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Case Report

Case Series: Cemiplimab and Nivolumab Immunotherapy as Promising Treatment in Advanced or Metastatic Cutaneous Squamous Cell Carcinoma

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Keywords

Cutaneous squamous cell carcinoma · Cutaneous oncology · Dermatology · Metastatic cutaneous squamous cell carcinoma · Immunotherapy · Immunotoxicities · Immune checkpoint inhibitors

Abstract

Cutaneous squamous cell carcinoma (CSCC) is the second most common skin cancer. Surgery is usually curative; however, some locally advanced or metastatic CSCC may be unresectable. Current novel therapeutic options with immune checkpoint inhibition (ICI) of programmed-death receptor 1 (PD-1) such as cemiplimab and nivolumab have demonstrated promising and sustained results with good tolerability in patients with CSCC. This study looks at 2 cases of CSCC treated with cemiplimab and nivolumab, respectively, demonstrating dramatic response within 2 cycles with significant reduction in tumour size and minimal toxicities or adverse outcomes reported. Immunotherapy has shown positive results as an effective treatment option for unresectable, recurrent, or metastatic CSCC. It is currently approved for use in the USA and Europe.

Introduction

Cutaneous squamous cell carcinoma (CSCC) is the second most common skin cancer globally with increasing incidence due to the ageing population along with better screening and awareness. It accounts for up to 75% of deaths from skin cancers excluding melanomas. CSCC arises from an uncontrolled proliferation of atypical keratinocytes, leading to tumour

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development. Most cases of CSCC rarely metastasize but can cause local soft tissue destruction. Treatment via resection is usually curative; however, 3–5% develop advanced or metastatic CSCC which may not be amenable for surgery or radiation therapy alone. These patients may be considered for systemic treatment. Recent studies have achieved good clinical responses by targeting immune checkpoints such as programme-death receptor 1 (PD-1) [1, 2]. PD-1 receptor is expressed on T cells, and T cells binding to its ligand (PD-L1) inhibit T-lymphocyte functions, limiting their cytotoxic function and anti-tumour activity [2].

CSCCs are tumours with high mutational burden with changes in the tumour microenvironment and immune checkpoint expression, allowing tumour cells to escape immune surveillance. Hence, they are more likely to be responsive to immune checkpoint inhibitors (ICIs) due to increased neoantigen expression. Most recently, cemiplimab and nivolumab, two examples of high-affinity human monoclonal antibody against PD-1 have shown good responses in the treatment of metastatic or locally advanced CSCC. They help enhance the T-cell response and have robust anti-tumour activity with good tolerability and sustained response in patients with unresectable CSCC [3, 4]. While cemiplimab is approved for use for advanced CSCC, nivolumab has traditionally been used in metastatic melanoma or advanced SCC of the head and neck. Evidence of its efficacy in advanced CSCC is mainly limited to phase 2 trial data [5].

Immunotherapy targeting different pathways including PD-1/PD-L1, epidermal growth factor receptor, and vascular endothelial growth factor have dramatically changed the standard of care in solid tumours. In particular, combination therapies with dual agents with different mechanism of action have shown improved morbidity and higher chance of achieving clinical remission compared to monotherapy with single agent ICI [6–9]. They work by enhancing the anti-tumour response and preventing immune suppression, limiting the risk of treatment resistance in advanced cancers. Of note, combination therapy with nivolumab and cetuximab, which are PD-L1 inhibitors and epidermal growth factor receptor inhibitors, respectively, has been shown to induce clinical remission in advanced CSCC, further highlighting the promising field of immunotherapies in future treatment pathways [10, 11].

This study identified 2 individual cases of unresectable or recurrent CSCC in a tertiary hospital in Waterford, Ireland. Data were collected prospectively over 3–4 months via clinical follow-up with a series of photographic images taken at intervals of treatment looking at outcomes including tumour response, adverse reactions, toxicities, or complications reported. Interim staging scans were also used to monitor treatment response.

Case Series

Case 1

A 71-year-old man initially diagnosed with CSCC on his left forehead in August 2021 was excised with split skin graft with lymphovascular and perineural invasion and involvement of the frontalis muscle. Due to multiple high-risk features, he underwent adjuvant radiotherapy. One year later, he unfortunately developed a biopsy-proven recurrence with a lesion in the superior orbit with perineural spread as far as the cavernous sinus, which was complicated by proptosis and ophthalmoplegia (Fig. 1, 2). He also developed intradermal recurrence lateral to the original grafted area on his left scalp (Fig. 3, 4). He was commenced on cemiplimab and showed promising response after 2 cycles with partial resolution of his diplopia and proptosis as well as visible improvement in intradermal recurrence (Fig. 5–8).

He developed a grade 3 transaminitis following cycle 3 of treatment. This was managed with 1 mg/kg of oral prednisolone. This liver derangement settled following steroid therapy which was weaned over the course of a month. He was rechallenged with cemiplimab but

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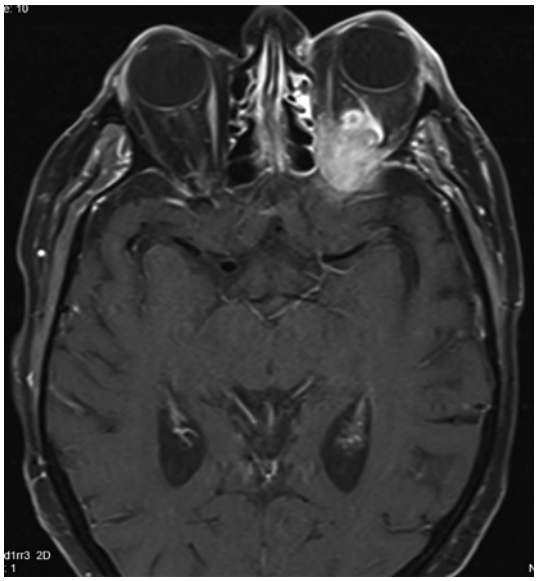

Fig. 1. Selected axial T1 fat-saturated contrast-enhanced images demonstrating a left-sided enhancing retroorbital mass involving superior rectus muscle and abutting the optic nerve prior to treatment.

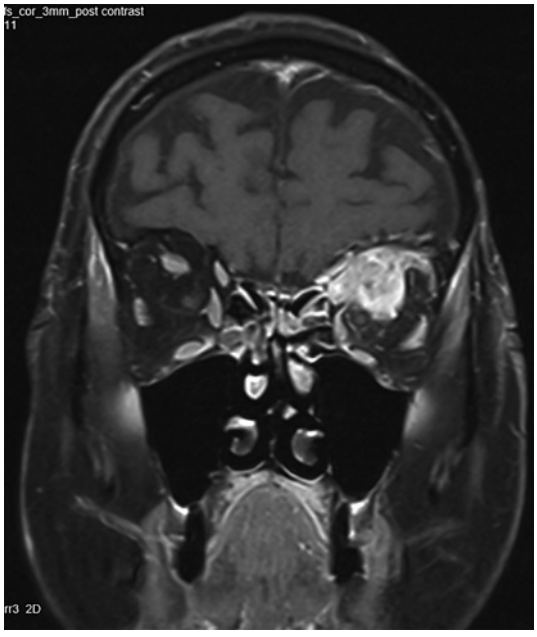

Fig. 2. Selected coronal T1 fat-saturated contrast-enhanced images demonstrating a left-sided enhancing retroorbital mass involving superior rectus muscle and abutting the optic nerve prior to treatment.

unfortunately developed a similar pattern of hepatotoxicity. Cemiplimab was permanently discontinued at this point and he was put on active surveillance. He continues to have a sustained response (see Table 1 for timeline of diagnosis and treatment received).

Case 2

A 75-year-old man with aggressive metastatic CSCC presented with a primary lesion in his right mastoid area (Fig. 9, 10). The lesion was initially excised in November 2022; however, a month later, he presented with two rapidly growing, fungating lesions on his posterior neck extending down to the supraclavicular fossa with muscle invasion demonstrated on CT neck (Fig. 11). Due to the extent of the lesions, they were not suitable for surgical resection. He was commenced on nivolumab in March 2023 and demonstrated dramatic response with >50% size reduction of his CSCC after 2 cycles of treatment (Fig. 12, 13). A grade 2 immune-mediated

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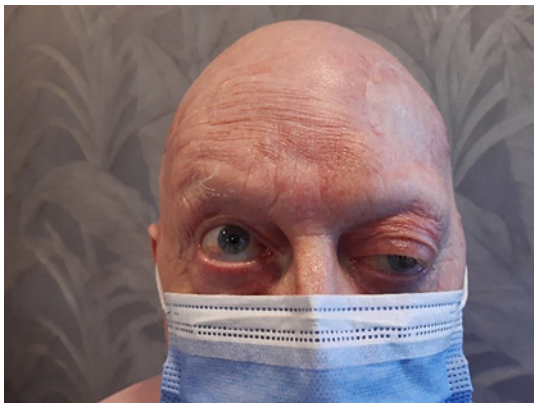

Fig. 3. Pre-treatment photos showing recurrence of metastatic CSCC adjacent to previously resected area on left scalp; partial ptosis of left eye from perineural invasion.

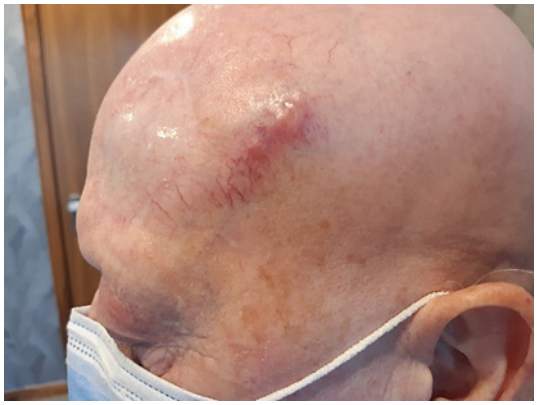

Fig. 4. Pre-treatment photos showing recurrence of metastatic CSCC adjacent to previously resected area on left scalp; partial ptosis of left eye from perineural invasion.

arthralgia was reported after cycle 7 which improved with steroids. He subsequently continued with further cycles of nivolumab with excellent tumour size response (Fig. 14). CT neck restaging scan following 6 cycles of nivolumab in June 2023 demonstrated significant interval reduction in the necrotic adenopathy in the right posterior neck with some small volume residual overlying skin thickening (Fig. 15) (see Table 2 for timeline of diagnosis and treatment received).

Discussion

Traditionally, advanced or metastatic CSCC confers a poor prognosis with only a few treatments available. Both cases described showed significant reduction of tumour size, making it a potential treatment in the future for these patients to induce long-term remission with good tolerability. Although in case 1, the patient experienced immune-mediated arthropathy following 2 cycles of cemiplimab, as well as immune-mediated hepatitis after the 3rd cycle. The immunotoxicities were resolved with course of tapering steroids and were otherwise tolerated well with marked improvement in his ptosis, pain, and eye movements. Moreover, the therapeutic potential of combination therapy using nivolumab and cetuximab in advanced CSCC also offers promising results in achieving tumour regression and tolerability, compared to monotherapy with cetuximab alone which is effective up to a limited time period [10, 11].

This case series adds to the evolving ICI treatment options in metastatic CSCC. In particular for CSCC in the head and neck region, ICI can be helpful to prevent disfiguring surgical resections and preserve organ function. Current literature mainly shows off-licence use of nivolumab in unresectable CSCC, or in combination with cetuximab following disease

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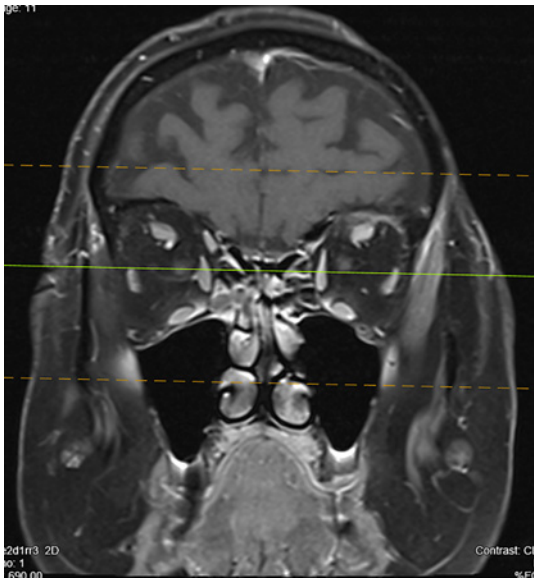

Fig. 5. Selected coronal T1 fat-saturated contrast-enhanced images demonstrating significant response in the retroorbital mass following three cycles of cemiplimab.

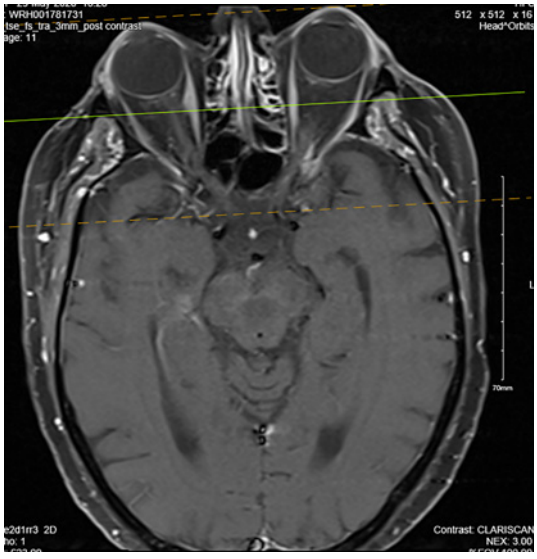

Fig. 6. Selected axial T1 fat-saturated contrast-enhanced images demonstrating significant response in the retroorbital mass following three cycles of cemiplimab.

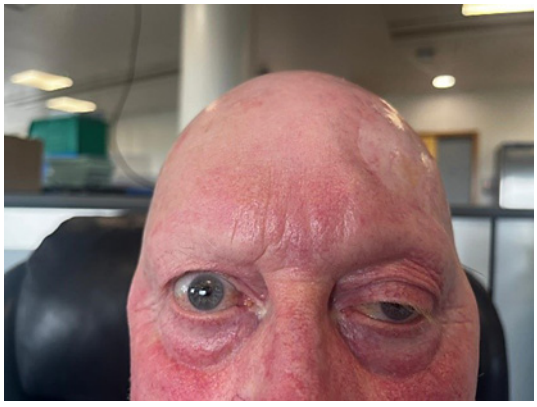

Fig. 7. Reduction in size of CSCC and improvement in left ptosis after 2 cycles of cemiplimab.

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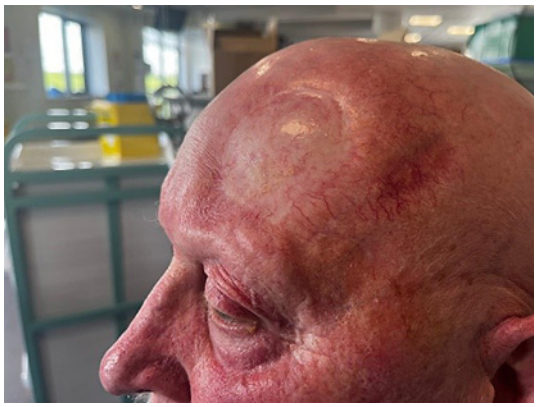

Fig. 8. Reduction in size of CSCC and improvement in left ptosis after 2 cycles of cemiplimab.

Table 1. Timeline of treatment received and response to cemiplimab in case 1

Timeline	Treatment received
Aug 2021	Initial diagnosis: CSCC of the left forehead, excision with split skin graft
Nov 2021	Completed adjuvant radiotherapy
Nov 2022	Recurrence of CSCC with soft tissue perineural invasion
Jan 2023	Recurrence of intradermal CSCC in the left scalp/forehead region
Mar 2023	Commenced cemiplimab
May 2023	Developed immunotherapy-mediated transaminitis post-cycle 3 cemiplimab
May 2023	MRI showed interval resolution of perineural invasion of CSCC and intradermal recurrence on the scalp

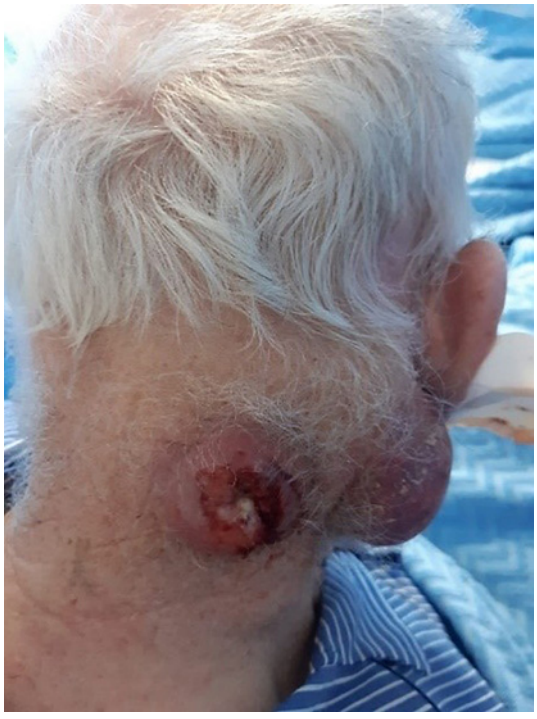

Fig. 9. Large ulcerated lesion on the right posterior neck area.

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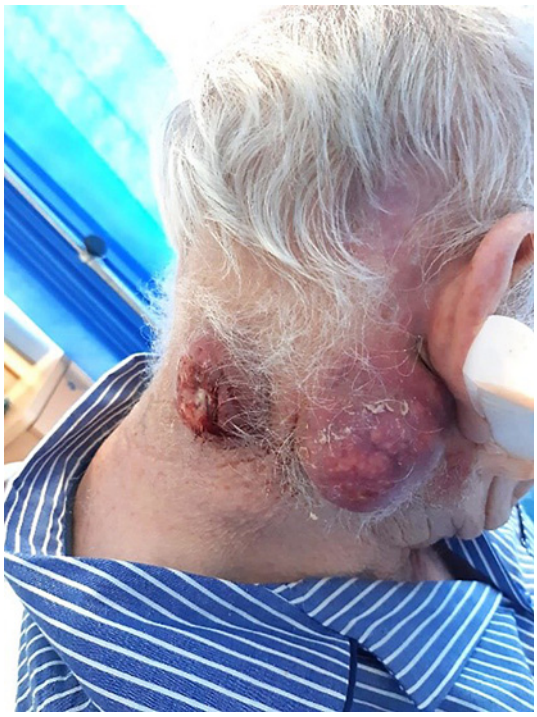

Fig. 10. Large ulcerated lesion on the right posterior neck area.

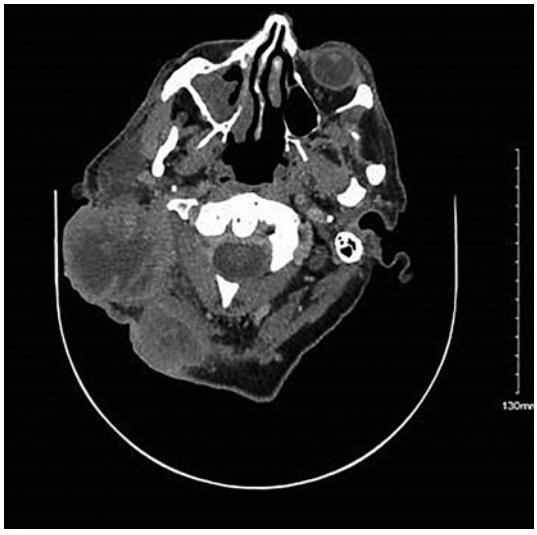

Fig. 11. Axial slice of contrast-enhanced CT neck pre-treatment showing large necrotic adenopathy in right posterior triangle with muscle invasion.

relapse on monotherapy. Cemiplimab demonstrated response in 50% of patients in phase 1 trials, and 47% of patients in phase 2 trials, with response duration exceeding 6 months in more than half of the study cohort [3]. In our first case, the patient continued to have sustained response after stopping cemiplimab for up to 3 months at time of data collection. In the second case, the patient showed excellent tumour response with single-agent nivolumab, suggesting its therapeutic potential as first-line option in suitable cohorts. Further research including phase 3 and 4 studies of efficacy of PD-L1 inhibitors is required to establish ICI as the new standard of care in advanced CSCC, in particular looking at timing of treatment induction and tumour response, as well as duration of disease-free survival following immunotherapy cessation. Finally, recurrence of aggressive CSCC usually occurs within 2 years,

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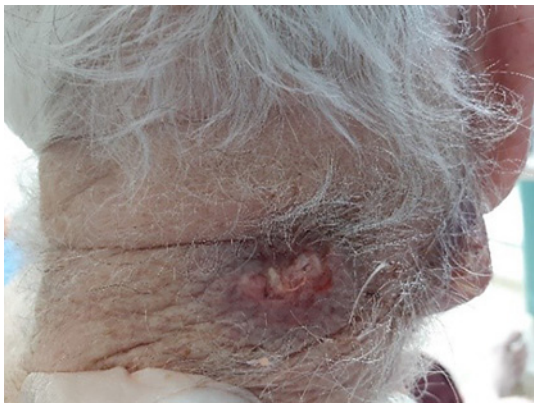

Fig. 12. Reduction in lesion size after 2 cycles of nivolumab.

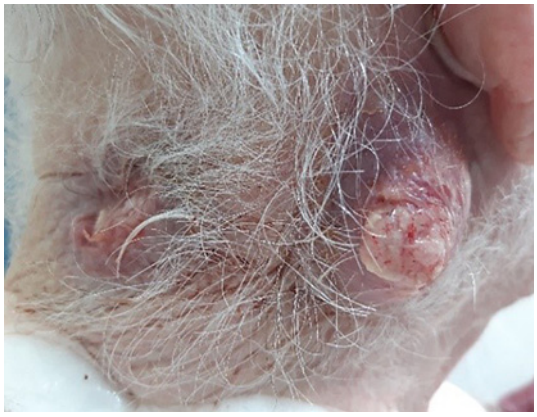

Fig. 13. Reduction in lesion size after 2 cycles of nivolumab.

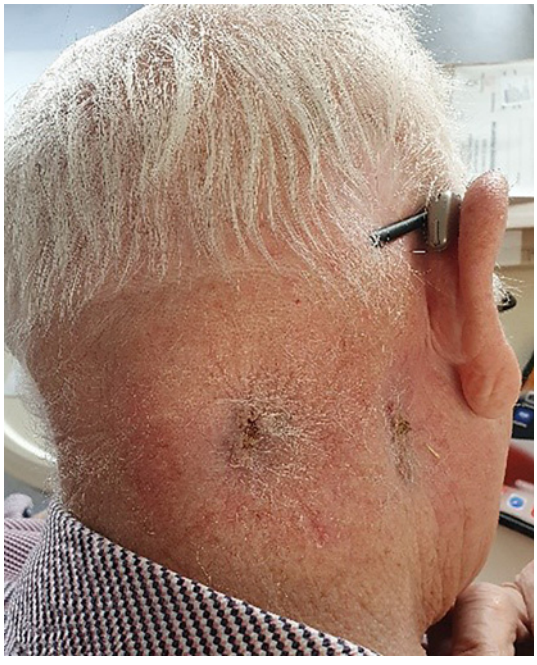

Fig. 14. Lesion size after cycle 8 nivolumab.

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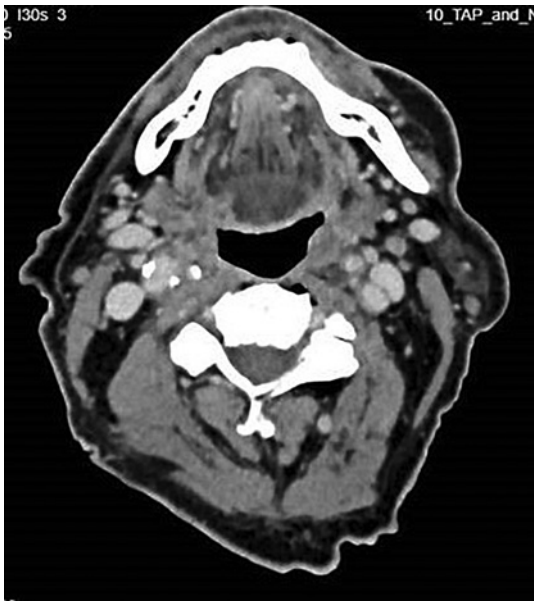

Fig. 15. Axial slice of contrast-enhanced CT neck post-cycle 6 nivolumab showing interval reduction in neck mass.

Table 2. Timeline of treatment received and response to nivolumab in case 2

Timeline	Treatment received
Nov 2022	Primary CSCC on right mastoid area, excised
Dec 2022	Multiple areas of CSCC on right posterior neck extending into supraclavicular fossa
Mar 2023	Commenced on nivolumab
Jun 2023	Restaging CT neck and TAP showed interval reduction in tumour size post-cycle 6 nivolumab

so regular skin and lymph node examination of the primary excision site and regional site should be performed every 3–6 months, depending on the initial stage at diagnosis and their medical history.

Conclusion

Cemiplimab and nivolumab have shown positive results as an effective treatment option for unresectable, recurrent, or metastatic CSCC. The immunotoxicities experienced in both of these cases were manageable, although one did lead to discontinuation. Furthermore, PD-1 expression during the course of the treatment of advanced or metastatic CSCC may potentially be used as a biomarker to monitor treatment response or disease progression. It is currently approved for use in the USA and Europe; however, in Ireland, it is available through compassionate access or individual hospital funding only. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533759).

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from both patients (cases 1 and 2) for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors declare no conflict of interest for the above study.

Funding Sources

The authors declare no funding or grant was received from any external agency for this study.

Author Contributions

Dr. Fei Ya Lai was responsible for the conception and design of manuscript, data review, collection, manuscript drafting, final approval, and agreement to be accountable for the work done as described. Dr. Rachel Clarke was involved in the review of data and methodology, interpretation, and final approval of manuscript. Dr. Patrick Cooper was responsible for reviewing radiological images taken during the course of treatment mentioned in the above report. Dr. John Stokes and Dr. Paula Calvert were responsible for supervising the analysis and interpretation of results.

Data Availability Statement

The authors confirm that the data supporting the findings are available in this article. Further enquiries can be directed to the corresponding author.

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