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Review

Immunotherapy in Head and Neck Squamous Cell Cancer

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Prognosis in relapsed metastatic head and neck squamous cell cancer (RM-HNSCC) is dismal. Platinum based chemotherapy in combination with Cetuximab is used in first-line setting, while no further validated options are available at progression. Immunotherapy has produced durable clinical benefit in some patients with RM-HNSCC although the premises are several patients are nonresponders. Studies are ongoing to determine predictive factors and the ideal setting/combination of novel immunotherapies. In this paper, we discuss the past and present of immunotherapy in head and neck cancer and provide an up-to-date information regarding the potential ways to improve immunotherapy outcomes in HNSCC.

Keywords. *Immunotherapy; Tumor Immune Escape; Squamous Cell Carcinoma; Head And Neck; Biomarkers*

INTRODUCTION

In the last 40 years, treatment of head and neck squamous cell cancer (HNSCC) did not change dramatically. Radiotherapy and platinum-based chemotherapy represent the backbone treatments for locally advanced HNSCC (LA-HNSCC) and are offered for resected high-risk LA-HNSCC [1-5]. In 2006, the trial by Bonner et al. [6] introduced a second standard treatment: bio-radiation. Relapsed metastatic head and neck cancer (RM-HNC) evolved even slower than LA-HNC.

Platinum combination was the standard treatment until the extreme study reported the benefit of Cetuximab combination [7]. Since then, the extreme regimen represents the new first-line standard of care for RM-HNC. An established second-line treatment has never existed in RM-HNC, up to the approval of immune checkpoint inhibitors (ICIs) [8]. Therefore, the 5-year prognosis remains around 50% at 5 years and median overall survival (OS) in RM-HNC is less than 11 months [7].

However, immune-modulating treatments appear to have a clear clinical benefit for RM-HNSCC and this benefit seems to be independent of previous treatment, even being observed among patients who have received multiple lines of therapy and who have been assumed to have exhausted all options. Two drugs targeting the PD-1/PD-L1 axis, Nivolumab and pembrolizumab, have achieved the approval for second-line treatment of RM-HNC (study KEYNOTE-012 [9] and CheckMate 141 [10]) [11]. Moreover, Durvalumab, an anti-PD-L1 drug, also showed a benefit in terms of disease control rate in pretreated HNSCC patients [12].

It is reasonable to think that these ICIs will move soon to first-line and will be introduced as companion drugs in the multi-agent treatment of LA-HNC. In the meanwhile, new immunotherapies are in clinical development and some of them have already reached the phase III [11]. However, although the results (slightly higher but longer responses) justify the enthusiasm, they are some warning on immune-resistance. Indeed, a high proportion of patients is resistant or acquires resistance to these therapeutic strategies. The latter findings may reflect, at least in some cases, the inability of the immunotherapeutic strategies used to eradicate (Table 1 summarizes published results with ICI in HNSCC; Table 2 reports a confront with standard methotrexate as published in LUX1 study) [9,10,13-15]. This paper addresses the new data on the therapy of HNSCC and discusses the biological basis of immunotherapy in this disease.

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Table 1. Study population and activity

Study		No. of patients	Treat	Line	ORR	PFS/OS	CR/PR	HPV
KEYNOTE-012	Seiwert et al. (2016) [13]	60	PEM	>I	21%, 12.2-Month duration of response	NR	NR	23 Patients
KEYNOTE-012	Chow et al. (2016) [9]	132	PEM	>I, 82%; 1° line, 18%	18% wp 32% (HPV positive) 22% (PD-L1 positive) 4% (PD-L1 negative)	6 mo PFS 23% OS 59%	NR	28 Patients
CheckMate 141	Ferris et al. (2016) [10]	361	Nivo vs. SOC	II	17% (PD-L1 positive) 12.3% (PD-L1 negative) 15.9% (p16 positive) 8% (p16 negative)	1 yr 16%/36% PFS 2 mo, OS 7.5 mo	6/26	275 Patients
Durvalumab	Segal et al. (2016) [12]	51	Durvalumab	III	12% wp 25% (PD-L1 positive)	NR	NR	NR
KEYNOTE-040	Cohen et al. (2017) [14]	495	PEM vs. SOC	III	NR	2.1 mo/8.4 mo	1/24	NR

ORR, overall response rate; PFS, progression-free survival; OS, overall survival; CR, complete response; PR, partial response; HPV, human papillomavirus; PEM, pembrolizumab; NR, not reported; wp, whole population; Nivo, Nivolumab; SOC, standard of care.

Table 2. Activity compared with second line

Outcome	CheckMate 141 Nivo	CheckMate 141 SOC	KEYNOTE-040 PEM	KEYNOTE-040 SOC	LUX H-N 1 afatinib	LUX H-N 1 methotrexate
mPFS (mo)	2.0	2.3	2.1	2.3	2.6	1.7
mOS (mo)	7.5	5.1	8.4	7.1	6.8	6.0
mPFS PD-L1 positive (mo)	-	-	2.2 (3.5)[a]	2.3 (2.2)[a]	2.6	1.7
mOS PD-L1 positive (mo)	8.7	4.6	8.7 (11.6)[a]	7.1 (7.9)[a]	6.8	6.0

Nivo, Nivolumab; SOC, standard of care; PEM, pembrolizumab; H-N, head & neck; mPFS, median progression-free survival; mOS, median overall survival.
[a]mPFS and mOS for patients with PD-L1 >50% in tumor prognostic score are in the parenthesis.

THE MUTATIONAL LOAD AND THE EFFECT OF THE VIRAL ETIOLOGY ON THE RESPONSE TO THE ICIs

According to Blank et al. [16], the mutational load (ML) of HNC is in between liver cancer and kidney cancer, tumors known for their high immunogenicity. This is related to the large number of mutations induced by smoking, the upmost risk factor for these tumors. However, the head and neck regions host two different virus-induced tumors: oropharynx cancer, related to human papillomavirus (HPV), and undifferentiated nasopharynx cancer, related to Epstein-Barr Virus (EBV).

HIGHLIGHTS

- Immunotherapy in head and neck squamous cell cancer represents a promising new opportunity of treatment.
- Unfortunately, only a small number of patients benefit from single approach/agent therapy (overall response rate remains around 20%).
- Combining immunotherapy and radiotherapy or biotherapy as well as reliable biomarkers for patients selection is expected to improve outcomes.

Looking at environmental induced tumors, it is expected that they are able to generate robust immune response, as supported by the high immune cells infiltration, due to their high ML [17]. Virus-induced HNC are different from the environmental-induced HNC. For example, both the virus-induced tumors show a much lower ML rather than those related to smoking abuse [18,19]. According to Seiwert et al. [19], there is a direct relationship between ML and benefit from immunotherapy.

However, clinical available data do not show any clear difference of the outcome between "environmental" and "virus-related" HNC. Generically, we might speculate that the virus immunogenicity could compensate for the lower mutational burden of virus induced HNC. Indeed, invading DNA viruses or transfected DNA, activate stimulator of interferon genes (STING), a signaling molecule located in the endoplasmic reticulum, leading to the transcription of many immune genes. This in turn promotes an immune response against pathogens and cancer cells starting an interferon (IFN) type I over expression which is toll-like receptor (TLR) independent [20]. In addition, STING, different from the TLRs, is widely expressed in various cell types, including endothelial, epithelial and haemopoietic, such as T cells, dendritic cells dendritic cells (DCs), and in particular, plasmacytoid DCs [21].

ICI COMBINATIONS

Combining anti-PD-1 and anti-CTLA-4 agents has been approved for melanoma, and it looks promising in lung cancer and renal cancer [22]. Several studies are ongoing both in first- and second-line combining anti-PD-1 and anti-CTLA-4. Immunomonotherapy regimens for HNSCC have yielded modest results, with few good responders (long-lasting and tumor response) [11]. It may be hypothesized that monotherapy is not able to overcome the numerous mechanism of immune escape. Combinatorial immunotherapy should increase response based on biological rationale of acting at a different ligand and function. It has been reported that HNSCCs have a high infiltration of Tregs, so although inflamed tumor immune phenotype, response might be unsatisfactory. Moreover, in immune excluded tumor, microenvironment is rich of immunosuppressive factors that avoid immune response (high interstitial pressure due to vascular endothelial growth factor [VEGF], metabolic alteration due to indoleamine 2, 3-dioxygenase [IDO], natural killer impairment related to several other immune regulators such as KIR, CD137, TIM3, LAG3) [23].

A promising approach is to combine IDO1 inhibitor with ICI: IDO1 over expression has been associated with poor survival in HNSCC. The role of this enzyme is very important, it transforms tryptophan in kynurenine, on the one hand, tryptophan deprivation affect cytotoxic lymphocytes, on the other hand, excess of kynurenine induce their apoptosis. Preliminary results of the combination epacadostat (a potent, selective oral IDO1 inhibitor) plus pembrolizumab reported encouraging response rates (34% and 14% in second and third lines and more heavily pretreated patients) [24]; epacadostat also demonstrated promising activity in combination with other checkpoint inhibitors in other solid tumors, including melanoma, urothelial carcinoma, renal cell carcinoma, and non-small cell lung cancer. Recent advances demonstrated the role of STING, TLR and retinoic induced gene receptors like to induce effective response. However, although TLRs are key mediators of immune responses, TLR agonists in combination with bio and chemotherapy failed to improve progression-free survival (PFS). In the Active 8 study, no advantage was reported with or without motolimod therapy, a selective small-molecule agonist of TLR8. It must be remembered that not all TLRs are the cytosolic and this might explain differences in efficacy [25]. Nevertheless, the combination of motolimod with Cetuximab in patients with HNSCC showed a disease control rate of 54% [26]. A phase IB is ongoing in the neoadjuvant setting.

COMBINATION WITH RADIOTHERAPY AND/OR CHEMOTHERAPY AND/OR ANTI-EPIDERMAL GROWTH FACTOR RECEPTOR

Based on biologic knowledge, immunotherapy has been associated respectively with radiotherapy or chemotherapy in order to induce cancer death and a self-vaccination; with vaccination to target viral antigens and with biotherapy to target proliferation pathways that crosstalk with immune system. The rationale is to elicit a strong immune response activating microenvironment while administering immunotherapy [27]. Preclinical evidence showed that radiotherapy upregulates PD-L1 within 24 to 48 hours; in animal models increase in survival has been reported [28].

A second partner with a strong biological rationale is anti-epidermal growth factor receptor (EGFR) Cetuximab (Erbitux) (https://clinicaltrials.gov). Several demonstrations evidenced that at least a part of Cetuximab effect depends on antibody-mediated cytotoxicity, this activity involves principally natural killer cells. Eight studies are ongoing combining ICI+Cetuximab ± respectively with Nivolumab (two studies), Pembrolizumab (two studies), Durvalumab (three studies) and Avelumab (two studies) [29-32].

There are also at least three phase III trials for LA-HNC. Early reports confirmed that pembrolizumab in combination with weekly cisplatin-based chemoradiotherapy (CRT) is safe and does not significantly impair radiation or chemotherapy dosing (ClinicalTrials.gov Identifier: NCT02586207) [33]. The goal of this combination (ICI+CRT) is to increase distant metastases free survival and OS in stage III–IV HNC. These studies will inform on the correct algorithm: providing evidence if sequential versus concomitant ICI has to be preferred.

In the neoadjuvant setting, extraordinary results point out the time of ICI therapy: earlier than recurrent/metastatic (R/M) disease? Benefit after one dose of pembrolizumab before surgery was obtained in 48% of patients (95% confidence interval, 26% to 70%; ClinicalTrials.gov Identifier: NCT02296684) while after two doses of Nivolumab 11 of 23 patients reported RECIST (Response Evaluation Criteria in Solid Tumors) disease

Table 3. Phase III combination studies in LA-HNC as of October 2017

Study	No. of patients	Treatment	Outcome	Expectation date
Rtog3504	120	Nivo+P+RT vs. Nivo+Cet+RT vs. Nivo+RT	PFS	Mar 2019
KEYNOTE-412	780 HPV negative	PEM+P+RT vs. PRT	EFS	Apr 2021
JAVELIN H&N100	640	Avelumab+PRT vs. PRT	PFS	Apr 2021
REACH	688	PRT vs. avelumab+cetuximab+RT vs. Cet+RT	PFS	Dec 2018

LA-HNC, locally advanced head and neck cancer; Nivo, Nivolumab; P, platin; RT, radiotherapy; Cet, Cetuximab; PFS, progression-free survival; HPV, human papillomavirus; PEM, pembrolizumab; PRT, platinum radiotherapy; EFS, event-free survival.

Table 4. Phase III combination studies in RM-HNC as of January 2018

Study	Setting	Treatment	Outcome	Expectation date
CheckMate 651 NCT 02741570	1° Line	Nivo+IPI vs. Extreme	OS Safety	Jan 2019
KESTREL NCT 02551159	1° Line	Durvalumab vs. durvalumab+tremelimumab vs. Extreme	OS, PFS Safety	Mar 2018
EAGLE NCT 02369874	1° Line +P-refractory	Durvalumab vs. durvalumab+tremelimumab vs. Extreme	OS	Feb 2018
KEYNOTE-034	1° Line	PEM+TVEC	OS Safety	Dec 2018
KEYNOTE-048	1° Line	PEM vs. PEM+PF vs. Extreme	PFS, OS	Mar 2018

RM-HNC, relapsed metastatic head and neck cancer; Nivo, Nivolumab; IPI, ipilimumab; Extreme, extreme regimen (PF+Cetuximab); OS, overall survival; PFS, progression-free survival; PEM, pembrolizumab; TVEC, talimogene laherparepvec; PF, platinum fluorouracil.

Table 5. Study's toxicity

Study		No. of patients	Toxicity	AE grade 3–4 (%)	Any grade (%)
KEYNOTE-012	Seiwert et al. (2016) [13]	60	Fatigue, pruritus, nausea, decreased appetite, rash	9	45
KEYNOTE-012	Chow et al. (2016) [9]	132	Fatigue, pruritus, nausea, decreased appetite, rash	15	53
CheckMate 141	Ferris et al. (2016) [10]	361	Fatigue, nausea, rash, decreased appetite, pruritus, diarrhea	13	58.9
KEYNOTE-055	Bauml et al. (2017) [37]	171	Fatigue, hypothyroidism, diarrhea, pneumonitis, aspartate, aminotransferase increase	15	64

AE, adverse events.

reduction [34]. Moreover, targeting HPV and EBV in association with ICI has showed enthusiastic preclinical results [35,36]. Several trials are ongoing combining definitive chemotherapy or CRT and HPV/EBV vaccines and ICI. Tables 3 and 4 summarize ongoing phase III trials in LA-HNC and RM-HNC.

COST/BENEFIT OF IMMUNE CHECK-POINT INHIBITORS IN RM-HNC

Clinical trials (CheckMate 141, KEYNOTE-012, 055, 040) published (and presented) so far focus on second-line treatment. Lessons learned from these trials allow drawing some initial information on toxicity and activity [9,10-14,37].

Patients population

A common feature of the patients included in these trials is the multiplicity of prior chemotherapy lines. Albeit the trials were designed for patients failing the first-line treatment, a large number of patients received immunotherapy as third or more treatment for their disease. In addition, most patients had Eastern Cooperative Oncology Group performance status 1 and were aged >80 years. The number of previous treatments and ages did not impact on safety and efficacy of treatment [38].

Although no clear data justify a selection of HPV positive patients, responses in some trials are higher than in HPV negative patients. Durvalumab in platinum refractory patients achieved a response of 26.5% in those HPV positive vs. 7.9% in those HPV negative [12]. However, these data are controversial as many HPV negative tumors are very immunogenic [39]. Pembrolizumab treatment leads to a better prognosis for HPV+HNSCC patients than for HPV-HNSCC patients [37].

Toxicity

Toxicity is reported mild to moderate. Grade 3–4 adverse events (AEs) are consistently reported in less than 15% of the population (Table 5). However, information regarding the tolerance of specific subgroups at possible higher risk of toxicity, such as those with a history of allergy, is missing. Moreover, it is not known the evolution of endocrine-AEs in patients with basal radio-induced hypothyroidism (at least three of four patients treated with chemoradiation). Fatigue is the most reported side effect, but usually is limited to grade I–II. Overall, the reported toxicity seems strongly lower than expected with chemotherapy, in particular in the heavily pretreated population enrolled in these trials.

Activity, PFS, OS

Average objective response rate is around 15%. This is larger than expected in second-line treatment (Tables 1, 2). However, activity remains well below desired and at least 80% of patients did not achieve any tumor size reduction. No significant difference between ICI and standard of care groups was observed with regard to the rate of PFS in both CheckMate and KEYNOTE studies; however, a late separation in the Kaplan-Meier was observed in these studies. Hyperprogression was observed in 29% of patients with RM-HNSCC treated with anti-PD-L1/PD-1 agents and correlated with a shorter PFS [40]. Treatment evaluation is a challenge in this population. At European Society for Medical Oncology 2017 meeting, Haddad et al. [41] report-

ed the results at a minimum follow-up of 11.4 months of CheckMate 141. What is not biological surprising is the response in 24% of patients who had experienced progression (ClinicalTrials.gov Identifier: NCT02105636). The suggestion is to continue treatment in those without clinical progression with good performance status [41].

WHY IS THE ACTIVITY OF ICIs LIMITED?

PD-1/PD-L1-targeted drugs have obvious advantages over traditional therapeutic regimens in terms of overall response rate, survival, and safety but their efficacy is still disappointing. As single agents, these therapies have response rated in the range of 14%–32% [11]. Several mechanisms can elicit the resistance of HNC cells to immunotherapy: (1) immunosuppressive factors in microenvironment: abundance of FoxP3+ and deregulation of CCL22-CCR4 axis has been reported [42]; constitutive activation of STAT3 and expression of VEGF, interleukin (IL)-6, IL-10. HNC inhibits chemokines in a transforming growth factor beta and VEGF dependent manner [43]. (2) Impaired human leukocyte antigen (HLA)-mediated cancer cell recognition: HNC over-express EGFR. Over-expression and over-activation of EGFR not only induces oncogenic transformations but also downregulates the expression of antigen presenting machinery. EGFR activates a protein phosphatase (SHP2) which dephophorilated STAT1 (signal transducer and activator of transcription 1) leading to reduced HLA class I dependent antigen presentation [44]. (3) PD-1/PD-L1 expression: a downregulation is mediated in a JAK2/STAT1 dependent manner. Moreover, EGFR blockade downregulated IFN-γ-dependent PD-L1 expression according to Concha-Benavente and Ferris [44]. Interestingly, EGFR also promotes stabilization of PD-L1 surface expression through glycosylation of its extracellular domain [45]. (4) Several immune modulators were reported to negatively affect T cells activity. For example, VISTA (V-domain Ig suppressor of T cell activation), a recently discovered protein involved in the checkpoint inhibitors, is overexpressed in HNSCC [23].

BIOMARKERS

ML and gene expression profile (GEP) were utilized in some American institution to assess in order to identify responders. ML and GEP are independently predictive of response to pembrolizumab in HPV−/EBV− patients with HNSCC; GEP was predictive regardless of viral status [11]. ML and GEP may have utility in characterizing responses to anti PD-1 therapies and novel cancer regimens in HNSCC. Mattox et al. [46] demonstrated, by analyzing archival tissue stained for PD-L1, that PD-L1 status in RM-HNC patients did not directly correlated, as in other solid tumors, with OS nor PFS NCT02543476.

In the randomized CheckMate 141 trial, PD-L1 expression was assessed on tumor cells of 72% of the patients. Patients were divided in two prespecified subgroups (expression ≥1% and <1%). The magnitude of survival benefit was greater in PD-L1 ≥1% population, hazard ratio for death 0.55 (0.36 to 0.86) vs. 0.89 (0.54 to 1.85), whereas no advantage was demonstrated for increasing PD-L1 expression [10]. The expanded cohort of the KEYNOTE-012 trial used two different methods to define PD-L1 positivity: the combined positive score (CPS) defined as ≥1% of expression in both tumor and mononuclear inflammatory cells, and the tumor proportion score defined as ≥1% of expression only in tumor cells [9]. The study identified a relation between PD-L1 positivity and relative ratio (RR) only with the combined positivity score (22% vs. 4%, P=0.021). Similarly, statistically significant differences for PFS and OS were observed for PD-L1 positive patients using CPS [13].

On the contrary, in the KEYNOTE-055 study, using the same CPS score, PD-L1 positivity was not demonstrated to be predictive of response, the response rate being 12% even in PD-L1 negative patients, compared to 18% in positive patients. Interestingly, RR was higher in patients with ≥50% [37]. In the KEYNOTE-040, Cohen et al. [14] presented the results among the difference in PD-L1 CPS score ≥1% versus the tumoral positive score ≥50%, these results confirm the role of this marker, but no comparison can be obtained among tumoral positive score and CPS as they used two different levels [14]. Therefore, PD-L1 is a marker but we cannot assume it is the marker; several factors contribute to the immune continuum and a better knowledge is required to have a reproducible and safe predictive marker. Muller et al. [47] reported a strong correlation between expression of PD-L1 and reduced OS time.

Other biomarkers appear fascinating such as PD-L1 evaluation in circulating cell (blood biopsy), characterization of tumor infiltrating cells and PD-L2. This latter was studied by Yearley et al. [48] on 180 HNSCC patients. They showed that response was greater in patients positive for both PD-L1 and PD-L2 (27.5%) than those positive only for PD-L1 (11.4%). PD-L2 status was also a significant predictor of PFS with pembrolizumab independent of PD-L1 status. Longer median times for PFS and OS were observed for PD-L2-positive than PD-L2-negative patients.

CONCLUSION

Immunotherapy clearly is active in head and neck cancer, both virally related/not related and heavily pre-treated patients. Head and neck cancer shows a prominent immune phenotype. Response rates are reasonable, but they are probably underestimating benefit, impact on survival is significant in responders. Anti-PD-1 and PD-L1 agents are well tolerated but awareness of potential immune-related AEs is important. We still need robust

and consistent biomarkers. From KEYNOTE studies, we should carefully select patients avoiding those with HPV negative and PD-L1 negative tumors.

Improvement in quality of life is reported compared with chemotherapy. Combination approaches are promising, first-line combinations studies are ongoing. It is important to learn how to integrate immunotherapy with other treatments. We should argue that, in the near future, the fastest run to register all combinations will probably determine the willingness to use (if economically allowed in any center) many combinations but without a personalized medicine. The cancer immunogram by Blank et al. [16] might suggest, if combinations are needed, which one is preferable, deserving a combination to patients without significant immune cell infiltration and absence of soluble inhibitors. New options for treatment in these patients will be soon available; we should have the ability to select them and to build a flowchart.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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