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Review

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Immunotherapy in head and neck tumors: new options in advanced disease and beyond

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Abstract

This article aims to review the role of immunotherapy in tumors of the head and neck, focusing primarily on US Food and Drug Administration (FDA) approved checkpoint inhibitors in squamous cell histology. The data showing superiority of checkpoint inhibitors over cytotoxic chemotherapy that led to FDA approval of two agents (Keytruda® Merck and Opdivo® Bristol-Myers-Squibb) in the recurrent and metastatic setting will be reviewed in detail, as well as summaries of ongoing trials for checkpoint inhibitor and combination therapies in both the curative and metastatic settings. Upcoming positive data regarding immunotherapy use and other innovative immune based therapies in rare histologies such as nasopharyngeal carcinoma and salivary gland tumors will also be reviewed. Additionally, data regarding management of immunotherapy side effects will be discussed and a brief review of recently published guidelines will be provided. Lastly, we will address risks to special patient populations that need further study.

Keywords: Head and neck cancer, immunotherapy, checkpoint inhibitor, pembrolizumab, nivolumab

INTRODUCTION

Head and neck cancers are a heterogeneous and diverse group of tumors with unique challenges related to the anatomic location of tumors, complex and often rare histologies, and potential loss of function and disfigurement caused by treatment. Historically, systemic therapies have been mainly limited to advanced stages where they can be used in combination with radiation for definitive treatment and in the palliative setting for non-curable recurrent and metastatic disease. Cisplatin with concurrent radiation has developed as an effective technique to preserve organ function in advanced but potentially curable tumors[1,2]. Debate continues as to the role of neoadjuvant chemotherapy in locally advanced head and neck squamous cell

tumors (LA-HNSCC); individual trials have shown benefit but large meta-analyses show no overall survival benefit[1,3,4]. Cytotoxic therapy plays a large role in palliation in the recurrent and metastatic setting, where options including multi-drug regimens may be toxic with modest benefit or single agent therapy with small benefit[5-7]. Overall survival for recurrent and metastatic head and neck squamous cell carcinoma (RM HNSCC) remains generally poor at less than 1 year with current cytotoxic therapeutic options[5-7]. The most commonly used first line chemotherapeutic regimen of cisplatin or carboplatin/5-FU/Cetuximab (Eribitux®, Eli Lilly) had a reported overall survival (OS) benefit of 10.1 months when the data was first published in 2008, and is the only one to have a level 1 recommendation from the National Comprehensive Cancer Network (NCCN)[6,8]. Cetuximab as a single agent use in second line has a 13% response rate and 7.5 month OS[9].

In the last several years, a new class of systemic therapies have been developed that harness the body's immune responses in fighting tumors. Classified broadly as immunotherapy, this is a heterogeneous group of therapies that target specific immune pathways to amplify the body's natural tumor fighting abilities. Vaccine therapies are also in development, and have been approved in other malignancies such as melanoma[10]. Another vaccine target is Epstein-Barr Virus (EBV) related malignancies, such as nasopharyngeal carcinoma. These are under development with ongoing trials looking at efficacy and safety.

One of the most successful groups of therapies to emerge is a class of drugs that target the programmed death-1/programmed death ligand-1 (PD-1 and PD-L1) pathway, as well as a co-regulatory pathway mediated through cytotoxic T-lymphocyte-associated protein 4 (CTLA 4). This pathway has been named the "checkpoint pathway" with agents acting on these proteins generally referred to as checkpoint inhibitors. Ipilumumab (Yervoy®, Bristol-Myers Squibb) is the first US Food and Drug Administration (FDA) approved CTLA-4 inhibitor which came to the market in 2011 for treatment of melanoma; the first PD-1 inhibitor, pembrolizumab (Keytruda®, Merck) was approved for melanoma in September 2014, and nivolumab (Opdivo®, Bristol-Myers Squibb) gained its first approval in December 2014, also in melanoma. Since then, these agents have gained approval in multiple tumor types and multiple settings, including head and neck squamous cell carcinoma.

This article will review the indications for checkpoint inhibitors in head and neck tumors, examining the data and discussing adverse events and their management, as well as review data on upcoming therapies.

PEMBROLIZUMAB

Pembrolizumab (Keytruda®) is a monoclonal IgG4 isotype antibody that binds to the programmed death-1 (PD-1) receptor on T-cells, preventing them from binding programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2) ligands expressed on tumor cells[11]. The first study done with pembrolizumab in recurrent or metastatic HNSCC is the phase I KEYNOTE 012, a multi-cohort trial looking at multiple tumor types, including HNSCC. It was conducted as a two-part safety and efficacy trial, with the primary outcome in both phases being safety and overall response rate (ORR). In the first phase (1a), 60 patients all with high PD-L1 expression (> 1%) were enrolled; 23 were human papillomavirus (HPV) positive, 37 HPV negative. Pembrolizumab was dosed at 10 mg/kg every 2 weeks. 17% of patients had grade 3 or 4 adverse events, and the ORR was 18%, further broken down as 25% in HPV positive and 14% in HPV negative patients[12].

In the second phase expansion cohort (1b), 132 patients were enrolled, this time regardless of PD-L1 expression[13]. Fifty-seven percent of these patients had received at least 2 prior lines of therapy. Primary outcomes were again safety and ORR; secondary outcomes were evaluated in this portion of the trial and included progression free survival (PFS), OS, and relationship of outcome to PD-L1 expression. In this cohort, the dose of pembrolizumab was changed to 200 mg every 3 weeks. ORR was again 18% and grade 3 or 4 adverse events dropped to 9%. PFS was 2 months, and OS was 8 months. In HPV positive patients, the ORR was 32%.

This led to a phase II study in HNSCC with pembrolizumab, KEYNOTE 055[14]. In this single arm study, patients were enrolled who had previously failed platinum and cetuximab therapy. A total of 171 patients were enrolled regardless of PD-L1 status and treated with the set dose of 200 mg every 3 weeks. The primary endpoints were safety and ORR. Twenty-two percent of these patients were HPV positive, and though not required for enrollment, 82% had > 1% PD-L1 positivity. Seventy-five percent of patients had received at least 2 prior lines of therapy. ORR was 16%, and grade 3 or 4 adverse events were 15%. The PFS was 2.1 months and OS 8 months.

Based on this data, the FDA granted accelerated approval to pembrolizumab on 5 August 2016. This approval is contingent upon completing a phase III study, which is the KEYNOTE 040 trial presented at the European Society for Medical Oncology (ESMO) annual meeting in September 2017[15]; the data has not yet been formally published as of this writing. In this prospective study, 495 platinum-treated patients were randomized 1:1 to pembrolizumab 200 mg every 3 weeks or standard therapy with docetaxel, methotrexate, or cetuximab. The primary endpoint was median OS in the intent to treat population; secondary endpoints included median PFS, ORR, PFS and OS in patients withPD-L1 combined positive score ≥ 1% (slightly different to the previously used definition of PD-L1 expression). A pre-specified efficacy boundary for OS in the intention to treat (ITT) population was set at one-sided $P = 0.0175$. The overall survival in pembrolizumab treated patients was 8.4 *vs.* 7.1 months in the standard therapy group, hazard ratio (HR) 0.81 (CI 0.66-0.99, $P = 0.0204$); this did not meet the pre-specified OS benefit, but did provide 19% reduction in the risk of death. PFS was 2.1 and 2.3 months respectively. Incidence of grade 3 or greater adverse events was 13.4% in the pembrolizumab group and 36.3% in the standard therapy group. Although the pre-specified statistical benefit was not met, the data is consistent with the phase 1 and 2 results, as is the toxicity profile.

PD-L1 status was again re-examined in this study, looking at two separate cut-offs not well described in the abstract: PD-L1 based on tumor proportion score, with the cut off being either greater than or less than 50%, and PD-L1 combined positive score ≥ 1%. There did appear to be some predictive benefit to these varying markers of expression, with PD-L1-TPS ≥ 50% suggesting an OS benefit of 11.6 *vs.* 7.9 months. It is unknown if this data will ultimately alter the FDA labeling for pembrolizumab in HNSCC to include PD-L1 expression testing similar to non-small cell lung cancer.

NIVOLUMAB

Nivolumab (Opdivo®) acts via a similar mechanism to pembrolizumab: it is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response[16]. It received FDA approval for advanced HNSCC in November 2016 based on the randomized phase III CHECKMATE 141 trial[17]. The trial randomized 361 patients in a 2:1 fashion to nivolumab 3 mg/kg or investigator's choice of methotrexate, docetaxel, or cetuximab. Primary endpoint in this trial was overall survival, with secondary endpoints including PFS, ORR, safety, and quality of life. Fifty-five percent of patients had at least two lines of prior systemic therapy. P16 expression was not available for every patient who participated, but in the nivolumab group 26% of 113 patients tested were positive; in the standard therapy group 24% of 65 patients were positive. Median OS was 7.5 months in nivolumab group *vs.* 5.1 months in the standard group ($P = 0.01$, HR 0.70). Interestingly, PFS was non-significant between the two groups, with nivolumab PFS being 2 months and standard therapy 2.3 months (HR 0.70, $P = 0.32$). ORR for nivolumab was 13.3% *vs.* 5.8% in standard therapy. However, looking at the median PFS and median OS curves, there is a late separation consistent with more durable responses to nivolumab therapy. Toxicity in these patients (grade 3 or higher) was 13.1% *vs.* 35.1%.

PD-L1 expression was not required for the CHECKMATE 141 trial, but a pre-specified analysis looked at the degree of expression to determine if there was any clear correlation. PD-L1 expression could be evaluated in 260 of the 361 patients; significant expression (considered ≥ 1%) was found in 57.3% of these patients.

Table 1. Summary of the key trial data leading to Food and Drug Administration approval or ongoing phase II/III trials

Study	Therapy	Phase	Number of patients	ORR	PFS	OS
KEYNOTE-055	Pembrolizumab	II	171	16%	2.1 months	8 months
KEYNOTE-040	Pembrolizumab	III	495	14.6%	2.1 months	8.4 months
CHECKMATE-141	Nivolumab	III	361	13.3%	2 months	7.5 months
HAWK	Durvalumab	II	112	13.5%	2.3 months	N/A
N/A	Atezolizumab	Ia	32	22%	N/A	N/A

ORR: overall response rate; PFS: progression free survival; OS: overall survival

P16 status was also evaluated, independently and in conjunction with PD-L1 expression. For patients with significant PD-L1 expression, the hazard ratio for death was 0.55 (95% CI; 0.36 to 0.83); in PD-L1 negative patients, it was 0.89 (95% CI; 0.54 to 1.45, $P = 0.17$). Patients with PD-L1 of ≥ 5% and ≥ 10% were also evaluated and had similar hazard ratios to those with PD-L1 ≥ 1%.

Similarly, a post hoc analysis of P16 status was done. One hundred and seventy-eight patients were positive; and overall survival was evaluated with regards to this status. Patients were found to respond to nivolumab regardless of P16 positivity. In P16 positive patients, median OS was 9.1 months for nivolumab *vs.* 4.4 months for standard therapy. In P16 negative patients, median OS was 7.5 *vs.* 5.8 months (HR 0.73, $P = 0.55$). This confirmed what has been previously demonstrated; that patients who are P16 tend to do better, but this is not necessarily a predictive biomarker for response to treatment.

Lastly, the investigators stratified patients by both PD-L1 expression and P16 expression. All the hazard ratios were < 1 but none were statistically significant based on the number of patients. Both PD-L1 expression and P16 expression are associated with better outcomes confirming their prognostic value, however even PD-L1 low and P16 negative patients had partial and complete responses to therapy, indicating these were not predictive biomarkers in this study.

Taken together, these trials with pembrolizumab and nivolumab demonstrate that checkpoint inhibitor therapy in the second line setting has improved overall survival at 7.5-8.4 months than 5.7-7.1 months with cytotoxic therapy, with manageable toxicity profiles. These response rates may be higher with prolonged OS for patients with high PD-L1 expression and HPV positive tumors [Table 1].

UPCOMING RESEARCH IN HNSCC

Other checkpoint inhibitors are being actively studied in RM HNSCC. Phase II durvalumab (Infinzi®, AstraZeneca) data from the HAWK trial was presented at ESMO in 2017[18], with similar results in terms of response rate and safety to pembrolizumab and nivolumab. Durvalumab is a monoclonal antibody inhibiting PD-L1, and in this study patients had progressed through first line platinum therapy and required 25% PD-L1 expression. One hundred and twelve patients were recruited, and ORR was 13.5% with HPV positive tumors showing ORR of 26.5% and HPV- tumors showing ORR of 7.9%. Median PFS was 2.3 months; median OS data was not mature. Interestingly, this is one of the first trials to show differential response to therapy based on PD-L1 expression. Based on this data, durvalumab is in phase III studies as single agent therapy for patients who progress after platinum therapy.

Atezolizumab (Tecentriq® Genentech), another monoclonal anti-PD-L1 antibody, is also under study for RM HNSCC with phase 1a safety results announced at ESMO as well. In a safety analysis of 32 patients, 9% had grade 3 or greater adverse events, and ORR was promising at 22%. Phase II and III studies are ongoing[19].

Table 1 summarizes some of the key immunotherapy trial data to date that have led to FDA approval or ongoing phase II/III trials. Table 2 summarizes several active trials that are recruiting or have finished accrual

Table 2. Selection of trials in head and neck squamous cell carcinoma active as of 29 March 2018

Agent	Phase	Name	Setting	NCT
Atezolizumab	III	A study of atezolizumab (anti-PD-L1 antibody) as adjuvant therapy after definitive local therapy in patients with high risk locally advanced squamous cell carcinoma of the head and neck	Adjuvant	NCT03452137
Atezolizumab, nivolumab, pembrolizomab	II	Priming immunotherapy with advanced disease with radiation	Relapsed	NCT03313804
Avelumab	III	Randomized trial of avelumab-cetuximab-radiotherapy *vs*. standard of care (SoC) in LA-HNSCC (REACH)	Curative	NCT02999087
Avelumab	III	Study to compare avelumab in combination with SoC chemoradiotherapy (CRT) *vs*. SoC CRT for definitive treatment in patients with locally advanced head and neck squamous cell tumors (LA-HNSCC) (javelin head and neck 100)	Curative	NCT02952586
Avelumab	I	Bioimmunotherapy (cetuximab/radiation/avelumab)	Curative	NCT02938273
Avelumab	II	A study of avelumab in combination with other cancer immunotherapies in advanced malignancies (javelin medley)	Advanced/ metastatic	NCT02554812
Durvalumab	II	Carboplatin, nab-paclitaxel, durvalumab before surgery and adjuvant therapy in HNSCC	Curative	NCT03174275
Durvalumab	II	Durvalumab before surgery in treating patients with oral cavity or oropharynx cancer	Curative	NCT02827838
Durvalumab, Tremelimumab	I/II	A trial of durvalumab and tremelimumab in combination with stereotactic body radiation (SBRT) in patients with metastatic cancer (ABBIMUNE)	Advanced/ metastatic	NCT03212469
Ipilumumab	I	Immunotherapy study of evofosfamide in combination with ipilumumab	Advanced/ metastatic	NCT03098160
Nivolumab	I	Safety testing of adding nivolumab to chemotherapy in patients with intermediate and high-risk local-regionally advanced head and neck cancer (EAGLE)	Locally advanced	NCT02764593
Nivolumab, Pembrolizumab	II	Reirradiation with pembrolizumab in locoregional inoperable recurrence or second primary squamous cell cancer CA of the head and neck	Recurrent/ metastatic	NCT02289209
Nivolumab	II	Nivolumab, carboplatin, and paclitaxel in treating patients with stage III-IV head and neck squamous cell carcinoma that can be removed by surgery	Neoadjuvant	NCT03342911
Nivolumab	III	Nivolumab or nivolumab plus cisplatin, in combination with radiotherapy in patients with cisplatin-ineligible or eligible locally advanced squamous cell head and neck cancer	Locally advanced	NCT03349710
Nivolumab, Ipilimumab	III	Study of nivolumab in combination with ipilimumab compared to the standard of care (extreme study regimen) as first line treatment in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (CHECKMATE 651)	Recurrent/ metastatic	NCT02741570
Pembrolizumab	II	Immunotherapy with MK-3475 in surgically resectable HNSCC	Neoadjuvant	NCT02296684
Pembrolizumab	III	Study of pembrolizumab (MK-3475) or placebo with chemoradiation in participants with locally advanced head and neck squamous cell carcinoma (MK-3475/ KEYNOTE-412)	Curative	NCT03040999
Pembrolizumab	II	Efficacy study of pembrolizumab in relapsed, locally recurrent squamous cell cancer of the head and neck	Relapsed	NCT02769520
Pembrolizumab	III	A study of pembrolizumab (MK-3475) for first line treatment of recurrent or metastatic squamous cell cancer of the head and neck (MK-3475-048/ KEYNOTE-048)	Recurrent/ metastatic	NCT02358031
Tremelimumab, MEDI4736	III	Study of MEDI4736 monotherapy and in combination with tremelimuab *vs*. SoC therapy in patients with head and neck cancer	Recurrent/ metastatic	NCT02369874
Tremelimumab, MEDI4736	III	Phase III open label study of MEDI 4376 with/without tremelimumab *vs*. SoC in recurrent/metastatic head and neck cancer	Recurrent/ metastatic	NCT02551159

Table 3. Trials for nasopharyngeal carcinoma and salivary gland tumors with immunotherapies

Histology	Trial name/NCT	Therapy	Phase	No. patients	Results
NPC	KEYNOTE 028	Pembrolizumab	IB	27	PFS 6.5 months, 26% partial response, 52% stable disease[22]
NPC	NCT02339558	Nivolumab	II	40	PR 19%, SD 33%, median overall survival (MOS) not reached[23]
NPC	KEYNOTE 122 (NCT02611960)	Pembrolizumab	III	230	Recruiting
NPC	NCT02605967	PDR001 (anti-PD-1 agent)	II	114	Recruiting
NPC	NCT01800071, NCT01094405	MVA EBNA1/LMP2	I/II	22 and 25	Completed; recruiting
Salivary gland	KEYNOTE 028	Pembrolizumab	IB	26	ORR 12%, m duration of response (DOR) 4 months[24]
Salivary gland	NCT03132038	Nivolumab	II	92	Recruiting
Salivary gland	NCT03172624, NCT03146650	Ipilimumab, nivolumab	II, II	64, 63	Recruiting
Salivary gland	KEYNOTE 158 (NCT02628067)	Pembrolizumab	II	N/A	Recruiting
Salivary gland	NCT03360890	Pembrolizumab, docetaxel	II	46	Recruiting

and are awaiting results. This list is a cross-section of various studies, but is not a complete representation due to the large number of ongoing trials. Many are evaluating agents already approved for HNSCC or other tumors in the neoadjuvant or adjuvant setting, or in combination with other agents, either cytotoxic or other immunotherapy agents.

Non-squamous cell head and neck cancers

Immunotherapy is being actively explored in non-squamous histology tumors of the head and neck. Both nasopharyngeal carcinoma and salivary gland carcinomas express PD-L1, and this has been independently associated with worse disease free survival in these tumor types[20,21]. There are published early phase I and II results as well as ongoing trials looking at various targets, both with checkpoint inhibitors and vaccine therapy. The preliminary results and ongoing trials are summarized in Table 3.

Role of PD-L1 testing

PD-L1 expression testing is not currently required for either FDA approved therapy, nivolumab or pembrolizumab in HNSCC, unlike some other tumor types. As reviewed previously, expression was included in the phase II and III trials with both agents but did not show a clear correlation between activity and response rates. There are several possible theories as to why this may be the case; some of it may be rooted in the assays used for testing themselves. There are at least 4 commercially available immunohistochemistry (IHC) assays, each used with a different checkpoint inhibitor to evaluate PD-L1 expression. Dako 22C3 (Agilent) was used in the KEYNOTE trials with pembrolizumab; Dako 28-8 (also IHC based) used in the CHECKMATE trials with nivolumab. Roche produces the other two available assays; Ventana SP142 is used with atezolizumab, and Ventana SP263 with durvalumab. Comparisons of these assays by testing the same specimen have yielded statistically significant differences in results; this may be related to the different cutoff values for positivity (> 1% *vs*. 50%)[25,26]. Most importantly, there does not appear to be a predictive correlation in many tumor types, head and neck tumors included, as patients with negative results can respond to therapy. One possible reason for this could be related to a co-regulatory pathway called programmed cell death ligand 2 (PDL2): data published in June 2017 looked at PDL2 expression in patients with HNSCC[27]. Even in patients who were PD-L1 negative, PDL2 positivity correlated with a statistically significant response to pembrolizumab therapy. Response rates were highest in patients who expressed both receptors. PD-L1 expression in tumor cells *vs*. tumor infiltrating lymphocytes (TILs) is also felt to be an important factor in interpreting response rates of tumors. Active research is ongoing looking at the prognostic implications, the role in predicting response to cytotoxic therapy, and the role in predicting response to checkpoint inhibitor therapy.

Adverse events and high risk patient populations

The immune related adverse events (irAEs) of immunotherapies are important due to their unique presentation and management compared to cytotoxic therapies. Due to the mechanism of "unleashing" the immune system via up-regulation of T-cell activity, most toxicities are immune mediated and treated with steroids and immune modulators. The unique mechanism of action of these drugs also raises concerns about their use in certain patient populations as well, who may be at increased risk for adverse events. In general toxicity rates are lower with immunotherapy in RM HNSCC; in most of the published trials, grade 3-4 adverse events range from 9%-18%[12-15,17] by comparison, the standard therapy arm in CHECKMATE 141 had a grade 3-4 reaction rate of 35%, more consistent with what is seen in clinical practice with traditional therapies.

The most common adverse events are usually mild and include fatigue, nausea, rash, and decreased appetite. Inflammatory processes such as colitis and pneumonitis are amongst the more common serious reactions; rarely, hepatitis, cardiomyopathy, autoimmune cytopenias, and nephritis have been reported. Endocrinopathies are also a recognized adverse event from these therapies, with hypothyroid the most common, necessitating routine monitoring. Hyponatremia, hypophysitis, hyperglycemia, and even new development of type 1 diabetes have all been reported with varying severities with the various checkpoint inhibitors.

Management of these reactions varies according to symptom and severity. Both the American Society for Clinical Oncology (ASCO) and the Society for Immunotherapy of Cancer (SITC) have created consensus practice guidelines to guide treatment, and have similar recommendations[28,29]. Grade 1 reactions can often be managed symptomatically with supportive care; for grade 2, therapy should be held and prednisone or equivalent started at 0.5-1 mg/kg, with either dose escalation or rapid taper depending on the patient's response. Therapy can be resumed when the reaction is ≤ grade 1 and the patient is off steroids. Grade 3 and 4 reactions necessitate stopping therapy and starting prednisone or equivalent at 1-2 mg/kg; once the patient responds, a slow taper can be done over 4-6 weeks, with appropriate GI and infectious prophylaxis depending on duration of steroid treatment. Generally, therapy can be resumed after resolution of symptoms to ≤ grade 1, except for grade 4 reactions where immunotherapy should be permanently discontinued. In patients with severe colitis that does not respond to steroids alone, the addition of infliximab, an anti-TNFa antibody, has improved symptoms and can be weaned off steroids faster[30].

Endocrinopathies require management related to the specific derangement; holding immunotherapy is not recommended unless the reaction is grade 3 or greater. The most common endocrinopathy that patients develop is hypothyroidism necessitating replacement therapy, though hyperthyroidism and thyroiditis can occur. If hypophysitis develops, patients should be screened for all possible complications including hypogonadism, hypothyroidism, and hypoadrenergic complications. In hyperglycemia, insulin therapy is generally preferred as these patients can develop type I diabetes and diabetic ketoacidosis; if these have been ruled out, oral hyperglycemic therapy can be considered. Referral to endocrinology for co-management is important in these patients to minimize long term impacts of these toxicities, and in some situations patients can be optimized and allowed to continue on immunotherapy if they are responding well, even if the reaction was initially grade 4.

Certain patient populations appear to be at increased risk for adverse events with the use of checkpoint inhibitors. Others may require further study of the impact these therapies could have. Immunotherapy adverse reactions mimic autoimmune phenomena, raising the question of how patients with pre-existing autoimmune diseases may respond. There is retrospective data examining patients with these conditions who go on to receive immunotherapy, especially with ipilumumab and melanoma. In these studies, exacerbations of autoimmune diseases occurred in 38%-75% of patients; most were managed with corticosteroids or immunosuppressive therapy and very few fatalities occurred[31-33]. Patients on immunosuppressive therapy prior to treatment appeared to have lower rate of flare/adverse events[33], as did patients with neurologic or gastrointestinal diseases as compared to arthritic or skin related autoimmune diseases[21]. Similarly, post organ-

transplant patients on immunosuppressive therapy are at increased risk of certain malignancies, especially cutaneous. These patients are mostly excluded from clinical trials so little prospective data exists. Retrospective case reports and analyses indicate that there is increased risk for organ rejection[34,35]. This risk varies with organ type and agent: renal transplants and PD-1 agents appear to have the highest risks. Lastly, patients with inherited mutations that increase the risk for head and neck cancers, such as Li Fraumeni Syndrome and Fanconi Anemia, may benefit from checkpoint inhibitor therapy, though there is no prospective or retrospective data identifying these patients and their response rates or adverse event profiles.

CONCLUSION

Head and neck tumors are a historically difficult group of tumors to treat due to variability in histology, location, and modest responses to systemic therapy. Response rates to systemic therapies are low, especially in recurrent and metastatic tumors, and overall survival remains dismal. Checkpoint inhibitors such as pembrolizumab and nivolumab provide an alternative to cytotoxic therapies in squamous cell tumors, with adequate response rates and a modest overall survival benefit, and overall better tolerability in terms of toxicities. Their use does require special attention to the unique irAEs that can occur. Other checkpoint inhibitors including durvalumab, avelumab, atezolizumab, tremelimumab, and ipilumumab are actively being explored in clinical trials. In addition, there are ongoing trials looking to move these agents into the curative setting and combine them with more traditional therapy options to gain more cumulative survival benefit. This is an interesting and exciting time for this field with potential advances that will hopefully significantly improve patient outcomes.

DECLARATIONS

Authors' contributions

Concept and design, data analysis: Costantini C, Quenelle N
Data acquisition, manuscript preparation: Quenelle N
Critical revision, finalizing of the manuscript: Costantini C

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Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Consent for publication

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