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Nivolumab: targeting PD-1 to reinforce antitumor immunity in platinum-refractory, recurrent, or metastatic Head and Neck Squamous Cell Carcinoma

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ABSTRACT:
Head and neck cancers are the sixth most common cancers worldwide, the majority of which are squamous cell carcinomas. These cancers are associated with high mortality and morbidity rates and significantly impact the patient's quality of life. Surgery, chemotherapy, and radiation have been the mainstay of oncological therapy. However, in advanced recurrent or metastatic cases, the prognosis and overall survival rates are very poor. Immunotherapy has been added to the rapidly evolving therapeutic landscape of HNSCC as these tumors are highly immune infiltrated and thus respond to changes in the immune system. Immunotherapy has benefitted oncological care by providing immune checkpoint inhibitors, vaccines, T call transfers, etc that have improved the survival rates of the patients. For platinum-refractory recurrent or metastatic HNSCC, cetuximab was approved by the US FDA as first-line treatment in cases that haven't progressed within 6 months. However, there was a clear unmet clinical need for a systemic therapeutic agent for cases that worsened after 6 months. Nivolumab was the first checkpoint inhibitor to be approved by the US FDA for this purpose based on the CheckMate 141 trial in 2016. Nivolumab has demonstrated superiority over standard single-agent systemic chemotherapy (methotrexate, docetaxel, or cetuximab) by improving the overall survival of patients and a better safety profile. The article is a review of immunotherapy in head and neck oncology highlighting the beneficial role of Nivolumab in the clinical operational setting.

Keywords: Nivolumab, HNSCC, PD-L1, Head and neck cancer, Immunotherapy

I. INTRODUCTION

Squamous cell carcinoma of the head and neck, including cancers of the oral cavity, pharynx, and larynx. [(1)] HNSCC form the sixth most common cancer type with a global incidence of 4,00,000 to 6,00,000 per year and mortality rates as high as 40%–50% i.e 2,23,000 and 3,00,000 deaths per year. 90% of these cancers are squamous cell carcinoma. (HNSCC) [(2)] HNSCC is responsible for approximately 3% of malignancies in the USA and 4% in Europe. [(3,4)]

Most patients with HNSCC present with locoregionally advanced disease, (stage III to IVB) at diagnosis, and more than 50% have a recurrence within 3 years. Maximizing the quality of life of patients with cancer is increasingly recognized as an important therapeutic goal, particularly in the context of improved survival. The morbidities associated with head and neck cancers as a result of damage to anatomic structures and functional impairments either due to the tumor itself or as a result of surgical resection, chemotherapy, radiation therapy can significantly impact mastication, deglutition, breathing and speech, etc that degrade the quality of life of these patients. HNSCC is thus associated with significant anatomic, functional, esthetic, social, and psychological ramifications. In addition to negative effects on quality of life, these patients have a dismal prognosis. Patients with recurrent or metastatic HNSCC might have residual toxicities caused by previous systemic therapies that can affect performance status, restrict the administration of subsequent treatments, and predispose patients to develop additional toxicities. [(5)]

Therapeutic options for HNSCC are based on tumor staging, the performance status, and related functional and physical comorbidities. Primary treatment of HNSCC consists of surgical

intervention and/ or radiation therapy. In more advanced stages (stages III and IV) adjuvant (chemo-)radiotherapy after surgery is administered, depending on established risk factors. The current first-line standard for recurrent and/or metastatic (R/M) HNSCC is a triple association of doublet chemotherapy (platinum, fluorouracil) and cetuximab (anti-EGFR agent), based on the EXTREME trial. [6] The toxicity of the EXTREME regimen is considerable, with an 82% rate of grade 3–4 adverse events (AE) Commonly applied second-line treatments include methotrexate, cisplatin, carboplatin, paclitaxel, docetaxel, and capecitabine. [7]

However, until the approval of Nivolumab, there was no second-line treatment that was able to improve the median overall survival beyond 6 months [8] in patients with HNSCC who have cancer progression within 6 months after platinum-based chemotherapy administered in the context of primary or recurrent disease. In the primary setting, despite all efforts, the 5 -year survival rate for the locally advanced disease was 50 -55%. The dire need to improve overall survival in advanced recurrent or metastatic cases without further exacerbating toxicity [9] paved the way for immunotherapy to foray into oncological therapy and ushered the use of Nivolumab, an immune checkpoint inhibitor that not only improved the overall survival but also the quality of life of patients with a better safety profile compared to chemotherapy. [10] This heralded a new era of anticancer treatment. [11]

Immunotherapy- The newest finding in medical oncology

Immunotherapy garnered enthusiasm because these agents use the patient's immune system, which can become suppressed by cancer cells, to fight the tumor. The hope was that by releasing suppressed immune cells and allowing these cells to be activated, immune cells could fight off tumors such as how the cells respond to an infection. The current armamentarium of immunotherapeutic strategies includes tumor-specific monoclonal antibodies, cancer vaccines, cytokines, adoptive T-cell transfer, and immune-modulating agents. [12,13]

History:

In the latter half of the 19th century, experimental attempts with streptococcal culture injections yielded sporadic remissions in patients with inoperable sarcomas. During that period, the Nobel Prize-winner Paul Ehrlich revolutionized the understanding of the role of the immune system in the fight against human diseases by suggesting the existence of specific receptors that can bind various antigens. This later evolved into his 'magic bullets' theory, which hypothesized the ability to seek out pathogens while sparing healthy tissues. Subsequently, in 1909, he postulated that tumors might be recognized by the immune system. In the 1950s, Thomas and Burnet proposed the concept of immunosurveillance, in which lymphocytes acted as sentinels to protect against transformed cells. In the 1970s, the NK were cells by Herbermann, which seemed to provide innate immune protection from the tumor. In the 1980s several cytokines (e.g. IL-2, IFN-α) entered clinical testing, new data on tumor-associated antigens appeared, and the adoptive T-cell transfer was used for the first time. [14]

The remaining doubts were dispelled in 2001 when Shankaran et al. published their paper showing that deeply immunocompromised mice lacking the recombination activating gene-2 did indeed experience a higher incidence of sarcomas. In the following years, with the arrival of tumor-specific monoclonal antibodies, medical oncology stepped into the era of targeted therapy, expanding the broad spectrum of immunotherapeutic approaches. In addition, as reported in 2010, sipuleucel-T, a vaccine based on autologous dendritic cells, reduced the risk of death in metastatic castration-resistant prostate cancer and became the first therapeutic cancer vaccine to be approved by the United States Food and Drug Administration (FDA). In parallel, allogeneic bone marrow transplantation was established as a standard treatment option for selected hematological malignancies.

The Immune System

The immune system is divided into two parts: adaptive and innate. The adaptive immune system is comprised of T cells and B cells and involves a directed response resulting from recognition of specific antigens loaded on a major histocompatibility complex (MHC) molecule. T cell activation is the result of two signals. within the context of a confirmatory third signal. Signal 1 occurs at the "immune synapse" where tumor

antigens bound to the MHC molecule on the surface of antigen-presenting cells (APCs) are presented to a T cell receptor (TCR). Signal 2 consists of either a co-stimulatory signal, such as the cluster of differentiation (CD) 28: B7 interaction, or an inhibitory signal.

The final signal, from immune-activating cytokines such as interleukin 12 (IL-12) or type I interferon (IFN), modulates the immune response, directing the cell towards inhibition or stimulation. Effective antigen presentation leading to T cell activation is enhanced and sustained by the induction of co-stimulatory cell surface molecules. To avoid an over-reactive immune system that leads to autoimmunity, immune cells express co-inhibitory receptors (immune checkpoints) that determine if a T cell is activated or becomes anergic, or nonresponsive, to the antigen displayed on the MHC molecule.

The Immune System and Cancer

An established hallmark of the multistep evolution of cancer is its ability to avoid immune destruction, particularly by T-lymphocytes and B-lymphocytes, macrophages, and natural killer cells. Consequently, cancer immunotherapy is based on the functional restoration of certain signaling cascades of the host immune system. These cascades help to counteract various tumor evasion strategies such as reduced antigen processing and presentation, increased tumor-permissive cytokine profiles, the establishment of an immunosuppressive microenvironment, cellular immune escape via regulatory T-cells or myeloid-derived suppressor cells (MDSCs), and induction of anergic T-cells either by an increase of co-inhibitory receptors (e.g. CTLA-4 or PD-1) or decreased co-stimulatory receptors.

The immunotherapeutic landscape for HNSCC encompasses a variety of targets that suppress or stimulate the immune system's ability to eliminate neoplastic cells. Activation of checkpoint receptors, such as programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte-associated protein (CTLA-4), causes T cell suppression. By contrast, activation of costimulatory receptors, such as CD40, glucocorticoid-induced tumor necrosis factor receptor (GITR), and toll-like receptors (TLRs) causes immune system stimulation. In addition to receptor signaling, certain enzymes, such as indoleamine 2,3-dioxygenase (IDO) and arginase 1 (Arg1), modify the tumor microenvironment by depleting nutrients essential for T cell proliferation while other enzymes, such as inducible nitric oxide (NO) synthase (NOS2), produce toxins that inhibit T cell proliferation. A functioning immune system with the capacity to eliminate neoplastic cells is dependent on T cell recognition of antigens along with costimulatory and inhibitory signals. Costimulatory signals contribute to the defense against pathogens while inhibitory signals prevent autoimmunity. [15]

Rationale for use of Immunotherapy in HNSCC

1. HNSCC tumors are among the most highly immune-infiltrated cancers with the highest median Treg/CD8+ T cell ratio and the highest levels of CD56dim NK cell infiltration.
2. HNSCC has a relatively high tumor mutation burden (TMB). This is relevant because high TMB is predictive of the efficacy of immune checkpoint inhibitors (ICIs), presumed due to the production from mutated DNA of altered proteins which are antigenic, and which serve as tumoral immune targets.
3. HNSCC can be immunosuppressive: many patients with HNSCC exhibit impaired tumor-infiltrating T lymphocytes via overexpression of PD-1 and other immune checkpoint receptors impaired natural killer cells, and poor antigen-presenting function.
4. A major advantage of immunotherapy over other forms of systemic cancer therapy is that the results of improved survival and reduced toxicity are durable with clinical benefits sometimes measured in years. [16]

Concepts in Immunotherapy

Cancer Immunoediting and Immune escape

Ideally, the immune system recognizes tumor cells and destroys them. However, tumor cells develop mechanisms to escape immunosurveillance by thwarting immune recognition and response. Thus, tumor cells escape elimination and continue to proliferate. This occurs by a dynamic process known as immunoediting by which the tumor selects cells that can evade the immune system. Immunoediting thus results in tumor escape or immune evasion.

Pathways of immune evasion:

Secretion of cytokines such as TGF-β, IL-10, or VEGF establishes a tumor-promoting immunosuppressive environment. Additional factors such as secretion of IL-6, which prevents the activation of T cells, NK cells, or dendritic cells maturation via STAT3, further modulates the cellular immune system resulting in conditions, which facilitate immune escape. Thus, they actively suppress signals of the antitumor immune response. HNSCC cells also reduce T-cell mediated recognition by decreasing their inherent immunogenicity by downregulating human leukocyte antigen (HLA) class I molecules and disrupting the antigen-processing machinery (APM). The HLA complex of the immune system presents processed tumor antigenic peptides to T lymphocytes. Cells with complete loss of HLA may evade the immune response by T-cell recognition but are a strong trigger for NK-cell activation, as the absence of HLA removes a key inhibitory signal for NK cells. Therefore, tumor cells use multiple mechanisms to realize immune evasion while avoiding total loss of HLA expression. In addition to oncogenic epidermal growth factor receptor (EGFR) expression and mitogenic signaling in HNSCC, immunosuppressive effects result from the downregulation of HLA, APM components, and STAT1 activation, while leading to suppressive STAT3 signaling, cytokines, and ligands on HNSCC cells.

Role of Immune Checkpoint Inhibitors:

HNSCC exploits the fact that the immune system is tightly regulated through immune checkpoints to avoid autoimmunity or immune system over-activation under physiological circumstances. [17]

Immune checkpoint inhibitors (ICIs) are among the most promising drugs in the field of immuno-oncology. The introduction of checkpoint inhibitors has dramatically changed the therapeutic approach in several cancers including melanoma, head, and neck, lung, renal and bladder cancers. They interrupt the immunosuppressive pathway of inhibitory checkpoints, which are used by tumor cells to prevent an immune reaction. [18] These checkpoint inhibitors represent monoclonal antibodies that modulate the effects of immune checkpoints, such as Programmed Cell Death Protein 1 (PD-1) which is a co-inhibitory signal responsible for immune suppression. Various drugs have demonstrated long-lasting and durable responses, with favorable toxicity profiles. [19]

Clinically, the inhibition of immune checkpoint receptors is well recognized since the landmark randomized study by Hodi et al. 2010 and approval in 2011 demonstrated that the use of ipilimumab, a cytotoxic T-lymphocyte antigen-4 (CTLA-4) blocker or anti -CTLA -4 antibody, resulted in an improvement in overall survival improved overall survival (OS) by 3.5 months compared with a glycoprotein 100 peptide vaccine and, importantly, for the first time induced long term responses in R/M melanoma. CTLA-4 is an inhibitory receptor that downmodulates the initial stages of T-cell activation. It is expressed by CD4 and CD8 cells and binds CD80 and CD86 expressed only in antigen-presenting cells, transmitting an inhibitory signal to T cells. This study established immune checkpoint blockade as a new avenue of immunotherapy. [20]Head and neck cancers are immunosuppressive, with a high proportion expressing PD-L1.

PD-1 receptor is an immune checkpoint receptor expressed on activated T cells, activated T cells, B cells, natural killer cells, and some myeloid cells. It is a type I transmembrane protein receptor belonging to the CD28 family of T cell receptors. It binds two distinct ligands, PD-L1 and PD-L2 on tumor cells to reduce T-cell effector activity and terminate immune response, to protect healthy cells from an excessive inflammatory or autoimmune response. Expression of both ligands is induced by extrinsic pro-inflammatory signals including IFN-γ, TNF-α, IL-4, and GM-CSF. Drugs such as Nivolumab, binding PD-1 or PD-L1 can turn off the inhibitory signal from the tumor, thus stimulating the immune system.

Thus, Inhibitory checkpoint receptors (IR) play an important role in the tumor microenvironment (TME). The PD-1 binding to PDL-1 indicates an exhausted T cell that has lost its normal function, including reduced proliferative capacity or cytolytic activity. However, this dysfunctional state can be reversed with IR blockade using immune checkpoint inhibitory receptors such as Nivolumab. [21,22]

PD-L1 was found to be expressed in up to 45-80% of HNSCC. After cetuximab, anti-PD1/PD-L1 agents were the first systemic drugs to demonstrate significant activity and efficacy in the second-line treatment of platinum-refractory R/M

HNSCC. Anti-PD1/PD-L1 agents resulted in better tolerated than chemotherapy.

Components of the Tumor Microenvironment (TME):

The tumor microenvironment consists of quantitative and qualitative alterations in the regular immune cells and houses these modified cells to carry out the antitumor activity. An understanding of the tumor microenvironment is paramount to achieving desired outcomes with the use of immunotherapy. The tumor microenvironment comprises regulatory T cells (Tregs), Myeloid depressor cells (MDSCs), and Tumor-associated macrophages (TAM) that inhibit cytotoxic T cells and thus decrease the immune response. Tumors arising in the oropharynx display generally higher levels of T cell infiltration and immune activation, but also higher levels of immunoregulatory influence as represented by their comparatively lower CD8+/Treg ratio. These findings are consistent with the rich lymphoid tissue in the oropharynx, and may also reflect the high prevalence of HPV-associated cancers in this site.

HNSCC induces an immune-suppressive state via various mechanisms. Patients with HNSCC have altered lymphocyte homeostasis (mainly reduced levels of CD3+, CD4+, and CD8+ T cells) compared to healthy controls. Consistently, a higher number of tumor-infiltrating CD4+ and CD8+ lymphocytes is associated with better overall survival in HNSCC patients. Additionally, natural killer cell (NK) function is impaired in HNSCC patients, which is accompanied by elevated levels of TGF-β and soluble MHC Class I chain-related peptide A. HPV-positive oropharyngeal carcinoma patients have an increased number of CD56+ cytotoxic NK cells that contributes to their favorable prognosis.

NK cell subpopulations:

The potent and early secretion of IFN-γ by NK cells helps shape the immune tumor microenvironment by activating the effectors of adaptive immunity, particularly Th1 and myeloid cells. This ability to influence adaptive immunity as well as their innate tumor cytolytic capability implicates NK cells as key effectors of antitumor immunity.

As a result, the blockade of immunoregulatory NK cell checkpoint receptors has garnered significant interest. Agents (e.g., lirilumab) targeting NK cell inhibitory receptors, such as killer cell immunoglobulin-like receptor (KIR), are the subject of intense preclinical/clinical investigation as a monotherapy or in combination with other checkpoint inhibitors. The CD56 bright subpopulation is predominantly found in lymph nodes and peripheral blood and is believed to be the likely precursor to CD56dim cells, which are far more cytotoxic and play a critical role in antitumor immunity. Strikingly, HPV-positive and HPV-negative HNSCC tumors had the numerically highest levels of infiltration with CD56dim NK cells, compared with other highly immune-infiltrated cancer types. [23]

MDSCs: They are a diverse cellular population of myeloid origin with T-cell suppressive functions i.e they inhibit activated T cells. Also, MDSCs produce nitric oxide and reactive oxygen species, which interact to catalyze the nitration of the T-cell receptor, which inhibits T-cell receptor and HLA interaction, signaling, and subsequent activation. Treatments such as antibody depletion, retinoic acid, gemcitabine, and STAT3 blockade, diminish MDSCs, restore immune surveillance, increase T-cell activation, and improve the efficacy of immunotherapy.

Tregs: They promote cancer progression by causing energy, apoptosis, and cell cycle arrest of activated T cells via production of IL-10, TGF, and direct cell-to-cell contact. They also inhibit the action of DCs, NK cells, and B cells. Tregs are increased in peripheral blood in patients with HNSCC. Tregs such as CD4+, CD25 high+, and FoxP3+ are upregulated in HNSCC and act as potent immunosuppressors.

TAMs in the tumor microenvironment may be strongly antitumor and possess a so-called M1 phenotype, which is characterized by the production of IFN and another type 1 cytokines. They produce EGF, IL-6, and IL-10 and have been associated with angiogenesis, local tumor progression, and metastasis. Through these immune/inflammatory cells and mediators, HNSCC induces an immunosuppressed state via multiple potent mechanisms, which is a barrier to effective cancer immunotherapy.

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Others- There are several other anti-PD-1 agents such as pembrolizumab, Atezolizumab durvalumab, etc that are in the focus of immunotherapeutic research. The anti -PD - 1 - antibody pembrolizumab extended the duration of response in recurrent and/or metastatic (R/M) HNSCC (by approximately 53 weeks) in a phase Ib study KEYNOTE-012. Based on its long-lasting effects, pembrolizumab was granted FDA approval for the treatment of platinum-refractory R/M HNSCC by the FDA. Atezolizumab and durvalumab have already shown similar benefits in phase Ia and II studies, respectively. [24]

PD-L1 expression as a potential biomarker

PD-L1 expression by tumors has been theorized to be a potential biomarker for patients who may have responses with nivolumab. PD-L1 is an inducible marker that can be up and downregulated, can be expressed by both tumor cells and/or tumor-infiltrating lymphocytes, and may be expressed differently by the primary tumor and metastases. Also, the sensitivity and specificity of PD-L1 detection can vary by the assay type and the quality of the tissue sample. Studies have shown that there may be increased nivolumab activity, longer PFS, and longer median OS in patients with PD-L1-positive melanoma.

Nivolumab:

Because immuno-evasion plays an essential role in the development of HNSCC, it became apparent that immune checkpoint inhibitors could be effective and might be useful in satisfying the unmet clinical need for patients with r/mHNSCC.

Nivolumab was the first PD-1 inhibitor approved by the US FDA in 2014 for the treatment of unresectable or metastatic melanoma. It got approved by the US FDA in November 2016 and the European Medicines Agency (EMA) in April 2017, as second-line therapy for platinum-refractory (disease progression within 6 months after the last dose of platinum) R/M HNSCC. The pivotal study for nivolumab was CheckMate-141.

Class: A fully human IgG4 anti–PD-1 monoclonal antibody that disrupts PD-1-mediated signaling to restore antitumor immunity.

Indications: Second-line treatment for patients with recurrent or metastatic HNSCC after platinum chemotherapy that has worsened in 6 months

Applications: It has been approved by the US FDA for advanced cases of Melanoma, Non-Small-Cell Lung Cancer, Renal Cell Carcinoma, Classical Hodgkin Lymphoma, Advanced HNSCC, Urothelial Carcinoma, and Metastatic Colorectal Cancer.

Nivolumab generation:

Nivolumab was engineered using transgenic mice, which express human heavy and light chain antibodies that can undergo class switching (e.g., from IgM to IgG1 or IgG2) and somatic hypermutation was used to generate human anti-PD-1 antibodies. These mice were immunized with Chinese hamster ovary cells expressing the full PD-1 protein on their surface, and with recombinant human PD-1-Fc fusion protein (booster immunizations) to generate an immune response against PD-1. Spleen cells from animals with detectable anti-PD-1 antibodies were fused with myeloma cells, and the resulting hybridomas were screened for those producing anti-PD-1 monoclonal antibodies.

One clone was selected based on its high affinity and specificity of PD-1 binding, ability to inhibit PD-1 binding to PD-1 ligands, and capacity to enhance T-cell proliferation and cytokine secretion. The variable region sequences from this clone were grafted onto human kappa and IgG4 constant (Fc) region sequences containing an S228P mutation. The S228P mutation reduces Fc exchange with serum IgG4 molecules to improve stability and reduce therapeutic variability. The antibody (hereafter referred to as nivolumab) was expressed in Chinese hamster ovary cells and was produced using standard mammalian cell cultivation and chromatographic purification technologies.

Pharmacokinetics and pharmacodynamics

The mean peak occupancy of nivolumab on T lymphocytes is 85% (range: 70–97%) and mean plateau occupancy of 72% (range: 59–81%) observed at 4–24 h and ≥57 days, respectively, after one infusion. After a single dose of nivolumab, its half-life was estimated to be between 12 days (for subjected

treated at the 0.3, 1, or 3 mg/kg dose) and 20 days (10 mg/kg). The median time to peak concentration was 1–4 h after the start of infusion. Nivolumab does not affect the cytochrome P450 activity, and its clearance was not affected by a renal impairment or mild hepatic impairment. [25]

The Checkmate 141 Trial

Type of trial: Randomized, open-label, phase 3 trial

Enrollment: Patients were enrolled between May 29, 2014, and July 31, 2015

Inclusion criteria:

1. Histologically confirmed, recurrent HNSCC (including metastatic disease) of the oral cavity, pharynx, or larynx that was not amenable to curative treatment
2. Tumor progression or recurrence within 6 months after the last dose of platinum-containing chemotherapy administered as adjuvant therapy or in the context of primary or recurrent disease
3. Age of at least 18 years;
4. Adequate bone marrow, hepatic, and renal function; and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.14

Exclusion criteria:

1. Active brain metastases, autoimmune disease, or systemic immunosuppression
2. Known human immunodeficiency virus or hepatitis B or C virus infection
3. Previous therapy targeting T-cell costimulating or immune checkpoint pathways.

Trial Design:

This trial was registered with ClinicalTrials.gov, number NCT02105636)

361 patients were randomly assigned in a 2:1 ratio via an interactive voice response system to receive either Nivolumab (Opdivo, Bristol-Myers Squibb) or the investigator's choice. Randomization was stratified by previous cetuximab use.

Nivolumab (n=240): 60 min i.v infusions 3 mg/kg body weight every 2 weeks until disease progression, intolerable toxicity, or withdrawal of consent.

Standard therapy (n=121): weekly i.v administration of methotrexate at a dose of 40-60 mg/m2 of body surface area, docetaxel 30-40 mg/m2, or cetuximab 250 mg/m2 after a loading dose of 400 mg/m2

Endpoints and assessments:

Primary endpoint: Overall survival (OS) (time from randomization to the date of death from any cause)

Secondary endpoints:

1. Progression-free survival (PFS) (time from randomization to date of disease progression or death)
2. Objective response rate (ORR) according to RECIST, version 1.1.

Additional prespecified endpoints: Time to response; associations between PD-L1 level and human papillomavirus (HPV) status and response rate; safety; and quality-of-life assessments.

Tumor response was assessed according to RECIST, version 1.1, every 6 weeks beginning at week 9. Patients were followed for overall survival every 3 months until death, loss to follow-up, or withdrawal of consent. At each treatment visit and for 100 days after receipt of the last dose, acute toxic effects were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0.

Patient-reported outcomes, including symptoms and health-related quality of life, were exploratory endpoints and were evaluated with the use of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 module (QLQ-C30) and the head-and-neck–specific module (QLQ-H&N35).

The proportion of patients reporting health problems was assessed with the use of the three-level version of the European Quality of Life–5 Dimensions (EQ-5D-3L) questionnaire. Patients also completed the EQ-5D-3L visual-analog scale.

Biomarker analysis:

PD-L1 expression by immunohistochemistry is the most widely used biomarker and is predictive of response to PD-(L)1 blockade in lung cancer and HNSCC.

For patients with oropharyngeal cancer, tumor HPV status was assessed using p16 immunohistochemical testing Dako North America) with the use of a rabbit antihuman PD-L1

antibody (clone 28–8, Epitomics) and defined as positive if diffuse staining was present in at least 70% of the tumor cells.

Immunochemical testing for p16 was not performed for non- oropharyngeal cancers because of the low prevalence of HPV-positive tumors and poor specificity for HPV status at these anatomical sites.

II. RESULTS:

The median overall survival was 7.5 months in the nivolumab group versus 5.1 months in the group that received standard therapy. Overall survival was significantly longer with nivolumab than with standard therapy and the estimates of the 1-year survival rate were approximately 19 percentage points higher with nivolumab than with standard therapy (36.0% vs. 16.6%).

The rate of progression-free survival at 6 months was 19.7% with nivolumab versus 9.9% with standard therapy. The objective response rate (ORR) was 13.3% in the nivolumab group versus 5.8% in the standard therapy group. This means that patients treated with nivolumab are more likely to benefit in terms of survival outcomes.

Survival was slightly worse in those who had been previously treated with cetuximab than in cetuximab-naive patients (7.1 vs. 8.2 months, respectively. This could be due to the PD-L1 downregulation mediated by EGFR-inhibition.

Quality of life improved during nivolumab treatment. including social function, swallowing, talking, eating, and xerostomia.

Patients treated with nivolumab appeared to have longer overall survival than those treated with standard therapy, regardless of tumor PD-L1 expression or p16 status.

Adverse events:

With regards to safety, nivolumab had a lower percentage of grade 3–4 adverse events in respect to SOC (13.1 vs. 35%, respectively)

In the nivolumab-treated group, fatigue (14%), nausea (9%), rash (8%), decreased appetite (7%), pruritus (7%), and diarrhea (7%) were the most common side effects. Apart from skin reactions, other adverse events comprised of endocrine (8%) primarily hypothyroidism, gastrointestinal, hepatic, pulmonary, infusion-related, and renal toxicities. There were two treatment-related deaths in the nivolumab cohort (caused by pulmonary embolism and hypercalcemia) and one in the standard therapy arm (lung infection).

Nivolumab stabilized physical, role, and social functioning from baseline to weeks 9 and 15 and delayed time to deterioration of patient-reported quality of life outcomes whereas IC led to clinically meaningful deterioration. [26, 27]

Other studies have also reported adverse effects with nivolumab therapy. 3 patients were reported by Hiroki Kagoshima et al [28] who complained of fatigue and appetite loss and were diagnosed with adrenal insufficiency based on the ACTH and cortisol levels. Another case of pituitary-adrenal dysfunction was reported by Kosuke Hihara et al [29] after 8 courses of nivolumab treatment in a 50-year-old man. Patients were switched to hydrocortisone and were successfully managed in all cases. Lichenoid skin reactions associated with anti-PD-1 therapy have been previously reported; the skin lesions often have a delayed onset and include typical lichen planus, hypertrophic or papulosquamous lesions that usually develop on the trunk and extremities. In the majority of these cases, lichen planus resolved with topical treatment, with no need for additional systemic therapy or discontinuation of immunotherapy. 'Hyperprogression' effect has also been observed with nivolumab wherein the disease paradoxically accelerates and 'flares up' on immunotherapy. [30]

Combination Therapy

The following have been associated with a significant survival benefit: radiotherapy, high-dose three-weekly cisplatin given concurrently with radiotherapy, and cetuximab, an anti-epidermal growth factor receptor (EGFR) monoclonal antibody. The use of various combination regimens is interesting since both chemotherapy (e.g. oxaliplatin, cyclophosphamide) and radiation can initiate effective antitumor immunity by inducing immunogenic alterations in dying and surviving cancer cells. The so-called 'immunogenic cell death' leads to dendritic cell activation, which facilitates the presentation of tumor antigens. Targeting CTLA-4 and PD-1/ PD-L1 axis in this setting allows for the lifting of inhibitory signals on effector T lymphocytes in the tumor

microenvironment, which then allows therapeutic synergy with cytotoxic or targeted agents.

Rarely, radiotherapy is associated with the abscopal effect, also known as the radiation-induced bystander effect, in which local treatment leads to a response in distant lesions. . This effect means that local irradiation results in regression of non -irradiated metastasis through anti-tumor immune reactions. Therefore, radiotherapy or chemotherapy may show synergistic effects with immunotherapy.

Another therapeutic combination strategy involves the use of HPV vaccines with checkpoint inhibitors. Preclinical models have shown more potent antitumor responses when anti-PD-1 therapy was combined with vaccines against HPV-specific antigens. Multiple trials are currently underway combining ICI with different HPV vaccines (ISA101/adjuvant mountainside, MEDI0457, ADXS11- 011, and TG4001).

Killer-cell immunoglobulin-like receptors (KIR) are other checkpoint receptors that suppress cytotoxic effects of natural killer (NK) cells on HLA-expressing tumor cells. Inhibition of these receptors could remove inhibitory signals on NK cells and further assist with antitumor immunogenic response. Two trials are investigating the combination of ipilimumab (NCT01750580) or nivolumab (NCT01714739) with anti-KIR antibody. Additionally, CD137 and OX40 are costimulatory tumor necrosis factor superfamily receptors primarily expressed on activated T cells, with OX40 also present on dendritic and activated NK cells. They both stimulate T-cell proliferation and enhance antitumor eradication. Therefore, stimulation of these receptors with monoclonal antibodies represents a future therapeutic target (with anti-OX40 and antiCD137 agonists) in HNSCC. Lymphocyte activation gene-3 (LAG-3) is another immune checkpoint protein that negatively regulates T cells and immune response by binding to MHC class II molecules and is overexpressed in HNSCC. Monoclonal antibodies against LAG-3 are also being explored in multiple trials in HNSCC. Other trials include combinations of PD-1 inhibitors with CTLA-4 inhibitors, cetuximab, and vorinostat (histone deacetylases inhibitor of the Fas/FasL-dependent activation-induced death of T cells).

III. CONCLUSION:

It has been more than 125 years since Dr. William Coley demonstrated that an induced streptococcal infection can stimulate anticancer immunity. Despite hurdles, it is now beyond doubt that a properly functioning immune system can effectively kill tumor cells.

There are 2 requirements for the successful response of a tumor to immune checkpoint blockade. The first requirement is immune cell infiltration and recognition of tumor cells by the immune system. Fortunately, HNSCC tumors are highly immune infiltrated tumors occurring in richly lymphovascular sites (such as the oropharynx and cervical lymph nodes) and thus are excellent candidates for immunotherapy. The second component of a successful sustained antitumor immune response requires freedom from the immunoinhibitory influences from the tumor itself and immunosuppressive cells. Collectively, these influences permit the use of immunotherapy in the management of HNSCC.

The introduction of checkpoint inhibitors has dramatically changed the therapeutic approach in several cancers including melanoma, head, and neck, lung, renal and bladder cancers. Various drugs have demonstrated long-lasting and durable responses, with favorable toxicity profiles. Results from The Checkmate 141 trial have shown a clear advantage for the first time with improved overall survival, response rate, and quality of life with fewer high-grade toxicities in recurrent or metastatic platinum-refractory HNSCC patients with nivolumab as second-line treatment. These emerging results suggest Nivolumab as one of the most promising frontiers for immunotherapy research that has changed state of the art approach in this patient's setting.

The ACTH and cortisol levels have to be monitored before and during nivolumab treatment and in case of a deficiency, the patients must be switched to hydrocortisone. Any complaints of dyspnea, cough, fever, fatigue, and loss of appetite must be noted and managed adequately and the risk of development of pneumonitis must be assessed.

More studies are required to identify robust biomarkers predictive of response to anti-PD1/PD-L1 is necessary to tailor immunotherapies on each patient thus exploiting these agents at the best and to make nivolumab therapy more cost-effective.

The next step will be to extend the observed benefit to first-line treatment, currently dominated by the EXTREME regimen (platinum/5-fluorouracil/cetuximab), and to the locoregionally advanced setting, where concurrent chemoradiation with cisplatin is standard. Regimens combining immunotherapy with other modalities will probably further improve outcomes. Harnessing the immune system has shown and will continue to show tremendous potential to become the real 'magic bullet' against cancer.

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