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Immunotherapy in head and neck cancer: The great challenge of patient selection

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ABSTRACT

The development of immune checkpoint inhibitors (ICIs) revolutionized the therapeutic landscape in head and neck cancer. However, the majority of patients present primary resistance to ICIs and do not benefit from use of these agents, highlighting the need of developing predictive biomarkers to better determine who will benefit from treatment with ICIs. Patient's related clinical characteristics, disease related features, pathological and molecular factors, as well as emerging immune predictive biomarkers can be considered for the selection of those patients who would be the best candidate for immunotherapy. We examined these factors, emerging from the results of currently available studies in head and neck squamous cell carcinoma (HNSCC), in order to provide a useful tool which could assist the oncologist in their clinical practice.

1. Introduction

Patients with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M-HNSCC) experienced a poor prognosis with a median survival less than 12 months (Marur and Forastiere, 2008; Pignon et al., 2009). However, the treatment of R/M-HNSCC is a rapidly evolving landscape. Until the publication of EXTREME trial (Vermorken et al., 2008), no further advances in the systemic therapy of R/M-HNSCC had been demonstrated and an established second-line treatment had never existed up to the approval of ICIs (Siano et al., 2017). Anti-programmed cell death protein (PD-1) monoclonal antibodies are the first immunotherapeutic agents to demonstrate evidence of response durability and survival benefit in platinum-pre-treated recurrent and metastatic disease (Lechner et al., 2017; Schoppy and Sunwoo, 2015). Two completed phase III randomized trials (CheckMate 141 and KEYNOTE-040) have consistently proved that two anti-PD-1 agents, nivolumab and pembrolizumab, significantly improved overall survival (OS) and quality of life (QoL) as compared with the investigators' choice (IC) of standard single-agent therapy (methotrexate, docetaxel or cetuximab) in patients who progressed to platinum-based chemotherapy (Cohen et al., 2019b; Ferris et al., 2016; Harrington et al., 2017). Moreover, survival benefit with nivolumab was also noted among patients who received nivolumab as first-line treatment after progressing during platinum therapy for locally advanced disease in the adjuvant or primary (i.e., with radiation) setting (Gillison et al., 2018). In 2016, the US Food and Drug Administration (FDA) approved nivolumab and pembrolizumab for the treatment of patients with R/M-HNSCC refractory to platinum-based therapy. Importantly, data reported on the results of KEYNOTE-048 confirmed the significant activity of anti-PD-1 in the first line R/M setting (Burtness and Harrington, 2018). This phase 3 randomized trial compared pembrolizumab monotherapy and pembrolizumab plus chemotherapy with the standard of care (EXTREME regimen) in patients who had not previously received systemic therapy for metastatic disease or with incurable recurrent disease. Pembrolizumab monotherapy conferred significantly longer OS compared to SOC in patients with PD-L1 combined positive score (CPS) ≥ 20 and ≥1, while the combination arm demonstrated improved survival over the EXTREME regimen in all patients, irrespective of PD-L1 status. Update final analysis of KEYNOTE-048, presented at ASCO 2019, demonstrated that patients treated with pembrolizumab plus chemotherapy had superior OS in the PD-L1 CPS ≥ 20, CPS ≥ 1, and total population and those treated with pembrolizumab alone confirmed superior OS in the CPS ≥ 20 and ≥1 patients, with non-inferior OS reported for the total population (Rischin and Harrington, 2019). Due to the improvement in survival benefit shown in this trial and the toxicity and logistical challenges of the EXTREME regimen, the FDA approved pembrolizumab for use in combination with chemotherapy for the first-line treatment of all patients with unresectable R/M-HNSCC and as a single agent for patients with a PD-L1 CPS ≥ 1 in 2019.

Moreover, several ongoing studies in R/M-HNSCC patients are testing the efficacy of the combination of ICIs with new targeted agents,

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such as EGFR inhibitors, indoleamine 2,3-dioxygenase-1 (IDO1) inhibitors, histone deacetylase inhibitors, multitarget kinase inhibitors and anti-B7-H3 monoclonal antibodies (Muratori et al., 2019). However, despite the promising results shown by immunotherapy, a high proportion of patients display primary resistance to ICIs and do not benefit from the use of these agents (Topalian et al., 2012). Based on the existing data, the effectiveness of nivolumab and pembrolizumab is similar in second-line treatment for R/M-HNSCC. The FDA approved both nivolumab and pembrolizumab in head and neck cancer for patients with R/M-HNSCC who have progressed on or after platinum-based chemotherapy without requiring PD-L1 expression analysis prior to treatment. The European Medicine Agency (EMA) approved Nivolumab in the same indication as FDA and pembrolizumab for the treatment of adult patients with R/M-HNSCC who progressed following platinum-based chemotherapy and whose tumors express PD-L1 with a ≥ 50% tumor proportion score (TPS) (Cohen et al., 2019a).

Translational biomarker research is critical for the future of immuno-oncology development and identifying selection criteria to guide clinical choice remains an urgent and unmet clinical need. In this review we reported all the existing evidence available in the literature to identify clinical/preclinical predictor factors of response in order to provide a useful tool for head and neck patient's selection for immunotherapy.

2. Patient's related clinical factors

2.1. Age

It's well known that immune-senescence induces differences on immune function and immune cell subsets between the younger and older population, thus it can play a role in cancer immune-therapy efficacy.

Overall, several papers and reviews discussed the impact of ageing and immune-senescence on immune system functions, assessing the safety and efficacy of immunotherapy in elderly patients, principally from the data of pivotal clinical trials with subgroup analysis and from retrospective cohort studies evaluating real-life setting (Ferrara et al., 2017; Grossi and Misino, 2016; Ray, 2016). Tolerance and toxicity in elderly patients appear to be similar to younger people, while the efficacy seems to be different between younger and elderly patients according to the type of cancer: some research showed no difference and others less or more efficacy in the elderly subgroup (Casaluce et al., 2018; Daste et al., 2017).

In particular, an interesting research showed differences in the response to PD-1 inhibitors between older (> 60 y/o) and younger patients affected by melanoma: patients over the age of 60 responded more efficiently to the therapy (Kugel et al., 2018). These findings seem to be confirmed by a recent metanalysis that showed a clinically age-dependent benefit of immunotherapy, suggesting that patients ≥ 65 y/o treated with ICIs had major benefit from treatment than younger ones (Wu et al., 2019). The potential effect of patients' age on the efficacy of immunotherapy was more evident in subjects treated with anti-PD-L1 and in those affected by melanoma. This data can be explained by an alteration between sub-populations of immune cells and an increased T-reg ratios observed in elderly patients, highlighting the importance of considering age as a factor for immunotherapy response.

In contrast, a second recent metanalysis evaluating the impact of ageing on ICIs' efficacy demonstrated generally that immune checkpoint inhibitors improved significantly OS in both younger and older patients, but less benefit was observed in patients aged 75 y/o and older (Nishijima et al., 2016).

In particular for head and neck cancer patients, the role of ICIs has been recently investigated: considering the age-related decline in the effectiveness of the immune system, the authors supposed that these therapies, based on T-cell abundance and activation, may be less efficacious in the context of elderly patients (Hartmann and Grandis, 2016).

Recently, a retrospective study compared efficacy and safety of ICIs in patients with R/M-HNSCC aged 70 y/o and older to younger patients. Among 226 patients enrolled, 67 were ≥70 y/o, with a median age of 75 y/o. Elderly patients treated with ICIs had significantly higher PFS but not OS compared to younger patients. Moreover grade ≥3 irAEs were associated with significantly higher ORR to ICIs in the whole population (Even et al., 2019).

Although no prospective studies have been carried out for immunotherapy in elderly head and neck patients, we may suppose that ICIs may be an effective treatment option also for this cancer patient population. However, limited data is available in this frail subgroup of patients due to the low number of patients aged between 65 years or older for these clinical trials. Additional specific clinical trials for elderly cancer patients are needed to clarify the influence of age on treatment efficacy in ICI treatment regimen.

2.2. Performance status

Some evidence identified a correlation between the performance status (PS) of the patient and the percentage of CD8+ and CD4+ cells: these findings hypothesized a potential relationship between PS and immune function, therefore between the patient physical state and his response to immunotherapy (Wang and Shen, 2013). At present, data on optimal management of ICIs according to PS are not available.

In non-small cell lung cancer (NSCLC) data from a post-hoc exploratory analysis of CheckMate 057 suggested that patients treated with nivolumab who had poorer prognostic features, such as ECOG PS 1, experienced a higher risk of death within 3 months when combined with lower or no PD-L1 expression, compared to those treated with chemotherapy (Peters and Capuzzo, 2017).

A recent Italian metanalysis investigated the predictive role of PS toward treatment with ICIs in cancer patients, reporting a better survival in all patients' subgroups (PS 0 and PS 1–2 subgroups) (Bersanelli et al., 2018). The authors concluded that PS should not influence the treatment choice for anticancer immunotherapy.

Although patients with PS 2 were generally excluded from clinical trials, data come from the Italian Expanded Access Program (EAP) of nivolumab for non-squamous NSCLC which also included patients with PS 2 demonstrated that ICI therapy was safe and efficacious in this population (Garassino et al., 2018). In contrast, an ECOG PS ≥2 in combination with the lack of response to previous chemotherapy has been associated with poor prognosis with ICI therapy in advanced NSCLC in some real-life experiences (Dudnik et al., 2018).

As far as the head and neck cancer is concerned, all pivotal clinical trials required an ECOG PS 0 or 1, without evidence of differences respect on PS from post-hoc subgroup analysis. At present no data from the real life is available in this setting, therefore we cannot consider PS a clinical predictor factor of response to immunotherapy.

2.3. Lifestyle habits: smoking and alcohol history

Smoking and alcohol consumption are two traditional risk factors for the development of HNSCC. The relationship between smoking history and the efficacy of immunotherapy is now object of study. Tobacco carcinogens create a specific mutational signature in tumors, increase overall mutation count and potentially alters the tumor immune microenvironment (Alexandrov et al., 2016; Hernandez et al., 2013). Mutational load and the tumor immune microenvironment have been associated with tumor response to immunotherapy (Ayers et al., 2017; Tumeh et al., 2014).

However, the clinical and immunologic correlates of tobacco use differ in smoking-associated cancer types, such as HNSCC and lung cancer.

Desrichard et colleagues analyzed the mutational signature of smoking and its association with tumor mutational load and the

immune microenvironment in squamous cell carcinomas arising in the head and neck and lung (Desrichard et al., 2018). In HNSCC, the mutational smoking signature was associated with poorer survival and strong immunosuppressive effects, while in lung squamous cell carcinoma smoking was associated with a more inflamed tumor microenvironment. This report confirmed that the genetic smoking signature is associated with higher mutational load, but variable effects on tumor immunity can occur, depending on anatomic site. Thus, it will be important to assess the effects of smoking separately in different cancer types.

These genetic findings are consistent with clinical data indicating that smokers with lung cancer tend to have higher response rates to ICIs. Rizvi et al. reported that in NSCLC patents treated with anti-PD-1 agent, the mutational smoking signature was a more precise determinant of response than clinical smoking history (Rizvi et al., 2015). A recent metanalysis investigated if the survival benefits of ICIs in NSCLC were different according to smoking status, showing that immunotherapy prolonged PFS and OS in ever-smoker patients and failed to improve survival in never-smokers (Kim et al., 2017).

Data in HNSCC is more limited and collected from the subgroup analysis of phase 3 trials. In particular, among these patients the survival benefit associated with nivolumab was numerically lower in current/former smokers compared with never-smokers (Ferris et al., 2016). Data from a retrospective analysis of 81 HNSCC patients treated with nivolumab provides additional support for the higher response rates seen in never-smokers (Desrichard et al., 2018).

Although Mandal et colleagues hypothesized that smoking signature-high HPV-negative HNSCC patients may benefit from immunotherapies due to their high mutational load (Mandal et al., 2016), preliminary evidence suggested that gene expression–based measures of tumor inflammation are more predictive of response than mutational load in head and neck cancer (Haddad, 2017).

Similar to smoking habit, alcohol consumption modulates many aspects of the immune system and its effect seems to depend on the individual daily dose. Over the past century, alcohol abuse has been associated with immunosuppression and host susceptibility to infectious disease, but it is also well known that chronic alcohol consumption can activate the immune cells (Meadows and Zhang, 2015). The little available data relating to the potential effect of alcohol on immune system in cancer patients suggested that patients with alcohol abuse have a decreased production of antigen-specific antibody, as result of the upregulation of suppressive cells in these patients (Pasala et al., 2015). Based on that, it is reasonable to assume that alcoholism may influence – in a positive or in a negative sense – the response to immunotherapy. This hypothesis must be verified from further investigation.

2.4. Nutritional aspects: body max index

Body Max Index (BMI) is a widely used parameter to describe the nutritional status of the patients associated to clinical outcomes in advanced cancer patients. A lot of evidence clearly indicated that obesity is an established risk factor for many malignancies, associated with worse outcomes in several cancers (Iyengar et al., 2016); thus, it may be interesting to value the relationship between BMI and response to immunotherapy. Body composition, especially, the distribution of fat max in the body, is strongly associated with the immune cell activity and the immune homeostasis. Indeed, white adipose tissue is involved in the induction and coordination of host defences, by releasing cytokines and chemokines. Adipose tissue has a pro-inflammatory role: it modulates lymphocytes Th1/Th2 balance, reduces T-reg activation and stimulates macrophages (Ouchi et al., 2011).

Bearing in mind the correlation between adipose tissue and immunity system, recent evidence revealed that adipose tissue may influence the individual response to immune checkpoint inhibitors in cancer patients. A recent Italian multicentre study showed how overweight may be favourable: patients with a BMI $\geq$ 25 experienced a better clinical outcome from the therapy with anti-PD-1/PD-L1 agents compared to those with a BMI < 25 (Cortellini et al., 2019). Patients were affected by NSCLC, melanoma, renal cell carcinoma and it was shown that obese patients experienced improved clinical outcomes, with higher ORR, while underweight patients had significantly lower outcome, confirming malnutrition as a negative prognostic factor. Moreover, a retrospective, multicohort analysis of patients affected by melanoma and treated with targeted therapy, chemotherapy or immunotherapy, demonstrated that obesity was associated with survival benefit (with improved PFS and OS) in patients treated with targeted therapy and immunotherapy, while there was no evidence of association between BMI and chemotherapy effectivity (McQuade et al., 2018). It is important to underline that a pronounced survival advantage was observed in male rather than in female patients, suggesting an additional role of hormonal mediators. A study about patients with hepatic metastases showed similar results: BMI > 30 was associated with improved survival in patients who received immunotherapy (Garje and Chennamadhavuni, 2018). This protective association has been termed the “obesity paradox” and it may be explained by the correlation between obesity and increased PD-1 expression mediated by leptin, a hormone whose levels increase in proportion with adipose tissue (Lysaght, 2019).

There are no studies about the impact of BMI on the effects of immunotherapy in patients affected by head and neck cancer, however, considering the studies mentioned and the fact that patients affected by HNSCC frequently experience loss of weight, muscle mass and malnutrition, it may be useful to discover the relationship between nutritional status and efficacy of ICIs in this specific subpopulation of patients. Up to now, there is not proven evidence of an interaction between BMI, sex and response to therapy; it should be explored with additional studies in order to discover new prognostic and/or predictive factors for patients treated with ICIs.

3. Disease related factors

3.1. HPV infection

HPV-related HNSCC is a biologically distinct disease characterized by favorable prognosis and improved locoregional and distant control with conventional therapies (Ang et al., 2010; Huang et al., 2018). Compared with non-viral related counterparts, HPV + HNSCC shows a less immunosuppressive TME, with a greater infiltration by tumor infiltrating lymphocytes (TILs), decreased CD4+/CD8+ ratio, lower numbers of T-regs, increased levels of INF-γ and high PD-L1 expression in immune cells (Lechner et al., 2017; Partlova et al., 2015; Solomon et al., 2018). These intrinsic characteristics suggest a potential major sensitivity of HPV + tumors to ICIs.

Several studies analyzed the effects of checkpoint inhibition regarding HPV status. In phase 1b trial KEYNOTE-012 with pembrolizumab, the percentage of HPV + patients was relatively small, with 23% being HPV + and 77% being HPV- (Chow et al., 2016; Seiwert et al., 2016). When stratified by HPV status, HPV + tumors had increased objective response rate (ORR) compared with those HPV- (25%–32% vs 14%) (Mehra et al., 2018). In the single-arm, phase 2 KEYNOTE-055 study, among 171 patients treated with pembrolizumab 22% were HPV positive. Response rates were similar regardless of HPV status, with ORR of 16% in HPV + patients and 15% in HPV- patients (Bauml et al., 2017). Similar results were reproduced in the phase 3 KEYNOTE-040 trial and in the CheckMate 141 study: pembrolizumab and nivolumab, respectively, did not yield significant differences in ORR or OS between HPV + and HPV- patients (Ferris et al., 2016). A recent update of CheckMate 141 confirmed a benefit of nivolumab compared to chemotherapy between both HPV + and HPV- patients (Ferris et al., 2018).

Further studies investigating other anti-PD-1/PD-L1 agents reported

mixed results. In an exploratory analysis of phase 2 HAWK trial with durvalumab, patients with HPV + tumors showed an ORR of 30% compared with 10.8% in those whose tumors HPV- (Zandberg et al., 2019), while no differences were seen in a phase I trial with atezolizumab (Bahleda and Braiteh, 2017).

A retrospective study on a cohort of 126 patients with R/M-HNSCC treated with anti-PD-1/PD-L1 agents revealed that HPV + patients had a lower tumor mutational burden, as expected, but similar response compared with non-HPV related counterpart (Hanna et al., 2018). This finding suggested that in virally induced tumors response to ICIs is higher than expected when adjusted for TMB, probably because virus-specific antigens, rather than tumor-neoantigens alone, can trigger an immune response.

Another retrospective chart review was performed in order to evaluate whether HPV-status is associated with duration of response in 54 patients with R/M-HNSCC receiving anti-PD-1 inhibitors. Both overall survival and time on anti-PD-1 inhibitor were significantly longer for patients with HPV-positive cancer than those with HPV-negative cancer (Kirtane et al., 2019).

At the current stage of knowledge, in the absence of strong data suggesting HPV-related tumors experience a distinct benefit from available ICIs, HPV-status should not affect selection of patients for immunotherapy.

3.2. Previous lines of treatment and disease state

KEYNOTE-012 assessed the safety and antitumor activity of pembrolizumab in an open-label phase 1b trial of patients with R/M-HNSCC. Although this trial did not mandate specific prior therapies, 15% of the patients had already received a prior one line of systemic therapy and 70%, two or more lines of systemic therapy (Mehra et al., 2018). Similar response rates were reported when analyses were restricted to patients whose disease progressed after prior platinum therapy or prior platinum and cetuximab therapy (17% and 15% respectively). In the phase 2 KEYNOTE-055 the majority of the patients were heavily pre-treated: 75% received at least two prior lines of systemic therapy (Bauml et al., 2017). Pembrolizumab showed significant antitumor activity and safety profile regardless prior treatment with platinum and cetuximab. The phase 3 CheckMate 141 evaluated the efficacy of nivolumab in the same setting (Ferris et al., 2016). Previous treatment included radiotherapy in 91.4% of the patients and two or more lines of systemic therapy in 54.5%. Similar to the other clinical trials, the study didn't show any significant association between outcomes and pre-treatments.

Known that cetuximab modulates immune responses, therefore its previous use may affect the efficacy of subsequent immunotherapy. A recently published post hoc analysis of CheckMate 141 investigated outcomes with nivolumab, by prior cetuximab exposure, in patients with R/M-HNSCC who had experienced progression within 6 months of platinum-based chemotherapy (Ferris et al., 2019). Nivolumab confirmed its benefit regardless the previous use of cetuximab, supporting its use across a broad population of patients with R/M-HNSCC post-platinum therapy. However, the reduction in risk of death with nivolumab was greater in patients without prior cetuximab exposure than with prior cetuximab use (48% and 16% respectively). Further research is needed to optimize treatment sequence in order to maximize therapy options and to understand the impact of prior treatments on response to ICIs.

The rapid expansion of immuno-oncology agents led researchers to investigate how conventional therapies may directly modulate the immune system and the tumor microenvironment in order to better understand the effects and combinatorial potential of these therapies in the era of immunotherapy. Regarding the radiation therapy, it is now evident that radiotherapy, through a plethora of diverse mechanisms, has the ability to generate anti-tumor immune responses which can be potentiated by immune checkpoint inhibition (Miyauchi et al., 2019). Recently post hoc analyses of KEYNOTE-040 were conducted to evaluate outcomes with pembrolizumab, by prior radiotherapy exposure and disease state in patients with R/M-HNSCC whose disease progressed during or after platinum-based therapy (Harrington et al., 2019). Prolonged survival benefit and trend toward improved PFS and ORR was observed with pembrolizumab in patients with prior radiotherapy, while for patients without radiotherapy, sample sizes were too small to draw any definitive conclusions. Moreover, survival benefit of pembrolizumab was demonstrated in patients with metastatic and R/M disease, but not in those whose disease recurred or progressed within 3–6 months of previous multimodal therapy containing platinum for locally advanced disease.

An interesting study presented at the 2019 ASCO Annual Meeting, with the proposal to determine whether primary site and metastatic tumor location was associated with initial response in non-irradiated lesions, evaluated the response in 144 non-irradiated lesions from 59 patients. The latter with metastatic HNSCC enrolled on a phase II randomized controlled trial of nivolumab with stereotactic body radiotherapy compared to nivolumab alone (Yu et al., 2019). On multivariate logistic regression controlling for PD-L1 and HPV-status, lymph node metastases were associated with decreased risk of progression, while live metastases and oral cavity primary site were associated with increased risk of early progression, using lung metastases and larynx/hypopharynx primaries as reference. Although the small sample size may prevent the findings from being extrapolated, the authors concluded that metastasis from oral cavity primaries and those to the liver were at increased risk of early progression following treatment with nivolumab. However, further research is needed to determine whether head and neck primary tumor subsite and metastasis tumor location are predictors of response to ICIs treatment.

4. Special populations

4.1. Autoimmune disease and steroid therapy

The use of ICIs in patients with pre-existing autoimmune diseases (AID) or in those who receive chronic steroid treatment remains an important issue. These subgroups of patients have been excluded from clinical trials of immune checkpoint inhibitors for cancer, but emerging evidence is now accumulating from retrospective studies and case reports. Alterations in the CTLA-4 and PD-1 checkpoints are associated with autoimmune diseases, raising concern that immune checkpoint inhibitors may confer a higher risk of toxicity among patients who have this condition (Kong and Flynn, 2014).

Johnson and colleagues investigated safety and efficacy of ipilimumab in patients affected by advanced melanoma with AID: 27% of patients treated with ipilimumab experienced exacerbations of their autoimmune condition requiring systemic treatment and 33% of patients had a grade ≥ 3 Immune Related Adverse Events (irAEs), reversible with corticosteroids or infliximab therapy (Johnson et al., 2016). In another similar study flare of the latent disorder requiring immunosuppression occurred in 38% of patients treated with anti-PD-1, although only 4% discontinued the treatment due to flare (Menzies et al., 2017). A recent retrospective study evaluated 56 patients with an AID who received a PD-L1 inhibitor: the 23% of patients developed an exacerbation of the underlying AID, but the incidence of irAEs was similar to that reported in clinical pivotal trials (Leonardi et al., 2018).

Recently, Kehl et al. identified 4438 patients treated with ICIs from 2011 to 2017 (including 216 HNSCC patients) using data from a large private national US health insurer (Kehl et al., 2019). Among all patients treated with ICIs 179 presented pre-existing AID selected by strict criteria and another 283 patients selected by relaxed criteria only. In this observational study pre-existing AID was not associated to any hospitalization after initiating ICI therapy, but it was associated with a modest increase in hospitalizations with irAEs diagnoses and with corticosteroid treatment.

Although there are currently no reliable biomarkers to predict occurrence of severe irAEs in response to ICI therapy, the development of high-throughput sequencing technologies led to the discovery of more than 300 susceptibility genetic loci associated with various autoimmune conditions (Hoefsmit et al., 2019). On the basis of the hypothesis that irAEs may be linked to susceptible loci related to ADI, the recognition of those susceptible loci could potentially function as a tool to identify predisposed patients who experience severe irAEs in response to ICI therapy.

At present, evidence regarding autoimmune disease is sparse and no data is yet available in head and neck cancer. However, the *Cancer Immunotherapy Guidelines – Head and Neck Cancer* subcommittee recommends that patients with autoimmune disease should not automatically be excluded, but the decision should be tailored to the specific disease (Cohen et al., 2019a).

Interestingly, several reports seem to suggest that the development of irAEs is associated with survival benefit and a longer median duration of response to anti-PD-1 in patients with advanced melanoma and NSCLC (Freeman-Keller et al., 2016; Haratani et al., 2018; Ricciuti et al., 2019a; Rogado et al., 2019). However, these analyses are flawed by several caveats including a short follow-up time, that could not correctly estimate the real predictive value of irAEs, and the mechanisms underlying this association are still not completely understood. The incidence of immune-related adverse events may reflect higher immune competence, thus leading to superior response rate, but future research of emerging immunotherapeutic agents should address this association to explore the underlying biological mechanisms of efficacy. In a prospective study of 73 NSCLC patients treated with anti-PD-1 therapy, autoimmune skin toxic effects were far more common in patients who achieved complete or partial remissions compared with those with progressive or stable disease as their best response (Berner et al., 2019). Notable, the authors identified nine T-cell antigens shared between tumor tissue and skin, suggesting that during checkpoint inhibitor therapy, T cells recognizing shared lung tumor and skin antigens simultaneously target both organs. This study raises the question of whether the identification of immunogenic tumor antigens may enable more effective immunotherapy while avoiding self-directed immune responses.

There is no data concerning the possible relationship between the development of immune-related toxicity and the efficacy of this innovative therapeutic regimen in HNSCC. However, a prospective phase IIIb clinical trial conducted in a real-life population of 127 patients with R/M-HNSCC treated with nivolumab recently showed that subjects experiencing any irAEs had an improved OS, suggesting also in this setting a strong correlation between toxicity and survival benefit (Bossi et al., 2019a).

Despite this preliminary evidence, the role of immune-related toxicity as potential markers of response and long-term survivors in head and neck cancer needs to be validated in larger prospective series. Moreover, several questions must be clarified, such as the incomplete overlap between response and nonresponse and the development or nondevelopment of irAEs which suggests to some measure of the host-specific tuning of immune response, a better understanding of which may serve to clarify who develops irAEs.

Corticosteroids are commonly used for treatment and prevention of acute or chronic inflammatory status, thus they could undermine the therapeutic action of ICIs with immune suppression mechanism. For this reason, patients receiving systemic steroids at baseline have been excluded from clinical trials (Scott and Pennell, 2018).

On-treatment, corticosteroids used for the management of immune-related adverse events, do not seem to negatively affect the efficacy, but the potential impact of baseline corticosteroids at the beginning of treatment is unknown. In a retrospective real-world series including 640 patients with NSCLC treated with ICIs, 14% of them received a dose of prednisone ≥10 daily at the start of immune treatment (Arbour et al., 2018). The most common indication for steroid treatment in this report were: fatigue, dyspnea and brain metastases. The use of corticosteroids was significantly associated with decreased ORR, PFS and OS.

However, because corticosteroids are often administered for palliation of cancer-related symptoms that are independently associated with a poor prognosis (fatigue, cachexia or brain metastases), in these patients the shorter survival times observed may not necessarily be due to a clinically significant corticosteroid-related blunting of the antitumor immune response to ICIs. An interesting study evaluated the impact of baseline corticosteroids on ICI efficacy in patients affected by NSCLC and treated with anti-PD-1 agents, comparing clinical outcomes in three different groups of subjects: patients who were on ≥ 10 mg of prednisone at the time of immunotherapy starting for cancer-related palliative indications; patients who were on ≥ 10 mg of prednisone at the time of immunotherapy starting for cancer-unrelated indications; and patients who were on 0 to < 10 mg of prednisone at the time of immunotherapy initiation (Ricciuti et al., 2019b). PFS and OS were significantly lower only among patients who received ≥ 10 mg prednisone for palliative indications compared with patients who received ≥ 10 mg prednisone for cancer-unrelated reasons and with patients receiving 0 to < 10 mg of prednisone. This data suggested that corticosteroids should not necessarily be decreased or discontinued before the start of treatment, as their impact on outcomes in patients treated with the latter immunotherapy seems to be driven by a poor-prognosis subgroup of patients who had received corticosteroids for palliative indications.

Further retrospective case series demonstrated that the overall survival of patients treated with steroid for adverse events was not worse than that of patients who not received steroid treatment (Postow et al., 2018).

More data from specific studies concerning the impact of baselines steroids on efficacy of immunotherapy is needed before drawing any definitive indications. Moreover, there is no data about the impact of corticosteroids on ICIs activity in patients with HNSCC, but it is known that these patients often need steroids treatment for dyspnea, fatigue, dysphagia and pain. The *Cancer Immunotherapy Guidelines – Head and Neck Cancer* subcommittee agreed that ICIs shouldn't be administered to patients receiving over 10 mg dose of daily prednisone (Cohen et al., 2019a).

4.2. Viral infections: HIV and HBV/HCV infection

Patients with chronic hepatitis have traditionally been excluded from clinical trials due to a possible hyperimmune response in HBV/HCV positive subjects treated with immunotherapy, potentially leading to the risk of an irreversible or fatal immune-mediated hepatic injury. Another problem is related to difficulty of distinguishing an immune-related hepatitis from a reactivation of a chronical viral hepatitis.

Case reports of patients affected by melanoma or lung cancer with the co-occurrence of chronic HCV infection detailed the use of ICIs, reporting a rapid antitumor response without any important issues regarding liver involvement (Davar et al., 2015; McCullar et al., 2017). Furthermore, some evidence comes from the use of nivolumab in patients HBV/HCV positive affected by hepatocellular carcinoma (HCC) in a phase 1/2 CheckMate 040 trial (El-Khoueiry et al., 2017). This study showed a similar disease control and objective response rates between patients infected and those non-infected. No hepatitis reactivation or seroconversion were reported among infected patients, while some of them had a transient reduction in viral load. There are many ongoing clinical trials of anti-PD-1 agents in patients with HCC that allow the enrollment of subjects with untreated HCV.

Some evidence suggested that a proportion of patients with HIV infection develop HNSCC, probably due to their immunodeficiency that could contribute to lower immune surveillance against a malignant process. However, HIV positive patients were historically excluded from clinical trials and the use of ICIs in this underrepresented

population remains a challenge.

It is known that in HIV positive people PD-L1 expression on the T cells is higher than in HIV unknown patients and its levels correlate with the severity of infection (Domblides et al., 2018). The increase in HIV-specific CD8 + T cells under ICIs therapy was also reported in patients treated with nivolumab, suggesting that anti-PD-1 therapy may have beneficial effects in patients with HIV infection (Guihot et al., 2018).

A systematic review was conducted in order to summarize results on the safety and efficacy of ICI therapy in HIV-infected patients with advanced-stage cancer, including NSCLC, melanoma and Kaposi sarcoma (Cook and Kim, 2019). Among 34 patients with known pre-treatment and post-treatment viral loads, HIV remained suppressed in 26 of the 28 patients (93%) with undetectable HIV load. Results showed that ICI therapy may be a safe and efficacious treatment option in this patient population, inducing grade ≥3 immune-related adverse events in 6 of 70 patients (8.6%). No association between adverse change and HIV load or CD4 cell count was found.

An open-label, multicenter, phase 1 study evaluating the safety of pembrolizumab in patients with HIV and advanced cancer was recently published (Uldrick et al., 2019). Thirty patients were enrolled from April 2016 to March 2018: 6 had Kaposi sarcoma, 5 had non-Hodgkin lymphoma, and 19 had non-AIDS-defining cancers (including NSCLC, melanoma and HCC). Pembrolizumab demonstrated an acceptable safety profile, although an unexpected treatment-emergent adverse event of Kaposi sarcoma herpesvirus-associated polyclonal B-cell lymphoproliferation was noted. Clinical benefit was observed in patients with Kaposi sarcoma, diffuse large B-cell lymphoma, and NSCLC. Interestingly, all participants continued anti-retroviral therapy.

Based on current knowledge, the *Cancer Immunotherapy Guidelines – Head and Neck Cancer* subcommittee recommends that patients with controlled disease, such as hepatitis C and HIV infection with normal CD4 + T cells count and who are on anti-retroviral therapy, are generally suitable for ICI treatment (Cohen et al., 2019a).

4.3. Antibiotics use

The composition and heterogeneity of gut microbiota plays a key role in ensuring a robust immune defense. Recent evidence suggested that primary resistance to ICIs can be attributed to abnormal gut microbiome composition (Routy et al., 2018b). Indeed, in pre-clinical models, the absence of an intact gut microbiome negatively impacted ICI efficacy (Vetizou et al., 2015). In parallel, many clinical studies including more than 1800 patients demonstrated that treatments with broad-spectrum antibiotics (ATB) resulted in poorer outcomes for patients treated with immunotherapy (Elkrief et al., 2019a). Both these findings have led to the hypothesis that ATB-induced symbiosis might influence the clinical response through the modulation of the gut microbiome (Matson et al., 2018).

To date a small number of retrospective case series, including different patient populations both in terms of tumor histology and different ATB use windows, evaluated the impact of ATB use in patients treated with ICIs. Derosa et al. examined patients with advanced renal cell carcinoma (RCC) and NSCLC treated with anti-PD-1 agents and compared patients who had received antibiotic within 30 days of beginning ICI with those who had not (Derosa et al., 2018). Among RCC and NSCLC patients treated the 13% and 20% received ATB respectively. In RCC patients ATB was associated with increased risk of primary progressive disease, lower PFS and OS. In patients with NSCLC ATB was associated with similar rates of primary progressive disease, but decreased PFS and OS. In another similar retrospective study on advanced melanoma patients treated with nivolumab, the impact of ATB use within 30 days prior to ICI starting adversely affected the PFS of patients (Elkrief et al., 2019b).

Recently, Tinsley et colleagues investigated the use of antibiotics during the periods 2 weeks before and 6 weeks after ICI treatment in a retrospective review of 291 patients affected by advanced cancer (including melanoma, RCC and NSCLC) treated with ICI (Tinsley et al., 2019). Antibiotic use, especially if multiple or prolonged courses, was confirmed an independent negative predictor of PFS and OS in patients with advanced cancer treated with ICIs. Similar results were reported in a retrospective series on lung cancer patients treated with immunotherapy, in which a detrimental effect was observed for patients with a higher Antibiotic-Immunotherapy Exposure Ratio (AIER) defined as days of antibiotic/days of immunotherapy during the whole period of treatment (Galli et al., 2019). Although the optimal ATB window has not been defined, prior ATB use within one month from ICI start seems to be associated with worse OS (regardless histotype, tumor burden, and ECOG PS), but not the concomitant use (Pinato, 2019).

The majority of studies investigated the role of early ATB use (1–2 months before and 1 month after the start of immunotherapy) in patients affected by melanoma, RCC and NSCLC. None of these had assessed the impact of ATB use in head and neck patients, although preliminary evidence on the importance of microbiota for also this setting of patients is now emerging (Hayes et al., 2018).

Put together, these studies suggested a negative impact on outcomes, deriving from the use of antibiotics, in patients receiving immune checkpoint inhibitors (Rossi et al., 2019). The timing of broad-spectrum antibiotic treatments with respect to the starting of ICIs seems to be important, and the antibiotics use seems to be independently associated with markers of poor prognosis (such as age, tumor stage, histology, prior lines of treatment, recent hospitalization) (Elkrief et al., 2019a).

Prospective studies are needed to elaborate guidelines for the optimal management of patients who do require ATB, to establish the minimum duration of ATB therapy, to define the specific ATBs that might induce favorable alterations in the host immune system or that are particularly negative for clinical outcome. It is also important to understand the potential impact of other concomitant medications and conditions that might alter the microbiome. Moreover, it should be advisable to understand if the current evidence is confirmed in patients with R/M-HNSCC, who are afflicted by an intrinsically poor prognosis and may often be in need of antibiotics.

5. Pathological and molecular factors

5.1. PD-L1

Most of clinical trials evaluating ICIs in R/M-SCCHN stratified PFS and OS on PD-L1 status, finding that patients with PD-L1 positive tumors responded with greater antitumor activity in comparison with PD-L1 negative patients. In the phase 1 study of pembrolizumab (KEYNOTE-012) analysis of PD-L1 showed more improved response rates in PD-L1 positive tumors than in PD-L1 negative tumors when membranous staining on tumor and mononuclear immune cells were used to score PD-L1 (Chow et al., 2016). With a CPS ≥ 1 (where CPS is determined by the number of PD-L1 staining cells – tumor cells, lymphocytes, macrophages- divided by total number of tumor cells evaluated, multiplied by 100) the response rates were 22% in PD-L1 positive patients compared with 4% in PD-L1 negative patients and similar trends were noted for PFS and OS. In contrast, PD-L1 expression on tumor cells alone (TPS – tumor proportion score > 1%) did not correlate with response, PFS or OS.

In KEYNOTE-040, a larger randomized study with pembrolizumab, the correlation with clinical outcome was strongly positive using PD-L1 expression on tumor cells alone (TPS ≥ 50%), but also using PD-L1 expression on tumor and immune cells (CPS ≥ 1) (Cohen et al., 2019b).

Recently, KEYNOTE-048 showed that pembrolizumab plus chemotherapy obtained superior OS in the PD-L1 CPS ≥ 20, CPS ≥ 1, and total population, while pembrolizumab monotherapy demonstrated superior OS in the CPS ≥ 20 and ≥ 1 groups and resulted non-inferior than SOC chemotherapy in the total population (Rischin and

Harrington, 2019).

In the CheckMate 141, a phase 3 study of nivolumab in platinum refractory R/M-HNSCC, for patients with less than 1% tumor PD-L1 expression median survival was similar between the immunotherapy and chemotherapy arms (Ferris et al., 2016). In contrast, patients with tumor PD-L1 expression ≥ 1% had longer survival and higher response rate with nivolumab than with chemotherapy. However, the 2-year follow-up data from CheckMate 141 indicated that over time the magnitude of benefit of nivolumab increased in patients with PD-L1 negative tumors, with a decrease in the HR, while remaining in patients with PD-L1 positive disease (Ferris et al., 2018). Moreover, with an increased PD-L1 expression (> 1% versus > 5% versus > 10%), nivolumab resulted in higher ORR, but had not impact on the OS. The assessment of PD-L1 expression in this trial was performed on tumor cells only, therefore the benefit observed in PD-L1 negative patients could be due to PD-L1 stromal cells. An exploratory analysis from CheckMate 141 evaluated the immune profile of patients, in context of tumor PD-L1 expression and showed that an increased abundance of tumor-associated immune cells (TAICs) expressing PD-L1 was associated with longer overall survival and greater likelihood of response to nivolumab, independent of tumor cell PDL-1 expression (Ferris, 2017).

In a phase 1/2 study with durvalumab, an anti-PD-L1 agent, ORR was 18% in patients with PD-L1-high tumor cell expression (defined as patients with ≥25% of tumor cells expressing PD-L1) compared to 8% in patients with PD-L1-low/negative tumor cell expression (Zandberg et al., 2019).

Generally, PD-L1 tumor expression correlates with improved outcomes in R/M-HNSCC treated with ICIs and its potential predictive value increase when including PD-L1 expression on immune cells (CPS more predictive than TPS). Nevertheless, the benefit from ICIs was also seen in some patients with PD-L1 negative tumors, indicating that PD-L1 was not a perfect biomarker for patient selection.

With the exception of results from KEYNOTE-048, mostly data available arose from exploratory retrospective analysis of prospective trials. Although the *Cancer Immunotherapy Guidelines – Head and Neck Cancer* subcommittee agreed that combined positive score (CPS) is the best score to use for PD-L1 testing in HNSCC patients treated with immunotherapy, the expression levels may differ according to the assay used for the test (for Dako: 28.8 or 22C3; for Ventana SP263 or SP142) and no concordance has been yet proven for the different FDA-approved tests. Recently, the FDA approved the use of pembrolizumab as a single agent for frontline setting with its companion diagnostic test (22C3 pharmDx kit). However, aside from this indication the level of tumor PD-L1 expression can be useful for decision making in special situations, such as in patients with high risk for toxicity with chemotherapy (e.g., with poor performance status, old age or comorbidities).

Another emerging predictive factor, which is currently under investigation, is PD-L2 (Bossi et al., 2019b). PD-L2 expression can be induced on multiple immune cells and, most importantly, is also expressed by tumor cells of many solid tumors, including HNSCC, which was the most PD-L2 enriched tumor type. Pembrolizumab-treated patients with PD-L2 positive tumor cells had a longer PFS and an improved OS respect to those with PD-L2 negative tumor cells, indicating that PD-L2 expression could be a predictive factor regardless the PD-L1 and partially explaining responses in PD-L1 negative patients (Yearley et al., 2017). Moreover, recent studies provided evidence of the predictive capacities of immune checkpoint gene methylation for response to ICIs in melanoma and gastric cancer (Goltz et al., 2018; Lingohr et al., 2019). The potential epigenetic regulation of PD-L2 and the association with known predictive biomarkers of response to anti-PD-1 immunotherapies, such as high mutational load, microsatellite instability and CD8 + T-cell infiltration, strongly suggests integration of PD-L2 methylation as an additional biomarker candidate also with ongoing trials for response to PD-1 immune checkpoint blockade in head and neck cancer. Further studies are needed to understand better the clinical relevance and predictive value of PD-L2 in this setting.

5.2. Tumor infiltrating lymphocytes (TILs) and others biochemical factors

Comprehensive characterization of heterogeneous immune tumor microenvironment (TME) could provide not only prognostic information, but also be predictive of response to therapies. The presence of strongly immunosuppressive tumor microenvironment in head and neck cancer has been widely demonstrated and allows tumors to evade immune recognition and elimination (Curry et al., 2014), but at the same time provides opportunity for therapeutic intervention (Gildener-Leapman et al., 2013). Despite the heterogeneity of the studies, the positive prognostic value of tumor infiltrating lymphocytes (TILs) in head and neck cancer has generally been recognized, although differences have been reported according to anatomic sub-site, tumor compartment (intra-tumoral vs. stromal) and HPV status (Solomon et al., 2018). In contrast with the growing evidence of its value as prognostic biomarker (de Ruiter et al., 2017), TILs assessment has not yet found a clinical application and limited data is available regarding its predictive value in head and neck cancer.

Studies using semi-quantitative scoring of IHC to describe TILs have suggested a potential role of infiltrating T cells in predicting the efficacy of chemoradiation (Balermpas et al., 2014, 2016). Balermpas et al. reported that high levels of CD3+ and CD8+ intra-tumoral TILs correlated with increased survival following definitive chemoradiotherapy, while stromal TILs showed no significant association (Balermpas et al., 2014). Subsequently, in another cohort of patients treated with surgery followed by adjuvant chemoradiation, CD3+ and CD8 + TILs in the stromal, intra-tumoral and tumor periphery compartments were all associated with improved outcome (Balermpas et al., 2016).

More recently, a retrospective evaluation of 126 patients treated with anti–PD-1/L1 therapies showed that higher CD8 + T cells infiltrates were positively correlated with treatment response among virus-negative tumors, suggesting their potential predictive role (Hanna et al., 2018). The dominant immunophenotype comprised an activated (CD38+ or CD69+) population enriched with effector memory T cells (CD45RO + CCR7-). These cells exhibited greater effector function and secrete high levels of IFN-γ with significant cytotoxic potential. The increase in B cells and myeloid-derived suppressor cells was additionally reported in PD-1 blockade responders, contributing the findings of an expanded CD8+ effector memory T cell population among responders (Ribas et al., 2016).

In this regard, another interesting observation was the pattern of checkpoint receptor co-expression among non-responders. A recent study showed intratumoral exhausted PD-1+ CD8 + T cells expressing TIM-3 or LAG-3 were higher among non-responders to anti-PD-1 therapy, suggesting a mechanism of adaptative immune resistance (Hanna et al., 2018). The inhibition of the PD-1/PD-L1 axis facilitates upregulation of other key checkpoint molecules to promote immune evasion. In a subgroup analysis of CheckMate 141 evaluating treatment with nivolumab beyond progression, responders had significantly lower levels of circulating PD-1+ CD8 + T cells at baseline and lower levels of PD-1+ T-regs at day 43, indicating that circulating exhausted T cells could be a negative predictive biomarker to anti-PD-1/PD-L1 drugs (Haddad et al., 2019).

Genomic analyses have also highlighted the importance of immune cell infiltrates in HNSCC. Keck and colleagues identified immune mesenchymal subtypes of HPV + and HPV- tumors, which were associated with increased expression of immune markers, CD8 + TILs and improved outcomes (Keck et al., 2015). Analyzing transcriptome data from 280 HNSCC from The Cancer Genome Atlas (TGCA), Mandal et colleagues identified different levels of immune infiltration and activation across tumors based on clinical and genetics features, such as HPV status, tumor site, molecular subtype, mutational smoking signature and genomic instability (Mandal et al., 2016). Both HPV + and HPV- HNSCC have the highest levels of T-regs and $CD56^{dim}$ NK cells,

which were also associated with superior survival. These findings suggested that immune composition may dictate a response to immunotherapy and that these tumors, then others, may benefit from T-reg-targeted therapies and inhibiting NK cells immunotherapeutic approaches.

Despite early data suggesting a correlation between TILs and response to ICIs, studies evaluating TILs in HNSCC have been limited by small cohort sizes, retrospective approaches, inclusion of heterogeneous populations, univariate analyses, and lack of standardized methodology for TIL quantification. This argues for the need for larger studies with prospective validation that take into account factors such as tumor site and HPV status, and also for identifying a T cell-inflamed phenotype and determining coexisting immune cells and co-expression of other inhibitory immune checkpoint molecules beyond PD-1/PD-L1 within the TME.

Another biochemical marker which has been investigated as a prognostic indicator for cancer patients is the neutrophil-to-lymphocyte ratio (NLR), an inflammatory- and immunologically-based index which may reflect host inflammatory responses and changes in the tumor microenvironment (Dumitru et al., 2012; Guthrie et al., 2013). Several studies have reported a relationship between the prognosis and the NLR in many solid tumors, including HNSCC (Salim et al., 2015; Takenaka et al., 2018). The most comprehensive meta-analysis investigating the prognostic value of NLR in HNSCC, with 28 cohorts involving 6847 patients, demonstrated that high level of pretreatment NLR was significantly associated with poor OS, DFS and PFS (Yang et al., 2019). Known the inclusion of only retrospective and observational studies with potential selection bias, prospective randomized controlled trials are warranted to confirm these findings. Although the exact mechanisms underlying the association between NLR and poor prognosis in cancer remains poorly understood, various hypotheses have been described. Neutrophils are a type of inflammatory cells that promote angiogenesis, cell growth, tumorigenesis, and tumor progression by secreting vascular endothelial growth factor, hepatocyte growth factor, IL-6, IL-8, and matrix metalloproteinases (Swierczak et al., 2015). In addition, neutrophils have been demonstrated to inhibit antitumor immune responses by suppressing activating T lymphocytes and natural killer cells through producing reactive oxygen species, arginase, and nitric oxide. Whereas, decreased lymphocyte counts often indicate suppression of lymphocyte-mediated antitumor immunity and poor clinical outcome (Coffelt et al., 2016).

However, the predictive value of the NLR in the immune and treatment responses of

HNSCC is still unclear. A recent published study revealed that an elevated NLR was significantly associated with higher locoregional recurrence and reduced overall survival in HNSCC patients who had received curative treatment (Chen et al., 2018). Furthermore, the authors examined the predictive value of aldehyde dehydrogenase 1 (ALDH1) for HNSCC prognosis and the correlation of the ALDH1 level with the myeloid-derived suppressor cells (MDSCs) levels and NLR, showing that the elevated expression of ALDH1 was correlated with a higher incidence of lymph node involvement and lower survival rate. Patients with a higher NLR had a higher ALDH1 level in their tumor specimens and more MDSCs in the peripheral circulation, which are associated with poor prognosis. These preliminary data suggest that the NLR could represent an important biomarker to assist the clinician and patient in making informed decisions regarding treatment options for HNSCC patients.

Another small retrospective study evaluated the clinical utility of the NLR in the management of patients with R/M-HNSCC treated with nivolumab, investigating whether the NLR kinetics could be used to predict the anticancer effect (Yasumatsu et al., 2019). Consistent with the results of previous studies concerning other malignant tumors, the authors found that the post-treatment NLR was significantly higher than the pretreatment value in 13 of 17 patients (76%) with progressive disease within the first 3 months, whereas the post-treatment NLR was lower than the pretreatment value in 10 of 11 patients (91%) with stable disease or partial response.

Although these findings need to be confirmed by prospective and large-scale studies, the NLR may represent a simple and economically feasible, earlier detection marker of disease progression in HNSCC patients treated with nivolumab. Thus, monitoring the NLR during ICIs therapy may guide the clinician in changing therapy at an early point in the disease course through the precocious confirmation of treatment failure.

5.3. Tumor mutational burden

Tumor mutational burden (TMB) has been recently emerged as a potential biomarker across many cancer types for identification of patients that will benefit from immunotherapy (Le et al., 2015; Rizvi et al., 2015; Snyder et al., 2014). Due to the fact that cancer cells have a high number of somatic mutations and produce neo-antigens, TMB may represent a useful estimation of tumor neo-antigenic load. Melanoma and squamous cell carcinoma of the skin followed by smoking-related cancers including NSCLC, urothelial cancer (UC) and HNSCC comprised malignancies with the highest levels of TMB (Alexandrov and Stratton, 2014). However, a significant TMB range is observed within the same cancer type (Chalmers et al., 2017).

Known that high TMB is associated with a greater probability of displaying tumor neoantigens on major histocompatibility complex (MHC) molecules on the cell surface, it is rational to hypothesize that tumors with the highest TMB stand to benefit most from immune checkpoint blockade. Consistent with this hypothesis, several studies have shown a correlation between TMB and response to ICIs in melanoma, urothelial cancer and NSCLC, but preliminary evidence is also emerging in HNSCC.

In a retrospective analysis of 126 HNSCC patients treated with anti-PD-1/PD-L1 agents TMB was found to be significantly higher among responders and was correlated with increased median OS in HPV– disease (Hanna et al., 2018).

Subsequently, a combined biomarker analysis of multiple studies with the proposal to evaluate the relationship between TMB, T-cell inflamed gene expression profile (GEP), PD-L1 expression by CPS and response to pembrolizumab in HNSCC showed no significant correlation between these two categories of biomarkers (TMB and inflammatory biomarkers – PD-L1 and GEP) (Cristescu et al., 2018). Although TMB and inflammatory biomarkers do not co-associate in multiple trials, greater benefit with ICIs is generally observed with high levels of both TMB and GEP or TMB and PD-L1 IHC expression, suggesting that TMB and inflammatory biomarkers have distinct and independent predictive values, and may be used orthogonally to identify responders.

A recent work evaluating the role of TMB for the efficacy of concurrent chemoradiation (CRTX) in locally advanced unresectable disease showed that high TMB identifies patients with poor outcome who might preferentially benefit from CRTX-ICI combinations (Eder et al., 2019).

The first FDA approval based on the concept of TMB was an anti-PD1 agent for patients with tumors characterized by mutations affecting DNA damage response, such as those with microsatellite instability high (MSI-H) or mismatch repair deficiency (dMMR), who have the highest mutational load, proving to be particularly sensitive to immune checkpoint blockade. Prospective clinical trials of pembrolizumab in adult and pediatric patients with MSI-H or dMMR solid tumors have been successful conducted, leading a rapid approval of pembrolizumab in this biomarker-defined group of patients (Le et al., 2017, 2015). The estimated frequency of MSI-H in HNSCC tumors is approximately 1–3%. However, Hanna et al. identified a subgroup of responders to ICIs whose tumors were enriched with somatic alterations derived from frameshift events in several genes with known tumor suppressor function, such as *NOTCH1* and *SMARCA4*. Similar to MMR

deficiency, these frameshift events may lead to errors in the genomic reading frame that yield an intermediate-to-high mutational load (Hanna et al., 2018).

Despite encouraged data, the interactions between the tumor, the microenvironment and the immune system are complex and dynamic, and TMB is not without limitations. Comparable to what occurred with the PD-L1 assay, defining standards to determine the mutational burden is not well established (Chan et al., 2019). Additionally, the variability of the thresholds used across studies are interferring with the interpretation and extrapolation of the results obtained. Moreover, the presence of immunogenic neoantigens is not only factor that influences the ability of T cells to recognize and kill tumor cells. Thus, important challenge is to understand how inactivating mutations in the antigen presentation pathway could modulate the overall effect of TMB on response to ICIs. Until calibration and standardization is not required for designing biomarker-validating studies, TMB analysis cannot be recommended in HNSCC.

5.4. Immune-gene signature

Gene-expression profiling (GEP) signatures, that identify tumors with an inflamed TME, represents a promising biomarker that may predict response to anti–PD-1 therapy in different tumor types. Through a rigorous multistep validation process, a composite score based on T-cell–inflamed GEP comprised of 18 genes indicative of a T-cell–activated TME was derived across a wide variety of solid tumors, demonstrating a positive correlation with response to pembrolizumab (Ayers et al., 2017). This study confirmed that a T-cell inflamed microenvironment, characterized by active INF-γ signalling, antigen presentation, cytolytic activity, and T-cell active cytokines, is a common feature of tumors that are responsive to anti PD-1/-L1 therapy.

The 18-gene profile was tested in two HNSCC cohorts from prospective clinical trials (KEYNOTE-012 and KEYNOTE-055) treated with pembrolizumab, showing a significant and independent association with increased response, PFS, and OS, regardless of HPV status (Haddad, 2017; Seiwert et al., 2018).

This signature has been subsequently validated in additional tumor cohorts from KEYNOTE-012 and -028 trials, including melanoma and HNSCC. The data confirmed its predictive value as a biomarker of response to pembrolizumab and showed also a positive correlation with PD-L1 expression by CPS, as expected for a gene co-expressed within the profile and consistent with the known PD-L1 upregulation in a T-cell–activated TME (Cristescu et al., 2018). Moreover, the study investigated the joint associations of inflammation (T-cell–inflamed GEP or PD-L1 CPS) and tumor mutational burden (TMB) with response rate and PFS, suggesting that the highest likelihood of clinical efficacy occurs in tumors with high levels of both inflammatory and mutational biomarkers. The TMB and GEP seems to be independent predictive biomarkers of response and demonstrated a low correlation, indicating that they capture distinct features of neo-antigenicity and T cell activation (Ott et al., 2019).

Despite these interesting results, assessment of these biomarkers in a randomized, comparative setting is required to provide a better understanding of how different components of the TME and mutational status may be used to predict clinical outcome with ICIs.

6. Emerging immune predictive biomarker: microbiota and CTCs

The microbiome may amplify or mitigate carcinogenesis, responsiveness to cancer therapy, and cancer-associated complications, thus potentially it represents an ideal immune biomarker predictor (Garrett, 2015; Goubet et al., 2018; Routy et al., 2018a).

The microbiota consists of a dynamic and complex community of microorganism (bacteria, fungi, viruses and other microbial and eukaryotic species) that are physiologically resident in the skin, gastrointestinal, respiratory and urogenital tracts; it plays a fundamental role on the induction, training and function of the host immune system, but also on the regulation of the quality and the magnitude of immune reactions, including antitumor responses (Guerrero-preston et al., 2017).

Retrospective cohort studies evaluated the composition of oral microbioma in the saliva of HNSCC patients showing a different microbiota composition compared with healthy controls, but also an association between the presence of specific bacteria and reduced risk of developing HNSCC (Hayes et al., 2018; Pushalkar et al., 2012; Wu et al., 2010).

Moreover, one of these studies that investigated the oral microbiota composition before and after treatment (including surgery, chemoradiotherapy and immunotherapy) proved an association between specific oral bacteria composition and down or up regulation of oncogenic and immune-signalling pathways (Guerrero-preston et al., 2017).

Chemotherapeutic interventions alter the balance between the gastrointestinal epithelium, the microbial community and the intestinal immunity; the perturbation of intestinal homeostasis may lead to the host immunization against some bacterial and to activation of the host's immunity, involved in the response after chemotherapy (Alexander et al., 2017).

Preclinical studies revealed that the efficacy of immune checkpoint inhibitors is strongly dependent on the gut microbiome, demonstrating an association between specific commensal intestinal flora (*Bacteroides* and *Bifidobacterium* species) and response to ICIs (Sivan et al., 2015; Vetizou et al., 2015). These findings have been recently confirmed by clinical data indicating that patients with melanoma and baseline gut microbioma enriched with *Faecalibacterium* and other *Firmicutes* had improved survival benefit from ICIs (Chaput et al., 2017; Gopalakrishnan et al., 2018; Routy et al., 2018b). The interpersonal variation within the gut microbiota is a plausible explanation for the range of clinical outcomes observed during ICI therapy.

The potential predictive role of microbiota in HNSCC is yet to be established. A sub-study from CheckMate 141 showed no significant association between the oral microbiota and treatment efficacy or survival, although this analysis was burdened by several limitations (Ferris et al., 2017). Intestinal and oral microbiota likely represent distinct entities with specific disease association, therefore an ongoing study will explore the correlation with both oral and intestinal microbiota using RNA sequencing in order to understand their role as predictors of response to ICIs in patients with HNSCC.

Overall, this preliminary evidence should be integrated into prospective clinical trials with the purpose of identifying a new tool to patient's stratification before the starting of anticancer therapies.

Another emerging research field is represented by a liquid biopsy analysing circulating tumor cells (CTCs), which provide a non-invasive and dynamic assessment of tumor specific alterations in "real time". This approach could significantly facilitate accurate patient risk stratification, guide treatment selection, predict response, and identify the failure of treatment early (Payne et al., 2019). The CTCs are cells derived from a primary or metastatic tumor mass that have shed into the vasculature or lymphatics and are carried around the body in the blood circulation. Several studies have investigated the survival outcomes and the CTC count as a prognostic biomarker in HNSCC, identifying a correlation between CTC positivity and decreased PFS and OS. In the largest study cohort to date, peripheral blood samples from 144 patients with locally advanced HNSCC patients, who had undergone previous primary tumor resection, were analyzed for CTC and detection of the latter was correlated with survival outcomes (Tinhofer et al., 2014). The authors demonstrated that CTC presence was a prognostic biomarker of worse DFS and OS in non-oropharyngeal carcinomas patients providing a useful tool for identification of patients who benefit from treatment intensification. In contrast, CTC positivity was associated with a good prognosis in patients with oropharyngeal carcinomas.

Most of the current research is focused on delivering intact single cells that can be characterised to provide protein-expression and

genetic level data, and thus identify actionable mutations and gene expression signature which can guide to understanding patient tumour heterogeneity and supporting the adoption of personalised medicine strategies. Preliminary evidence suggested a benefit of single-cells sequencing to identify tumor heterogeneity of PD-L1 expression between tumor samples and CTCs (Chikamatsu et al., 2019). Furthermore, in locally advanced HNSCC patients treated with curative intent the CTCs overexpressing PD-L1 at end of treatment was associated with shorter PFS and OS, suggesting that CTC PD-L1 status could be used as a prognostic marker to guide adjuvant-immunotherapy in this setting (Strati et al., 2017). Further research may clarify if CTC derived biomarkers provide more accurate prognostic and predictive risk stratification than tissue derived biomarkers, although most likely a combination of compartmental markers will be required. Subsequently, large clinical trials are needed to validate CTC multi-omic biomarkers, correlating to clinical outcome, in order to guide treatment decision making.

7. Conclusions

The development of immune checkpoint inhibitors has revolutionized the therapeutic landscape in head and neck cancer. Anti PD-1 therapies have become the standard of care for the treatment of patients with R/M-HNSCC and multiple ongoing studies are currently exploring the opportunity of incorporating immunotherapy in early-stage disease.

Known that only a minority of patients currently benefit from approved ICIs, an appropriate selection is crucial. At present, no validate predictive biomarkers of response are established in this disease, but many candidate markers have shown promising results. Up to now, PD-L1 testing is the only one that is used by regulatory agencies to guide ICIs approval in head and neck cancer therapy (i.e. FDA approval of pembrolizumab in first line setting). However, most of these clinical or molecular marker have been investigated retrospectively, thus prospective clinical trials will be critical to generate robust data and to advantaging the field.

This review, examining the most clinical and molecular factors associated with efficacy or resistance to ICIs in head and neck cancer, provides a practice guide to assist clinicians in the selection of patients to candidate to immunotherapy based on the current evidence.

This review examines the most clinical and molecular factors associated with efficacy or resistance to ICIs, however the data is as a whole to immature for the head and neck cancer and the points brought up in this paper will be important for clinicians and for researchers to take along in their clinical trial design and analysis in order to define a practice guide to assist medical oncologist in the selection of patients for immunotherapy treatment.

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Declaration of Competing Interest

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