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REVIEW

Pembrolizumab for the Treatment of Locally Advanced Cutaneous Squamous Cell Carcinoma: Patient Selection and Special Considerations

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Abstract: The treatment of locally advanced cutaneous squamous cell carcinoma (cSCC) has shifted with the advent of immune checkpoint inhibitors (ICIs). Traditional treatment methods have been met with limited efficacy and durability. Recently, ICIs such as pembrolizumab and cemiplimab have emerged as effective alternatives for treating advanced cSCC. Pembrolizumab, approved by the FDA in 2020 for recurrent or metastatic cSCC not amenable to curative surgery or radiation, has shown promising results in clinical trials. Immunotherapy is also being explored in neoadjuvant settings, with ongoing trials evaluating its potential to improve outcomes for high-risk patients with recurrent or metastatic disease. However, patient selection remains crucial, with the tumor microenvironment playing a key role in predicting treatment response. With many patients achieving a complete response, immunotherapy presents a promising option; however, ongoing research is needed to refine its use, especially in immunocompromised or high-risk patients.

Keywords: cutaneous squamous cell carcinoma, cSCC, immunotherapy, pembrolizumab

Introduction

Cutaneous squamous cell carcinoma (cSCC), a keratinocyte carcinoma, composes the second most common type of nonmelanoma skin cancer after basal cell carcinoma, together with Merkel cell carcinoma, comprising non-melanoma skin cancers (NMSC). Although NMSCs are not tracked by the Centers for Disease Control (CDC), cSCC is estimated to account for at least 33% of cases, with approximately 1.8 million cases diagnosed annually in the United States.[1]

The most significant risk factor for cSCC is chronic exposure to ultraviolet radiation from the sun. Frequent and prolonged exposures place patients at higher risk, as do fair skin and older age. The immune system is a clear regulator in the cSCC disease process: immunosuppression is a well-established and significant risk factor for developing cSCC.[2–4] Immunos-suppressed individuals, particularly solid organ transplant recipients, face a significantly higher risk of developing cSCC, with studies indicating a 5- to 113-fold increased risk in these patients.[5] In addition, immunosuppression from lymphoma, leukemia, HIV, and chronic immunosuppressive therapies also increase the risk of developing cSCC. Immunosuppression is generally associated with a more aggressive clinical course, including faster tumor growth, deeper invasion, higher recurrence rates, greater metastatic potential, and poorer prognosis.[5]

While the majority of cases of cSCC can be eradicated by surgical excision alone and feature cure rates >90%,[6] there are some cases that have features that put them at higher risk for recurrence, metastasis, and death. Advanced cSCC is typically stratified into two categories: locally advanced and metastatic. Locally advanced disease comprises cases where the tumor has invaded deeper tissues and invaded nearby structures, without metastasizing to distant organs. Metastatic cSCC, on the other hand, includes cases where disease involves distant organs, but also notably includes when disease spreads to regional lymph nodes. Regional nodal metastases, the most common form of metastatic cSCC, are a significant prognostic factor, with worse outcomes compared to locally advanced disease.[7]

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cSCC Treatment Approaches

Treatment for advanced cSCC is often multidisciplinary, and the modalities commonly employed include surgical resection, radiation therapy, and systemic therapy. In cases where surgical resection with curative intent is feasible for locally advanced disease, the first-line treatment and standard of care is surgical excision with clear margins. In some cases, where function, cosmesis, and patient preference are of concern, an alternative primary treatment can be radiotherapy.[8,9] Adjuvant radiation is often recommended following surgery, particularly in cases with high-risk features such as positive surgical margins, perineural invasion, lymphovascular invasion, extracapsular spread, and poor differentiation. For patients with locally advanced disease not amenable to curative surgery due to factors such as proximity to major nerves, organs, or blood vessels, large tumor size, concerns over functional deficits, age, frailty, or other patient-related factors, radiotherapy with or without systemic therapy becomes the standard of care.[9,10] Notably, in advanced disease, a combination of both surgery and post-operative radiation (PORT) is often recommended to improve locoregional control and survival outcomes. PORT is recommended for perineural spread, positive margins that cannot reasonably be further corrected by surgery, and recurrence in the setting of a prior margin-negative resection.[10]

For patients where surgical excision is not an option, the NCCN guidelines list definitive chemoradiotherapy (CRT) as a treatment option. Cisplatin is the preferred systemic agent of choice, with carboplatin as an alternative for those who cannot tolerate cisplatin. These chemotherapy options have shown limited efficacy in treating locally advanced disease, with both reduced response rates and limited response durability. Additionally, the toxicity profiles of these agents can often limit their use, particularly in the case of elderly or frail patients. Notably, however, definitive CRT is controversial due to limited high-quality evidence (available studies are often small, retrospective, or lack randomization), mixed clinical outcomes, as well as toxicity concerns as previously mentioned.[11,12]

When it comes to adjuvant CRT in locally advanced, resected cSCC, the NCCN guidelines do not routinely recommended it based on evidence from the TROG 05.01 trial. However, this is controversial as there are concerns over study design. The TROG 05.01 trial concluded that concurrent carboplatin with postoperative radiotherapy did not improve locoregional recurrence, disease-free survival, or overall survival.[13] However, it is important to note that the study's design limits the generalizability of these conclusions. The trial included the use of carboplatin over the widely considered more efficacious cisplatin, which has been suggested to improve outcomes when added to radiotherapy in patients with high risk resected cSCC.[14] Patient eligibility is another important limitation of the study, as evidenced by the favorable outcomes in the control arm of the study. Those patients excluded had the highest-risk disease features, including chronic immunosuppression, more advanced tumor stage and nodal staging, and other histologic markers known to confer high-risk disease such as lymphovascular invasion and satellitosis.[15,16] Including these patients, in addition to using cisplatin, may have afforded different results in favor of a concurrent chemoradiotherapy approach.

Given the limited efficacy and toxicity concerns associated with CRT, newer systemic therapies, such as immune checkpoint inhibitors, have garnered attention for advanced cSCC treatment. In a study by Pickering et al, they identify a high mutation rate as being characteristic of aggressive cSCC, as is the case with advanced cSCC.[17] Given that a high mutational burden, which correlates with an increased number of neoantigens, has been associated with better responses to immune checkpoint inhibitors in other cancers, it goes on to follow that the same principle would apply to cSCC.[18] In recent years, this understanding has significantly altered the landscape of systemic therapy for the treatment of advanced cSCC that is unresectable or not amenable to radiotherapy. Programmed cell death protein 1 inhibitors (PD-1), such as cemiplimab and pembrolizumab, are immune checkpoint inhibitors that have distinct indications for treatment of cSCC. Cemiplimab was approved by the FDA in 2018 for the treatment of patients with metastatic cSCC or locally advanced cSCC who are not candidates for curative surgery or curative radiation. Pembrolizumab, on the other hand, was approved by the FDA in 2020 for the treatment of patients with recurrent or metastatic cSCC that is not curable by surgery or radiation, with locally advanced disease a notable exception.

Immunotherapy in cSCC: Efficacy and Safety

Several studies have demonstrated cemiplimab as a highly effective and safe treatment for patients with locally advanced cSCC. A pivotal study by Migden et al published in the New England Journal of Medicine in 2018 demonstrated that

cemiplimab was able to achieve an objective response rate (ORR) of 47% in patients with metastatic disease and 57% of responding patients maintained their response for over 6 months.[19] For locally advanced disease specifically, Migden et al published a study in 2020 that demonstrated an ORR of 44%; 13% of whom achieved a complete response (CR).[20] The safety profile demonstrated limited side effects and good tolerability, especially when compared to EGFR inhibitors and cytotoxic chemotherapy.

While cemiplimab has demonstrated impressive response rates, pembrolizumab has also shown promising efficacy, as seen in the KEYNOTE-629 trial. At the time of initial publication, KEYNOTE-629 demonstrated a 34% ORR, with a 10% CR.[21] The duration of response was not reached at the time of initial data cut off, suggesting that a significant proportion of patients who responded continued to do so for an extended period. However, preliminary 5-year follow-up data from 2024 updated the ORR to 52% in patients with locally advanced disease, with 22% achieving CR.[22]

Incorporating Immunotherapy in Locally Advanced Disease

Adjuvant

Historically, 40–50% of patients with high-risk, locally advanced cSCC experience local recurrence and regional metastasis despite receiving standard-of-care surgical resection and adjuvant radiation.[13] The use of immunotherapy as an adjuvant treatment in patients in this setting is an area of active investigation, with the aim of improving these outcomes. Patient selection, particularly for high-risk, locally advanced disease, is critical; it includes characteristics such as tumor size >2 cm, poor differentiation, perineural invasion, lymphovascular invasion, depth of invasion >6 mm or beyond subcutaneous fat, and tumors located in high-risk areas like the ear, lip, or temple.[23–25] In a study by Kus et al, lymphovascular invasion (LVI) in particular was shown to be an independent predictor of poor outcomes; the study found that tumors with LVI had significantly higher rates of metastasis and disease-specific death as compared to cSCC without LVI.[15] Furthermore, satellitosis or in-transit metastasis, which is not currently part of the staging system of cSCC, was associated with a significantly higher risk of recurrence, similar to the prognosis for patients with nodal involvement.[16] Two ongoing trials, NCT03969004 and NCT03833167, are currently evaluating the addition of immunotherapy following resection and post-operative radiotherapy. Both trials are nearing completion of accrual, and results are eagerly anticipated.

Neoadjuvant

Gross et al published Phase II results of neoadjuvant cemiplimab in patients with resectable stage II to IV cSCC.[26] Patients received cemiplimab every three weeks for up to four doses before undergoing surgery with curative intent. The study's primary end point was a pathological complete response (absence of viable tumor cells in the surgical specimen), and a notable secondary endpoint was pathological major response (presence of viable tumor cells that constitute ≤10% of the surgical specimen). Following the surgery, patients received either adjuvant cemiplimab for up to 48 weeks, radiotherapy, or observation alone, at the investigator's discretion.[27] Of the 79 patients included in the study, 51% (n=40) showed a pathologic complete response, with long-term follow-up data demonstrating no recurrences at data cut off (approximately 18 months following the conclusion of study enrollment). Thirteen percent (n=10) had a major pathologic response, with long-term data showing that only one patient experienced recurrence.[26,27] To further underscore Gross et al's findings, another study by Kim et al conducted a cohort study involving 27 patients, investigating the use of neoadjuvant cemiplimab or pembrolizumab in patients with advanced but resectable cSCC. The study found that 47.4% of patients had a pathologic complete response or near complete response.[28] Table 1 lists ongoing and upcoming clinical trials registered through ClinicalTrials.gov that are exploring the usage of pembrolizumab in the neoadjuvant setting.

The RAMPART trial (NCT05574101) is an actively recruiting study that aims to use cemiplimab as a neoadjuvant treatment in unresectable disease, followed by radiotherapy. The study hypothesizes that combining immune checkpoint inhibitors with radiotherapy may lead to synergistic effects through immune modulation, potentially enhancing tumor control and improving outcomes over radiotherapy alone.[18]

Table 1 Clinical Trials Listed on ClinicalTrials.gov Exploring the Usage of Pembrolizumab in the Neoadjuvant Setting

ClinicalTrials.gov ID	Name of Trial	Sponsor	Enrollment	Primary Completion Date
NCT04808999	*Neoadjuvant Study of PD-1 Inhibitor Pembrolizumab in PD-1 Naive Cutaneous Squamous Cell Carcinoma (cSCC)*	Diwakar Davar	30 (actual)	2024–04-12 (actual)
NCT05025813	*Neoadjuvant Pembrolizumab in Cutaneous Squamous Cell Carcinoma (DESQUAMATE)*	Queensland Health	27*	2025–06-01*
NCT06295809	*A study of (Neo)Adjuvant V940 and Pembrolizumab in Cutaneous Squamous Cell Carcinoma (V940-007)*	Merck Sharp & Dohme LLC	1012*	2029–04-30*
NCT06036836	*Study of Favezelimab Coformulated With Pembrolizumab (MK-4280A) in Participants With Selected Solid Tumors (MK-4280A-010)*	Merck Sharp & Dohme LLC	160*	2027–03-09*
NCT06580054	*Pembrolizumab for the Treatment of Locally Advanced and/or Recurrent Orbital or Periocular Cutaneous Squamous Cell Carcinoma*	University of Michigan Rogel Cancer Center	22*	2027–10-01*

Notes: *Estimated.

Discussion

Pembrolizumab was initially approved by the FDA in 2020 for the treatment of recurrent or metastatic cSCC that is not amenable to curative surgery or radiation. This approval was based on the results of the KEYNOTE-629 study which demonstrated an ORR of 50% in the local advanced cohort and durable responses in patients with advanced cSCC overall. Following its initial approval, pembrolizumab has been further evaluated in various settings, including adjuvant therapy after surgical resection and in combination with other modalities like radiation therapy. KEYNOTE-630 is exploring pembrolizumab's efficacy in the adjuvant setting for patients with locally advanced cSCC, aiming to prevent recurrence in high-risk individuals. Further, there are numerous studies that are exploring pembrolizumab's possible role as a neoadjuvant treatment for locally advanced cSCC. These trials continue to expand the understanding of pembrolizumab's role in managing cSCC, with the potential to improve outcomes across different stages of the disease. However, despite its established efficacy, safety, and promising upcoming trial data, patient selection remains critically important for treatment success.

Despite the promising results of the KEYNOTE-629's study, approximately half of the patients did not respond, and this underscores the importance of patient selection and exploring possible reasons that limit efficacy in select patients.[21] Factors influencing how a patient may respond to ICI therapy are numerous, but notably include PD-L1 expression, tumor mutational burden (TMB), and variability within the tumor microenvironment. As noted above, high tumor mutational burden (TMB) has been associated with better responses to ICIs – in cancers on a broader scale, but also specifically in cSCC.[18,19,21] What is notable, however, is that early cemiplimab studies, as well as KEYNOTE-629, demonstrated that virtually all cSCC tumors exhibit high TMB, even those that do not respond to immunotherapy.[19,21] One plausible theory is that cancer cell plasticity and the tumor microenvironment (TME) play a critical role in resistance to ICIs. In a study by Lorenzo-Sanz et al, cancer cells can acquire epithelial/mesenchymal plasticity which can thereby alter their immune checkpoint ligand profiles.[29] This is important because although epithelial cells primarily utilize the PD-1/PD-L1 pathway for immune evasion, mesenchymal cancer cells utilize the CTLA-4/CD80 and TIGIT/CD155 pathways.[30] Thus, different expression of the checkpoints could theoretically lead to partial responses to PD-1 inhibitors. In other words, some patients may need treatments that target different ligands beyond PD-1/PD-L1.

The TME is a dynamic environment that is composed of immune cells, stromal cells, and signaling molecules. Differences in the makeup of a patient's TME could theoretically impact how a patient responds to ICIs. In a study by Thai et al, memory B-cell-like populations in the peritumoral stroma were associated with better prognosis and better response to ICIs.[31] This suggests that the overall host immune response significantly impacts response to ICIs and not just the tumor's mutational profile. Additionally, when considering the TME, there is a concept called "persistent" tumor mutational burden, or pTMB, as introduced by Niknafs et al.[32] This suggests that mutations in particular regions of the genome that are unlikely to be lost may

contribute to persistent anti-tumor immune responses, which can thereby increase ICI effectiveness. Niknafs et al goes to suggest that tumors with high pTMB are characterized by a more "inflamed" TME, which could be crucial for the effectiveness of ICIs.[32] More study is needed here to better understand the role the TME has on ICI response; however, recognizing the TME's impact on patient responses is crucial for making treatment decisions.

There are notable studies that demonstrate clinical outcomes of combining ICIs and other treatment modalities, namely local therapies such as radiotherapy. In particular, the RAMPART study currently underway takes into account that not all patients will have a robust response to ICI therapy alone. As described above, the study is evaluating a possible synergistic effect of radiation therapy on the increasing efficacy of ICIs. Radiation therapy induces cell death, increasing the release of tumor antigens, which may enhance the immune response. This cell death recruits immune cells within the TME, and this could theoretically "convert" an immunologically less active tumor to an immunologically very active tumor (ie, inflamed environment). This more active environment could theoretically make the tumor more responsive to ICIs. Additionally, a Phase I trial exploring the combination of cemiplimab with hypofractionated radiotherapy reported durable partial and complete responses in a subset of patients with advanced solid tumors, including CSCC.[33] Therefore, integrating radiation therapy with ICIs could be a strategic approach to improve local tumor control, but also stimulate antitumor immunity when a patient does not initially respond to ICI treatment. This may be particularly effective for patients with advanced, inoperable disease. This multimodal approach emphasizes a personalized approach that considers both the TME as well as the tumor's genetic profile.[34–38]

As for patients who are to receive ICI treatment, it must be underscored that there is a cohort of patients who are generally not able to receive PD-1 treatment for locally advanced cSCC, namely organ transplant recipients. Immune checkpoint inhibitors like pembrolizumab are contraindicated due to triggering immune responses that can lead to acute rejection of the transplanted organ. Some studies have shown allograft rejection as high as 65% in patients treated with PD-1 inhibitors.[39] Elderly and frail patients are also patients that need special consideration in evaluating candidacy for ICI treatment. In a study by Yakobson et al, they retrospectively studied the efficacy and safety of PD-1 inhibitors, including both cemiplimab and pembrolizumab, in patients over 75 years old. They compared outcomes in immunocompromised versus immunocompetent individuals. The median progression-free survival of the entire cohort was 8.9 months overall, with immunosuppressed patients faring better (10.6 months) as compared to immunocompetent patients (7.5 months). A complete response was achieved in 17% of patients, and a partial response was achieved in 51%. Despite its efficacy, 86% of patients experienced an immune-related adverse event (irAE), most of which were grades 1 or 2. There were no deaths reported. The most common irAEs were fatigue, rash, thrombocytopenia, and myalgias.[40] Although there was a high rate of irAEs in this population, the high antitumor activity shown was significant. Despite this, caution and extensive counseling for patients in both the elderly and immunocompromised populations is strongly advised.

The usage of ICIs like pembrolizumab has significantly improved outcomes for patients with advanced cSCC, offering many the possibility of curing disease. This is a stark change from the poor outcomes seen with traditional systemic therapy. However, despite these advances, there is a need to improve outcomes for specific patient populations, particularly those who are immunosuppressed or have tumors refractory to currently available immune checkpoint inhibitors. To address these challenges, improved patient selection is necessary to identify those who will benefit most from ICIs, which is backed by ongoing trials continuing to explore novel uses of pembrolizumab. Continued research and personalized approaches are essential to fully realize the potential of pembrolizumab in improving outcomes for patients with advanced cSCC.

Disclosure

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References

1. Foundation SC. Our new approach to a challenging skin cancer statistic. 2023.;
2. Zavdy O, Coreanu T, Bar-On DY, et al. Cutaneous squamous cell carcinoma in immunocompromised patients-A comparison between different immunomodulating conditions. *Cancers*. 2023;15(6):1764. doi:10.3390/cancers15061764

3. Kreher MA, Noland MMB, Konda S, Longo MI, Valdes-Rodriguez R. Risk of melanoma and nonmelanoma skin cancer with immunosuppressants, part I: calcineurin inhibitors, thiopurines, IMDH inhibitors, mTOR inhibitors, and corticosteroids. *J Am Acad Dermatol*. 2023;88(3):521–530. doi:10.1016/j.jaad.2022.11.044
4. Granger EE, Groover M, Harwood C, et al. Cutaneous squamous cell carcinoma tumor accrual rates in immunosuppressed patients with autoimmune and inflammatory conditions: a retrospective cohort study. *J Am Acad Dermatol*. 2024;90(4):731–738. doi:10.1016/j.jaad.2023.11.039
5. Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. *J Am Acad Dermatol*. 2002;47 (1):1–17;quiz18–20. doi:10.1067/mjd.2002.125579
6. Brougham ND, Dennett ER, Cameron R, Tan ST. The incidence of metastasis from cutaneous squamous cell carcinoma and the impact of its risk factors. *J Surg Oncol*. 2012;106(7):811–815. doi:10.1002/jso.23155
7. Kim JYS, Kozlow JH, Mittal B, Moyer J, Olenecki T, Rodgers P. Guidelines of care for the management of cutaneous squamous cell carcinoma. *J Am Acad Dermatol*. 2018;78(3):560–578. doi:10.1016/j.jaad.2017.10.007
8. Stratigos AJ, Garbe C, Dessinioti C, et al. European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: part 2. *Treatment Eur J Cancer*. 2020;128:83–102. doi:10.1016/j.ejca.2020.01.008
9. Inc. NCCN. NCCN guidelines version 1. 2024 Squamous Cell Skin Cancer.Accessed August 29, 2024.
10. Likhacheva A, Awan M, Barker CA, et al. Definitive and postoperative radiation therapy for basal and squamous cell cancers of the skin: executive summary of an American society for radiation oncology clinical practice guideline. *Pract Radiat Oncol*. 2020;10(1):8–20. doi:10.1016/j.prro.2019.10.014
11. Gyawali B, Shimokata T, Honda K, Ando Y. Chemotherapy in locally advanced head and neck squamous cell carcinoma. *Cancer Treat Rev*. 2016;44:10–16. doi:10.1016/j.ctrv.2016.01.002
12. Nottage MK, Lin C, Hughes BG, et al. Prospective study of definitive chemoradiation in locally or regionally advanced squamous cell carcinoma of the skin. *Head Neck Apr*. 2017;39(4):679–683. doi:10.1002/hed.24662
13. Porceddu SV, Bressel M, Poulsen MG, et al. Postoperative concurrent chemoradiotherapy versus postoperative radiotherapy in high-risk cutaneous squamous cell carcinoma of the head and neck: the randomized phase III TROG 05.01 trial. *J Clin Oncol*. 2018;36(13):1275–1283. doi:10.1200/jco.2017.77.0941
14. Tanvetyanon T, Padhya T, McCaffrey J, et al. Postoperative concurrent chemotherapy and radiotherapy for high-risk cutaneous squamous cell carcinoma of the head and neck. *Head Neck*. 2015;37(6):840–845. doi:10.1002/hed.23684
15. Kus KJB, Murad F, Smile TD, et al. Higher metastasis and death rates in cutaneous squamous cell carcinomas with lymphovascular invasion. *J Am Acad Dermatol Apr*. 2022;86(4):766–773. doi:10.1016/j.jaad.2021.11.002
16. Smile TD, Ruiz ES, Kus KJB, et al. Implications of satellitosis or in-transit metastasis in cutaneous squamous cell carcinoma: a prognostic omission in cancer staging systems. *JAMA Dermatol*. 2022;158(4):390–394. doi:10.1001/jamadermatol.2022.0001
17. Pickering CR, Zhou JH, Lee JJ, et al. Mutational landscape of aggressive cutaneous squamous cell carcinoma. *Clin Cancer Res*. 2014;20 (24):6582–6592. doi:10.1158/1078-0432.CCR-14-1768
18. Samstein RM, Lee CH, Shoushtari AN, et al. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. *Nat Genet*. 2019;51(2):202–206. doi:10.1038/s41588-018-0312-8
19. Migden MR, Rischin D, Schmults CD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. *N Engl J Med*. 2018;379(4):341–351. doi:10.1056/nejmoa1805131
20. Migden MR, Khushalani NI, Chang ALS, et al. Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, Phase 2, single-arm trial. *Lancet Oncol*. 2020;21(2):294–305. doi:10.1016/s1470-2045(19)30728-4
21. Hughes BGM, Munoz-Couselo E, Mortier L, et al. Pembrolizumab for locally advanced and recurrent/metastatic cutaneous squamous cell carcinoma (KEYNOTE-629 study): an open-label, nonrandomized, multicenter, phase II trial. *Ann Oncol*. 2021;32(10):1276–1285. doi:10.1016/j.annonc.2021.07.008
22. Couselo EM, Hughes BGM, Mortier L, et al. Pembrolizumab (pembro) for locally advanced (LA) or recurrent/metastatic (R/M) cutaneous squamous cell carcinoma (cSCC): long-term results of the phase 2 KEYNOTE-629 study. *J Clin Oncol*. 2024;42(16_suppl):9554. doi:10.1200/JCO.2024.42.16_suppl.9554
23. Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma: incidence, risk factors, diagnosis, and staging. *J Am Acad Dermatol*. 2018;78(2):237–247. doi:10.1016/j.jaad.2017.08.059
24. Petre A, Pommier P, Brahmi T, et al. Benefit from adjuvant radiotherapy according to the number of risk factors in cutaneous squamous cell carcinoma. *Radiother Oncol*. 2022;168:53–60. doi:10.1016/j.radonc.2022.01.015
25. Trosman SJ, Zhu A, Nicolli EA, Leibowitz JM, Sargi ZB. High-risk cutaneous squamous cell cancer of the head and neck: risk factors for recurrence and impact of adjuvant treatment. *Laryngoscope*. 2021;131(1):E136–E143. doi:10.1002/lary.28564
26. Gross ND, Miller DM, Khushalani NI, et al. Neoadjuvant cemiplimab for stage II to IV cutaneous squamous-cell carcinoma. *N Engl J Med*. 2022;387(17):1557–1568. doi:10.1056/NEJMoa2209813
27. Gross ND, Miller DM, Khushalani NI, et al. Neoadjuvant cemiplimab and surgery for stage II-IV cutaneous squamous-cell carcinoma: follow-up and survival outcomes of a single-arm, multicentre, phase 2 study. *Lancet Oncol*. 2023;24(11):1196–1205. doi:10.1016/S1470-2045(23)00459-X
28. Kim EY, Ruiz ES, DeSimone MS, et al. Neoadjuvant-intent immunotherapy in advanced, resectable cutaneous squamous cell carcinoma. *JAMA Otolaryngol Head Neck Surg*. 2024;150(5):414–420. doi:10.1001/jamaoto.2024.0259
29. Lorenzo-Sanz L, Lopez-Cerda M, da Silva-Diz V, et al. Cancer cell plasticity defines response to immunotherapy in cutaneous squamous cell carcinoma. *Nat Commun*. 2024;15(1):5352. doi:10.1038/s41467-024-49718-8
30. Nicolazzo C, Gradilone A, Carpino G, Gazzaniga P, Raimondi C. Molecular characterization of circulating tumor cells to study cancer immunoevasion. *Methods mol Biol*. 2019;1884:247–258. doi:10.1007/978-1-4939-8885-3_17
31. Thai AA, Young RJ, Bressel M, et al. Comprehensive profiling identifies tumour and immune microenvironmental differences in clinical subsets of cutaneous squamous cell carcinoma. *Br J Dermatol*. 2023;189(5):588–602. doi:10.1093/bjd/ljad250
32. Niknafs N, Balan A, Cherry C, et al. Persistent mutation burden drives sustained anti-tumor immune responses. *Nat Med*. 2023;29(2):440–449. doi:10.1038/s41591-022-02163-w
33. Papadopoulos KP, Johnson ML, Lockhart AC, et al. First-in-human study of cemiplimab alone or in combination with radiotherapy and/or low-dose cyclophosphamide in patients with advanced malignancies. *Clin Cancer Res*. 2020;26(5):1025–1033. doi:10.1158/1078-0432.CCR-19-2609

34. Chi A, Nguyen NP. Mechanistic rationales for combining immunotherapy with radiotherapy. *Front Immunol*. 2023;14:1125905. doi:10.3389/fimmu.2023.1125905
35. Procureur A, Simonaggio A, Bibault JE, Oudard S, Vano YA. Enhance the immune checkpoint inhibitors efficacy with radiotherapy induced immunogenic cell death: a comprehensive review and latest developments. *Cancers*. 2021;13(4):678. doi:10.3390/cancers13040678
36. Donlon NE, Power R, Hayes C, Reynolds JV, Lysaght J. Radiotherapy, immunotherapy, and the tumour microenvironment: turning an immunosuppressive milieu into a therapeutic opportunity. *Cancer Lett*. 2021;502:84–96. doi:10.1016/j.canlet.2020.12.045
37. McLaughlin M, Patin EC, Pedersen M, et al. Inflammatory microenvironment remodelling by tumour cells after radiotherapy. *Nat Rev Cancer Apr*. 2020;20(4):203–217. doi:10.1038/s41568-020-0246-1
38. Martinez-Zubiaurre I, Chalmers AJ, Hellevik T. Radiation-induced transformation of immunoregulatory networks in the tumor stroma. *Front Immunol*. 2018;9:1679. doi:10.3389/fimmu.2018.01679
39. Ferrandiz-Pulido C, Leiter U, Harwood C, et al. Immune checkpoint inhibitors in solid organ transplant recipients with advanced skin cancers-emerging strategies for clinical management. *Transplantation*. 2023;107(7):1452–1462. doi:10.1097/TP.0000000000004459
40. Yakobson A, Abu Jama A, Abu Saleh O, Michlin R, Shalata W. PD-1 inhibitors in elderly and immunocompromised patients with advanced or metastatic cutaneous squamous cell carcinoma. *Cancers*. 2023;15(16):4041. doi:10.3390/cancers15164041