Clinical Oncology: Case Reports

Case Report

A SCITECHNOL JOURNAL

Pembrolizumab as a First Line Therapy in a Patient with Extensive Mucoepidermoid Salivary Gland Carcinoma: A Complete Clinical, Radiological And Pathological Response: A Very Specific Case

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Abstract

Background: The treatment options for patients with advanced Salivary Gland Cancers (SGCs) are limited. Results from recently published studies indicate a possible use for checkpoint inhibition in a subset of patients, but there are no established criteria for Programme Cell Death Ligand 1 (PD-L1) scoring in SGCs. The benefit of chemotherapies was reported to be minimal with a prognosis that remains poor in unresectable and high grade SGC.

Immunotherapies have shown remarkable success in various entities not limited to non-small cell lung cancer and malignant melanoma. Pembrolizumab, an anti-PD-1 antibody, has been proven to have strong anti-tumor activity in a variety of clinical studies.

Case Presentation: We report a unique case of advanced high grade mucoepidermoid carcinoma of the parotid salivary gland after Pembrolizumab treatment as a first line therapy.

Pembrolizumab treatment resulted in downstaging of the tumor which lead to its successful surgical resection with no facial nerve sacrifice and no serious side effects of the neoadjuvant treatment, and the final specimen pathology was free of tumor. A similar strategy that resulted in Complete Response (CR) radiologically and pathologically has never been mentioned before in these kind of tumors.

Conclusions: Pembrolizumab has demonstrated a promising antitumor activity in pretreated patients with high grade salivary gland mucoepidermoid carcinoma, and offered a clinically, radiological and pathological response with a meaningful therapeutic option. Further studies that move the treatment of Pembrolizumab to front-line are necessary. These studies should include the time and duration of the pharmacotherapy in relation to the needed time of surgery.

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Received: January 16, 2022, Manuscript No: COCR-21-51739; **Editor assigned:** January 19, 2022, PreQC No: P-51739; **Reviewed:** February 14, 2022; QC No: Q-51739; **Revised:** February 20, 2022, Manuscript No: R-51739; **Published:** February 27, 2022, DOI: 10.4172/cocr.5(2).218

Keywords

Pembrolizumab; Salivary Gland Cancers (SGCs) Immunotherapy; Complete Response (CR)

Introduction

Salivary Gland Carcinoma (SGC) is a rare tumor and represents ~6% of head and neck cancers [1]. Regardless of its histological subtype, curative treatment consists of a surgical resection with or without postoperative adjuvant radiation therapy [2-4] .

Mucoepidermoid Carcinoma (MEC) is a malignant tumor predominantly arising from the salivary glands; the minor glands preferentially give rise to MEC [5,6]. MEC is the most frequent malignant salivary gland tumor in children and adults6.

Although adjuvant treatment options like chemotherapy or radiation do not have a detectable impact on survival in highly aggressive subtypes like salivary duct carcinomas [7]. There is also no standard treatment or proven efficacy for patients with unresectable primaries/recurrences or patients with distant metastasis [8]. The benefit of chemotherapies like combinations of cisplatin, doxorubicin and cyclophosphamide was reported to be minimal with a prognosis that remains poor [2,9,10].

Immunotherapies have shown remarkable success in various entities not limited to non-small cell lung cancer and malignant melanoma. All these therapies share a similar mode of action directing the body's own immune system to dispose of tumor cells [11,12] .

Pembrolizumab is a fully humanized immunoglobulin G4/κ anti-PD-1 monoclonal antibody. Pembrolizumab has demonstrated robust antitumor activity and a favorable safety profile in multiple tumor types and is currently approved in over 60 countries for 1 or more advanced malignancies, including in the United States for recurrent or metastatic head and neck squamous cell carcinoma that progressed on or after platinum containing chemotherapy [13-15].

The recently published keynote-048 trial established a new standard in this setting with the introduction of immunotherapy, either alone or in combination with chemotherapy [16].

This article reports a unique case of unresectable advanced high grade mucoepidermoid carcinoma of the salivary gland with complete response after Pembrolizumab treatment as a first line therapy. A similar strategy has never been tried in high grade salivary gland tumors, and complete radiological and pathological responses have never been reported before in this kind of tumors. This treatment resulted in downstaging of the tumor and led to its successful surgical resection.

Case Presentation

A 68-year-old male, diabetic with a forty pack-year smoking history presented with an enlarging left, slightly tender, rapidly progressive swelling of the left parotid gland during the previous 6 months before our first examination. The patient was referred to head and neck clinic, Department of Otolaryngology Head and Neck

Surgery, Ziv Medical Center in Safed, in the north of Israel.

Physical examination showed a firm, immobile, slightly tender, 3 cm × 3 cm left parotid mass with overlying skin change (Figure 1), with multiple hard, immobile lymph nodes, 3 cm × 2 cm, at level II,III,V of the left neck, the remainder of the head and neck examination was unremarkable. Flexible nasendoscopy findings of the nasopharynx, oropharynx, and larynx were unremarkable.

Fine Needle Aspiration (FNA) of the left parotid mass was consistent with positive malignant cells for high grade mucoepidermoid carcinoma with mitosis.

Contrast-enhanced Magnetic Resonance Imaging (MRI) revealed a lobulated, irregular mass, 37 mm × 39 mm × 47 mm located in the posteroinferior segment of the superficial and deep lobe in the left parotid gland, with areas of extensive central necrosis, septation, and peripheral wall enhancement contiguous with the anterior portion of external auditory canal and SCM muscle with subcutaneous tissue and skin involvement, several nodules in the left infraparotid area and level II were calcified (Figure 2).

The 18F-FDG PET/CT revealed hypermetabolic activity within the mass in the left parotid gland with involvement of the skin, SCM muscle and several nodules in the left infraparotid area and level II,III in the left neck (Figure 3). The final diagnosis was clinical stage IV (T4aN2bM0).

The patient was considered as high-grade MECs which progressed rapidly and caused pain, soft tissue invasion; these MECs are associated with poor overall survival, which approaches 40% to 50% at 5 years, and with an increased risk for locoregional and distant failures [17-19].

The recommended therapy for high-grade MECs includes surgical resection with selective neck dissection followed by adjuvant radiotherapy [20].

In our case, the high morbidity and mortality associated with the need of extensive surgical resection with free flap reconstruction and the massive loss of tissue with possible facial nerve sacrifice, in addition to increased risk for locoregional and distant failures led us to think about neoadjuvant treatment.

Pembrolizumab monotherapy was generally well tolerated in advanced Salivary Gland Carcinoma (SGC), with a safety profile that reflects previous experience of pembrolizumab in patients with advanced cancers [21].

Treatment plan was made by a multidisciplinary team and after multiple discussions with the goal of maximizing survival with preservation of form and function. The patient received pembrolizumab intravenously at 200 mg every 2 weeks, with a good compliance. From September 2021 to November 2021, he underwent 2 cycles of pembrolizumab with no side effects.

The MRI scan after 3 cycles revealed a significant decrease in the tumor or even its disappearance, and on examination WHEN? The patient had attained a complete remission in the clinic examination (Figure 4, Figure 5).

Restaging with 18FDG PET-CT at 6 weeks after completion of immunologic treatment demonstrated a full resolution of the parotid gland metabolic activity. In the left neck, the nodal status had generally improved with no signs of hypermetabolic activity. High metabolic uptake was not seen elsewhere (Figure 6).

As a precaution, left parotidectomy and unilateral neck dissection levels I, II, III, IV were recommended for locoregional control and

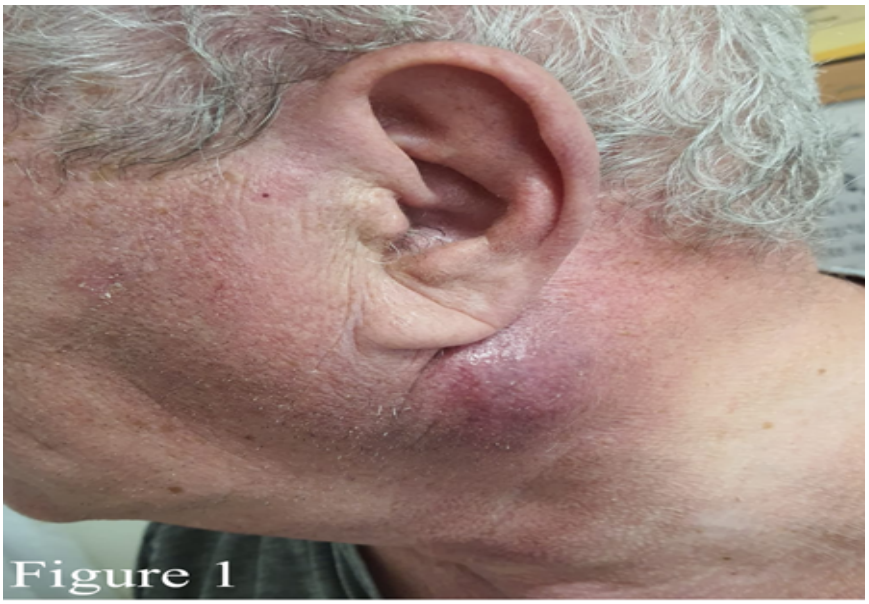

Figure 1: Firm, immobile, slightly tender, 3 cm × 3 cm left parotid mass with overlying skin changes.

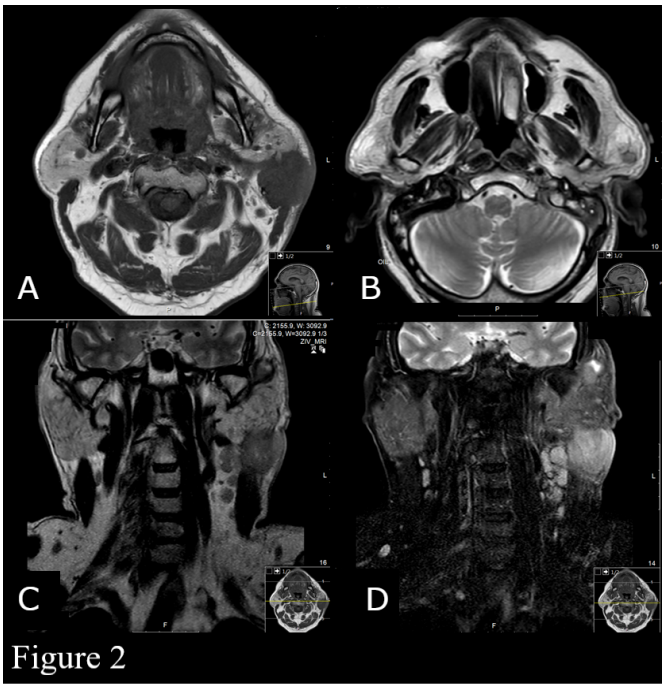

Figure 2: A) MRI T1 lobulated irregular mass, located in the posteroinferior segment of the superfacial lobe in the left parotid gland; B) MRI T2 with areas of extensive central necrosis, septation; C) several suspected lymph nodule in the left infraparotid area and level II and III; D) peripheral wall enhancement.

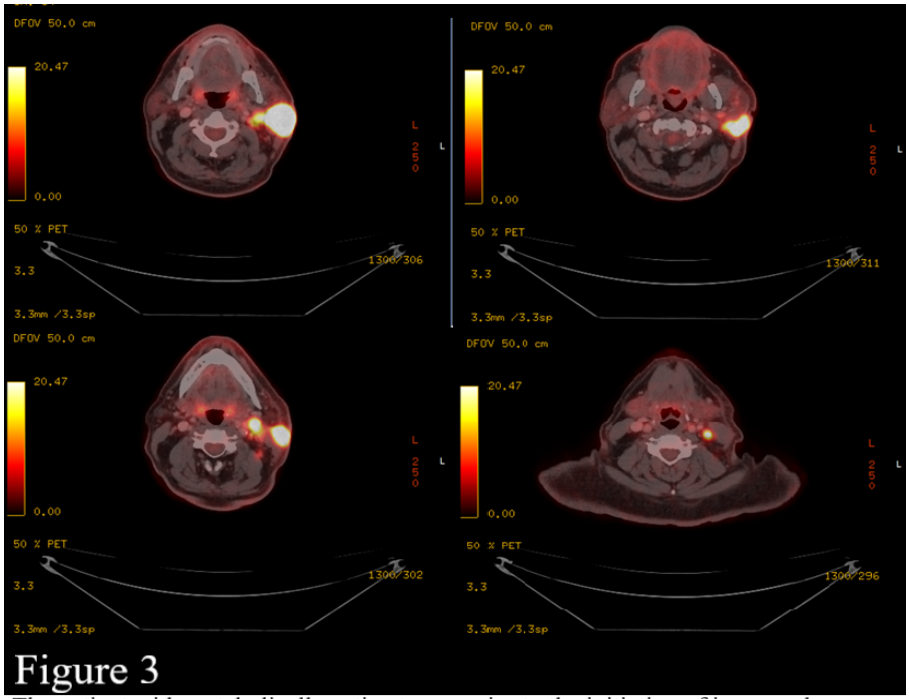

Figure 3: The patient with metabolically active prior to the initiation of immunotherapy with Pembrolizumab.

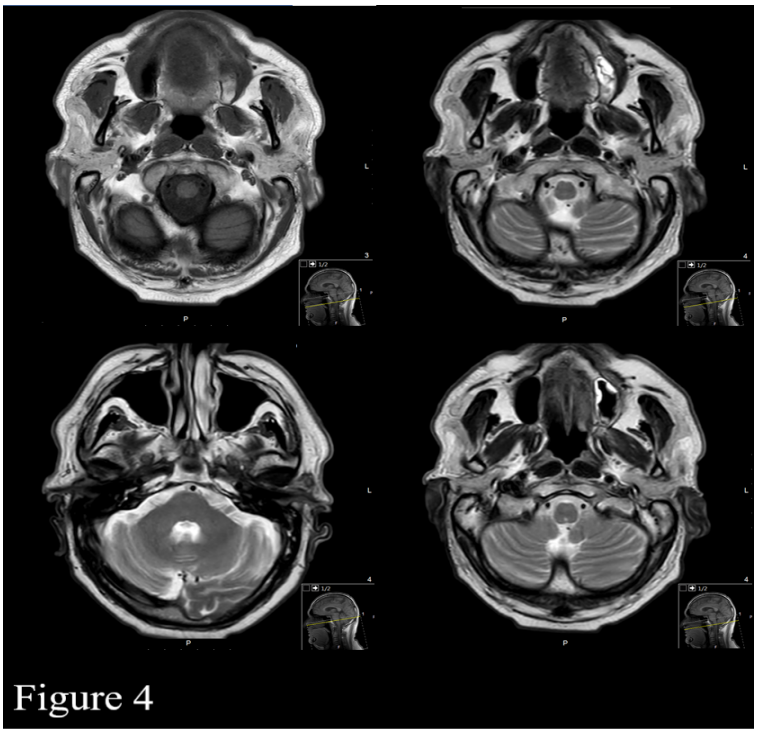

Figure 4: MRI T1 and T2 - after 2 cycles of the neoadjuvant treatment shows significant decrease in the tumor or even its disappearance attained a complete remission.

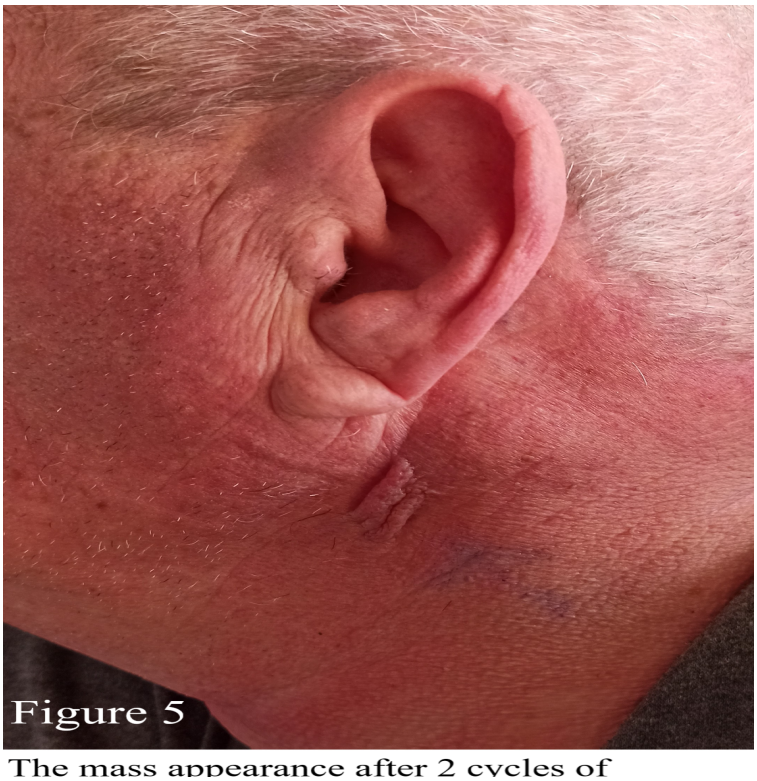

Figure 5: The mass appearance after 2 cycles of neoadjuvant treatment.

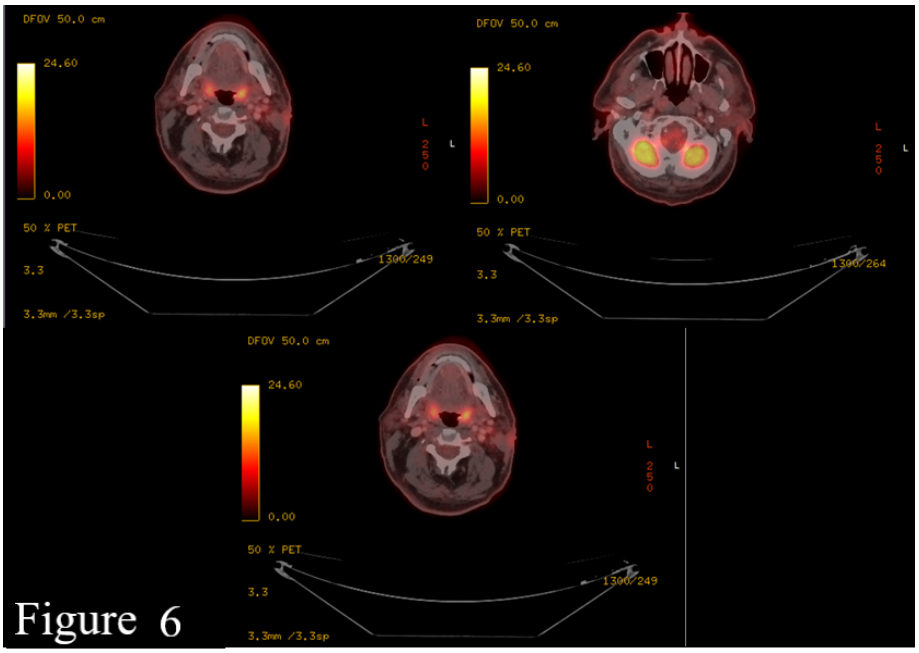

Figure 6: A complete metabolic response already 8 weeks after immunotherapy of Pembrolizumab initiation despite remaining morphological masses on CT.

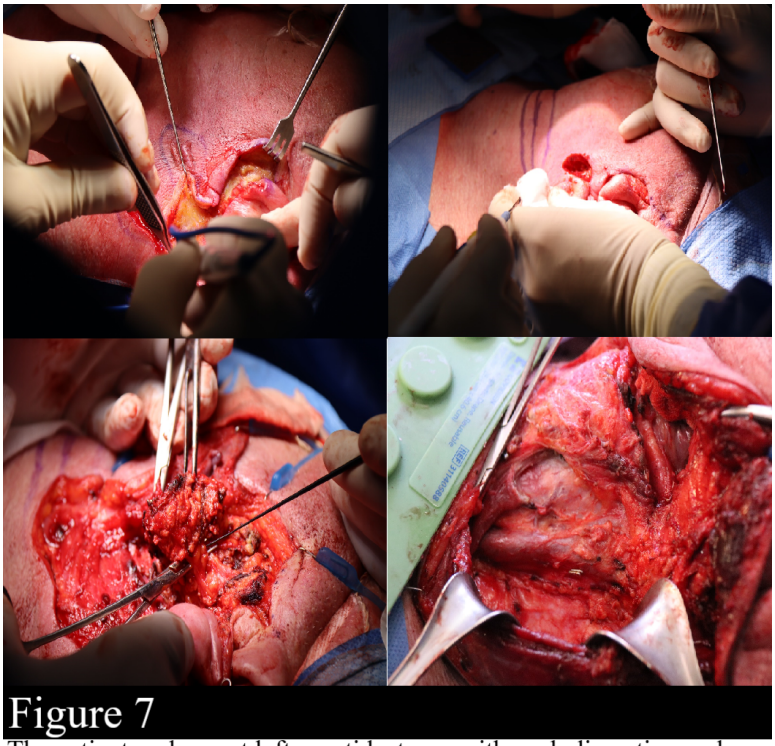

Figure 7: The patient underwent left parotidectomy with neck dissection and excision of the involved skin.

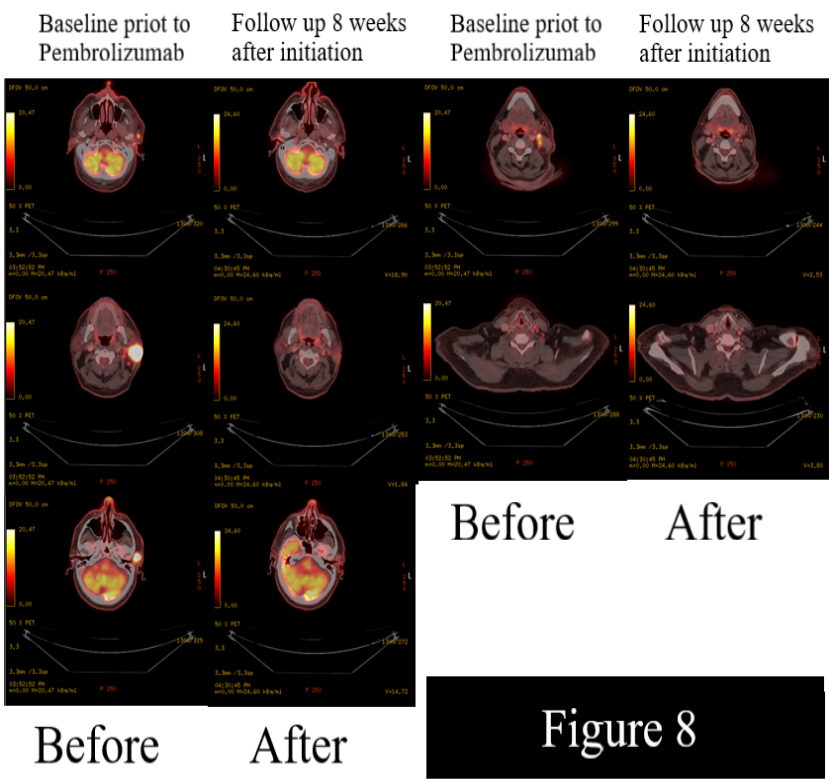

Figure 8: 18 FDG PET-CT scans

because of remaining morphological masses on CT (Figure 7). All the 18 FDG PET-CT scans performed are summarized in (Figure 8).

Final pathological results showed no evidence of carcinoma neither in the parotid gland nor in the neck lymph nodes and had free margins.The patient has continued to be supervised with CT scans and serum tumor marker measurements every 3 or 4 months and is still in complete remission at this time.

Discussion

This is the first report that describes complete resolution of high grade malignant salivary gland mucoepidermoid carcinoma with Pembrolizumab as a “first line” therapy treatment.

Cohen et al. [21] reported the phase Ib KEYNOTE-28 experience using single-agent pembrolizumab 10 mg/kg once every 2 weeks in 38 PDL1 expressing recurrent-metastatic salivary gland carcinomas. This study did not report evidence of progression before participation, and the majority of enrolled participants had adenocarcinomas. Among 38 patients enrolled, three had a Partial Response (PR) with an overall response rate of 12% with a 3-month median duration of response. There were no complete remission responses.

There is no gold standard for management of advanced SGC, and existing therapies generally lack significant clinical benefit. Available data supporting use of traditional cytotoxic chemotherapy are based on small studies, many of which were conducted before contemporary analytical concepts (e.g, RECIST) [22].

The prospective experience with the anti PD1 checkpoint inhibitors in salivary gland carcinoma consists of small phase I and II clinical trials, again with heterogenous histologies and variations in design and eligibility for such treatment.

Although pembrolizumab carries a primary site agnostic US Food and Drug Administration approval for mismatch repair–deficient tumors, it is important to note that this was based on a nine-patient cohort of non-colorectal cancer patients, none of whom had salivary gland malignancies [23].

The role of Tumor Mutation Burden (TMB) is unclear in SGCs. The subgroup analysis by TMB from the KEYNOTE-158 trial led to the approval of pembrolizumab for patients with TMB >10 mut/Mb as an agnostic treatment. There were three patients with salivary histology and high TMB, one of whom achieved partial response [23].

Although the current data from salivary gland malignancies trials are limited, our result in using Pembrolizumab as a first line agent in advanced high grade mucoepidermoid carcinoma suggests that this treatment remains a promising cancer therapy .

Further research studies which will evaluate the treatment of Pembrolizumab to front-line, maintenance settings, and trials of combinations with chemotherapy, radiotherapy or other immune checkpoints are very necessary.

Conclusion

In conclusion, Pembrolizumab has demonstrated a promising antitumor activity in pre-treated patients with high grade salivary gland mucoepidermoid carcinoma, and offered a clinically,

radiological and pathological response with a meaningful therapeutic option.

Further studies that move the treatment of Pembrolizumab to front-line, maintenance settings and combinations with other treatment methods are necessary. These studies should include the time and duration of the pharmacotherapy in relation to the needed time of surgery. Side effects of the drugs should also be followed as well as patient compliance.

Acknowledgment

We would like to thank the entire department of Otolaryngology head and neck surgery and Oncology Department for their help and support.

Conflicts of interest statement and funding:

None

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