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COMMENTARY

Top advances of the year: Developments of immunotherapy in cutaneous squamous cell carcinoma, 2023–2024

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Abstract

Antibodies against PD-1 (PD1i), such as cemiplimab and pembrolizumab, have demonstrated significant efficacy in advanced, unresectable cutaneous squamous cell carcinoma (cSCC). These agents elicit durable responses in approximately 45% of patients, contributing to improved aesthetic, functional, and survival outcomes in a subset of individuals with advanced cSCC. This review highlights recent and ongoing research investigating the safety and efficacy of immune checkpoint inhibitors for cSCC in the curative intent perioperative settings, advanced/metastatic setting, and within the immunocompromised patient populations.

KEYWORDS
cutaneous squamous cell carcinoma, immune checkpoint inhibitors (ICI), immunosuppression, neoadjuvant, PD-1 inhibitors (PD1i)

INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin malignancy and represents 20% of all nonmelanoma skin cancers.[1,2] Incidence is rising, which is attributable to an aging population and increased cancer screening.[1,3] Notably, immunosuppression is associated with a significantly increased risk of developing cSCC, a more aggressive tumor biology, and poorer prognosis.[4,5] These observations implicate a critical role for impaired immunosurveillance in the genesis of this disease.

Because of association with ultraviolet-induced mutagenesis, cSCC generally carries a high tumor mutation burden (TMB), which is a predictive biomarker of response to inhibitors of programmed cell death protein 1 (PD1i) or programmed death-ligand 1 (PDL1i) in advanced malignancies. This is due to its association with increased neoantigen load and higher tumor immunogenicity.[6–8] The PD1i cemiplimab received Food and Drug Administration approval in 2018 for unresectable locally advanced and metastatic cSCC after phase 1 and 2 clinical trials demonstrated an objective response rate (ORR) of 46.1%. Notably, these responses were durable, with 87.8% ongoing at 12 months.[9–11] Pembrolizumab, another PD1i, demonstrated similar efficacy and toxicity profile than cemiplimab, and was subsequently approved in 2020 for recurrent and metastatic cSCC, with approval later expanded to locally advanced disease.[12–15]

Mateus Trinconi Cunha and Neil Wallace contributed equally to this article.

Based on the encouraging activity of PD1i in the locally advanced unresectable and metastatic setting, recent research efforts were directed at expanding the role of immune checkpoint inhibitors (ICI) for advanced resectable disease, exploring its safety and efficacy in immunocompromised patients, and evaluating other immunotherapeutic approaches such as oncolytic virus and therapeutic vaccines. This review will summarize these recent developments and discuss their potential to change the treatment paradigm of cSCC.

RESECTABLE CSCC

Neoadjuvant immune checkpoint inhibitors

Nearly 85% of cSCC arise in the head and neck area.[16] Although local interventions can be curative in the majority of localized cases, potential adverse cosmetic and functional outcomes must be considered as they can significantly impact patients' quality of life. After high response rates were observed in advanced cSCC, PD1i were investigated in the neoadjuvant setting. The aims not only included establishing whether they may improve tumor response and patient survival, but also whether they could decrease morbidity and improve cosmetic and functional outcomes via preservation of critical anatomical structures.

Neoadjuvant PD1i for resectable cSCC was introduced in a phase 2 study that included 20 patients with stage III or IV head and neck cSCC with no distant metastasis (M0). Patients received two cycles of neoadjuvant cemiplimab every 3 weeks followed by surgery.[17,18] All patients underwent surgical resection and the treatment was generally well tolerated. Adverse events (AE) possibly related to the drug included one grade 3 event of diarrhea, four grade 2 toxicities of fatigue, myalgia, joint pain, and hypothyroidism, and nine grade 1 events (all pruritus or maculopapular rash). The ORR per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 was 30%, however, pathologic response rate was 75%, including 55% pathologic complete response (pCR) and 20% major pathologic response (MPR). Preplanned postoperative radiotherapy (PORT) was omitted in 60% of patients and 80% of pathologic responders. At a median follow-up time of 42.3 months, 15% of patients had recurred, none of whom had been pathologic or radiologic responders, and all had received PORT with or without concurrent chemotherapy. Notably, all pathologic responders remained disease-free, including those who did not receive PORT. These findings suggested that pathologic response to neoadjuvant PD1i is a predictor of improved oncologic outcomes. Furthermore, these data generate the hypothesis that the omission of PORT for pathologic responders may be a safe strategy.

A subsequent phase 2 trial including 79 patients further studied the strategy. This evaluated the administration of up to four doses of neoadjuvant cemiplimab (as opposed to two doses in the pilot study) for resectable stage II disease of at least 3 cm in an aesthetically unfavorable area or stage III-IV (M0) cSCC, followed by surgery and either PORT, adjuvant cemiplimab for up to 1 year, or observation, per investigator discretion.[19,20] The primary end point was pCR rate based on independent review, whereas secondary end points included MPR on independent review, pathologic response (pCR or MPR) on investigator assessment, radiologic response per RECIST 1.1, and safety. Of the 79 treated patients, 62 received four doses of PD-1i and 70 underwent surgery. Nine patients did not undergo resection due to withdrawal of consent or loss to follow-up in the context of radiographic response (4), death due to adverse events (2), progression to inoperability (2), or nonadherence to protocol visits (1).

The pCR rate was 51% and MPR rate was 13% on independent central assessment, validating the pathologic response rate seen in the pilot study. ORR was 68%, with 6% radiologic complete response. Although more radiologic responses were reported after four versus two cycles of neoadjuvant cemiplimab (68% vs. 30% in the pilot study), the data suggest that radiologic response on average underestimates pathologic response. Regarding safety, treatment-emergent AEs of grades 1–2 were observed in 70% of treated patients, the most common of which were fatigue (29%), nausea (15%), rash (14%), diarrhea (13%), and pruritus (10%). Grade 3 and 4 AEs were observed in 11% and 3% of patients, respectively, and grade 5 in 5%. One grade 5 event was considered potentially related to cemiplimab (exacerbation of congestive heart failure in a 93-year-old female with multiple baseline cardiovascular comorbidities). After a median follow-up of 29.4 months,[21] the 24-month event-free survival (EFS) was 86%. EFS was defined as time from first dose of neoadjuvant cemiplimab to progressive disease that precluded surgery, inability to undergo complete resection, disease recurrence by imaging criteria, or death due to any cause. The 24-month EFS for patients who had pCR was 92% and 89% for those with MPR. Nonresponders or not evaluable patients exhibited a 24-month EFS of 64%, once again suggesting that pathologic response to PD-1i is a predictor of improved oncologic outcomes. The data supporting improved prognosis in complete responders to PD-1i is in line with evidence from other cutaneous malignancies, such as melanoma and Merkel cell carcinoma.[22,23] Two-year overall survival (OS) was 86% for all patients and compares favorably with results from surgery and PORT in patients with high-risk cSCC.[24–26]

Aside from cemiplimab, other ICI are currently under investigation in the advanced, curative intent setting. The MATISSE trial, a randomized phase 2 study, explored the use of neoadjuvant PD1i nivolumab, either as a single agent or combined with the CTLA-4 inhibitor ipilimumab, administered over a 4-week period for patients with T1-4, N0-3 or Tx, N1-3, M0 cSCC with an indication for extensive surgery.[27] Publication of the final trial report is awaited but preliminary results presented at the 2023 American Society for Clinical Oncology meeting revealed a MPR rate of 40% with single-agent nivolumab and 53% for the combination. Deep responses (defined as MPR or clinical complete response in the absence of surgery) were seen in 50% and 61% of patients, respectively. Ten patients withdrew consent for surgery and radiotherapy, nine of those due to significant clinical remission, each of whom remained disease-free after median follow-up of 12 months. Grade 3–4 immune-related AEs occurred in 12% of patients and were

manageable. The authors also reported that post-neoadjuvant ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)-computed tomography (CT) scans were predictive of major or partial pathologic response.[28]

More recently, the De-Squamate study, a multicenter, single-arm phase 2 clinical trial evaluated the feasibility of a risk-adapted surgical de-escalation approach. This was guided by clinical, radiological, and pathological response in resectable cSCC of all sites in patients who received at least two of four planned cycles of neoadjuvant pembrolizumab every 3 weeks.[29] Patients underwent imaging with CT or magnetic resonance imaging (MRI) as well as ^{18}F-FDG PET-CT scans at baseline and after the fourth cycle of pembrolizumab to assess metabolic response. Patients who exhibited complete metabolic response and negative biopsies of target sites had surgery and PORT omitted; whereas those with residual disease underwent resection, with PORT omitted in case of MPR or pCR. The primary end point was the combined rate of pCR, MPR, and complete clinical response, and secondary end points included treatment de-escalation and safety. A total of 17 of 27 (63%) enrolled patients met the primary end point (15% pCR, 0% MPR, and 48% complete clinical response), which resulted in the omission of both surgery and PORT in 48% and omission of PORT alone in 15% of patients. Two patients had pembrolizumab-related AEs, grade 2 arthritis and hypophysitis, and there were no grade 3–5 AEs attributable to pembrolizumab.

Finally, a phase 2 single-institution study evaluated the PDL1i atezolizumab in the neoadjuvant setting in patients with stage II–IV (M0) cSCC of the head and neck.[30] The primary end point was the number of patients who completed neoadjuvant treatment and underwent surgery. Secondary end points included ORR (evaluated after 6 weeks), and rates of pCR and MPR. Twenty patients were recruited, of whom 16 (80%) completed three planned doses of atezolizumab; 19 underwent surgical resection, while one patient declined surgery due to the possibility of orbital exenteration. There was one AE leading to drug discontinuation, a grade 3 pneumonitis successfully treated with corticosteroid taper. Seven patients (35%) experienced pCR, while four (20%) experienced MPR, and eight (40%) had no response. By RECIST 1.1, one (5%) patient had complete response, seven (35%) had partial response, and 10 (50%) had stable disease, with one disease progression. Of the 19 patients submitted to surgery, 10 were treated with PORT. Of the seven pCR patients, only one received PORT, while three of the four MPR patients underwent radiotherapy.

Despite the growing evidence suggesting an important role for neoadjuvant PD1i or PDL1i in improving functional and cosmetic outcomes of advanced cSCC patients, it is not yet known if it improves oncologic outcomes compared to standard-of-care surgery and PORT. These classes of drug demonstrate high response rates and attractive toxicity profiles, but disease progression or adverse events, although infrequently, can occur and may preclude curative-intent surgery. Furthermore, predictors of pathologic response are yet to be established and there have been reports of delayed response after initial apparent disease progression with or without clinical deterioration.[31,32] To address these important questions, NRG-HN014 (ClinicalTrials.gov identifier NCT06568172), a phase 3, randomized clinical trial was designed and recently activated. Patients with resectable stage III/IV cSCC will be randomized to either standard of care surgery with PORT, or the experimental arm, consisting of neoadjuvant cemiplimab, followed by response-adapted surgery, ± PORT (at clinician discretion), and four additional cycles of cemiplimab every 3 weeks for patients who exhibit pCR. Notably, formal criteria regarding use of PORT are not specified in the available trial description.[33]

Other ongoing neoadjuvant approaches

Although uncommon, ICI can lead to serious AEs that can be permanent or fatal. A phase 1 clinical trial is currently evaluating whether intralesional cemiplimab injection in patients with recurrent cSCC has potential to reduce the incidence of AEs.[34]

Attempts to improve on the efficacy of single agent PD1i with combinatorial strategies are also under active investigation. INTerpath-007 is a phase 2/3 study evaluating V940, an individualized neoantigen vaccine therapy plus pembrolizumab for patients with stage II–IV (M0) cSCC, and is currently accruing patients.[35]

Adjuvant therapy with immune checkpoint inhibitors

Adjuvant cemiplimab is under investigation in NCT03969004 (C-POST trial),[36] which includes patients whose surgical specimen included high-risk pathologic features. Patients were randomized to receive either adjuvant cemiplimab or placebo for 1 year. The protocol was later amended to include patients with chronic lymphocytic leukemia who were not on active treatment.[37] Study accrual has been completed and the data have been locked. The publication is awaited.

Adjuvant pembrolizumab was investigated in a similar setting in KEYNOTE-630, which included patients whose specimens had high-risk pathologic characteristics.[38,39] The study has also completed accrual and final results are yet to be presented.

Pre-clinical and clinical data in other solid tumors suggest that ICI administered pre-surgery, while the tumor is in situ, is more likely to elicit an antitumor immune response than when the tumor is removed.[40] In melanoma, neoadjuvant administration of PD1i has been found to be more effective than its adjuvant counterpart.[41,42] It remains to be seen whether these results will apply to cSCC.

Table 1 summarizes currently ongoing and upcoming clinical trials investigating peri-operatory ICI strategies for cSCC, and Figure 1 illustrates a proposed algorithm for the treatment of resectable cSCC according to currently published evidence.

TABLE 1 Ongoing or registered, not withdrawn, clinical trials investigating neoadjuvant or adjuvant treatments for cSCC.

NCT number	Study title	Phase	Status	Interventions
NCT04154943	Study of Cemiplimab in Patients with Type of Skin Cancer Stage II to IV Cutaneous Squamous Cell Carcinoma	II	Active, not recruiting	Neoadjuvant cemiplimab
NCT04632433	Neoadjuvant Plus Adjuvant Treatment with Cemiplimab in Cutaneaous Squamous Cell Carcinoma	II	Active, not recruiting	Perioperatory cemiplimab
NCT03889912	Intralesional Cemiplimab for Adult Patients with Cutaneous Squamous Cell Carcinoma or Basal Cell Carcinoma	I	Recruiting	Neoadjuvant cemiplimab (intralesional)
NCT03969004	Study of Adjuvant Cemiplimab versus Placebo after Surgery and Radiation Therapy in Patients with High Risk Cutaneous Squamous Cell Carcinoma	III	Active, not recruiting	Adjuvant cemiplimab versus placebo
NCT04975152	Neoadjuvant Cemiplimab in Newly Diagnosed or Recurrent Stage I-II Merkel Cell Carcinoma and Locoregionally Advanced Cutaneous Squamous Cell Carcinoma	I	Recruiting	Neoadjuvant cemiplimab
NCT06418724	Neoadjuvant PD-1 Inhibitor and EGFR Inhibitor in Locally Advanced Cutaneous Squamous Cell Carcinoma	II	Not yet recruiting	Neoadjuvant cemiplimab plus cetuximab
NCT04428671	Cemiplimab before and after Surgery for the Treatment of High Risk Cutaneous Squamous Cell Cancer	I	Recruiting	Perioperatory cemiplimab
NCT03565783	Cemiplimab in Treating Patients with Recurrent and Resectable Stage II-IV Head and Neck Cutaneous Squamous Cell Cancer before Surgery	II	Recruiting	Neoadjuvant cemiplimab
NCT04315701	A PD-1 Checkpoint Inhibitor (Cemiplimab) for High-Risk Localized, Locally Recurrent, or Regionally Advanced Skin Cancer	II	Recruiting	Neoadjuvant cemiplimab
NCT06568172	Testing the Addition of an Immunotherapy Drug, Cemiplimab (REGN2810), Plus Surgery to the Usual Surgery Alone for Treating Advanced Skin Cancer	III	Not yet recruiting	Standard of care surgery (± radiotherapy) with or without neoadjuvant cemiplimab
NCT04808999	Neoadjuvant Study of PD-1 Inhibitor Pembrolizumab in PD-1 Naive Cutaneous Squamous Cell Carcinoma (cSCC)	II	Active, not recruiting	Neoadjuvant pembrolizumab
NCT05025813	Neoadjuvant Pembrolizumab in Cutaneous Squamous Cell Carcinoma	II	Recruiting	Neoadjuvant pembrolizumab
NCT03833167	Pembrolizumab (MK-3475) versus Placebo following Surgery and Radiation in Participants with Locally Advanced Cutaneous Squamous Cell Carcinoma (MK-3475-630/KEYNOTE-630)	III	Active, not recruiting	Adjuvant pembrolizumab versus placebo
NCT06295809	A Study of (Neo)Adjuvant V940 and Pembrolizumab in Cutaneous Squamous Cell Carcinoma (V940-007)	II/III	Recruiting	Arm A: perioperatory pembrolizumab + V940 Arm B: surgery Arm C: perioperatory pembrolizumab
NCT06288191	Neoadjuvant Nivolumab and Relatlimab in Cutaneous Squamous Cell Carcinoma	II	Not yet recruiting	Neoadjuvant nivolumab plus relatlimab
NCT04620200	Neo-adjuvant Nivolumab or Nivolumab with Ipilimumab in Advanced Cutaneous Squamous Cell Carcinoma Prior to Surgery (Matisse Trial)	II	Unknown	Neoadjuvant nivolumab + ipilimumab
NCT04710498	Neoadjuvant Atezolizumab in Surgically Resectable Advanced Cutaneous Squamous Cell Carcinoma	II	Active, not recruiting	Neoadjuvant atezolizumab
NCT05858229	Neo-adjuvant Treatment for Squamous Cell Carcinoma Using Direct Tumor Injection with RP1	I/II	Recruiting	Neoadjuvant RP1 (intratumoral)
NCT06014086	Intratumoral PH-762 for Cutaneous Carcinoma	I	Recruiting	Neoadjuvant PH-762 (intralesional)

Abbreviations: cSCC, cutaneous squamous cell carcinoma; NCT, National Clinical Trial.

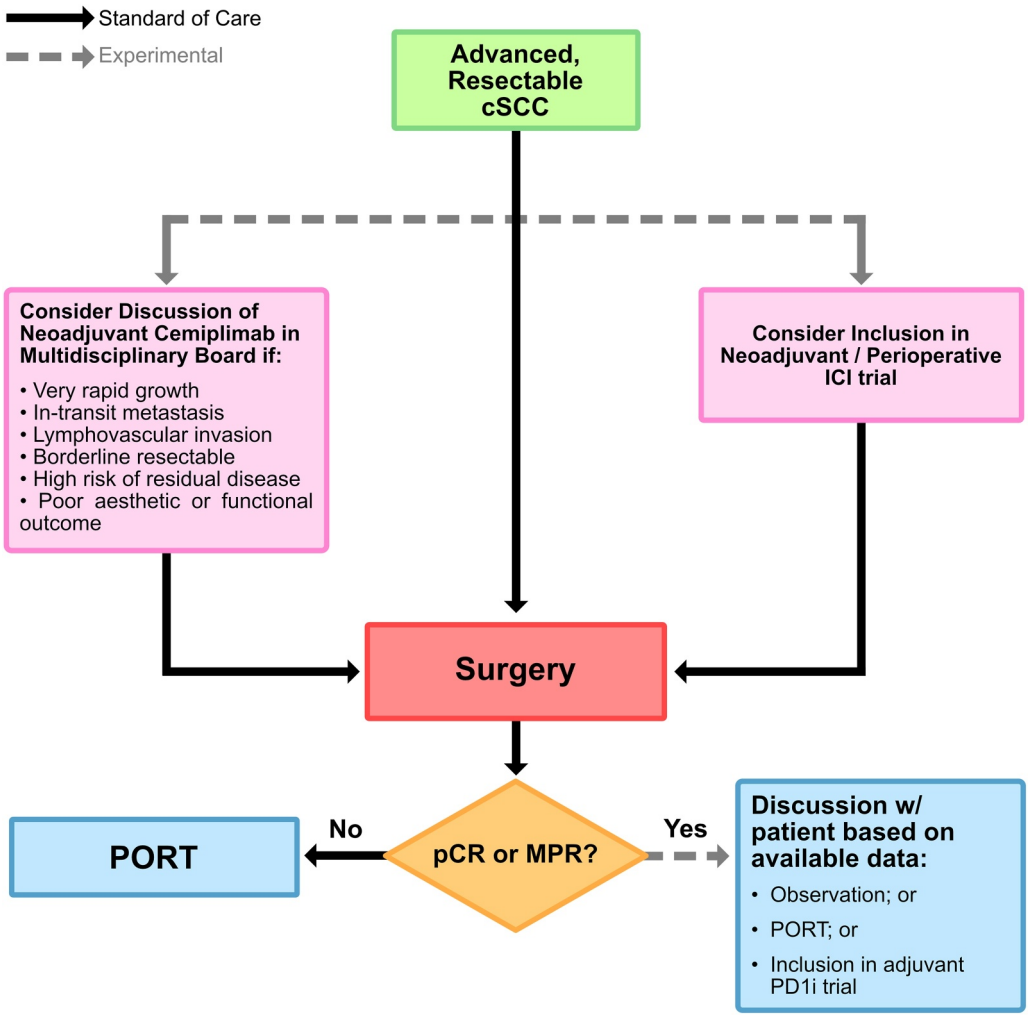

FIGURE 1 Proposed algorithm for the treatment of resectable cutaneous squamous cell carcinoma (cSCC). Currently, omission of resection and/or PORT should only be considered in an experimental setting. cSCC indicates cutaneous squamous cell carcinoma; ICI, immune checkpoint inhibitor; MPR, major pathological response; pCR, pathological complete response; PD1i, PD-1 inhibitor; PORT, postoperative radiotherapy.

Locally advanced or metastatic disease

Results published in the latest 2 years include investigations of oncolytic virus alone or in combination with PD1i, and anti-epidermal growth factor receptor (EGFR) inhibitors in combination with PD1i.

The intratumoral injection of RP1, an enhanced potency oncolytic HSV-1 with expression of GALV-GP R−, a fusogenic glycoprotein, and granulocyte macrophage colony stimulating factor, is being studied as single agent in the ARTACUS trial and in combination with nivolumab or cemiplimab in the IGNYTE and CERPASS studies, respectively. ARTACUS will be described in the 'Immunosuppressed patients' section.

IGNYTE is a phase 1/2 multi-cohort clinical trial investigating the combination of nivolumab and intratumoral RP1 in patients with skin cancers.[43] The report on the nonmelanoma skin cancer cohort included 26 patients, 15 of whom had cSCC. For this subgroup, ORR was 60% and complete response rate was 46.6%. Median duration of response was not reached. Two patients experienced RP1-related AEs, namely dehydration and hypotension, both of which resolved without sequelae.

CERPASS is a randomized phase 2 trial including ICI-naive patients with metastatic or unresectable locally advanced cSCC who were either not suitable for, or refused, surgery and/or radiotherapy. Patients were randomized 2:1 to receive intravenously cemiplimab with intratumoral RP1 or cemiplimab alone.[44] Final results are awaited.

Given the known activity of EGFR inhibitors in cSCC and the potential synergistic effect with PD-1 inhibitors,[45] research on anti-EGFR drugs has also advanced. The Alliance A091802 phase 2 randomized trial is investigating the PD-L1i avelumab with or without cetuximab in the first-line setting[46]; accrual has been completed and results awaited. Meanwhile, I-TACKLE, a phase 2 clinical trial, investigated the addition of cetuximab to pembrolizumab after disease progression on pembrolizumab.[47] Preliminary results reported in 2022 showed an ORR of 44%, with 1-year progression-free survival (PFS) of 42% for patients after starting the combination. Final publication is awaited.

Immunocompromised patients

The risk of developing cSCC is significantly higher in immunocompromised patients (i.e., solid organ or hematopoietic stem cell transplant recipients, people with hematologic malignancies, patients with autoimmune diseases requiring chronic immunosuppressive therapies, or those living with chronic viral infections). However, these categories of patients were largely excluded from the clinical trials of cemiplimab and pembrolizumab due to concerns about potential complications, including severe immune-related AEs and treatment-associated organ rejection. This lack of robust prospective data leaves a gap in understanding the safety and efficacy of PD1i in immunocompromised individuals. In subsequent years, real-world data with a limited number of patients suggested that immunocompetent and immunosuppressed patients had similar outcomes regarding response rate and OS.[48–51]

More recently, evidence on PD1i use in immunocompromised patients has been expanded in both the advanced and early-stage setting. In the advanced disease scenario, a retrospective observational study involving 15 Australian institutions described patient outcomes following PD-1i treatment.[52] The study included 286 patients, 88 (31%) of whom were immunocompromised, of whom 14 (5%) had received renal transplants, and 63 (22%) had concurrent hematological malignancies. Additionally, 27 (9%) had autoimmune diseases, including rheumatoid arthritis (30%) and psoriasis (18%). The primary end point was investigator-assessed ORR, and secondary end points included OS, PFS, and toxicity. ORR was 51% in immunocompromised patients, compared to 64% in immunocompetent patients. After a median follow-up of 12.2 months, OS and PFS were statistically shorter for immunocompromised patients, hazard ratio (HR) 1.8 (95% confidence interval [CI], 1.1–3.0) and 1.8 (95% CI, 1.2–2.7), respectively. Twenty (23%) immunocompromised patients reported immune-related AEs, which was similar to the rates observed for immunocompetent patients ($n = 35$, 18%). Patients with autoimmune disease had significantly more immune-related AEs (12 of 27, or 44%) compared to those who did not have such diseases (43 of 259, or 17%), $p = .001$. Of the 14 renal transplant recipients, two experienced allograft rejection and subsequent graft loss and both continued PD1i treatment while on dialysis.

A smaller retrospective observational study reported the outcomes of 27 patients who received neoadjuvant PD1i, including nine who had a history of lymphoma and four with active disease.[53] The majority of patients (22, or 81%) were exposed to cemiplimab, whereas the remainder received pembrolizumab. Five patients (19%) declined to undergo planned surgery due to clinical responses or stability and one did not undergo surgery due to progressive disease. For the overall population, pathologic response rate was evaluable in 19 patients, with nine (47%) responses, including seven pCR. For the eight pathologically evaluable patients with history of lymphoma, pathologic response rate was 37%, including two pCR and one mPR. Notably, the only two patients who experienced disease recurrence after surgery had active lymphoma at the time of treatment.

Two prospective studies also expanded the current body of evidence regarding safety of PD1i for kidney transplant recipients. A multicenter phase 1/2 trial included adult recipients of a kidney transplant who had a functioning allograft and unresectable advanced cSCC or other skin malignancies. The study tested the immunosuppressive regimen of tacrolimus and prednisone with nivolumab as anticancer therapy, with the option of adding ipilimumab to nivolumab at disease progression.[54] The primary composite end point was disease control rate (partial or complete response or stable disease per RECIST v1.1) without allograft loss at 16 weeks. Secondary end points included ORR, PFS, OS, and rate of allograft loss. Donor-derived cell-free DNA (dd-cfDNA) levels were investigated as a potential predictor of allograft rejection. Twelve patients were enrolled, eight of whom were evaluable after 8 weeks of therapy. Of those patients, five had cSCC. All eight patients experienced disease progression on the first regimen of tacrolimus, prednisone, and nivolumab. After progression, six patients received the combination of ipilimumab and nivolumab without altering the immunosuppression regimen. Among these six patients, there were two CR and four PD, with median PFS of 3 months (95% CI, 1.4–NE [not estimable]). The median OS of the patients was 9.1 months (95% CI, 3.9–NE). Overall, three patients experienced treatment-related allograft loss: one during the first-line phase, and two during the post-progression treatment phase (one of the two experienced a CR). Two of the three patients had elevations in dd-cfDNA levels 10 and 15 days earlier than increases in serum creatinine. The remaining patients who did not experience rejection were not found to have dd-cfDNA elevations.

A phase 1, single-arm, single-center clinical trial investigated the role of the combination of immunosuppression with an mTOR inhibitor (everolimus or sirolimus) and prednisone, and cemiplimab for up to 2 years in kidney transplant recipients with advanced cSCC.[55] The primary end point was safety and toxicity, specifically the rate of kidney allograft rejection or loss. Efficacy was a secondary end point. Twelve patients enrolled and no kidney allograft rejection events were observed. However, there were two grade 5 events (two deaths attributed to comorbid conditions). A response was observed in five of 11 evaluable patients; of those, three were CR. Seven of 11 patients had either tumor response or stable disease, with a median duration of response of 11.4 months (95% CI, 4.9–29.7). Biomarker analysis revealed a trend toward increased CD3+ and CD8+ T lymphocytes and decreased total myeloid cells in tumor specimens of treatment responders.

Finally, ARTACUS is a phase 1b/2 clinical trial evaluating RP1 single agent in transplant recipient patients with cutaneous malignancies.[56] An interim report showed that 20 of 23 evaluable patients had cSCC, eight experienced responses (five CR and three PR), and there was no allograft rejection reported.[57]

Overall, the growing body of evidence shows the nuanced outcomes of immunocompromised patients who receive PD1i for cSCC. Despite the worse outcomes when compared to the immunocompetent population, these drugs appear to have some biological effect on immunocompromised patients. The small number of analyzed

patients and the diversity of scenarios grouped together (i.e., history of hematologic malignancy, solid organ or bone marrow transplant, or autoimmune disease under iatrogenic immunosuppression) precludes strong conclusions and warrants extreme care in risk-benefit analyses. For organ-transplant patients, the uncertain benefit of neoadjuvant PD1i along with the risk of transplant rejection and adverse events makes this a precarious choice. On the other hand, in an advanced disease scenario, with no therapeutic alternatives, PD1i may play a role. Notably, the population with autoimmune conditions requires additional care, as they have a greater likelihood of exhibiting immune-related AEs, as well as flares in their conditions.[58]

CONCLUSIONS

The addition of PD1i to more established therapeutic options has marked an advance toward improved oncological outcomes for patients with cSCC. Neoadjuvant strategies have demonstrated that a notable proportion of patients achieve major or complete pathological responses, which have been associated with improved clinical outcomes. These findings suggest the potential for de-intensification of local therapies, especially for patients whose surgical resection would risk unfavorable functional or aesthetic results. These encouraging results, however, warrant confirmatory research. In the adjuvant setting, results from ongoing trials evaluating PD1i for high-risk resected cSCC are anticipated. In advanced disease, combination strategies of PD1i with cetuximab or RP1 may add to currently available therapeutic options.

Further exploration of the safety and efficacy of PD1i in immunocompromised patients has increased treatment options for this diverse population. Real-world evidence indicates that, although PD1i may have some anticancer activity, survival outcomes for immunocompromised patients are poorer compared to the immunocompetent population. The risk–benefit ratio may vary according to the nature of immunosuppression, and individualized approaches are encouraged. Notably, clinical trials in advanced cSCC demonstrated the safety of these medications in renal transplant recipients. In all cases, ongoing and future clinical trials will further add to the evidence base.

AUTHOR CONTRIBUTIONS

Mateus Trinconi Cunha: Conceptualization, writing–original draft, and writing–review and editing. **Neil Wallace**: Conceptualization, writing–original draft, and writing–review and editing. **Sandro Porceddu**: Conceptualization, writing–original draft, and writing–review and editing. **Renata Ferrarotto**: Conceptualization, writing–original draft, and writing–review and editing.

CONFLICT OF INTEREST STATEMENT

Renata Ferrarotto reports personal advisory board fees from Prelude Therapeutics, Regeneron, Elevar Therapeutics, Coherus Bioscience, Eisai, and Remix Therapeutics; personal fees from Sanofi/Aventis for educational talk; personal fees for answers in CME educational talk; personal fees from Labcopr Drug Development DSMC outside the submitted work; and royalties from UpToDate (olfactory neuroblastoma chapter). The other authors declare no conflicts of interest.

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