

## Advanced squamous cell carcinoma and immunotherapy: new therapeutic perspectives

*Carcinoma espinocelular avançado e imunoterápicos: novas perspectivas terapêuticas*

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### ABSTRACT

Squamous cell carcinoma (SCC) has the second highest incidence rate among non-melanoma skin cancers. About 5% of cases progress to locally advanced and/or metastatic lesions, making the surgical approach often unfeasible. Based on this, we performed a literature review on the use of immunotherapy drugs to treat advanced SCC. The results showed that immunotherapy is a potential therapeutic strategy due to the antitumor activity promotion through the individual immune response, reducing the adverse events of surgeries, chemotherapy, and radiotherapy.

**Keywords:** Squamous cell carcinoma; Tumor Evasion; Immunotherapy; Skin neoplasms

### RESUMO

O carcinoma espinocelular (CEC) apresenta a segunda maior taxa de incidência entre os cânceres de pele não melanoma. Cerca de 5% desses casos evoluem para lesões localmente avançadas e/ou metastáticas, tornando a abordagem cirúrgica muitas vezes inviável. Com base nisso, foi realizada uma revisão na literatura sobre o uso de imunoterápicos no tratamento do CEC avançado. Observou-se, então, que a imunoterapia é uma potencial estratégia terapêutica devido à promoção da atividade antitumoral por meio da própria resposta imunológica individual, o que contribui para a redução dos efeitos colaterais de cirurgias, quimioterapias e radioterapias.

**Palavras-chave:** Carcinoma de células escamosas; Evasão tumoral; Imunoterapia; Neoplasias cutâneas

## Review

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## INTRODUCTION

Non-melanoma skin cancers (NMSCs) represent one of the most prevalent groups of malignancies in the world. Worldwide, an estimated 18 million new cancer cases occurred in 2018, causing around 100,000 deaths. Of these, approximately 1 million were NMSCs.<sup>1-3</sup> In Brazil, the National Cancer Institute estimates near 625,000 cancer cases in the country, of which 177,000 are NMSCs. Thus, this is the group of malignant neoplasms with the highest incidence.<sup>3</sup>

NMSCs include several malignant neoplasms, including basal cell carcinoma (BCC), the most common skin cancer, and squamous cell carcinoma (SCC), the second most frequent skin malignancy.<sup>3</sup> BCCs and SCCs originate from the neoplastic proliferation of epidermal keratinocytes exposed to carcinogenic factors, including exposure to ultraviolet (UV) radiation, chronic immunosuppression, burn scars, contact to ionizing radiation, among others.<sup>1,2</sup>

UV radiation stands out among the carcinogenic factors. It is recognized for its high mutagenic potential, providing BCCs and SCCs with the highest mutation load among all types of cancer. However, SCCs are a matter of greater concern given their more aggressive behavior: about 5% of cases evolve to locally advanced or metastatic conditions, with uncontrollable growth and substantial disfigurement.<sup>4-6</sup>

Regarding treatment, early surgical excision is considered the therapeutic option of choice, allowing the tumor type confirmation, histological differentiation degree, and free margins analysis. Nevertheless, some SCC cases are diagnosed in elderly patients with comorbidities that limit the adoption of more invasive therapeutic alternatives.<sup>5,6</sup> The tumors' location and size can also restrict surgical therapies, such as lesions with a diameter greater than 20 mm in periocular, auricular, labial, and temporal regions, as well as in cases of metastatic diseases.<sup>7,8</sup>

Locally advanced cutaneous SCC represents a significant therapeutic challenge. For unresectable, unsuitable for radiotherapy SCC, standard systemic treatment options include chemotherapy (usually platinum or fluoropyrimidine-based) or targeted therapy with epidermal growth factor receptor inhibitors.<sup>6</sup> The responses often have a short life and may be associated with significant adverse events in an elderly and frail population.

Despite the relevance of the surgical approach in advanced SCCs, cases of greater clinical complexity can adopt therapeutic alternatives. These alternatives include radiotherapy and chemotherapy with cisplatin, 5-fluorouracil, paclitaxel, and methotrexate (often used in inoperable and advanced lesions).<sup>5,6</sup>

Improved understanding of the immunological control mechanisms involved in skin cancer pathogenesis led to the development of specific immunotherapeutic treatments to promote antitumor activity. In this sense, immunotherapy provides individualized treatment to patients, with minimal adverse events, as it acts in the tumor microenvironment through molecular and cellular mechanisms.<sup>9,10</sup>

Given the new therapeutic approach proposed by im-

muno-therapy for malignant skin neoplasms, this study aimed to conduct an integrative review of immunotherapy drugs to treat advanced squamous cell carcinomas and/or in patients with comorbidities that limit other therapies.

## METHODS

The study aimed to overview the current scientific production on the use of immunomodulators to treat advanced cutaneous squamous cell carcinoma and/or in patients with comorbidities that limit conventional therapies. It adopted the integrative review as a research method. Integrative reviews consist of research methods that aim to provide a synthesis of knowledge about a particular subject or field to integrate concepts, ideas, and results from original and/or secondary studies.<sup>11,12</sup>

We conducted the literature review in three databases: Medline (Medical Literature Analysis and Retrieval System Online), Lilacs (Latin American and Caribbean Center on Health Sciences Information), and Scopus (SciVerse Scopus – Elsevier) adopting as search strategy the keywords: “cutaneous squamous cell carcinoma” AND “immunotherapy”. The search used the filters “10 years” – to select studies published from 2010 to 2020 – and “full text” – to retrieve articles with the full version available.

From the results obtained with the search strategy, we started the article selection process, using as inclusion criteria studies on the use of immunomodulators to treat cutaneous squamous cell carcinoma (SCC), with text in Portuguese or English available, and primary focus related to cutaneous immunology in SCCs and/or the use of immunotherapy drugs in SCC treatment. The exclusion criteria adopted were: studies addressing SCC systemic treatments generically or broadly, with full texts not available, and relating immunotherapeutic treatment with other therapeutic alternatives. Such standards aimed to allow the data synthesis to be more targeted and specific to the study objectives.

We assessed the selected studies separately, dividing them into two thematic areas: “Immune system and immunotherapy in cutaneous squamous cell carcinoma” and “Immunotherapy drugs in cutaneous squamous cell carcinoma”. Then, the articles' contents were analyzed and summarized through a conceptual synthesis.

## RESULTS

The search in the databases identified a total of 123 publications. The titles and abstracts preliminary assessment through eligibility criteria allowed the selection of 59 studies, from which 24 were excluded due to duplicity. Thus, 35 publications comprised the sample analyzed in the review and conceptual synthesis (Figure 1).

We distributed the assessed studies in two thematic areas: 17 studies in “Immune system and immunotherapy in cutaneous squamous cell carcinoma” and 18 studies in “Immunotherapy drugs in cutaneous squamous cell carcinomas”. Most of these

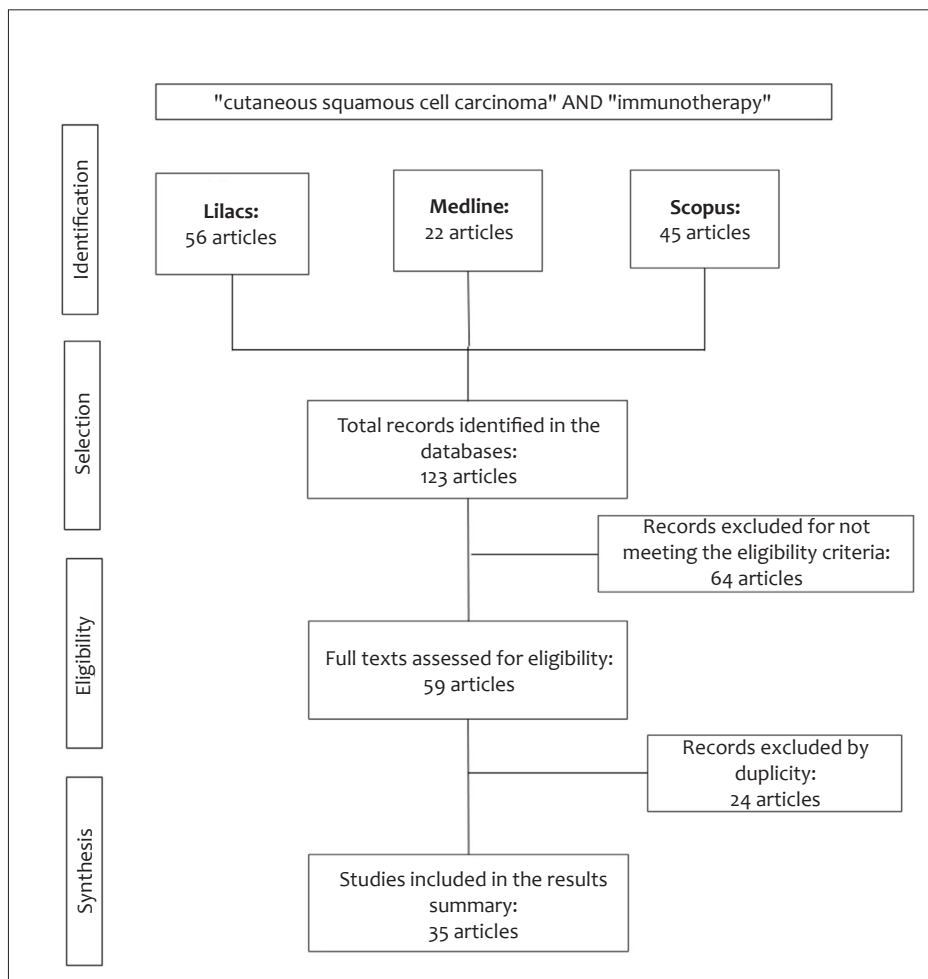


FIGURE 1: Search in three databases

studies were composed of narrative reviews (16 articles) and case reports (five studies), and the year 2019 had the highest number of publications, with 13 studies (Table 1).

## DISCUSSION

Cutaneous squamous cell carcinoma (SCC) is the second most frequent among non-melanoma skin cancers (NMSC). More than 90% of SCCs have a favorable prognosis, and early surgical treatment can cure it through the excision of the lesions. However, the disease progresses locally in about 4-5% of cases, becoming unresectable and/or metastatic and requiring alternative therapeutic approaches such as radiotherapy, chemotherapy, and, more recently, immunotherapy.<sup>5,18,31</sup>

The use of immunomodulators to treat squamous cell carcinomas is based on the ability of the immune system to control the carcinogenesis process.<sup>39</sup> The high NMSC incidence among immunocompromised individuals, such as in HIV infection cases, or immunosuppressed patients, condition of solid organ transplant recipients, supports this perspective. Thus, the immunological surveillance role to control neoplasms is highlighted, making it relevant to understand the relationship be-

tween the immune system and cutaneous carcinogenesis.<sup>2</sup>

### The immune system and skin cancers

The skin plays essential roles in the homeostasis of the human body, acting to maintain body temperature, protect against environmental agents (physical and chemical), and produce nervous and endocrine stimuli, in addition to working in the body's immune defense. Such defense can occur in the form of innate immunity, characterized by the absence of immunological memory, represented by neutrophils, eosinophils, natural killer (NK) cells, mast cells, cytokines, complement, and antibacterial peptides; or in the form of adaptive immunity, through antigen-presenting cells (dendritic cells), T-lymphocytes (regulators, CD8 and CD4) and B-lymphocytes.<sup>8</sup>

The immune system, under physiological conditions, can recognize and destroy antigens from infectious agents and/or neoantigens from neoplastic cells, acting through innate and adaptive immunities. The neoantigens formation results from the cell mutation process, through which unrepaired damage to cellular DNA sequences promote mutations that lead to changes in cell functions and carcinogenesis.<sup>2,8,27,30</sup>

Cutaneous squamous cell carcinomas (SCCs) originate

TABLE 1: Synthesis of studies analyzed by the systematic review

Authors	Year	Title	Journal	Type of study	Subject Area
Ascierto PA, Garbe C. <sup>5</sup>	2020	Updates and new perspectives in nonmelanoma skin cancer therapy: highlights from 'Immunotherapy Bridge'	Immunotherapy	Narrative review	Immune system and immunotherapy
Hall ET <i>et al.</i> <sup>2</sup>	2020	Immunologic Characteristics of Nonmelanoma Skin Cancers: Implications for Immunotherapy	American Society of Clinical Oncology Educational Book	Narrative review	Immune system and immunotherapy
Choi FD <i>et al.</i> <sup>13</sup>	2020	Programmed cell death 1 protein and programmed death-ligand 1 inhibitors in the treatment of non-melanoma skin cancer: A systematic review	Journal of the American Academy of Dermatology	Systematic review	Immune system and immunotherapy
Lima PO <i>et al.</i> <sup>4</sup>	2020	Epidermal Growth Factor Receptor's Function in Cutaneous Squamous Cell Carcinoma and Its Role as a Therapeutic Target in the Age of Immunotherapies	Current Treatment Options in Oncology	Narrative review	Immune system and immunotherapy
Salzmann M <i>et al.</i> <sup>14</sup>	2020	Programmed cell death protein 1 inhibitors in advanced cutaneous squamous cell carcinoma: real-world data of a retrospective, multicenter study	European Journal of Cancer,	Retrospective cohort study	Immunotherapy drugs in SCC
Hanna GJ <i>et al.</i> <sup>15</sup>	2020	Real-world outcomes treating patients with advanced cutaneous squamous cell carcinoma with immune checkpoint inhibitors	British Journal of Cancer	Prospective cohort study	Immunotherapy drugs in SCC
Pezeshki S <i>et al.</i> <sup>16</sup>	2020	Novel treatments using PD1 inhibitors for advanced and metastatic cutaneous squamous cell carcinoma	Journal Expert Review of Anticancer Therapy	Narrative review	Immune system and immunotherapy
Rischin D <i>et al.</i> <sup>17</sup>	2020	Phase 2 study of cemiplimab in patients with metastatic cutaneous squamous cell carcinoma: primary analysis of fixed-dosing, long-term outcome of weight-based dosing	Journal for Immunotherapy of Cancer	Clinical trial	Immunotherapy drugs in SCC
Barrios DM <i>et al.</i> <sup>18</sup>	2020	Immune checkpoint inhibitors to treat cutaneous malignancies	Journal of the American Academy of Dermatology	Narrative review	Immune system and immunotherapy
Desilets A <i>et al.</i> <sup>19</sup>	2020	Safety evaluation of pembrolizumab for treating recurrent head and neck squamous cell carcinoma	Expert Opinion on Drug Safety	Narrative review	Immunotherapy drugs in SCC
Lee A <i>et al.</i> <sup>20</sup>	2020	Cemiplimab: A Review in Advanced Cutaneous Squamous Cell Carcinoma	Drugs	Systematic review	Immunotherapy drugs in SCC
Ferris RL <sup>21</sup>	2019	Nivolumab in Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck: Efficacy and Safety in CheckMate 141 by Prior Cetuximab Use	Clinical Cancer Research	Clinical trial	Immunotherapy drugs in SCC
Habib LA <i>et al.</i> <sup>8</sup>	2019	Advances in Immunotherapy and Periocular Malignancy	Seminars in Ophthalmology	Systematic review	Immune system and immunotherapy
Guminski A, Stein B <sup>9</sup>	2019	Immunotherapy and other systemic therapies for cutaneous SCC	Oral Oncology	Narrative review	Immune system and immunotherapy
Liebl MC, Hofmann TG <sup>22</sup>	2019	Identification of responders to immune checkpoint therapy: which biomarkers have the highest value?	Journal of the European Academy of Dermatology and Venereology	Narrative review	Immune system and immunotherapy
Ahmed SR <i>et al.</i> <sup>23</sup>	2019	Cemiplimab-rwlc as first and only treatment for advanced cutaneous squamous cell carcinoma	Expert Review of Clinical Pharmacology	Narrative review	Immunotherapy drugs in SCC
van Baar MLM <i>et al.</i> <sup>24</sup>	2019	Pembrolizumab for cutaneous squamous cell carcinoma: Report of a case of inoperable squamous cell carcinoma with complete response to pembrolizumab complicated by granulomatous inflammation	JAAD Case Reports	Case report	Immunotherapy drugs in SCC
Kacew AJ <i>et al.</i> <sup>25</sup>	2019	Chromosome 3q arm gain linked to immunotherapy response in advanced cutaneous squamous cell carcinoma	European Journal of Cancer	Retrospective cohort study	Immunotherapy drugs in SCC
Ogata D, Tsuchida T <sup>26</sup>	2019	Systemic Immunotherapy for Advanced Cutaneous Squamous Cell Carcinoma	Current Treatment Options in Oncology	Narrative review	Immunotherapy drugs in SCC

Continuation...

TABLE 1: Synthesis of studies analyzed by the systematic review

Authors	Year	Title	Journal	Type of study	Subject Area
Paulson KG <i>et al.</i> <sup>27</sup>	2019	Immunotherapy for skin cancer	International Immunology	Narrative review	Immune system and immunotherapy
Liu Y <i>et al.</i> <sup>28</sup>	2019	Prolonged Response to Pembrolizumab in Spindle Cell Squamous Cell Carcinoma Metastatic to the Central Nervous System	Journal of Investigative Medicine High Impact Case Reports	Case report	Immunotherapy drugs in SCC
Di Nardo L <i>et al.</i> <sup>29</sup>	2019	Molecular genetics of cutaneous squamous cell carcinoma: perspective for treatment strategies	Journal of the European Academy of Dermatology and Venereology	Narrative review	Immune system and immunotherapy
Barber BR <sup>30</sup>	2019	Immune Status and Immunotherapy in Advanced Cutaneous Squamous Cell Carcinoma-What Are Our Next Steps?	JAMA Otolaryngology-Head & Neck Surgery	Letter to the editor	Immune system and immunotherapy
Bottomley <i>et al.</i> <sup>31</sup>	2019	The Role of the Immune System in Cutaneous Squamous Cell Carcinoma	International Journal of Molecular Sciences	Narrative review	Immune system and immunotherapy
Chen A <i>et al.</i> <sup>7</sup>	2018	Clinical Remission of Cutaneous Squamous Cell Carcinoma of the Auricle with Cetuximab and Nivolumab.	Journal of Clinical Medicine	Case report	Immunotherapy drugs in SCC
Amoils M <i>et al.</i> <sup>32</sup>	2018	PD-L1 Expression and Tumor-Infiltrating Lymphocytes in High-Risk and Metastatic Cutaneous Squamous Cell Carcinoma	Head and Neck Surgery	Cross-sectional study	Immunotherapy drugs in SCC
Migden MR <i>et al.</i> <sup>33</sup>	2018	PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma	New England Journal of Medicine	Clinical trial	Immunotherapy drugs in SCC
Degache E <i>et al.</i> <sup>34</sup>	2018	Major response to pembrolizumab in two patients with locally advanced cutaneous squamous cell carcinoma	Journal of the European Academy of Dermatology and Venereology	Letter to the editor	Immunotherapy drugs in SCC
Yanagi T, Kitamura S, Hata H <sup>35</sup>	2018	Novel therapeutic targets in cutaneous squamous cell carcinoma	Frontiers in Oncology	Narrative review	Immune system and immunotherapy
Ilyas M, Costello CM, Sharma A <sup>36</sup>	2017	Exploring the relationship between natural killer cells and cutaneous squamous cell carcinoma development	JAAD Case Reports	Case report	Immunotherapy drugs in SCC
Falchook GS <i>et al.</i> <sup>37</sup>	2016	Responses of metastatic basal cell and cutaneous squamous cell carcinomas to anti-PD1 monoclonal antibody REGN2810	Journal for Immunotherapy of Cancer	Case report	Immunotherapy drugs in SCC
Chang ALS <i>et al.</i> <sup>38</sup>	2016	A case report of unresectable cutaneous squamous cell carcinoma responsive to pembrolizumab, a programmed cell death protein 1 inhibitor	JAMA Dermatology	Letter to the editor	Immunotherapy drugs in SCC
Macdonald JB <i>et al.</i> <sup>39</sup>	2015	Cutaneous adverse effects of targeted therapies: Part II: Inhibitors of intracellular molecular signaling pathways	Journal of the American Academy of Dermatology	Narrative review	Immune system and immunotherapy
Yanofsky VR <i>et al.</i> <sup>40</sup>	2013	Understanding dendritic cells and their role in cutaneous carcinoma and cancer immunotherapy	Clinical and Developmental Immunology	Narrative review	Immune system and immunotherapy
Fujita H <i>et al.</i> <sup>41</sup>	2012	Langerhans cells from human cutaneous squamous cell carcinoma induce strong type 1 immunity	Journal of Investigative Dermatology	Experimental study	Immune system and immunotherapy

from mutations in keratinocytes of the epidermal squamous cell layer, which expand into tissues through neoplastic clones. Tumor promoters stimulate clonal tumor expansion. They can be exogenous, such as ultraviolet radiation (UVR), chemical agents, medications, and infections, or endogenous, such as diet and immune suppression. SCCs carry one of the highest tumor

mutation loads among all types of cancer, which increases their immunogenicity due to the expression of tumor neoantigens, mutations, and/or viral gene expression.<sup>2,27,30</sup>

Natural killer (NK) cells represent one of the main cell lines of innate immunity, and they're found mainly in the dermis.<sup>31</sup> NK cells are responsible for the neoantigens immu-

nosurveillance, controlling tumor progression through cytolytic response.<sup>36</sup> Tissue macrophages also constitute another crucial lineage in the antitumor immune response, identifying damaged keratinocytes and promoting leukocyte recruitment and pro-inflammatory mediator in the neoplastic site to eradicate cancer cells. However, when infiltrated into neoplastic tissue, tumor-associated macrophages act as stimulating agents for tumor development by secreting pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMP).<sup>31,36</sup>

Dendritic cells (DCs) also promote antigens recognition in peripheral tissues, and they're differentiated into six subtypes of cutaneous dendritic cells. The Langerhans cells, present in the corneal and granular layers of the epidermis, and the dermal myeloid dendritic cells, found in the dermis, can be highlighted. Dendritic cells recognize neoplastic neoantigens in the cutaneous tissue, introducing them to CD8+ and CD4+ naive T-lymphocytes located in regional lymph nodes.<sup>31,40,41</sup>

T cells make up about 10% of the cellular infiltrate of skin tumors, thus playing an essential role in neoplastic immunological control. Dendritic cells introduce tumor neoantigens through the major histocompatibility complex (MHC). They promote the activation of naive T cells into effector T cells and the polarization of T cell responses into Th1, Th2, Th9, and Th17.<sup>31,40</sup> The T response pattern is crucial to prevent the development of cutaneous malignancy and metastases. The Th1 pattern (cytotoxic response) is the main responsible for controlling tumor progression, and the Th2 pattern is generally associated with neoplastic development.<sup>31,40</sup>

In addition to cellular immunity, the humoral response of effector B cells is also an essential component of neoplastic control. B cells act through the immunoglobulins and cytokines production, contributing to the T-lymphocyte responses polarization, and to pro-inflammatory mechanisms chemotaxis and activation that will lead to carcinogenesis failure.<sup>31</sup>

Despite the immune control mechanisms, some neoplasms can evade the immune system, proliferating and invading adjacent structures and spreading to other tissues.<sup>8</sup> The neoplastic evasion process is strongly influenced by the tumor microenvironment through its cellular, molecular, and environmental characteristics.

### The tumor microenvironment and the immune escape

The tumor microenvironment comprises several malignant and non-malignant cell types that establish complex and dynamic interactions through chemotactic agents, such as cytokines, growth factors, and inflammatory enzymes.<sup>31</sup> In this perspective, the balance or imbalance between such biological interactions will determine tumor progression or suppression through mechanisms intrinsic or extrinsic to neoplastic cells (Figure 2).

Among the intrinsic factors is the tumor's surface proteins expression, hindering recognition and phagocytosis by DCs, and the cytokines secretion, promoting DC dysfunction

and inhibiting specific tumor T cells activation. It results in an increased SCCs tumor burden.<sup>31,40,41</sup>

The immune status is one of the extrinsic factors that influence the tumor microenvironment.<sup>27</sup> It can also affect the Th1 and Th2 immunity patterns. Immunocompetent individuals tend to demonstrate gene expressions associated with Th1 and Th2 responses, while immunosuppressed individuals show a Th2 immunity predominance, an immune response more related to cell infiltration and tumor progression.<sup>27,31</sup>

Another extrinsic factor is ultraviolet (UV) radiation, which acts in the tumor microenvironment inducing dendritic cells' apoptosis and reducing their lymphatic migration. Thus, it impairs the CD8+ T-lymphocyte cytotoxic response mediated by CD8. UV radiation also stimulates the pro-inflammatory mediators released by infiltrating keratinocytes and leukocytes that favor the SCCs initial development.<sup>27,31</sup>

From another perspective, Bottomley et al. proposed the concept of "immunoediting", a process where the tumor cells' elimination by immune defense mechanisms would lead to the neoplastic cells selection without specific immunogenic antigens. These cells, when not recognized by the immune system, would then have the ability to proliferate in the tumor microenvironment.<sup>31</sup>

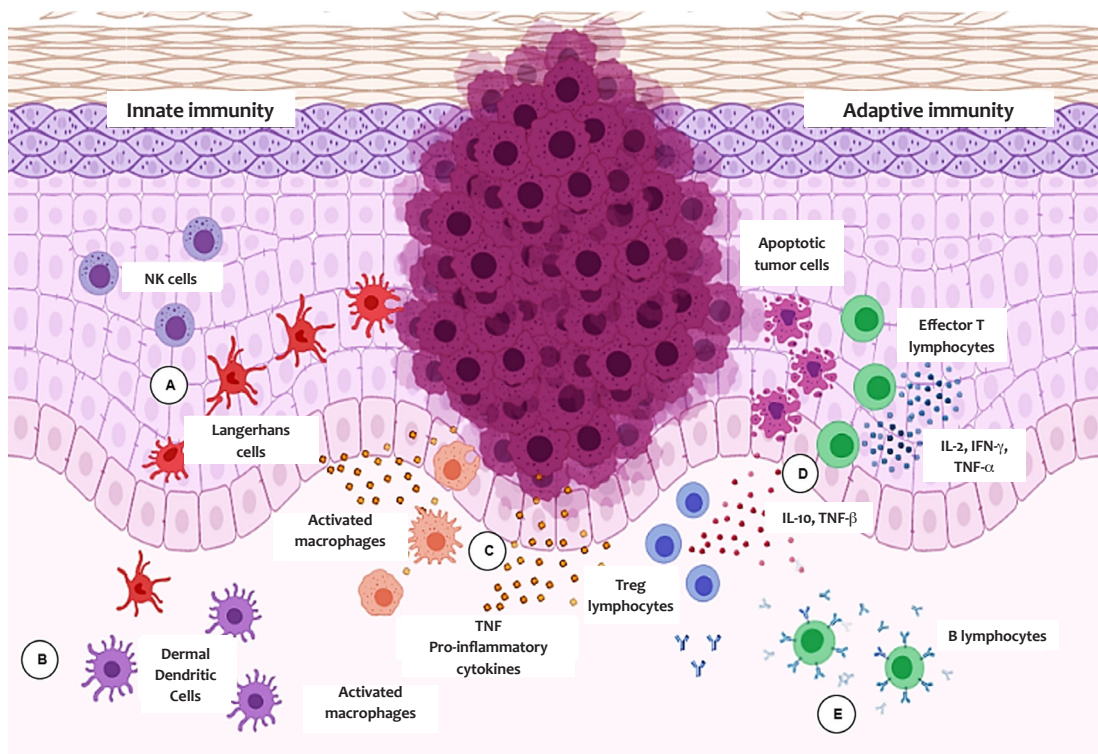
However, the "immunoediting" of the Treg cells, -main 'e governan de modo globalismo todo. Nao podemos , deppois so caminho e os. Os monstros uqe q' does not consist of an "escape" mechanism per se and may result in three types of outcomes: elimination, where the immune system can totally eliminate the tumor cells; equilibrium, where the immune mechanisms control the tumor progression but fail to eradicate the cancer cells completely; and escape, where tumor cell lines proliferate, combining characteristics of immune evasion and resistance to apoptosis.<sup>31</sup>

Immunological tolerance has also been recognized as one of the main "escape" tumor cells mechanisms. Under physiological conditions, inactivated and immature dendritic cells stimulate the regulatory T cells (Treg) differentiation, which acts by inhibiting the effector T cells cytotoxic responses, limiting excessive immune reactivity.<sup>31,40</sup>

Nevertheless, Treg cells act by preventing the secretion and proliferation of dendritic cells in the tumor microenvironment. It reduces the presentation quality of neoplastic neoantigens and results in an imbalance towards the inhibition of effector T activation.<sup>22,31,40</sup> Regulatory T cells are identified in tumor infiltrates of BCCs and SCCs.<sup>2</sup> This fact can be explained by the ability of tumor cells to recruit immunosuppressive cells, such as Treg cells and myeloid-derived suppressor cells (MDSCs), favoring neoplastic evolution.<sup>8</sup>

It is worth highlighting the influence of individual variants on the tumor microenvironment composition - cytokines, interleukins, interferons, and infiltrating immune cells (T, Treg, and B-lymphocytes), determining the immune response pattern and tumor progression control.<sup>22</sup>



**FIGURE 2:**

**A** – NK cells and Langerhans cells recognizing tumor antigens and initiating the innate immune response.  
**B** – Dermal dendritic cells recognizing tumor antigens.  
**C** – Macrophages phagocytizing tumor cells and secreting pro-inflammatory cytokines.  
**D** – Effector T cells triggering the tumor cells apoptosis through a cytotoxic response, in addition to secreting pro-inflammatory cytokines. Treg cells secreting cytokines that inhibit the activity of effector T cells.  
**E** – Activated B cells producing antitumor immunoglobulins.

### Immune checkpoints and immunomodulation

Self-tolerance represents an essential element of the immune system. It promotes immune response regulation, preventing excessive inflammatory and cytotoxic processes that would cause the degradation of healthy tissues adjacent to the lesions. Under physiological conditions, immune modulation results from the activity of cellular molecules and receptors called immune checkpoints.<sup>8,9</sup>

Nevertheless, cancer cells have acquired the ability to overexpress molecules and receptors of immune checkpoints, evading the antitumor mechanism and, consequently, progressing uninhibitedly.<sup>8</sup> Programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), and epidermal growth factor receptor (EGFR) represent the main immune checkpoints expressed in SCC tumor cells, signaling their relevance as potential therapeutic targets.<sup>8,9,14</sup>

CTLA-4 is expressed on the surface of cytotoxic T-lymphocytes and acts to prevent these cells' activation, triggered by the binding with CD80 and CD86 dendritic cells proteins. However, T cells also have the surface protein CD28, which promotes the stimulation of cytotoxic T activity through CD80 and CD86 ligands. Therefore, the effector T-lymphocyte's response will depend on the balance of the bindings between CD80 and CD86 with the CTLA-4 ("inhibitory") and CD28 ("stimulator") receptors.<sup>8</sup>

PD-1 is a cell surface receptor found on T and B cells, NK cells, dendritic cells, and monocytes. In T cells, PD-1 is only expressed after their activation, promoting effector T cells apoptosis. Also, it inhibits Treg cells apoptosis by binding to PD-L1 and PD-L2 proteins (programmed cell death ligands 1 and 2) present on the surface of tumor cells.<sup>8,14,31,32</sup> Thus, cancer clones can increase their PD-L1 surface presentation, avoiding immunological surveillance.<sup>19,32</sup> Amoils et al. corroborated this understanding, emphasizing the association of increased PD-L1 expression with metastatic and recurrent SCCs. From another perspective, Pezeshki et al. highlighted the PD-1 and PD-L1 role in the "T cell exhaustion" phenomenon, resulting from the potency reduction in the T cell clones from chronic exposure to a particular antigen.<sup>16</sup>

The EGFR gene is another important tumor checkpoint component, encoding a transmembrane glycoprotein receptor responsible for activating multiple downstream signaling pathways – including MAPK/ERK and PI3K/AKT/mTOR – that control processes of maturation, proliferation, apoptosis inhibition, and cells angiogenesis.<sup>29</sup> EGFR deregulation has been observed in head, neck, ovary, breast, bladder, colon, and lung carcinomas, and it is related to tumor proliferation. In cutaneous SCC cases, despite the low incidence of EGFR mutations – ranging from 2.5% to 5% – this gene overexpression has been associated with metastases and a worse prognosis.<sup>21,29</sup> In this respect, the study of the immune response role in the tumor microenvironment in recent years has stimulated the de-

velopment of target therapies aimed at overexpressed ligands in tumor tissue.<sup>8</sup> The mechanisms of inhibition of CTLA-4 and PD-1 receptors on immune cells and PD-L1 on neoplastic cells were described for the first time in 2018. It enabled the interruption of the mechanism of the tumor evasion, allowing the effector T cells action to control the cancers' progression (Figure 3).<sup>8,9,18,22,32</sup>

In this perspective, CTLA-4 blocking would allow the effector T-lymphocytes activation, while blocking PD-1 or PD-L1 would inhibit the effector T-lymphocytes apoptosis, as well as the phenomenon of "T cell exhaustion". Thus, both therapeutic pathways would promote increased cellular immunity activity mediated by T cells.<sup>8</sup> On the other hand, blocking the EGFR would inhibit one of the mechanisms of tumor cells "evasion", allowing the immune system to act on them.<sup>21,29</sup>

Still, it is noteworthy that the immune activity stimulation by immunotherapy drugs can trigger nonspecific immune responses, in the form of autoimmune diseases such as vitiligo. Furthermore, these medications also demonstrate the potential to cause adverse events such as pruritus, lichenoid rash, papulopustular eruptions, among other skin manifestations, as well as diarrhea and hypothyroidism.<sup>19,24,39</sup>

Understanding the immune surveillance of cancers and the mechanisms of tumor "evasion" allowed the development of drugs that block the receptors involved in these pathways, with greater emphasis on the CTLA-4, PD-1, and EGFR receptors.<sup>8</sup>

Due to the high mutational load of SCCs, they become very susceptible to blocking immune checkpoints.<sup>8</sup>

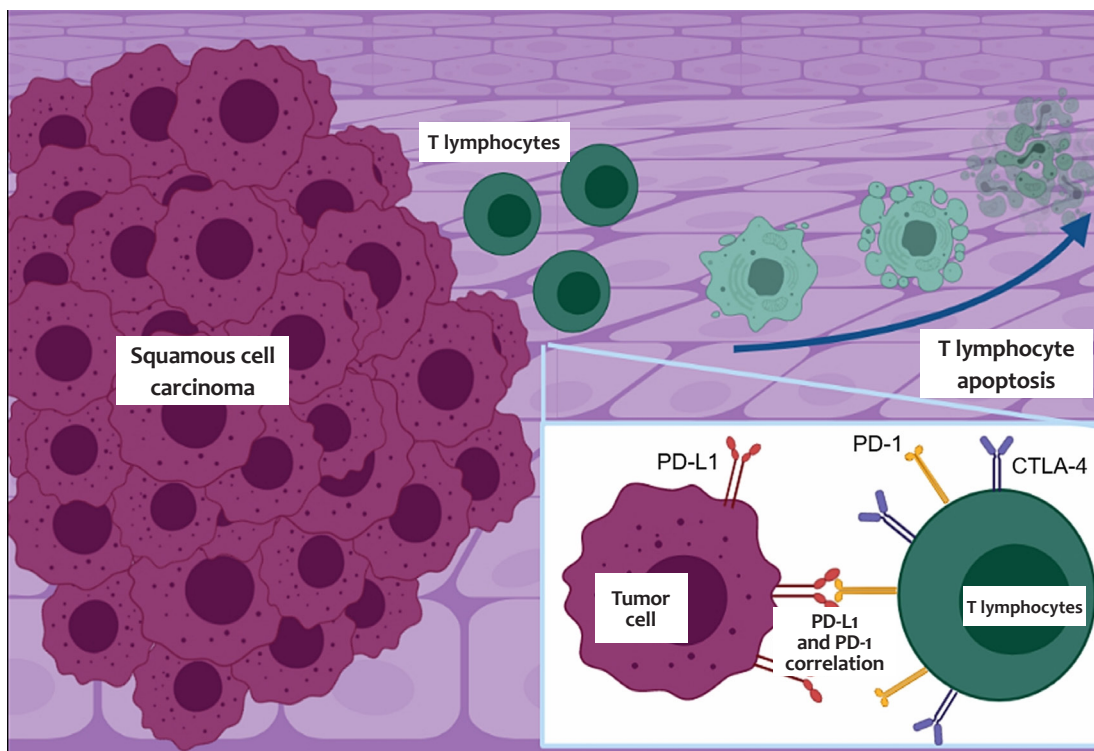
The main indications for immunotherapy are locally advanced, unresectable, incurable, metastatic SCCs and cases of good tolerability to medications with potential increased survival.<sup>15</sup> The combination of anti-CTLA-4 and anti-PD-1 medications has been reported in specific cases of melanoma, renal cell carcinoma, and recurrent and metastatic SCCs of head and neck, demonstrating better therapeutic responses.<sup>8,25</sup> However, such combinations have higher toxicity, with the risk of triggering colitis and hypophysitis.<sup>24</sup>

The advent of checkpoint inhibitor therapy has raised promising expectations for the treatment of locally advanced, recurrent, and metastatic SCCs, with improved patient overall survival as well as progression-free survival.<sup>8,25</sup> Ipilimumab, CTLA-4 inhibitor, nivolumab, pembrolizumab, cemiplimab, PD-1 inhibitors, cetuximab, and anti-EGFR are the immunological checkpoint inhibitors currently approved for skin neoplasms (Table 2).<sup>8,18,35</sup>

## IMMUNOTHERAPY DRUGS AND TREATMENT OF SQUAMOUS CELL CARCINOMA:

### Ipilimumab

Ipilimumab can cause adverse events such as autoimmune dermatitis, colitis, and diarrhea, in addition to skin reactions such as pruritus, morbilliform eruption, nodular pruritus, lichenoid rash, and photosensitivity. In general, these adverse events present after three to six weeks from the start of the medication, being dose-dependent and reversible with the end of the treatment.<sup>39</sup>



**FIGURE 3:** T-lymphocytes recruited to the tumor site. PD-L1 ligands of tumor cells activating PD-1 receptors on T-lymphocytes, triggering apoptosis of these cells



**TABLE 2: Immunotherapy drugs used in the squamous cell carcinomas treatment**

Immunotherapy drugs	Class	Clinical Applications	Adverse Events
Cemiplimab	PD-1 inhibitor	Metastatic and/or locally advanced cutaneous SCC	Diarrhea, fatigue, nausea, constipation, and rash.
Cetuximab	Anti-EGFR	Colorectal cancer, head and neck SCC, and unresectable cutaneous SCC.	Papulopustular eruption, desquamative rash, eczema, xerosis, paronychia, and alopecia.
Ipilimumab	Anti-CTLA-4	Metastatic melanoma, non-melanoma skin cancer, renal cell carcinoma, and colorectal cancer	Mild diarrhea, mild rash or itching, hypopituitarism, hypothyroidism, reduced appetite, dizziness, headache, fatigue.
Nivolumab	PD-1 inhibitor	Non-small cell lung cancer, renal cell carcinoma, recurrent or metastatic cutaneous SCC of the head and neck, and advanced melanoma	Diarrhea, nausea, rash, itching, fatigue, headache, mental status changes, abdominal pain, hypotension.
Pembrolizumab	PD-1 inhibitor	Non-small cell lung cancer, melanoma, and advanced cutaneous SCC	Diarrhea, hypothyroidism, rash, and rare immunological adverse events, especially grade 3 to 5 pneumonitis.

### Nivolumab

Nivolumab is a PD-1 receptor inhibitor that prevents the T-lymphocyte's deactivation and preserves the cellular immunity function. The FDA approved the drug in 2017 to treat recurrent or metastatic head and neck SCCs, and advanced melanoma.<sup>21,26</sup> However, nivolumab's role in non-melanoma skin cancers has not yet been fully elucidated.<sup>7</sup>

Chen et al. reported a case of complete remission of an invasive and poorly differentiated SCC in the auricle. The treatment was based on immunotherapy using a combination of nivolumab and cetuximab – antibody against the epidermal growth factor receptor (EGFR). The case reported by Chen et al. avoided extensive surgery with a potential risk of facial nerve palsy through these immunotherapy drugs and showed promising results.<sup>7</sup>

Regarding adverse events, mild fatigue represented the most common condition. However, the literature has also reported dermatological disorders such as vitiligo, skin rash, itching, endocrine hypofunction, and hip fracture.<sup>26,39</sup>

### Cemiplimab

Cemiplimab is a human IgG4 monoclonal antibody with a high affinity for the PD-1 receptor. It promotes the blocking of PD-L1 (expressed in tumor cells) and stimulates the effector T cells' action. It was the first systemic therapy approved to treat metastatic or locally advanced SCCs not suitable for curative surgery or radiotherapy.<sup>17,20,23,26,37</sup>

Several studies have demonstrated the effectiveness of cemiplimab use to treat SCCs, reducing the diameters of target lesions.<sup>17,23,37</sup> Ahmed et al. demonstrated a cemiplimab response rate of 50% in advanced SCC cases – in a phase 1 study – and a response rate of 47% in metastatic disease cases – in a phase 2 study.<sup>23</sup>

Regarding the adverse events, the most common are diarrhea, fatigue, nausea, constipation, and rash,<sup>23,33</sup> which are solved by adjusting the therapeutic doses and/or discontinuing the treatment.<sup>23</sup> Despite the adverse events, cemiplimab has a clinically significant lasting effect, with acceptable safety and tolerability profile.<sup>20</sup>

### Cetuximab

Cetuximab is a chimeric immunoglobulin (IgG1mAb) that binds to domain 3 of the extracellular domain of the epidermal growth factor receptor (EGFR), leading to innate and adaptive immune responses in tumors dependent on this oncogenic pathway.<sup>13,21</sup> The response to cetuximab correlates to the tumor's EGFR expression. It can restore the anti-tumor immune response, lead to cell cytotoxicity of NK cells, in addition to maturation and crosstalk between NK and dendritic cells.<sup>13,21</sup>

Cetuximab was initially approved to treat colorectal cancer. Currently, it has been approved for advanced head and neck and/or platinum-refractory SCCs, and it can be adopted as adjuvant therapy to surgery and radiotherapy.<sup>4</sup> Cetuximab has been described as the most effective anti-EGFR in SCC treatment, with promising results when combined with other therapeutic alternatives.<sup>4,13</sup>

A 2014 study on the treatment of unresectable SCCs compared the use of cetuximab in monotherapy with combinations of the drug with carboplatin or radiotherapy. The results showed control rates of 50% for monotherapy, 87.5% for cetuximab + carboplatin, and 100 % for cetuximab + radiotherapy.<sup>4</sup> Another phase 2 clinical trial study on the use of cetuximab in monotherapy to treat unresectable SCCs observed disease stabilization in 58% of cases.<sup>21</sup> However, the medication still presents unpromising cure rates: 3% of complete remission and 8% partial response in advanced SCC cases.<sup>21</sup>

## CONCLUSIONS

The treatment of cutaneous neoplasms is at an advanced stage, benefiting patients affected with tumors that are challenging to access surgically and reconstruct anatomically. The use of many of these therapies is still under investigation, clinical trial, or approval. Still, the literature already presents evidence to support the consideration of the great importance and benefit of these new therapeutic strategies.

It's essential to understanding the physiopathogenesis of SCCs to promote the development of new therapeutic approaches that may soon benefit a more significant number of patients. ●

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