cerroni L, Lebbé C, Veness M, et al. Merkel cell carcinoma. Nat Rev Dis Primers. 2017;3:17077.

4. Nghiem P, Bhatia S, Lipson EJ, Sharfman WH, Kudchadkar RR, Brohl AS, 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(9):693–702.

5. Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol. 2016;17(10):1374–85.

6. Indini A, di Guardo L, Cimminiello C, Prisciandaro M, Randon G, de Braud F, et al. Immune-related adverse events correlate with improved survival in patients undergoing anti-PD1 immunotherapy for metastatic melanoma. J Cancer Res Clin Oncol. 2019;145(2):511–21.

7. Nagase K, Narisawa Y. Immunotherapy for Merkel cell carcinoma. Curr Treat Options in Oncol. 2018;19(11):57.

8. Robert C, Ribas A, Hamid O, Daud A, Wolchok JD, Joshua AM, et al. Durable complete response after discontinuation of pembrolizumab in patients with metastatic melanoma. J Clin Oncol. 2018;36(17):1668–74.

9. Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol. 2014;32(10):1020–30.

10. Nghiem PT, Bhatia S, Lipson EJ, Kudchadkar RR, Miller NJ, Annamalai L, et al. PD-1 blockade with pembrolizumab in advanced Merkel-cell carcinoma. N Engl J Med. 2016;374(26):2542–52.

11. Jansen YJL, Rozeman EA, Mason R, Goldinger SM, Geukes Foppen MH, Hoejberg L, et al. Discontinuation of anti-PD-1 antibody therapy in the absence of disease progression or treatment limiting toxicity: clinical outcomes in advanced melanoma. Ann Oncol. 2019;30(7):1154–61.

12. Blasig H, Bender C, Hassel JC, Eigentler TK, Sachse MM, Hiernickel J, et al. Reinduction of PD1-inhibitor therapy. Melanoma Res. 2017;27:321–5.

13. Lipson EJ, Sharfman WH, Drake CG, Wollner I, Taube JM, Anders RA, et al. Durable cancer regression off-treatment and effective reinduction therapy with an anti-PD-1 antibody. Clin Cancer Res. 2013;19(2):462–8.

14. Bernard-Tessier A, Baldini C, Martin P, Champiat S, Hollebecque A, Postel-Vinay S, et al. Outcomes of long-term responders to anti-programmed death 1 and anti-programmed death ligand 1 when being rechallenged with the same anti-programmed death 1 and anti-programmed death ligand 1 at progression. Eur J Cancer. 2018;101:160–4.