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PD-1 and PD-L1 inhibitors in the treatment of non-melanoma skin cancer: a systematic review

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ABSTRACT

Background: Immunotherapy using PD-1 or PD-L1 inhibitors has been increasingly reported in a variety of non-melanoma skin cancers (NMSCs).

Objective: To analyze the evidence of PD-1 and PD-L1 inhibitors in the treatment of non-melanoma skin cancer.

Methods: A primary literature search was conducted with PubMed, Cochrane Library EMBASE, Web of Science, and CINAHL through October 28, 2018 to include studies on the use of PD-1 or PD-L1 inhibitor in human subjects for non-melanoma skin cancer. Two reviewers independently performed study selection, data extraction and critical appraisal.

Results: Fifty-one articles were included in this systematic review. The most robust evidence was in the treatment of Merkel cell carcinoma and cutaneous squamous cell carcinomas, as supported by phase 1 and 2 clinical trials. Treatment of basal cell carcinoma, cutaneous sarcoma, sebaceous carcinoma and malignant peripheral nerve sheath tumor also showed benefit with PD-1/PD-L1 inhibitors but data is limited. There does not appear to be efficacy for PD-1/PD-L1 inhibitors in cutaneous lymphomas.

Limitations: More investigation is needed to determine the efficacy, tumor responsiveness, and the safety profile of PD-1 and PD-L1 inhibitors in NMSC.

Conclusion: PD-1 and PD-L1 inhibitors exhibit treatment efficacy in a variety of non-melanoma skin cancers.

Abbreviations – CR: complete response, PR: partial response, SD: stable disease, DP: disease progression; LMS: leiomyosarcoma, UPS: undifferentiated pleomorphic sarcoma

CAPSULE SUMMARY

- PD-1 and PD-L1 inhibitors have been demonstrated to treat a variety of non-melanoma skin cancers.
- We found PD-1 and PD-L1 inhibitors to be efficacious in treating advanced squamous cell carcinoma, basal cell carcinoma, Merkel cell carcinoma, cutaneous soft tissue sarcomas, malignant peripheral nerve sheath tumors, and sebaceous carcinomas.

ABBREVIATION AND ACRONYM LIST

- AE: adverse event
- BCC: basal cell carcinoma
- CR: complete response
- cSCC: cutaneous squamous cell carcinomas
- CTCL: cutaneous T-cell lymphoma
- CTLA-4: cytotoxic T lymphocyte associated protein 4
- DP: disease progression
- EGFR: epidermal growth factor
- FDA: Food and Drug Administration
- HIV: human immunodeficiency virus
- ICOS: inducible T cell costimulatory
- KS: Kaposi sarcoma
- LAG3 : lymphocyte activation gene 3
- MCC: Merkel cell carcinoma
- MPNST: malignant peripheral nerve sheath tumor
- NMSC: non-melanoma skin cancers
- PD-1: programmed cell death 1 protein
- PD-L1: programmed death ligand-1
- PFS: progression-free survival
- PR: partial response
- PRISMA: Preferred Reporting Items for Systematic Reviews ad Meta-Analyses
- RECIST: Response Evaluation Criteria in Solid Tumors
- SD: stable disease
- TIL: tumor infiltrating lymphocytes
- UPS: undifferentiated pleomorphic sarcoma

INTRODUCTION

Treatment landscape for skin cancer has expanded rapidly recently due to development of targeted immunotherapy that enhances the immune system's recognition of cancer cells.[1] Immune checkpoints such as cytotoxic T lymphocyte associated protein 4 (CTLA-4) and programmed cell death 1 protein (PD-1) are part of a complex signaling network that play crucial role in maintaining self-tolerance and in controlling the magnitude of immune responses to minimize autoimmunity.[2,3] Cancer cells hijack these pathways to evade immune response. Work in the 1990s demonstrated that targeted inhibition of these pathways led to enhanced tumor recognition and subsequent tumor regression.[4] Since then, clinical trials with immune checkpoint inhibitors have shown efficacy and improved survival in patients with melanoma, non-small cell lung cancer, Hodgkin's lymphoma and other malignancies.[5–12]

Non-melanoma skin cancers (NMSCs) are attractive targets for immune checkpoint inhibitors, and immunotherapy use has been increasingly reported. Often occurring on sun-exposed areas and resulting from ultraviolet damage, NMSCs demonstrate high mutational and neoantigen burden.[13] On histology, lymphocytes are often seen in the surrounding area, particularly in cutaneous squamous cell carcinomas (cSCCs), suggesting a potential immune response system primed to be stimulated.[14]

The purpose of this review is to analyze the evidence of using PD-1 and programmed death-ligand 1 (PD-L1) inhibitors in the treatment of NMSCs— cSCC, basal cell carcinoma (BCC), Merkel cell carcinomas (MCC), dermatofibrosarcoma protuberans, sebaceous carcinoma, atypical fibroxanthoma, pleomorphic dermal sarcoma, Kaposi sarcoma (KS), leiomyosarcoma, clear cell sarcoma, angiosarcoma, malignant peripheral nerve sheath tumor (MPNST), cutaneous lymphoma and extramammary Paget's disease.

METHODS

This study was done in accordance to the Preferred Reporting Items for Systematic Reviews ad Meta-Analyses (PRISMA).[15] A primary literature search was conducted with the databases PubMed, Cochrane Library, Web of Science and CINAHL on October 28, 2018. Two authors independently

screened with the search terms: (pd-L1 OR pd-1 OR pd1 OR pdl1 OR programmed death) AND (squamous OR basal OR NMSC OR merkel OR dermatofibrosarcoma OR sebaceous OR dermal sarcoma OR kaposi OR leiomyosarcoma OR clear cell sarcoma OR angiosarcoma OR undifferentiated pleomorphic sarcoma OR fibroxanthoma OR MPNST OR lymphoma OR extramammary). Medical Subject Headings (MeSH®) controlled vocabulary and text words were both utilized to develop the search terms.

Two reviewers independently screened all article titles and abstracts to include clinical trials, cohort studies, case series, cross-sectional studies, or case reports, published in English, on the use of PD-1 or PD-L1 inhibitor in human subjects for NMSCs as enumerated in the introduction. Meeting abstracts (from the June 2018 American Society of Clinical Oncology Annual Meeting, and the October 2018 European Society for Medical Oncology Congress) on unpublished or preliminary reports from ongoing trials were also included. Animal studies and articles not published in English were excluded. Subsequently identified studies were then subjected to full-text review. Bias risk and methodological quality were assessed according to the Cochrane Handbook for Systematic Reviews of Interventions.[16] Rationales for exclusion and article appraisals were recorded at every stage. References of included and excluded studies were reviewed for potential studies not identified through initial search strategy.

Included studies were summarized using a data extraction form. Outcomes of interest included treatment response graded using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 such as CR: complete response, PR: partial response, SD: stable disease, DP: disease progression[17]; progression-free survival (PFS) and treatment-related adverse events (AEs). Studies were graded using the Oxford Center for Evidence-Based Medicine 2011 Levels of Evidence.[18]

RESULTS

Through full-text screening of 5039 non-duplicate articles from 1972 to 2018, fifty-one studies were included in this systematic review as depicted by the PRISMA flow diagram (Figure 1).[15] PD-1/PD-L1 inhibitors used for each NMSC are listed in Table 1 with corresponding patient characteristics, response and adverse effects for each study included in this review.

Cutaneous Squamous Cell Carcinoma

Cemiplimab

An ongoing pivotal phase 2 trial (NCT02760498, EMPOWER) evaluating the use of cemiplimab 3 mg/kg every 2 weeks in 59 patients with metastatic cSCC revealed 7% CR, 41% PR, and 5% DP (Table 1).[19,20] Cemiplimab is also being used in another ongoing expansion cohort phase 1 trial (NCT02383212) in 26 patients with either metastatic or locally advanced cSCC. Initial reports from the trial described 50% PR and 12% DP.[19,21–23] PFS were not reported for either trial. On September 2018, cemiplimab was granted Food and Drug Administration (FDA) approval for metastatic or locally advanced cSCC based on these two trials.

Nivolumab

Nivolumab administered at a dose of 3 mg/kg or a fixed dose of 200 mg every 2 weeks over a range of 8-78 weeks in 7 cases reported 6-19.5 months PFS. CR was noted in a case of invasive, poorly differentiated recurrent cSCC treated with nivolumab and weekly cetuximab[24]. PR was noted in 5 cases, PFS was 28-48 weeks[25–27]. One case reported stable disease with PFS of 24 weeks[25].

Pembrolizumab

Pembrolizumab is being studied in an open-label phase 2 trial at 200 mg every 3 weeks up to 2 years in 19 patients (NCT02883556, CARSKIN) with unresectable chemotherapy-naive cSCC. Initial reports from the trial described 5% CR, 37% PR, 16% SD and 42% DP; median PFS 28 weeks. One patient discontinued due to grade 2 colitis. Other AEs (rash, pruritus, fatigue, dysthyroidism, diarrhea)

were noted in 63%,[28] as detailed in Table 1. Case reports also described CR in 3 cases[26,29,30], PR in 11 cases[25,26,31–34], DP in 2 cases[26,35]; (PFS 12-48 weeks).

Summary

The use of PD-1 inhibitors cemiplimab (FDA approved for metastatic or locally advanced cSCC in September 2018), nivolumab, and pembrolizumab for metastatic, locally advanced or recurrent cSCC has been reported in two phase 2 trials, one phase 1 trial, one retrospective cohort study and nineteen case reports (age 22-93 years, 19 females, 104 males, 8 unreported sex) as shown in Table 1. Responses with cemiplimab were as follows: 0-7% CR, 41-50% PR and 5-12% DP, while pembrolizumab had a higher DP rate: 5% CR, 37% PR, 16% SD, 42% DP (Table 2). The differences in the severity of cSCC may account for the wide range of response rates seen with different inhibitors.

Basal Cell Carcinoma

Cemiplimab

A patient with recurrent metastatic BCC, resistant to hedgehog inhibitors, achieved PR with cemiplimab 10mg/kg every two weeks for 24 weeks; PFS 32 weeks.[23]

Nivolumab

Two patients with metastatic BCC were treated with nivolumab.[25,36,37] One achieved PR with PFS 116 weeks.[36,37] The other patient (with prior liver transplant) showed SD with PFS 22 weeks.[25]

Pembrolizumab

Pembrolizumab 2 mg/kg every three weeks was used in five case reports – two patients had CR[38,39] and three had PR[33,35,40]; PFS 12-72 weeks. AEs reported include subclinical hypothyroidism and sarcoid-like lymph node reaction.[33,35]

More recently, a non-randomized open-label phase1b trial by Chang *et al*.[41] for sixteen subjects with unresectable or metastatic BCC refractory to or recurrent after use of Hedgehog pathway inhibitors concluded that pembrolizumab is active against BCCs. Nine patients (six with metastatic disease) received pembrolizumab monotherapy 200 mg every three weeks and seven (three with metastatic disease)

received pembrolizumab with oral vismodegib 150 mg. The pembrolizumab monotherapy group reported 11% CR, 33% PR, 44% SD, 11% DP; while the pembrolizumab-vismodegib combination group reported 29% CR, 14% PR, 57% SD. PFS in weeks was not reported but one-year PFS was noted to be 70%. Additionally, although the monotherapy and combination therapy groups were not directly compared due to the trial's non-randomized study design, the authors concluded that the response rate of the pembrolizumab-vismodegib combination therapy group was not subjectively superior compared to the pembrolizumab monotherapy group. Only one of the severe AEs, hyponatremia, was attributed to pembrolizumab.

Summary

The use of PD-1 inhibitors cemiplimab, nivolumab and pembrolizumab for BCC has been reported in one phase 1 trial and eight case reports (age 58-81 years, 5 females, 3 males, 16 unreported sex). CR has not been reported with cemiplimab nor nivolumab. The non-randomized open label trial reported CR in two patients (29%) who received pembrolizumab monotherapy and in one patient (11%) who received pembrolizumab-vismodegib combination therapy.

Merkel Cell Carcinoma

Avelumab

Avelumab received accelerated FDA-approval based on the JAVELIN Merkel 200 trial, a phase 2 prospective, open-label, multicenter trial (NCT02155647) of 88 subjects with metastatic MCC that reported 11% CR, 22% PR, 10% SD, 36% DP; and PFS of 6-28 weeks (1.4-6.9 months). Grade 3 or 4 AEs occurred in 11% which included lymphopenia and interstitial nephritis. [42,43,44] Individual case reports described one CR case[45] and one PR[46] case for metastatic MCC treated with avelumab.

Nivolumab

A phase 1/2 trial of 25 metastatic MCC patients treated with nivolumab 240 mg every 2 weeks reported 14% CR, 55% PR, 18% SD and 14% DP.[47] PR was noted in two other metastatic MCC case reports; PFS 32-40 weeks. Grade 3 or 4 AEs occurred in 20%.[48,49]

Pembrolizumab

A phase 2 multicenter trial of pembrolizumab for 26 patients with advanced MCC, with no prior systemic therapy use, reported 15% CR, 38% PR, 8% DP, PFS 9-39 weeks (2.2-9.7 months). Grade 3 or 4 AEs occurred in 15% which included grade 4 myocarditis.[50] Five other case reports demonstrated three with CR and two with PR, PFS 12-68 weeks.[51-55] Therapy was discontinued after 3 cycles in one case where the patient developed oral mucous membrane pemphigoid.[54] Three cases reported DP.[56,57]

Summary

The use of the PD-L1 inhibitor avelumab, and PD-1 inhibitors nivolumab and pembrolizumab have been reported for the treatment of advanced MCC in three phase 2 trials and eleven case reports (age 33-88, 94 males, 31 females, 26 unreported sex). Treatment response and AE profiles were similar for all three molecules. Avelumab achieved 11% CR, 22% PR, 10% SD, 36% DP; while nivolumab had 14% CR, 55% PR, 18% SD, 14% DP; and pembrolizumab had 15% CR, 38% PR, 8% DP. Of these three immunotherapies, only avelumab is FDA-approved for the treatment of metastatic MCC.

Cutaneous Lymphoma

There has been one phase 1b clinical trial using nivolumab up to 2 years for cutaneous T-cell lymphoma (CTCL); this was in a broader trial for B- and T-cell lymphomas that included 13 patients with mycosis fungoides and 2 with Sézary syndrome. Within the subset of mycosis fungoides patients, 15% PR, 69% SD, 15% DP were reported; PFS 7-35 weeks were reported. Sézary syndrome patients had 0% CR/PR and 100% DP over the treatment course.[58] Pneumonitis, sepsis, and myositis were adverse events reported that led to the discontinuation of medication in 15% of patients.

Soft Tissue Sarcoma

PD-1 inhibitors have been utilized in a variety of sarcomas including leiomyosarcoma, undifferentiated pleomorphic sarcoma, liposarcoma, Kaposi sarcoma, and angiosarcoma.

Leiomyosarcoma has been treated with PD-1 inhibitors in two phase 2 trials and two reported cases. Thirteen patients with leiomyosarcoma were treated with pembrolizumab in combination with cyclophosphamide in one phase 2 trial that reported 23% SD, 77% DP, and no patients achieved PR/CR.[59] In another phase 2 trial, 10 patients received 200 mg pembrolizumab every 3 weeks resulting in 60% SD, 40% DP.[60] One case from the phase 1 KEYNOTE-001 trial reported SD with pembrolizumab.[51] Overall, pembrolizumab alone or in combination with cyclophosphamide for leiomyosarcoma revealed 0% CR/PR, 23-60% SD and 67-77% DP (Table 2). One case of refractory leiomyosarcoma treated with 3mg/kg nivolumab every 2 weeks reported PR.[61]

Pembrolizumab in combination with cyclophosphamide was also used for twelve patients with undifferentiated pleomorphic sarcoma (UPS). The trial reported 42% SD and 58% DP, with one case of death.[59]Another phase 2 trial of pembrolizumab alone for 10 patients with UPS reported 10% CR, 30% PR, 30% SD and 30% DP.[60] Overall, pembrolizumab alone or in combination for UPS revealed 0-10% CR, 0-30% PR, 30-42% SD and 30-58% DP. In addition, pembrolizumab in 10 patients with liposarcoma reported 20% PR, 40% SD, 40% PD.[60] In this trial, 6% of patients discontinued therapy due to toxicity, which included nephritis and pneumonitis, and the most frequent grade 3 or worse AE was anemia and other hematologic abnormalities.

A single cohort of 9 patients and four cases of Kaposi sarcoma (KS) have been treated with PD-1 inhibitors nivolumab or pembrolizumab. In this cohort study, 8 patients with HIV-related KS were treated with nivolumab and one with pembrolizumab, resulting in 11% CR, 56% PR, 33% SD; PFS 6-26 weeks.[62] No drug-related AE's greater than grade 2 severity were reported. One case series reported PR in two cases of endemic KS that received nivolumab 3mg/kg every 2 weeks.[63] In this case series, the medication was relatively well-tolerated, and the only AE noted was adrenal insufficiency with hyponatremia. Additionally, one case of KS treated with pembrolizumab 10mg/kg every 2 weeks reported SD at 8 weeks[51], and another case of classic KS resulted in PR after 12 to 18 weeks of pembrolizumab.[64]

Angiosarcoma of the nose with liver metastasis was treated with pembrolizumab, resulting in marked shrinkage in metastatic lesions and no progression of cutaneous lesions (PR).[65] This patient

developed autoimmune hepatitis during therapy. Additionally, complete responses were reported with use of pembrolizumab for scalp angiosarcoma[66] and with nivolumab-cetuximab combination therapy for sarcomatoid carcinoma.[67]

Sebaceous Carcinoma

One case of widely metastatic sebaceous carcinoma treated with pembrolizumab 2mg/kg every three weeks demonstrated PR after 24 weeks, PFS of 48 weeks.[68] This was despite dose interruption for treatment of secondary adrenal insufficiency.

Malignant Peripheral Nerve Sheath Tumor

PD-1 inhibitors have been utilized in two cases of MPNST – a case of SD within the phase 1 KEYNOTE-001 trial of pembrolizumab 10mg/kg every 3 weeks for 21 weeks and a case report of CR with pembrolizumab 200mg every 3 weeks for 18 weeks.[51,69] No AEs were reported for the case of pembrolizumab-induced CR. Objective response (CR or PR cases) have been reported with UPS, liposarcoma, KS, angiosarcoma, sarcomatoid carcinoma, sebaceous carcinoma and MPNST; but not in leiomyosarcoma.

DISCUSSION

A review of the literature reveals the utility of PD-1 and PD-L1 inhibitors for difficult to treat NMSCs. The most robust evidence for use of these checkpoint inhibitors was in treatment of MCC (multiple completed phase 1 and 2 clinical trials), cSCCs (ongoing phase 1 and 2 clinical trials), and BCC (one non-randomized phase 1 clinical trial) showing overall benefit (Table 2). Most patients included in clinical trials of MCC, cSCC and BCC either had metastatic, locally advanced disease, or disease unresponsive to conventional therapies. The heterogeneity may account for the differences seen in the response rates. To date, only two PD-1/PD-L1 inhibitors have been FDA-approved for NMSCs –

avelumab for metastatic MCC (March 2017) based on the completed multicenter JAVELIN MERKEL 200 trial[46,48], and cemiplimab for metastatic or locally advanced cSCC (September 2018) based on two ongoing trials[16,25-28]. Pembrolizumab and nivolumab have been FDA approved (2014) for treatment of unresectable or metastatic melanoma, but have yet to be approved for any NMSC. PD-1 inhibitors were also found to have benefit in the treatment of Kaposi sarcoma, angiosarcoma, UPS, liposarcoma, sarcomatoid carcinoma, sebaceous carcinoma and MPNST, although current evidence consists of mostly case reports and one small-scale phase 2 trial for UPS and liposarcoma. It is worth noting that soft tissue sarcoma trials included in this review involved advanced or metastatic soft tissue sarcomas and the extents of cutaneous disease were not reported extensively; however case reports included all reported skin involvement. The role of PD-1 inhibitors in CTCL or leiomyosarcoma is less promising with no CR/PR ever reported. Interestingly, there has been a case of CD56+ CTCL development during pembrolizumab treatment for metastatic melanoma.[70]

Several clinical studies are underway investigating immune-checkpoint inhibitors for advanced NMSC. In the list of 71 active clinical trials for NMSCs published online by the National Institutes of Health National Cancer Institute in December 2018[71], there are 17 active trials looking at PD-1/PD-L1 inhibitors with no published reports to date, 8 active trials with preliminary reports published, and 3 completed trials (Table 2). The majority of active clinical trials are for advanced SCCs and MCCs. Other tumors of investigation include advanced BCCs (for individuals with progression on, or failure after, hedgehog inhibitor therapy), mycosis fungoides, leiomyosarcoma and UPS. Of note, there is currently an active trial involving a new molecule atezolizumab, a PD-L1 inhibitor, for soft tissue sarcoma. Trials are looking at PD-1/PD-L1 inhibitors as both primary and adjuvant therapy, as well as their utility in combination therapy with radiotherapy, other immunomodulators such as anti-CTLA-4 antibodies, indoleamine 2,3-dioxygenase-1 inhibitors, tumor microenvironment modulators, and personalized cancer vaccines.

Only a percentage of patients with advanced tumors benefit from PD-1/PD-L1 immunotherapy currently. Epidermal growth factor receptor (EGFR) trials have found control rates of 60-70% in

cSCCs— cetuximab, erlotinib, gefitinib and panitumumab.[72] Future studies of interest would evaluate dual immune-targeted therapy combining EGFR and PD-1 inhibitors. Other future therapeutic areas of interest involve intralesional anti-PD1 treatment. A recent pilot study conducted in patients with metastatic melanoma showed efficacy of anti-PD-1 injections.[73] Intratumoral IL-12 treatment with concurrent systemic anti–PD-1 therapy is also under investigation for melanoma.[74]

Gaps remain in the knowledge and use of PD-1 and PD-L1 inhibitors. A primary concern is that some patients can develop resistance to immunotherapy through mutations in genes like inducible T cell costimulatory (ICOS), 4-1BB, lymphocyte activation gene 3 (LAG3) that would affect T cell activation and exhaustion.[12,75] Identifying patients who will respond remains paramount, yet biomarkers to predict response to checkpoint inhibitors is still ill-defined in NMSCs.[76] In melanoma, there is evidence that specific $CD8^+$ T cell phenotypes are associated with positive response to checkpoint inhibitors but whether similar T cell phenotypes are important in NMSCs are unknown.[77] Melanoma patients that express PD-L1 are more likely to respond to combination therapy than patients who do not express high levels of PD-1.[7] There is mixed data on NMSC PD-1 and PD-L1 expression and response, with conflicting findings for both MCCs and BCCs.[43,78] Domingo-Musibay *et al.* assessed sebaceous carcinoma metastatic tumor tissue for PD-L1 expression and found it to be 100% reactive.[68] Other than PD-1 and PD-L1 expression, studies have also shown that higher amount of CD8+ tumor infiltrating lymphocytes (TILs) are associated with a positive response to anti-PD-1 immunotherapy.[79] Whether these parameters also predict response to immunotherapy in NMSCs is unclear and future larger studies are necessary.

Additional insight into the safety profile of checkpoint inhibitors is also necessary, as many patients who develop advanced NMSCs are immunosuppressed and/or elderly. The rate of grade 3-4 adverse events in clinical trials of anti-PD-1 inhibitors in melanoma is estimated at 15%[14]. Again, this demographic tends to be younger than those with NMSCs. Of note, PD-1 efficacy and safety in the treatment of non-small cell lung cancer was recently reported in HIV patients.[80] In this case series, Borradori *et al*. reported PR of cSCC with no reported AEs in an HIV patient[25]; and Galanina *et al*.

reported 11% CR, 56% PR and 33% SD among patients with HIV-associated Kaposi sarcoma treated with nivolumab or pembrolizumab[62].

Transplant patients represent another challenging group for checkpoint inhibitor use as enhanced T cell activation can lead to allograft rejection.[81,82] Limited data exists as transplant patients were often excluded from checkpoint inhibitor trials due to chronic immunosuppression and only data from case studies are available. Sadaat and Jang reported CR to pembrolizumab in a patient receiving sirolimus and prednisone as immunosuppression for prior kidney transplant.[30] Lipson *et al*. reported PR for cSCC treated with pembrolizumab in a kidney transplant patient (on prednisone immunosuppression). This patient experienced acute allograft rejection two months after pembrolizumab initiation.[81] Based on a review of current reported cases, Chae *et al.* suggested that CTLA-4 inhibitors may have a lower risk of rejection than PD-1 inhibitors but further studies are needed to determine the safety profile of checkpoint inhibitors in immunosuppressed populations at high risk for developing NMSCs.[82] Currently, given the significant risk of allograft rejection in this population, an in-depth discussion with the patient is necessary before the initiation of checkpoint inhibitors.

CONCLUSION

The role of PD-1 and PD-L1 inhibitors in advanced NMSCs is promising; with utility in advanced cSCC, BCC, MCC, cutaneous soft tissue sarcomas, sebaceous carcinoma and malignant peripheral nerve sheath tumors. The role of PD-1 inhibitors in cutaneous lymphomas is less impressive. More investigation is needed to determine the efficacy, tumor responsiveness, and the safety profile of PD-1 and PD-L1 inhibitors.

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599 **FIGURE LEGEND**

600 Figure 1. PRISMA diagram[21] for the systematic review of PD-1/PD-L1 inhibitors for the treatment of
601 non-melanoma skin cancers.

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603 **TABLE LEGEND**

604 Table 1. Systematic Review of PD-1 and PD-L1 Inhibitors in the Treatment of Non-Melanoma Skin
605 Cancer

606

607 Table 2. Clinical Trials Utilizing PD-1 and PD-L1 Inhibitors in the Treatment of Non-Melanoma Skin
608 Cancer

Table 1. Systematic Review of PD-1 and PD-L1 Inhibitors in the Treatment of Non-Melanoma Skin Cancer

Authors, Year	Study Design, LOE[a]	Patient Condition, Age, Sex	Intervention	Response[b], PFS[c]	Adverse Effects
Cutaneous SCC (cSCC)					
Rischin et al. 2018[20], Migden et al. 2018[19]	ongoing pivotal phase 2 trial (n=59) [NCT02760498, EMPOWER] LOE 2	metastatic cutaneous SCC 38-93, 54M, 5F	cemiplimab 3 mg/kg IV q2w	4 (7%) CR, 24 (41%) PR, 3 (5%) DP not reported	most common AEs (all grades, ≥Grade 3): diarrhea (27.1%, 1.7%), fatigue (23.7%, 1.7%), and nausea (16.9%, 0.0%); immune-related AEs ≥grade 3 in 10.2%
Papadopoulos et al. 2018[21], Owonikoko et al. 2018[22], Falchook et al. 2016[23]; Migden et al. 2018[19]	ongoing expansion cohort phase 1 trial (n=26) [NCT02383212] LOE 2	cutaneous SCC with distant metastases (n=10), locally advanced cutaneous SCC (n=16) 56-88, 21M, 5F	cemiplimab 3 mg/kg IV q2w for up to 48 weeks	13 (50%) PR, 6 (23%) SD, 3 (12%) DP not reported	most common treatment-related adverse event of any grade was fatigue (26.9%); the following ≥ grade 3 AEs occurred once: asthenia, maculopapular rash, liver enzymes elevation, adrenal insufficiency, myalgia
Borradori et al. 2016[25]	case series (n=5) LOE 4	Case B: cutaneous SCC with bone and lymph node metastases (n=1) 65, M	nivolumab 3 mg/kg q2w x 28+ wks	PR skin ulcerations, lymph nodes, face mass 28 wks	none reported
Borradori et al. 2016[25]	case series (n=5) LOE 4	Case D: cutaneous SCC with lymph, bone and lung metastases (n=1) 66, M	nivolumab 3 mg/kg q2w x 8 wks	SD, patient death due to arrhythmia 24 wks	weight loss, nausea, fatigue, grade 1 hyponatremia, deceased after 6 months due to arrhythmia
Tran et al. 2017[26]	case series (n=6) LOE 4	Case C: recurrent cutaneous SCC with lymph node metastasis (n=1) 60-82, M	nivolumab 3 mg/m2 q2w x 50+ wks	PR 48 wks	mild fatigue, moderate hip pain, moderate hyperglycemia
Blum et al. 2018[27]	case series (n=3) LOE 4	Case A: advanced cutaneous SCC with parotid gland and lung metastases (n=1) 66, M	nivolumab 3 mg/kg q2w x 78+ wks	PR 78 wks	none reported
Blum et al. 2018[27]	case series (n=3) LOE 4	Case B: advanced cutaneous SCC with lymph node and lung metastases (n=1) 72, M	nivolumab 3 mg/kg q2w x 78+ wks	PR (near complete) 78 wks	none reported

[a] Level of Evidence (LOE) graded using the Oxford Center for Evidence-Based Medicine 2011 Levels of Evidence
[b] Response graded using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; CR: complete response, PR: partial response, SD: stable disease, DP: disease progression
[c] Progression-Free Survival (PFS)

Blum et al. 2018[27]	case series (n=3) LOE 4	Case C: advanced cutaneous SCC with lymph node lung and bone metastases (n=1) 81, F	nivolumab 200mg q2w x 34+ wks	PR 34 wks	none reported
Chen et al. 2018[24]	case report (n=1) LOE 5	invasive, poorly differentiated recurrent SCC of pre-auricular region with external auditory canal involvement; renal failure (n=1) 74, M	nivolumab q2w and cetuximab q1w x 52+ wks	CR 48 wks	none reported
Maubec et al. 2018[28]	ongoing open-label phase 2 trial (n=19) [NCT02883556, CARSKIN] LOE 2	unresectable, chemotherapy-naive cutaneous SCC (n=19) 61-88, 15M, 4F	pembrolizumab 200 mg q3w up to 104 wks	1 (5%) CR, 7 (37%) PR, 3 (16%) SD, 8 (42%) DP 28 wks	one patient discontinued due to grade 2 colitis AE in 63%: rash (32%), pruritus (16%), fatigue (26%), dysthyroidism (10%), and diarrhea (10%)
Hermel et al. 2018[34]	retrospective cohort study (n=8) LOE 3	locally advanced cutaneous SCC (n=8) 22-85	pembrolizumab 2 mg/kg q3w at least 1 cycle	4 (50%) PR, 2 (25%) SD not reported	no grade 3 or 4 toxicity observed
Borradori et al. 2016[25]	case series (n=5) LOE 4	Case A: cutaneous SCC with brain and lymph node metastases (n=1) 79, M	pembrolizumab 2 mg/kg q3w x 28+ wks with stereotactic radiation to the brain lesion	PR skin ulcerations, brain mass, lymph nodes 28 wks	transient mild grade 1 fatigue, transient brain edema
Borradori et al. 2016[25]	case series (n=5) LOE 4	Case E: cutaneous SCC with lymph node metastases; HIV infection (n=1) 65, M	pembrolizumab 2 mg/kg q3w x 16+ wks	PR neck mass, SD lung nodules 16 wks	none reported
Tran et al. 2017[26]; Chang et al. 2017[31]	case series (n=6) LOE 4	Case A: unresectable recurrent cutaneous SCC with perineural invasion (n=1) 70s, M	pembrolizumab 2 mg/kg q3w x 78+ wks	PR 84 wks	severe weakness with hypocortisolism and thyroid hypofunction (recovered), chills, mild arthralgia, mild weight loss

[a] Level of Evidence (LOE) graded using the Oxford Center for Evidence-Based Medicine 2011 Levels of Evidence
[b] Response graded using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; CR: complete response, PR: partial response, SD: stable disease, DP: disease progression
[c] Progression-Free Survival (PFS)

Tran et al. 2017[26]	case series (n=6) LOE 4	Case B: cutaneous SCC with lymph node metastasis (n=1) 60-82, M	pembrolizumab 2 mg/kg q3w x 45+ wks	CR 42 wks	mild fatigue
Tran et al. 2017[26]	case series (n=6) LOE 4	Case D: cutaneous SCC with lymph node, brain and lung metastases (n=1) 60-82, M	pembrolizumab 2 mg/kg q3w x 27+ wks	PR 22 wks	mild fatigue, mild xerosis, mild appetite loss
Tran et al. 2017[26]	case series (n=6) LOE 4	Case E: cutaneous SCC with lymph node and lung metastases (n=1) 60-82, F	pembrolizumab 2 mg/kg q3w x 24+ wks	PR axillary lymph nodes, SD lung nodules 22 wks	mild fatigue, mild neuropathy, hip fracture
Tran et al. 2017[26]	case series (n=6) LOE 4	Case F: cutaneous SCC with brain metastasis (n=1) 60-82, F	pembrolizumab 2 mg/kg q3w x 15+ wks	DP 12 wks	mild fatigue, mild increased salivation, mild dull headache, mild short-term memory loss, mildly unsteady gait
Winkler et al. 2017[35]	case series (n=2) LOE 4	Case B: cutaneous SCC with lymph node metastases (n=1) 74, F	pembrolizumab 2 mg/kg q3w x 15 wks	DP 12 wks	n/a
Assam et al. 2016[29]	case report (n=1) LOE 5	unresectable stage 4 cutaneous SCC with lung metastases and perineural invasion (n=1) 67, M	pembrolizumab 2 mg/kg IV q3w x 104+ wks	CR 96 wks	mild fatigue
Lipson et al. 2016[33]	case report (n=1) LOE 5	metastatic cutaneous SCC; on immunosuppression for prior kidney transplant (n=1) 57, F	pembrolizumab 2 mg/kg q3w x 32+ wks	PR 32 wks	acute allograft rejection 2 months after pembrolizumab initiation
Sadaat and Jang. 2018[30]	case report (n=1) LOE 5	cutaneous SCC with lymph node metastasis; on immunosuppression for prior kidney transplant (n=1) 63, M	pembrolizumab 2 mg/kg q3w x 12 wks	CR 12 wks	none reported

[a] Level of Evidence (LOE) graded using the Oxford Center for Evidence-Based Medicine 2011 Levels of Evidence
[b] Response graded using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; CR: complete response, PR: partial response, SD: stable disease, DP: disease progression
[c] Progression-Free Survival (PFS)

Stevenson et al. 2018[32]	case report (n=1) LOE 5	locally advanced cutaneous SCC (n=1) 70s, M	pembrolizumab 2 mg/kg q3w x 12 wks	PR (near complete) 12 wks	none reported
Basal Cell Carcinoma (BCC)					
Falchook et al. 2016[23]	case series (n=2) LOE 4	Case A: recurrent desmoplastic BCC with bone, lung, lymph node metastasis (n=1) 66, F	cemiplimab (REGN2810) 10 mg/kg IV q2w x 24 wks	PR 32 wks	none reported
Ikeda et al. 2016[37], Cohen et al. 2017[36]	case report (n=1) LOE 5	refractory BCC with brain, bone, liver, lung metastasis (n=1) 58, M	nivolumab 240 mg q2w	PR 116 wks	new primary cutaneous superficial BCC with no PD-L1 amplification that also responded to nivolumab
Borradori et al. 2016[25]	case report (n=1) LOE 5	Case D: BCC with lung metastasis and prior liver transplant (n=1) 61, F	nivolumab 4 infusions	SD of several metastatic nodules, PR of left upper lobe lesion 22 wks	fatigue
Chang et al. 2018[41]	non-randomized, open-label phase 1b trial (n=16) [NCT02690948] LOE 2	unresectable or metastatic BCC refractory or recurrent to Hedgehog pathway inhibitors (n=16) 56-77, 13M, 3F	pembrolizumab 200 mg q3w IV with (n=7) or without (n=9) vismodegib 150 mg PO	combination: 2 (29%) CR, 1 (14%) PR, 4 (57%) SD monotherapy: 1(11%) CR, 3 (33%) PR, 4 (44%) SD, 1(11%) DP (70% PFS at one year)	only one out of the 98 severe AEs was attributed to pembrolizumab (hyponatremia); 23 immune-related AEs (irAEs): grade 1-2 dermatitis and fatigue as the most common
Winkler et al. 2017[35]	case series (n=2) LOE 4	Case A: BCC with lung metastasis (n=1) 62, F	pembrolizumab stopped after 4 cycles	PR 12 wks	sarcoid-like lymph node reaction
Lipson et al. 2017[33]	case report (n=1) LOE 5	recurrent BCC with lung metastasis (n=1) 67, F	pembrolizumab 2 mg/kg q3w	PR 40 wks	subclinical hypothyroidism
Cannon et al., 2018[39]	case report (n=1) LOE 5	recurrent BCC with lung metastasis (n=1) 50s, M	pembrolizumab 2 mg/kg q3w	CR of original lung nodules, DP of new vertebral mass 16 wks	none reported

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[c] Progression-Free Survival (PFS)

Fischer et al. 2018[40]	case report (n=1) LOE 5	BCC with lung metastasis (n=1) 81, M	pembrolizumab 2 mg/kg q3w (total dose 150 mg)	PR 72 wks	none reported
Moreira et al. 2018[38]	case report (n=1) LOE 5	Gorlin-Goltz syndrome with more than 50 BCC on head and upper trunk (n=1) 77, F	pembrolizumab 2 mg/kg q3w x 12wks	CR of nose BCC and right forehead, PR of left nasolabial fold BCC, PR of left retroauricular lesions	none reported
Merkel Cell Carcinoma (MCC)					
Kaufman et al. 2016[42]; D'Angelo et al. 2018[44]; Kaufman et al. 2018[43]	multicenter, international, prospective, single-group, open-label phase 2 trial (n=88); LOE 2 [NCT02155647, JAVELIN Merkel 200]	chemotherapy-refractory, stage IV MCC (n=88) 33-88, 65M, 23F	avelumab 10 mg/kg IV q2w	10 (11%) CR, 19 (22%) PR, 9 (10%) SD, 32 (36%) DP 6-28 wks (1.4-6.9 mos)	7 (10.1%) discontinued due to treatment-related AE (ileus, transaminitis) grade 3 (5%): lymphopenia (2), blood creatine phosphokinase increase (1), aminotransferase increase (1), blood cholesterol increase (1); other serious (6%): enterocolitis (1), infusion-related reaction (1), aminotransferase increase (1), chondrocalcinosis (1), synovitis (1), interstitial nephritis (1)
Eshghi et al. 2017[45]	case report (n=1) LOE 5	MCC with liver and lymph node metastasis (n=1) 85, M	avelumab	CR not reported	n/a
Zhao et al. 2017[46]	case report (n=1) LOE 5	MCC with lymph node metastasis (n=1) 73, M	avelumab 10 mg/kg IV q2w	PR 14 wks	central diabetes insipidus that resolved with avelumab discontinuation and desmopressin
Topalian et al. 2017[47]	phase 1/2 trial (n=25) [NCT02488759, CheckMate 358] LOE 2	advanced MCC (n=25) median 66, 17M, 8F	nivolumab 240 mg q2w until progression or unacceptable toxicity	3 (14%) CR, 12 (55%) PR, 4 (18%) SD, 3 (14%) DP 82% PFS at 12 wks	Grade 3 or 4 AEs occurred in 20%, AEs led to discontinuation in 12%
Matripragada and Birnbaum. 2015[48]	case report (n=1) LOE 5	MCC with metastasis to heart and pancreas (n=1) 42, M	nivolumab 3 mg/kg IV q2w x 12 wks	PR 40 wks	none reported
Walocko et al. 2016[49]	case report (n=1) LOE 5	MCC with metastasis to lymph node, pancreas (n=1) 80s, M	nivolumab 3 mg/kg IV q2w x 12 wks	PR 32 wks	pneumonia and autoimmune hepatitis by 12 weeks managed with IV corticosteroids

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Nghiem et al. 2016[50]	multicenter, noncontrolled, phase 2 trial (n=26) [NCT02267603] LOE 2	advanced MCC with no previous systemic therapy (n=26) 57-91, M/F	pembrolizumab 2 mg/kg q3w	4 (15%) CR, 10 (38%) PR, 2 (8%) DP 9-40 wks (2.2-9.7 mos)	treatment-related adverse events in 77% patients; grade 3 or grade 4 in 15%; grade 4: myocarditis (1), elevated liver enzymes (1)
Xu et al. 2018[56]	case series (n=2) LOE 4	Case A: MCC with metastasis to lymph node, pancreas (n=1) 69, M	pembrolizumab x 10 wks, palliative radiotherapy later added for 12 months	initial DP with pembrolizumab; PR after addition of radiotherapy 68 wks	n/a
Xu et al. 2018[56]	case series (n=2) LOE 4	Case B: MCC with metastasis to lymph node, pancreas (n=1) 72, M	pembrolizumab x 20 weeks, radiotherapy single fraction given after	initial DP with pembrolizumab; PR after addition of radiotherapy 48 wks	n/a
Patnaik et al. 2015[51]	case report (n=1) from a phase 1 trial (n=13) LOE 5 [NCT01295827, KEYNOTE-001]	Case D: merkel cell carcinoma previously untreated (n=1) age not reported, M	pembrolizumab 2 mg/kg q3w x 63+ wks	CR 100 wks	treatment related AE in 70% patients; no grade 3 or 4; 10% discontinued due to grade 2 fatigue (1), pneumonitis (1), decreased weight (1); death in 1 case due to cryptococcal infection
Roche et al. 2017[55]	case report (n=1) LOE 5	MCC with metastasis to liver; psoriatic arthritis (n=1) 59, M	pembrolizumab 2 mg/kg q3w x 24+ wks	CR 24 wks	none reported; no flare of psoriatic plaques nor joint symptoms
Winkler et al. 2017[53]	case report (n=1) LOE 5	MCC with lymph node, intestine and adrenal gland metastasis (n=1) 80, M	pembrolizumab 2 mg/kg q3w x 12 wks, stopped for 16 wks, resumed for 12 wks after DP, therapy-free period of 2 mos	PR 68 wks	autoimmune hyperthyroidism after 1 cycle
Cugley et al. 2018[52]	case report (n=1) LOE 5	MCC with metastasis to orbit, liver, bone; CLL previously treated; metastatic SCC; hypogammaglobulinemia; CKD due to type II MPGN (n=1); 64, M	pembrolizumab 2 mg/kg IV q3w + external beam radiotherapy after 2 weeks	CR 12 wks	n/a

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Haug et al. 2018[54]	case report (n=1) LOE 5	MCC with lymph node metastasis (n=1) 62, M	pembrolizumab 2 mg/kg q3w stopped at 13 weeks	PR 24 wks	oral mucous membrane pemphigoid after 13 weeks
Barker et al. 2018[57]	case report (n=1) LOE 5	recurrent MCC with lymph node metastasis; untreated CLL (n=1) 65, M	pembrolizumab 2 mg/kg q3w x 9 weeks; palliative radiotherapy added later on	DP 0 wks	precipitation of low grade fever within hours of infusion; grade 3 Cytokine Release Syndrome related to addition of palliative radiotherapy
Cutaneous Lymphoma, Soft Tissue Sarcomas, Sebaceous Carcinoma, and Malignant Peripheral Nerve Sheath Tumor					
Lesokhin et al. 2016[58]	open-label, dose-escalation, cohort-expansion phase 1b trial for refractory or relapsed lymphoma and multiple myeloma (n=81) [NCT01592370] LOE 2	T-cell lymphoma: mycosis fungoides (n=13), Sezary syndrome (n=2) 23-81, 34F, 47M	nivolumab 1 or 3 mg/kg q2w for up to 2 years	mycosis fungoides: 2 (15%) PR, 9 (69%) SD; Sezary syndrome: 0% response mycosis fungoides: 10wks (7-35 wks); Sezary sydrome: 7 wks	treatment related AE in 65% patients; fatigue (17%), pneumonia (11%), decreased appetite, pruritus, rash (9% each)
Toulmonde et al. 2018[59]	open-label, multi-center phase 2 trial for advanced soft-tissue tumor (n=57) [NCT02406781] LOE 2	leiomyosarcoma (LMS) (n=13), undifferentiated pleomorphic sarcoma (UPS) (n=12) 18-84, 33M, 24F	pembrolizumab 200 mg q3w; cyclophosphamide 50 mg twice daily 1 week on and 1 week off	LMS: 10 (77%) DP, 3 (23%) SD UPS: 7 (58%) DP, 5 (42%) SD 5.6 wks	UPS: toxicity (4), death (1) most frequent: grade 1 or 2 fatigue, diarrhea or anemia; grade 3 or 4: fatigue, oral mucositis, anemia
Tawbi et al. 2017[60]	two-cohort, single-arm, open-label, phase 2 trial (n=84) [NCT02301039, SARC028] LOE 2	LMS (n=10), UPS (n=10), liposarcoma (n=10) 18-81, 31F, 53M	pembrolizumab 200 mg q3w	LMS: 60% SD, 40% PD; UPS: 10% CR, 30% PR, 30% SD, 30% PD liposarcoma: 2 (20%) PR, 4 (40%) SD, 4 (40%) PD UPS: 30 (8-68) wks; liposarcoma: 25(8-42)wks	grade 3 or worse AE in soft tissue sarcoma patients: anemia (7%), decreased lymphocyte count (7%), and prolonged activated partial thromboplastin time (7%)
Patnaik et al. 2015[51]	case report from phase 1 trial (n=17) [NCT01295827, KEYNOTE-001] LOE 5	Case B: leiomyosarcoma (n=1) 81, F	pembrolizumab 3 mg/kg q2w stopped at 33wks	SD 35 wks	grade 2 pneumonitis

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Heine et al. 2010[61]	case report (n=1) LOE 5	refractory leiomyosarcoma (n=1) 39, M	nivolumab 3 mg/kg q2w	PR 24 wks	none reported, most notably no autoimmune-related symptoms
Galanina et al. 2018[62]	retrospective cohort study (n=9) LOE 3	HIV-associated Kaposi sarcoma (n=9) 33-63, 9M	nivolumab (n=8), or pembrolizumab (n=1)	1 (11%) CR, 5 (56%) PR, 3 (33%) SD 6-26 wks	no drug-related grade >2 toxicities; most common: fatigue (56%), pruritus (44%), muscle/joint ache (22%), abdominal discomfort (11%), onycholysis (11%)
Delyon et al. 2018[63]	case series (n=2) LOE 4	Case A: monomelic endemic HIV(-) Kaposi sarcoma with muscular, bone and lymph node extension (n=1) 74	nivolumab 3 mg/kg q2w x 24 wks	PR 24 wks	at 16 weeks: hyponatremia associated with low cortisol requiring hormone replacement therapy
Delyon et al. 2018[63]	case series (n=2) LOE 4	Case B: monomelic endemic HIV(-) Kaposi sarcoma with bone and lymph node extension (n=1) 64	nivolumab 3 mg/kg q2w x 24 wks	PR 24 wks	none reported
Saller et al. 2018[64]	case report (n=1) LOE 5	advanced classic HIV(-) chemotherapy-refractory Kaposi sarcoma; history of atrial fibrillation (n=1) 75, M	pembrolizumab for 12-18 weeks	PR 42 wks	none reported
Patnaik et al. 2015[51]	case report from phase 1 trial (n=17) [NCT01295827, KEYNOTE-001] LOE 5	Case A: Kaposi sarcoma (n=1)	pembrolizumab 10 mg/kg q2w stopped at 6wks	SD 8 wks	treatment related AE in 70% patients; no grade 3 or 4; 10% discontinued due to grade 2 fatigue (1), pneumonitis (1), decreased weight (1); death in 1 case due to cryptococcal infection
Hamacher et al. 2017[66]	case report (n=1) LOE 5	angiosarcoma of the scalp (n=1)	pembrolizumab 200 mg q3w x 24+ wks	CR 24 wks	n/a
Sindhu et al. 2017[65]	case report (n=1) LOE 5	angiosarcoma of the nose (n=1) 63, M	pembrolizumab 2 mg/kg q3w x 39 wks	PR 39 wks	autoimmune hepatitis
Chambon et al. 2017[67]	case report (n=1) LOE 5	xeroderma pigmentosum presenting as scalp sarcomatoid carcinoma with bone lysis, vascular and meningeal contact 6, F	nivolumab 3 mg/kg q2w x 12 wk; then nivolumab 3 mg/kg q4w + cetuximab q1w	PR 52 wks	two large skin melanomas and several SCC managed with nivolumab, cetuximab, large excision

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Domingo-Musibay et al. 2018[68]	case report (n=1) LOE 5	widely disseminated sebaceous carcinoma with metastases to brain, lungs, liver, bowel, lymph nodes, bone 73, M	pembrolizumab 2mg/kg q3w x 52+ wks	PR of primary lesions; DP in liver, mediastinum and abdominal lymph nodes 24 wks	adrenal insufficiency requiring high-dose systemic corticosteroids and later adrenal replacement therapy
Payandeh et al. 2017[69]	case report (n=1) LOE 5	recurrent malignant peripheral nerve sheath tumor (n=1) 48, M	pembrolizumab 200 mg q3w x 18 wks with procarbazine hydrochloride 50 mg/m2 twice daily	CR 18 wks	n/a
Patnaik et al. 2015[51]	case report from phase 1 trial (n=17) [NCT01295827, KEYNOTE-001] LOE 5	Case C: peripheral nerve sheath tumor (n=1)	pembrolizumab 10 mg/kg q3w stopped at 21wks	SD 2 wks	treatment related AE in 70% patients; no grade 3 or 4; 10% discontinued due to grade 2 fatigue (1), pneumonitis (1), decreased weight (1); death in 1 case due to cryptococcal infection

[a] Level of Evidence (LOE) graded using the Oxford Center for Evidence-Based Medicine 2011 Levels of Evidence
[b] Response graded using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; CR: complete response, PR: partial response, SD: stable disease, DP: disease progression
[c] Progression-Free Survival (PFS)

Table 2. Active and Completed Clinical Trials Utilizing PD-1 and PD-L1 Inhibitors in the Treatment of Non-Melanoma Skin Cancer

Intervention	NCT Identifier	Phase	Published Findings
Cutaneous Squamous Cell Carcinoma			
Cemiplimab (PD-1)	NCT02760498 [EMPOWER]	2	Migden et al. 2018[19], Rischin et al. 2018[20] 7% CR, 41% PR, 5% DP
	NCT02383212	1	Papadopoulos et al. 2018[21], Owonikoko et al. 2018[22] 50% PR, 12% DP
Nivolumab (PD-1)	None		
	Other literature: 7 case series/reports		CR: 1, PR: 5, SD: 1 [24-25,27]
Pembrolizumab (PD-1)	NCT02721732	2	
	NCT02883556 [CARSKIN]	2	Maubec et al. 2018[28] 5% CR, 37% PR, 16% SD, 42% DP
	NCT02964559	2	
	NCT03057613	2	
	NCT03284424	2	
	Other literature: 1 cohort study, 13 case series/reports		CR: 3, PR: 11, DP: 2 [25-34]
Basal Cell Carcinoma			
Cemiplimab	NCT03132636	2	
	Other literature: 1 case series/reports		PR: 1 [23]
Nivolumab	None		
	Other literature: 2 case series/reports		PR: 1, SD: 1 [25,36-37]
Pembrolizumab	NCT02690948 (completed)	1	Chang et al. 2018[41] Monotherapy: 29% CR, 14% PR, 57% SD; Combination: 11% CR, 33% PR, 44% SD, 11% DP
	Other literature: 1 case series/reports		CR: 2, PR: 3 [35,38-40]
Merkel Cell Carcinoma			
Avelumab (PD-L1)	NCT03271372 [ADAM]	3	
	NCT02155647 [JAVELIN Merkel 200] (completed)	2	Kaufman et al. 2018[43]; D'Angelo et al. 2018[44] 11% CR, 22% PR, 10% SD, 36% DP
	Other literature: 2 case series/reports		CR: 1, PR: 1 [45-46]
Avelumab + cellular adoptive immunotherapy	NCT02584829	1/2	
INCMGA00012 (PD-L1/L2)	NCT03599713	2	
Nivolumab	NCT02488759 [CheckMate358]	1/2	Topalian et al. 2017[47] 14% CR, 55% PR, 18% SD, 14% DP
	Other literature: 2 case series/reports		PR: 2 [48-49]
Nivolumab + ipilimumab	NCT03071406	2	
	NCT02196961 (ADMEC-O)		
Pembrolizumab	NCT03712605	3	
	NCT02267603	2	Nghiem et al. 2016[50] 15% CR, 38% PR, 8% DP
	Other literature: 8 case series/reports		CR: 3, PR: 2, DP: 3 [51-57]
Pembrolizumab + stereotactic body radiation therapy	NCT03304639	2	

Abbreviations – CR: complete response, PR: partial response, SD: stable disease, DP: disease progression; LMS: leiomyosarcoma, UPS: undifferentiated pleomorphic sarcoma

Cutaneous Lymphoma			
Nivolumab	NCT01592370	1	Lesokhin et al. 2016[58] 15% PR, 69% SD
Soft Tissue Sarcoma			
Pembrolizumab	NCT02301039 [SARC028]	2	Tawbi et al. 2017[60] LMS – 60% SD, 40% DP UPS – 10% CR, 30% PR, 30% SD, 30% DP liposarcoma – 20% PR, 40% SD, 40% DP
	NCT03092323	2	
	NCT01295827 [KEYNOTE-001] (completed)	1	Patnaik et al. 2015[51] LMS – SD: 1 Kaposi sarcoma – SD: 1
Pembrolizumab + cyclophosphamide	NCT02406781	2	Toulmonde et al. 2018[59] LMS – 20% SD, 67% DP UPS – 31% SD, 44% DP
Pembrolizumab/nivolumab	Other literature: 1 cohort study, 6 case series/reports		CR: 2, PR: 10, SD: 3 [61-66]
Malignant Peripheral Nerve Sheath Tumor			
Pembrolizumab	None		
	Other literature: 2 case series/reports		CR: 1, SD: 1 [51,69]
Sebaceous Carcinoma			
Pembrolizumab	None		
	Other literature: 1 case report		PR: 1 [68]
Variety of NMSC types			
Atezolizumab (PD-L1) + personalized cancer vaccine	NCT03289962	2	
Nivolumab + talimogene laherparepvec	NCT02978625	2	
Nivolumab + INCAGN01876	NCT03126110	1/2	
Nivolumab + pembrolizumab + trigriluzole	NCT03229728	1