Curr. Treat. Options in Oncol. (2019) 20: 30
DOI 10.1007/s11864-019-0629-2

Skin Cancer (T Ito, Section Editor)

Systemic Immunotherapy for Advanced Cutaneous Squamous Cell Carcinoma

Dai Ogata, MD, PhD[*]
Tetsuya Tsuchida, MD, PhD

Address
[*]Department of Dermatology, Saitama Medical University, Morohongo 38, Moroyama-machi, Iruma-gun, Saitama, 350-0495, Japan
Email: dai.ogata@gmail.com

Published online: 14 March 2019

This article is part of the Topical Collection on *Skin Cancer*

Keywords Squamous cell carcinoma of the skin · Chemotherapy · Targeted therapy · Immunotherapy · Radiotherapy · Metastasis · Unresectable

Opinion statement

Advanced (i.e., unresectable) cutaneous squamous cell carcinoma (cSCC) is a rare condition with a dismal prognosis. Although less than 5% of cSCC patients develop metastases or local recurrence after complete excision, advanced cSCC is difficult to treat. These conditions tend to develop in elderly patients, although, at times, metastases are noted in middle-aged patients. Once metastasis occurs in cSCC, the 10-year survival rates fall to less than 20% for patients with regional lymph node involvement and less than 10% for patients with distant metastases, indicating that cSCC can be difficult to treat effectively when it is advanced. Traditionally, platinum-based therapy has been considered as a conventional option for advanced cSCC. It is efficacious to some degree, but the toxic effects of the combination treatments often prohibit their use in elderly patients. It has been a decade since the development of epidermal growth factor receptor (EGFR) inhibitors as agents that are less toxic. However, evidence regarding systemic therapy for advanced cSCC is limited because of a lack of high-quality prospective studies. Remarkably, the US Food and Drug Administration (FDA) approved an anti-PD-1 antibody treatment (cemiplimab) for the treatment of patients who are not candidates for curative surgery or curative radiation. It will be a promising treatment option for these types of rare conditions.

Introduction

Treatment options for advanced cutaneous squamous cell carcinoma

For regional (nodal) disease, the current management approach is surgical excision and consideration of adjuvant radiation [1, 2]. Whether adjuvant radiation therapy (RT) should be added to improve local disease control remains controversial [3–6]. Surgery may be performed in patients with metastasis if the number, size, and location allow for complete removal [2]. The combination of RT and systemic chemotherapy may be selected as an alternative option when surgery is not feasible (Fig. 1). Conventional systemic therapy for advanced cutaneous squamous cell carcinoma (cSCC) are cytotoxic agents with mainly cisplatin-based chemotherapies [7]. Furthermore, EGFR-targeted therapy has been used gradually for over 10 years [8, 9]. However, evidence supporting the efficacy of both these approaches is limited. Moreover, the general condition of the patient, patient's age, associated comorbidities, and immunosuppression state are important variables that should be considered for appropriate management [10]. In this setting, checkpoint immunotherapies are also being tested. Recently, preliminary data from phase 1 and 2 studies have shown that cSCC responds to anti-PD-1 therapy [11••].

Immunotherapy for advanced cutaneous squamous cell carcinoma

Rationale for checkpoint blockade

cSCC is particularly prevalent in patients with chronic sun exposure as well as in immunosuppressed patients [12, 13]. The tumors diagnosed in immunosuppressed organ transplant recipients are more likely to show unfavorable prognostic features and to metastasize [14]. UV-induced inflammation results in recruitment of infiltrating leukocytes secreting a variety of proinflammatory cytokines [15], and chronic inflammation, plays a crucial role in all the three stages of tumor development: initiation, promotion, and progression [16]. There are some reports to support the benefits of checkpoint

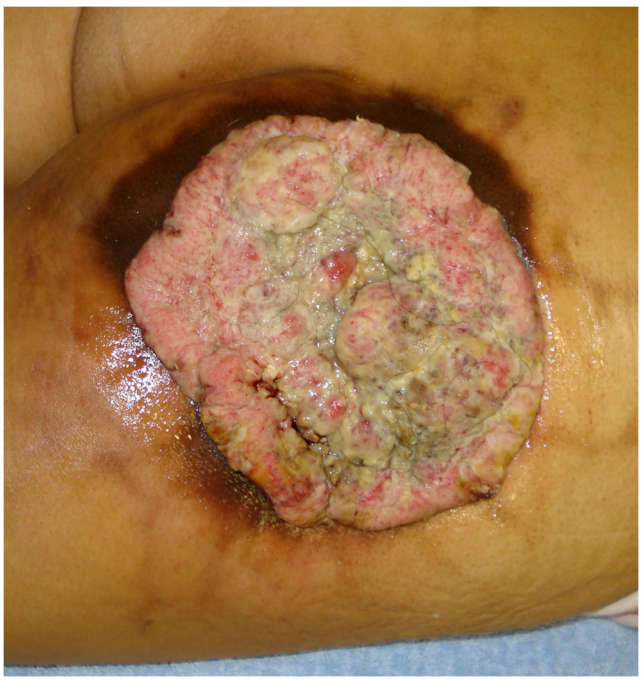

Fig. 1. Advanced cutaneous squamous cell carcinoma developing on the right hip of a 56-year-old woman. The tumor showed large ulcerated, partially necrotic, destructive lesions and invaded retroperitonea. We chose combination of RT and cisplatin-based systemic chemotherapy at first, then performed surgery. It has passed 3 years without recurrence

Table 1. Checkpoint inhibitor case reports and trials for advanced SCC

Drug name	Drug class	Dose and schedule	Study type	Number of patients	Best overall response or ORR (%)	Reference
Trial						
Cemiplimab	Anti-PD-1	3 mg/kg, q2w	Phase 1	26	50%	Migden 2018 [11••]
Cemiplimab	Anti-PD-1	3 mg/kg, q2w	Phase 2	59	47%	
Case report						
Pembrolizumab	Anti-PD-1	2 mg/kg, q3w	Case	1	PR	Chang 2016 [22]
Pembrolizumab	Anti-PD-1	–	Case	1	PR	Lipson 2016 [23]
Pembrolizumab	Anti-PD-1	2 mg/kg, q3w	Case	2	PR, SD	Borradori 2016 [24]
Nivolumab	Anti-PD-1	3 mg/kg, q2w		2	2PR	
Pembrolizumab	Anti-PD-1	–	Case	1	PR	Winkle, 2017 [25]
Pembrolizumab	Anti-PD-1	2 mg/kg, q3w	Case	1	PR	Hauschild 2017 [26]
Pembrolizumab	Anti-PD-1	2 mg/kg, q3w	Case	1	PR	Deinlein 2017 [27]
Pembrolizumab	Anti-PD-1	2 mg/kg, q3w	Case	1	CR	Stevenson 2017 [28]
Pembrolizumab	Anti-PD-1	2 mg/kg, q3w	Case	5	1CR, 3PR, 1PD	
Nivolumab	Anti-PD-1	3 mg/kg, q2w		1	PR	Tran 2017 [29]
Pembrolizumab	Anti-PD-1	2 mg/kg, q3w	Case	2	1CR, 1PR	Degache 2018 [30]
REGN2810 (=cemiplimab)	Anti-PD-1	1 mg/kg, q2w	Case	1	CR	Falchook 2016 [31]
Ipilimumab	Anti-CTLA4	--, q3w	Case	1	PR	Day 2017 [32]

inhibitors; cSCC is characterized by a reduced number of $CD8^+$ T cells and increased number of regulatory T cells compared to those in the peripheral area [17]. Roper et al. demonstrated that of the 74 primary head and neck cSCC (HNcSCC) cases, PD-L1 expression was seen in tumor cells in 39 cases (52.7%), of which 29 (39.2%) demonstrated PD-L1 expression in > 5% of the cells. Furthermore, PD-L1 expression in > 5% of primary tumor cells, primary tumor-infiltrating lymphocytes (TILs), and metastatic TILs is associated with longer disease-free survival in HNcSCC [18]. Patel and Kurzrock also suggest that tumor types classically responding to PD-1/PD-L1 inhibitors tend to have higher rates of PD-L1 expression, as shown by immunohistochemistry, than those in tumor types with typically poor responses [19]. These findings indicate a strong biological rationale for using immunotherapy in patients with advanced cSCC.

Cemiplimab

Cemiplimab is a human programmed death receptor-1 (PD-1) monoclonal antibody that binds to PD-1 and blocks its interaction with programmed death ligands 1 (PD-L1) and 2 (PD-L2) [20•]. In

September 2018, the FDA approved cemiplimab as an option for patients with metastatic or locally advanced cSCC who are not candidates for surgery or RT [21]. The decision was based on the results of two early-phase clinical trials involving 108 patients (75 with metastatic disease and 33 with locally advanced disease) [11••] (Table 1). In one of the trials, 13 of 26 patients responded to cemiplimab. The response rate was 50% and the median observed time to response was 2.3 months. The duration of response exceeded 6 months in seven of the 13 patients who showed a response (54%). The most common adverse events of any grade were fatigue (occurring in 27% of the patients) and constipation, decreased appetite, diarrhea, hypercalcemia, hypophosphatemia, nausea, and urinary tract infection (each occurring in 15% of the patients). One patient died due to an adverse event. In the second trial, tumors shrank or disappeared in 28 of 59 patients with metastatic disease who were treated with cemiplimab. The response rate was 47% and the rate of durable disease control was 61%. A partial response was observed in 24 patients and a complete response in 4 patients. The estimated probability of progression-free survival (PFS) at 12 months was 53%, and the estimated probability of overall survival at 12 months was 81%. The most common adverse events were diarrhea (occurring in 27% of the patients), fatigue (24%), nausea (17%), constipation (15%), and rash (15%). Three patients died due to adverse events. The phase 2 part of this study for locally advanced cSCC is ongoing (NCT02760498).

Nivolumab and pembrolizumab

In 2017, the FDA approved nivolumab and pembrolizumab monotherapy for the treatment of patients having recurrent or metastatic head and neck squamous cell cancer with disease progression during or after platinum-based chemotherapy [33, 34]. However, neither the phase 3 trial supporting the nivolumab approval (Checkmate 041) nor the phase 1b trial supporting the pembrolizumab approval (KEYNOTE-012) included any patients with cSCC [35••, 36•, 37•]. A literature review revealed up to 18 patients with advanced cSCC treated with nivolumab and pembrolizumab, of whom 17 responded well to treatment (Table 1) [22–32]. Tran et al. [29] reported six consecutive cases of unresectable and metastatic cSCCs treated with pembrolizumab (2 mg/kg every 3 weeks) or nivolumab (3 mg/m^2 every 2 weeks). Five of the six patients (83%) showed a clinical response, and the longest PFS was 21 months. With regard to adverse events, the most common was mild fatigue, observed in five patients (83%), and two patients experienced severe adverse events such as fatigue caused by endocrine hypofunction and hip fracture, both of which were treated and resolved. There was obvious reporting bias in these reports; these reports suggest that nivolumab and pembrolizumab may represent promising new treatment options for advanced cSCC.

Ipilimumab

Cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) is an immune checkpoint molecule that downregulates T cell activation pathways [38]. Ipilimumab is a fully human monoclonal antibody (IgG1) that blocks CTLA-4 to promote antitumor immunity [39, 40]. Although it has already been used as an adjuvant or a combination therapy for melanoma, there is only one case report wherein advanced cSCC responded to ipilimumab [32]. In this case report, ipilimumab was used to accidentally treat metastatic cSCC and melanoma. After 4 cycles of ipilimumab, nodular cSCC metastases and facial lymphedema showed clinical improvement with PFS of 8 months. Although many potential biomarkers having been described, no candidate biomarkers for ipilimumab efficacy have been introduced in clinical practice [41].

Ongoing clinical trials of immunotherapies

Currently, only one tumor-specific trial of PD-1/PD-L1 inhibitor in cSCC has been published [11••] and the phase 2 part of this trial for locally advanced cSCC is ongoing (NCT02760498). Since immunotherapy for

Table 2. Ongoing clinical trials of immunotherapy in cSCC

NCT identifier	Official title	Phase	Recruitment status	Conditions	Intervention
NCT02760498	Study of REGN2810 in patients with advanced cutaneous squamous cell carcinoma	1	Recruiting	Advanced cutaneous squamous cell carcinoma	REGN2810 a monoclonal, fully human antibody to programmed death receptor-1 (PD-1)
NCT02883556	Study of pembrolizumab as first-line therapy in patients with unresectable squamous cell carcinoma of the skin (CARSKIN)	2	Active, not recruiting	Locally advanced or metastatic squamous cell carcinoma of the skin	Pembrolizumab
NCT03565783	Cemiplimab in treating participants with recurrent stages III and IV head and neck squamous cell cancer before surgery	II	Recruiting	Stages III and IV cutaneous squamous cell carcinoma of the head and neck AJCC v8 and HNSCC	Cemiplimab
NCT02721732	Pembrolizumab in treating patients with rare tumors that cannot be removed by surgery or are metastatic	II	Recruiting	Skin squamous cell carcinoma and others	Pembrolizumab
NCT03458117	T-VEC in non-melanoma skin cancer (20139157 T-VEC)	I	Recruiting	Non-melanoma skin cancer	Talimogene laherparepvec (T-VEC)
NCT03212404	Phase 1 study of CK-301 as a single agent in subjects with advanced cancers	I	Recruiting	Cutaneous squamous cell carcinoma and others	CK-301 a fully human monoclonal IgG1 antibody targeting PD-L1
NCT03737721	The UNSCARRed Study: UNresctable Squamous Cell Carcinoma treated with Avelumab and Radical Radiotherapy (UNSCARRed)	II	Not yet recruiting	Squamous cell carcinoma of the skin	Avelumab and radical radiotherapy
NCT03082534	Pembrolizumab combined with cetuximab for treatment of recurrent/metastatic head and neck squamous cell carcinoma	II	Recruiting	HNSCC and cutaneous squamous cell carcinoma	Pembrolizumab, cetuximab
NCT02978625	Talimogene laherparepvec and nivolumab in treating patients with refractory lymphomas or advanced or refractory non-melanoma skin cancers	II	Recruiting	Skin squamous cell carcinoma and others	Nivolumab and talimogene laherparepvec
NCT03590054	A Phase 1b dose escalation/expansion study of abexinostat in combination with pembrolizumab in patients with advanced solid tumor malignancies	Ib	Recruiting	Cutaneous squamous cell carcinoma of the head and neck and others	Abexinostat pembrolizumab
NCT03773744	Trial of MG1-MAGEA3 with Ad-MAGEA3 and pembrolizumab in patients with previously treated metastatic melanoma or cutaneous squamous cell carcinoma (Pelican)	I	Not yet recruiting	Squamous cell skin carcinoma and metastatic melanoma	Ad-MAGEA3, MG1-MAGEA3, pembrolizumab, cyclophosphamide
NCT03108131	Cobimetinib and atezolizumab in advanced rare tumors	2	Recruiting	Cutaneous squamous cell carcinoma and others	Cobimetinib or atezolizumab

cSCC is still in the process of development (Table 2), unlike that for melanoma and non-small cell lung cancer, it is necessary to verify the effectiveness of a single agent. Clinical trials of immunotherapy administered as monotherapy are ongoing: a triple-arm, open-label phase 2 study of cemiplimab in 182 participants [42]; and a single-arm, open-label, phase 2 study of pembrolizumab in 39 participants [43].

As PD-L1 expression by tumor cells was revealed to be the strongest single predictor of response to anti-PD1 therapy [44], both trials intend to determine the efficacy and safety of a single agent and whether efficacy of these agents is correlated to PD-L1 expression in advanced cSCC. Furthermore, a single-arm, open-label, phase 2 study of cemiplimab in 22 participants [45] aims to verify how well cemiplimab works before surgery in treating participants with advanced HNcSCC and a single-arm, open-label, phase 2 study of pembrolizumab 275 patients [46] aims to show how well pembrolizumab works in treating patients with rare tumors including cSCC. There are also early-phase trials of talimogene laherparepvec (T-Vec) [47] and CK-301, which is a fully human monoclonal antibody of the IgG1 subtype that directly binds to PD-L1 and blocks its interactions with the PD-1 and B7 [48].

There are also some ongoing phase II trials. Avelumab and RT [49] and pembrolizumab combined with cetuximab [50] are specialized treatments for SCC. Nivolumab and T-VEC [51], abexinostat in combination with pembrolizumab [52], MG1-MAGEA3 with ad-MAGEA3 and pembrolizumab [53], and cobimetinib and atezolizumab [54] are targeted for mixed rare tumors.

Discussion or conclusion

In the past 10 years, novel targeted therapeutic agents, like EGFR and tyrosine kinase inhibitors, for cSCC have been developed [8, 9, 55]. However, most studies were performed for head and neck SCC, not specialized for cSCC. Immunotherapy might deliver promising results in the near future. Furthermore, these novel treatments can be used as a monotherapies or combination therapies. With increasing treatment options, we have a further responsibility of providing better treatment by assessing patients' conditions and disease progression.

Compliance with Ethical Standards

Conflict of Interest
Dai Ogata and Tetsuya Tsuchida declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Jambusaria-Pahlajani A, Miller CJ, Quon H, Smith N, Klein RQ, Schmults CD. Surgical monotherapy versus surgery plus adjuvant radiotherapy in high-risk cutaneous squamous cell carcinoma: a systematic review of outcomes. Dermatol Surg. 2009;35:574–85.
2. Stratigos A, Garbe C, Lebbe C, Malvehy J, del Marmol V, Pehamberger H, et al. Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline. Eur J Cancer. 2015;51:1989–2007.
3. Hirshoren N, Danne J, Dixon BJ, Magarey M, Kleid S, Webb A, et al. Prognostic markers in metastatic cutaneous squamous cell carcinoma of the head and neck. Head Neck. 2017;39(4):772–8.
4. Wang JT, Palme CE, Wang AY, Morgan GJ, Gebski V, Veness MJ. In patients with metastatic cutaneous head and neck squamous cell carcinoma to cervical lymph nodes, the extent of neck dissection does not influence outcome. J Laryngol Otol. 2013;127(Suppl 1):S2–7.
5. Forest VI, Clark JJ, Veness MJ, Milross C. N1S3: a revised staging system for head and neck cutaneous squamous cell carcinoma with lymph node metastases: results of 2 Australian Cancer Centers. Cancer. 2010;116(5):1298–304.
6. Schmidt C, Martin JM, Khoo E, Plank A, Grigg R. Outcomes of nodal metastatic cutaneous squamous cell carcinoma of the head and neck treated in a regional center. Head Neck. 2015;37(12):1808–15.
7. Bejar C, Maubec E. Therapy of advanced squamous cell carcinoma of the skin. Curr Treat Options in Oncol. 2014;15(2):302–20.
8. Maubec E, Petrow P, Scheer-Senyarich I, Duvillard P, Lacroix L, Gelly J, et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. J Clin Oncol. 2011;29(25):3419–26.
9. Lewis CM, Glisson BS, Feng L, Wan F, Tang X, Wistuba II, et al. A phase II study of gefitinib for aggressive cutaneous squamous cell carcinoma of the head and neck. Clin Cancer Res. 2012;18(5):1435–46.
10. Weinberg AS, Ogle CA, Shim EK. Metastatic cutaneous squamous cell carcinoma: an update. Dermatol Surg. 2007;33:885–99.
11. •• Migden MR, Rischin D, Schmults CD, Hauschild A, Lewis KD, Chung CH, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. N Engl J Med. 2018;379(4):341–51

This article is the first cemiplimab, an anti-PD-L1 antibody, prospective trial in patients with advanced cSCC for evaluating efficacy and safety. It indicates anti-PD-L1 antibody therapy significantly improves the prognosis of advanced cSCC patients.

12. Ribero S, Stucci LS, Daniels GA, Borradori L. Drug therapy of advanced cutaneous squamous cell carcinoma: is there any evidence? Curr Opin Oncol. 2017;29(2):129–35.
13. Boukamp P. Nonmelanoma skin cancer: what drives tumor development and progression? Carcinogenesis. 2005;26:1657–67.
14. Barrett WL, First MR, Aron BS, Penn I. Clinical course of malignancies in renal transplant recipients. Cancer. 1993;72:2186–9.
15. Kim Y, He YY. Ultraviolet radiation-induced nonmelanoma skin cancer: regulation of DNA damage repair and inflammation. Genes Dis. 2014;1:188–98.
16. Mukhtar H, Elmets CA. Photocarcinogenesis: mechanisms, models and human health implications. Photochem Photobiol. 1996;63(4):356–7.
17. Freeman A, Bridge JA, Maruthayanar P, Overgaard NH, Jung JW, Simpson F, et al. Comparative immune phenotypic analysis of cutaneous squamous cell carcinoma and intraepidermal carcinoma in immune-competent individuals: proportional representation of CD8þ T-cells but not FoxP3þ regulatory T-cells is associated with disease stage. PLoS One. 2014;9:e110928.
18. Roper E, Lum T, Palme CE, Ashford B, Ch'ng S, Ranson M, et al. PD-L1 expression predicts longer disease free survival in high risk head and neck cutaneous squamous cell carcinoma. Pathology. 2017;49(5):499–505.
19. Patel SP, Kurzrock R. PD-L1 expression as a predictive biomarker in cancer immunotherapy. Mol Cancer Ther. 2015;14:847–56.
20. • Markham A, Duggan S. Cemiplimab: first global approval. Drugs. 2018;78(17):1841–6

This article summarizes the milestones in the development of cemiplimab and ongoing clinical trials.

21. FDA. FDA approves first treatment for advanced form of the second most common skin cancer. 2018. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm622044.htm. Accessed 2 Jan 2019.

22. Chang AL, Kim J, Luciano R, Sullivan-Chang L, Colevas AD. A case report of unresectable cutaneous squamous cell carcinoma responsive to pembrolizumab, a programmed cell death protein 1 inhibitor. JAMA Dermatol. 2016;152:106–8.
23. Lipson EJ, Bagnasco SM, Moore J Jr, Jang S, Patel MJ, Zachary AA, et al. Tumor regression and allograft rejection after administration of anti-PD-1. N Engl J Med. 2016;374(9):896–8.
24. Borradori L, Sutton B, Shayesteh P, Daniels GA. Rescue therapy with anti-programmed cell death protein 1 inhibitors of advanced cutaneous squamous cell carcinoma and basosquamous carcinoma: preliminary experience in five cases. Br J Dermatol. 2016;175(6):1382–6.
25. Winkler JK, Schneiderbauer R, Bender C, Sedlaczek O, Fröhling S, Penzel R, et al. Anti-programmed cell death-1 therapy in nonmelanoma skin cancer. Br J Dermatol. 2017;176(2):498–502.
26. Hauschild A, Eichstaedt J, Möbus L, Kähler K, Weichenthal M, Schwarz T, et al. Regression of melanoma metastases and multiple non-melanoma skin cancers in xeroderma pigmentosum by the PD1-antibody pembrolizumab. Eur J Cancer. 2017;77:84–7.
27. Deinlein T, Lax SF, Schwarz T, Giuffrida R, Schmid-Zalaudek K, Zalaudek I. Rapid response of metastatic cutaneous squamous cell carcinoma to pembrolizumab in a patient with xeroderma pigmentosum: case report and review of the literature. Eur J Cancer. 2017;83:99–102.
28. Stevenson ML, Wang CQ, Abikhair M, Roudiani N, Felsen D, Krueger JG, et al. Expression of programmed cell death ligand in cutaneous squamous cell carcinoma and treatment of locally advanced disease with pembrolizumab. JAMA Dermatol. 2017;153(4):299–303.
29. Tran DC, Colevas AD, Chang AL. Follow-up on programmed cell death 1 inhibitor for cutaneous squamous cell carcinoma. JAMA Dermatol. 2017;153(1):92–4.
30. Degache E, Chrochet J, Simon N, Tardieu M, Trabelsi S, Moncourier M, et al. Major response to pembrolizumab in two patients with locally advanced cutaneous squamous cell carcinoma. J Eur Acad Dermatol Venereol. 2018;32(7):e257–e258s. https://doi.org/10.1111/jdv.14371.
31. Falchook GS, Leidner R, Stankevich E, Piening B, Bifulco C, Lowy I, et al. Responses of metastatic basal cell and cutaneous squamous cell carcinomas to anti-PD1 monoclonal antibody REGN2810. J Immunother Cancer. 2016;4:70.
32. Day F, Kumar M, Fenton L, Gedye C. Durable response of metastatic squamous cell carcinoma of the skin to ipilimumab immunotherapy. J Immunother. 2017;40(1):36–8.
33. Merck & Co., Inc. Prescribing information: KEYTRUDA (pembrolizumab) injection, for intravenous use. 2017. https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf. Accessed 2 Jan 2019.
34. Bristol-Myers Squibb Company. Prescribing information: OPDIVO (nivolumab) injection, for intravenous use. 2017. https://packageinserts.bms.com/pi/pi_opdivo.pdf. Accessed 2 Jan 2019.
35.•• Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med. 2016;375(19):1856–67

This article describes randomized, open-label, phase 3 trial with recurrent squamous-cell carcinoma of the head and neck and nivolumab prolonged survival, as compared with standard therapy.

36.• LQM C, Haddad R, Gupta S, Mahipal A, Mehra R, Tahara M, et al. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: Results from the phase Ib KEYNOTE-012 Expansion Cohort. J Clin Oncol. 2016;34(32):3838–45

This article describes a phase Ib, multicenter, nonrandomized, multicohort study of pembrolizumab in patients with advanced solid tumors.

37.• Seiwert TY, Burtness B, Mehra R, Weiss J, Berger R, Eder JP, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol. 2016;17(7):956–65

This article describes an open-label, multicenter, phase 1b trial of patients with recurrent or metastatic squamous cell carcinoma of the head and neck.

38. Melero I, Hervas-Stubbs S, Glennie M, Pardoll DM, Chen L. Immunostimulatory monoclonal antibodies for cancer therapy. Nat Rev Cancer. 2007;7:95–106.
39. O'Day SJ, Hamid O, Urba WJ. Targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4): a novel strategy for the treatment of melanoma and other malignancies. Cancer. 2007;110:2614–27.
40. Fong L, Small EJ. Anticytotoxic T-lymphocyte antigen-4 antibody: the first in an emerging class of immunomodulatory antibodies for cancer treatment. J Clin Oncol. 2008;26:5275–83.
41. Manson G, Norwood J, Marabelle A, Kohrt H, Houot R. Biomarkers associated with checkpoint inhibitors. Ann Oncol. 2016;27:1199–206.
42. Study of REGN2810 in patients with advanced cutaneous squamous cell carcinoma. ClinicalTrials.gov. 2019. Accessed 2 Jan 2019. https://clinicaltrials.gov/ct2/show/NCT02760498
43. Study of pembrolizumab as first line therapy in patients with unresectable squamous cell carcinoma of the skin. ClinicalTrials.gov. 2019. Accessed 2 Jan 2019. https://clinicaltrials.gov/ct2/show/NCT02883556
44. Taube JM, Klein A, Brahmer JR, Xu H, Pan X, Kim JH, et al. Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. Clin Cancer Res. 2014;20(19):5064–74.
45. Cemiplimab in treating participants with recurrent stage III-IV hand neck squamous cell cancer before

surgery. ClinicalTrials.gov. 1999. Accessed 2 Jan 2019. https://clinicaltrials.gov/ct2/show/NCT03565783
46. Pembrolizumab in treating patients with rare tumors that cannot be removed by surgery or are metastatic. ClinicalTrials.gov. 2019. Accessed 2 Jan 2019. https://clinicaltrials.gov/ct2/show/NCT02721732
47. T-VEC in non-melanoma skin cancer (20139157 T-VEC). ClinicalTrials.gov. 2019. Accessed 2 Jan 2019. https://clinicaltrials.gov/ct2/show/NCT03458117
48. Phase 1 study of CK-301 as a single agent in subjects with advanced cancers. ClinicalTrials.gov. 2019. Accessed 2 Jan 2019. https://clinicaltrials.gov/ct2/show/NCT03212404
49. The UNSCARRed study: UNresctable Squamous Cell Carcinoma treated with Avelumab and Radical Radiotherapy (UNSCARRed). ClinicalTrials.gov. 2019. Accessed 2 Jan 2019. https://clinicaltrials.gov/ct2/show/NCT03737721
50. Pembrolizumab combined with cetuximab for treatment of recurrent/metastatic head & neck squamous cell carcinoma. ClinicalTrials.gov. 2019. Accessed 2 Jan 2019. https://clinicaltrials.gov/ct2/show/NCT03082534
51. Talimogene laherparepvec and nivolumab in treating patients with refractory lymphomas or advanced or refractory non-melanoma skin cancers. ClinicalTrials.gov. 2019. Accessed 2 Jan 2019. https://clinicaltrials.gov/ct2/show/NCT02978625
52. A Phase 1b dose escalation/expansion study of abexinostat in combination with pembrolizumab in patients with advanced solid tumor malignancies. ClinicalTrials.gov. 2019. Accessed 2 Jan 2019. https://clinicaltrials.gov/ct2/show/NCT03590054
53. Trial of MG1-MAGEA3 with Ad-MAGEA3 and pembrolizumab in patients with previously treated metastatic melanoma or cutaneous squamous cell carcinoma (Pelican). ClinicalTrials.gov. 2019. Accessed 2 Jan 2019. https://clinicaltrials.gov/ct2/show/NCT03773744
54. Cobimetinib and atezolizumab in advanced rare tumors. ClinicalTrials.gov. 2019. Accessed 2 Jan 2019. https://clinicaltrials.gov/ct2/show/NCT03108131
55. William WN Jr, Feng L, Ferrarotto R, Ginsberg L, Kies M, Lippman S, et al. Gefitinib for patients with incurable cutaneous squamous cell carcinoma: a single-arm phase II clinical trial. J Am Acad Dermatol. 2017;77:1110–3.