International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

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ARTICLE TITLE	IMMUNOTHERAPY IN THE FIGHT AGAINST MELANOMA: CHALLENGES AND DEVELOPMENT PERSPECTIVES- A LITERATURE REVIEW
ARTICLE INFO	Paulina Redel, Aleksandra Dzwonkowska. (2025) Immunotherapy in The Fight Against Melanoma: Challenges and Development Perspectives - A Literature Review. *International Journal of Innovative Technologies in Social Science*. 3(47). doi: 10.31435/ijitss.3(47).2025.3504
DOI	https://doi.org/10.31435/ijitss.3(47).2025.3504
RECEIVED	18 June 2025
ACCEPTED	25 July 2025
PUBLISHED	30 July 2025
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IMMUNOTHERAPY IN THE FIGHT AGAINST MELANOMA: CHALLENGES AND DEVELOPMENT PERSPECTIVES- A LITERATURE REVIEW

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ABSTRACT

Melanoma is a highly malignant skin cancer with a high propensity to metastasize and a very poor prognosis. Melanoma is considered a multifactorial disease resulting from the interaction between genetic susceptibility and environmental exposure. The rate of increase in incidence worldwide is much higher than any other cancer and comparable to an epidemic. Prompt diagnosis, detection and treatment are crucial in melanoma diagnosis. Traditional treatment methods, such as surgical removal of the tumor, sentinel node biopsy and chemotherapy, often show limited efficacy. Chemotherapy offers little benefit in prolonging survival, and in 15-20% of patients leads to recurrence and relapse. Advances in knowledge of the molecular mechanisms of melanoma development and the discovery of the role of immune molecules such as PD-1, PD-L1 and CTLA - 4 have made modern immune therapies possible. The 2018 Nobel Prize recognized the discovery of these mechanisms, resulting in new drugs such as immune checkpoint inhibitors (ipilimumab, pembrolizumab, nivolumab). Modern immunotherapy in recent years has become the fourth (next to surgery, chemotherapy and radiotherapy) pillar of systemic treatment of melanoma. The purpose of this review is to summarize the available immune therapies for the treatment of melanoma.

KEYWORDS

Melanoma, Immunotherapy, CTLA-4, PD-1, Ipilimumab, Pembrolizumab, Niwolumab

CITATION

Paulina Redel, Aleksandra Dzwonkowska. (2025) Immunotherapy in The Fight Against Melanoma: Challenges and Development Perspectives - A Literature Review. *International Journal of Innovative Technologies in Social Science*. 3(47). doi: 10.31435/ijitss.3(47).2025.3504

Introduction.

Malignant melanoma is one of the most aggressive, heterogeneous and treatment-resistant cancers, characterized by high mutation rates [1]. It accounts for about 5% of all cancers [2]. It arises from melanocytes, which are found in the epidermis, hair follicles, mucous membranes, meninges and the choroidal layer of the eye [3]. Melanoma can arise in any area of the body where melanocytes are present. Most cases occur on the skin [4]. About 4% of cases occur in less-exposed areas, such as the choroidal membrane of the eye, the mucous membranes of the gastrointestinal and genitourinary tracts, and the meninges [4,5,6,7]. Melanoma occurring outside the skin, including uveal and mucosal melanoma, are rare tumors with unique epidemiology, biological behavior and molecular profile [8]. Uveal melanoma accounts for only 5% of all cases, but is the most common primary intraocular neoplasm. Unlike cutaneous melanoma, which is often associated with BRAF, NRAS and KIT mutations, uveal melanoma usually contains GNAQ/GNA11, EIF1AX, SF3B1, BAP1 mutations and chromosomal alterations [9]. Mucosal melanoma is the rarest type of this cancer, accounting for 1 to 3% of all cases [8,9]. It is associated with melanocytes found in the mucous membranes of the gastrointestinal tract, genitourinary tract and respiratory tract [8]. Mucosal melanoma has a distinctive genomic profile, characterized by a higher prevalence of SF3B1 and KIT mutations and lower levels of BRAF and NRAS mutations [9,10].

Materials and Methods

A comprehensive review of articles published in scientific journals was conducted using online research platforms such as PubMed and Google Scholar. Articles were identified using the following search terms: „melanoma", „immunotherapy", „CTLA-4", „PD-1".

Discussion

Modern melanoma incidence rates have increased dramatically, despite the fact that melanoma has been a disease known since antiquity. The first documented case of melanoma dates back to the fifth century and was described by Hippocrates of Kos, although earlier physical evidence of the disease was found in the bones of pre-Columbian mummies, which are about 2,400 years old. The first references to melanoma in Western medical literature date back to 1651, in the writings of Drs. Highmore and Bonet, and to 1757, in the work of Henrici and Nothnagel, who described fatal black tumors occurring in the bodies of patients. The first surgical removal of a melanoma tumor occurred in 1787, when Scottish surgeon John Hunter performed surgery on a 35-year-old man, removing a recurrent tumor from his jaw. At the time, Hunter, like many other doctors, thought melanoma was a fungal growth, and the true nature of the disease was not discovered until later. After that, surgical removal of melanoma became the standard treatment. Norris pointed out that melanomas originate from nevi, and people with a family history of melanoma tend to have more of them. He was the first to recommend removing melanoma lesions with wide margins, stressing that too narrow margins can lead to recurrence, and that surgical excision is ineffective if the cancer has already spread. In 1892, Dr. Herbert Snow proposed removing lymph nodes, viewing it as a mechanism to prevent the cancer from metastasizing into the blood. For nearly 100 years, melanoma treatment did not change significantly, with surgical excision and lymph node removal remaining the main treatments [10]. In the mid-20th century, the development of chemotherapy introduced new therapeutic options, but chemotherapy, as applied to melanoma, had limited effects due to the high resistance of the tumor to cytostatics [11]. A breakthrough in the treatment of melanoma was the discovery of the role of the immune system in the fight against cancer and the development of immunotherapy. The 1980s and 1990s saw the first treatment trials using interleukin-2 and interferon alpha, which showed that stimulation of the immune system could improve treatment outcomes. However, the real revolution came with the introduction of immune checkpoint inhibitors, such as CTLA-4 and PD-1 blocking antibodies, which enable T-cell activation and an effective anti-tumor response [12].

Epidemiology

Melanoma is one of the most treatment-resistant types of cancer. Over the past few decades, there has been a systematic increase in melanoma cases worldwide, especially in countries with high ultraviolet radiation and light-skinned populations [8]. The increase is much greater worldwide than for any other cancer [5]. According to the World Health Organization (WHO), the annual incidence of melanoma has more than doubled over the past 30 years [11,12]. Melanoma incidence varies widely from country to country, and these differences in incidence are attributed to factors such as racial skin phenotype and varied sun exposure [4]. The highest incidence rates are observed in Australia, New Zealand, and northern and western European countries, where the incidence is as high as 40-50 cases per 100,000 inhabitants per year. In Poland, the incidence of melanoma is lower, but there is also an increasing trend, especially among young and middle-aged people [13]. Melanoma is the fifth most common cancer in men and the seventh among women [4]. Preferential sites for melanoma vary by gender: in men it is most common on the back, while in women it occurs on the arms and legs [12]. Unlike other solid tumors, melanoma affects mostly young and middle-aged people, with a median age at diagnosis of 57 years [14]. The 5-year survival rate is over 90% for early-stage melanoma, but drops to only 16% for metastatic disease, indicating that metastasis is the main cause of poor treatment outcomes [1].

Classification

In the 1960s, famed dermatologist Wallace Clark suggested classifying melanoma based on histologic features, which had a profound impact on how it was diagnosed. He initially described three main histological variants of melanoma: superficial spreading melanoma (SSM), lentiginous malignant melanoma (LMM) and nodular melanoma (NM). Although several new variants have since been introduced, such as acral lentiginous melanoma, mucosal melanoma, desmoplastic melanoma and nevus melanoma, SSM, LMM and NM remain the recognized types of melanoma to this day. In 1966, Clark proposed a melanoma grading system based on the depth of invasion of tumor cells into the dermis and subcutaneous fatty tissue. He distinguished five levels:

Level 1: melanoma cells confined to the epidermis (melanoma in situ),
Level 2: single melanoma cells or their small clusters in the papillary dermis,
Level 3: melanoma cells filling and expanding the papillary layer of the dermis,
Level 4: invasion into the reticular layer of the dermis,
Level 5: invasion into subcutaneous fat.

Clark's research has changed the approach to treating patients in the early stages of melanoma. He noted that patients with deeper skin infiltration (Levels III-V) were more likely to have lymph node metastasis, leading him to conclude that lymph node excision should only apply to patients whose melanoma had crossed the papillary layer of the dermis. In 1970, Alexander Breslow developed a more precise way of classifying melanoma, based on measuring the depth of infiltration, which took into account the thickness of the tumor. Breslow's classification system, known as Breslow's depth, was based on millimeters of infiltration depth rather than anatomical compartments, the thickness of which can vary in different parts of the body. Breslow divided melanoma into five grades:

Grade I: less than or equal to 0.75 mm,
Grade II: 0.76-1.5 mm,
Grade III: 1.51-2.25 mm,
Grade IV: 2.26-3.0 mm,
Grade V: greater than 3.0 mm.

Breslow proved that patients with thinner tumors (grades I and II) have a significantly higher chance of survival and a lower risk of regional and distant metastasis. This discovery allowed for smaller resections than had been previously practiced, and enabled doctors to assess the risk of melanoma spreading to lymph nodes and decide whether to remove them. According to his study, patients with a Breslow thickness of 1.5 mm or more were more likely to benefit from prophylactic lymphadenectomy. Breslow depth remains to this day one of the best predictors of patient outcomes. Over the next 40 years, new staging systems were developed based on patient treatment data and improvements in statistical methods. The American Joint Committee on Cancer (AJCC) played a key role in developing the TNM (tumor, lymph node, metastasis) staging system [10]. The TNM system developed by the American Joint Commission on Cancer is the most widely used method for evaluating melanoma staging, taking into account the histologic features of the primary tumor (T), the status of the lymph nodes (N) and the presence of distant metastases (M) [10,15]. The stage of the disease depends on factors such as the thickness of the tumor and possible involvement of lymph nodes or other organs [16]. As tumor thickness increases, the risk of lymph node involvement increases, with an increase of 2-5% for tumors with a Breslow depth of ≤ 1.00 mm. The 5-year survival rates for stage IIIA, IIIB and IIIC melanoma are 78%, 59% and 40%, respectively. Patients with distant metastases to skin, subcutaneous tissue and lymph nodes (M1a), lung metastases (M1b) and extrapulmonary metastases to other organs (M1c) have one-year survival rates of 62%, 53% and 33%, respectively [16]. Extensive metastases to the liver, lung, brain, bone and lymphatic system are the leading cause of death for melanoma patients [17]. The average survival time for patients with AJCC stage IV melanoma is about 8 months (± 2 months), and only about 10% survive longer than 5 years from diagnosis [18]. The prognosis of melanoma is closely related to the depth of the tumor, which usually increases over time, so early detection is crucial [13].

The immune environment of melanoma

Melanoma is one of the most prominent examples of an immunogenic tumor. As early as the late 19th century, William B. Cooley observed that injecting patients with dead Streptococcus pyogenes and Serratia marcescens bacteria led to remission of their tumors [19]. In the last 20 years, immune cells in the tumor microenvironment (TME) have been shown to be crucial in the success or failure of cancer treatment. The tumor microenvironment includes immune cells (T cells, macrophages, dendritic cells), fibroblasts, endothelial cells, and extracellular matrix (ECM) elements. The immune system plays a dual role in cancer progression, as there is a dynamic interaction between immune cells and tumor cells, involving three phases: elimination, equilibrium and escape. Once activated, immune responses must be controlled temporally and spatially to avoid tissue damage and ensure peripheral tolerance [20]. Infiltrating T lymphocytes (TILs) are a key component of the anti-tumor response. The presence of CD8+ TILs correlates with the efficacy of immunotherapy. Myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) suppress the immune response and are associated with treatment resistance. M2 macrophages promote angiogenesis and immunosuppression in melanoma TME, making them a target for new therapeutic strategies [19]. The advent of effective systemic therapies in the form of checkpoint-blocking immunotherapy for the treatment of

melanoma patients represented a revolution in modern patient care. The discovery of anti-CTLA4-Ig antibodies and the subsequent approval of ipilimumab for systemic treatment in melanoma patients ushered in a new era. Treatment advances were rapid, and newer therapies showed better efficacy and less toxicity. PD-1 inhibitors quickly became the standard of care for adjuvant treatment and non-operative relapses [21]. The breakthrough evidence of objective responses in checkpoint blockade therapy caused a real revolution in oncology, as evidenced by the 2018 Nobel Prize in Physiology or Medicine awarded to James P. Allison and Tasuku Honjo [20]. The purpose of this review is to summarize the different types of immunotherapeutic agents, as well as discuss various treatment strategies, complementary treatment regimens and possible biomarkers of treatment response [19].

Risk factors

Cutaneous melanoma arises from malignant transformation of melanocytes, which are located in the basal layer of the epidermis [1,8]. The primary risk factor for melanoma is exposure to UV radiation, which leads to direct DNA damage. In response to UV radiation, keratinocytes produce the α-melanocyte-stimulating hormone, which activates the melanocortin 1 receptor (MC1R) on melanocytes, stimulating the production of melanin, a pigment that protects the skin from the damaging effects of UV [8]. Melanocytes transport melanin to keratinocytes, and the latter accumulate it to protect the nuclei from UV-induced mutations. Keratinocytes, as they mature and die over time, form a dead protective layer of skin that acts as a barrier [10]. Individuals with low MC1R activity are more prone to mutations as a result of stronger UV exposure [8]. Melanocyte transformation is a process of sequential accumulation of genetic and molecular changes [22,23]. There are two forms of melanin produced by melanocytes: black/brown eumelanin and red/yellow pheomelanin. Skin color depends on the proportion of these two pigments, not on the number of melanocytes, which is similar in all skin types. Eumelanin provides better protection against UV radiation, which reduces the risk of skin cancer in people with darker skin. In contrast, pheomelanin not only provides weaker UV protection, but its production leads to the production of carcinogens. Pheomelanin generates more reactive oxygen species (ROS) when exposed to UV radiation, leading to more severe DNA damage [10]. The risk of melanoma is closely related to the level of UV radiation, especially UV-B. A history of sunburn in childhood and adolescence also plays an important role. People who have experienced more than five episodes of sunburn have twice the risk of developing melanoma in the future. The increased risk also applies to people who use tanning beds, regardless of age [22,23,24]. Solaria emit ultraviolet radiation, which is similar to natural sunlight, but often with higher intensity and concentration. Epidemiological studies have unequivocally shown that tanning bed use increases the risk of melanoma, especially when exposure begins at an early age. Consequently, many health organizations, including the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC), classify tanning beds as a Group 1 carcinogen, a confirmed cancer-causing agent in humans.In Poland and many other countries, regulations have been introduced restricting access to tanning beds, especially for minors, as a preventive measure to reduce the incidence of melanoma [25,26]. Periodic sunburns in childhood are a strong risk factor for melanoma on the trunk and extremities, while long-term radiation exposure and occupational exposure are associated with a higher risk of melanoma of the head and neck [26]. The incidence of melanoma varies by geographic region. As early as 1956, Lancaster noted that melanoma-related mortality increases as one approaches the equator, referring to this phenomenon as a “latitude gradient.” There are also suggestions that changes in altitude affect the incidence of melanoma, as higher areas have less shading, reduced ozone absorption and greater reflection of UV radiation from snow-covered surfaces, which can lead to increased UV exposure [1]. Other risk factors associated with malignant transformation of melanocytes include age, gender, race, genetic factors, environmental conditions and the number of nevi [8]. Light complexion, freckles, numerous dysplastic or atypical nevi, increase the risk of developing melanoma [4,26]. A large number of common nevi correlates with a 7-fold increased risk of melanoma [4].

Treatment of early-stage melanoma

Surgery remains the primary treatment for melanoma, especially for early stages of the disease. Primary removal of the tumor with an adequate margin of healthy tissue is key to reducing the risk of local recurrence and regional metastasis. The chances of cure decrease as the thickness of the tumor increases. Therefore, early and accurate diagnosis is crucial [5,10]. Surgical resection of the tumor is the main method of treatment for patients with stage I-IIIB primary melanoma that does not metastasize to regional lymph nodes [18,28].Standard excision includes a margin depending on the depth of tumor infiltration, determined according to the Breslow classification [29]. For lesions up to 1 mm thick, a margin of 1 cm is recommended,

while for thicker lesions the margin should be 2 cm or more [28]. If regional lymph node metastasis is suspected or confirmed, a sentinel lymph node biopsy is performed. Sentinel lymph node biopsy is a key diagnostic and prognostic procedure in the treatment of cutaneous melanoma [15,29]. The procedure identifies and removes the first lymph node into which cancer cells from the primary tumor can enter. The result of SNB allows an accurate assessment of the presence of lymphatic metastases, which is important for further therapy planning and prognosis assessment [30]. The introduction of SNB has revolutionized the approach to melanoma treatment, making it possible to avoid prophylactic lymphadenectomy in patients without nodal metastases, significantly reducing the risk of complications associated with the procedure, such as lymphedema [31]. SNB biopsy is indicated in patients with a tumor with a thickness according to Breslow of 0.8-1.0 mm or less than 0.8 mm, but with ulceration and a mitotic index of ≥1/mm2, classified as T1b melanoma according to the AJCC. The presence of ulceration increases the risk of a positive SNB [5]. If the biopsy shows the presence of metastases, the standard of care is extended lymph node excision (lymphadenectomy) [29]. Surgical treatment of melanoma is most effective in stages limited to the skin and regional lymph nodes. In more advanced cases with distant metastasis, surgery often has a palliative role or is used as part of combination therapy with immunotherapy and targeted therapy [31].

Chemotherapy in metastatic melanoma

For patients with metastatic cancer, surgery will not be curative, and further treatment options will include drug therapies. Before the introduction of new treatments, chemotherapy was the only treatment option for patients with metastatic melanoma [10]. The most commonly used drug for chemotherapeutic treatment of melanoma is dacarbazine (DTIC), approved by the FDA in the 1970s [10]. Other drugs used in melanoma chemotherapy include temozolomide, which is a derivative of dacarbazine with better oral bioavailability, and drug combinations such as paclitaxel in combination with carboplatin [26]. Dacarbazine has antitumor activity, but contemporary studies show that its efficacy is moderate and treatment responses are usually short-lived. Response to dacarbazine treatment is achieved in about 15-20% of patients, with limited disease progression-free survival, and median survival has ranged from 5 to 11 months [5,10]. Five-year survival was reported by only 2-6% of patients [32]. The most common side effects of chemotherapy include mild nausea, vomiting, bone marrow suppression and fatigue [31]. In recent years, the role of chemotherapy in the treatment of melanoma has significantly diminished in favor of targeted therapies and immunotherapies, which show higher efficacy and a better safety profile. Nevertheless, chemotherapy remains a therapeutic option for patients who are ineligible for treatment with modern therapies or when other therapies fail [32].

Immunotherapy in metastatic melanoma

Tumor immunotherapy includes a variety of approaches aimed at modulating the patient's immune system response to fight cancer. This involves activating immune responses against tumors or delivering effector cells to help fight the cancer. For many years, the main research on manipulating the immune response focused on T cells [20]. Over the past few years, there have been significant advances in the treatment of metastatic melanoma as a result of a better understanding of the role of the immune system in the cancer response. It has been demonstrated that the immune system can be an effective therapeutic target in the treatment of solid tumors, including melanoma [32]. Therapies based on blocking immune checkpoints, which have yielded clear results in melanoma, have revolutionized approaches to cancer treatment, as recognized by the 2018 Nobel Prize awarded to James P. Allison and Tasuku Honjo [20]. Melanoma, whose tumor antigens were among the first to be identified, has become a key model in immuno-oncology research, allowing a better understanding of the mechanisms of the anti-tumor response [33]. Thanks to its high mutation rate, melanoma produces numerous tumor antigens that are easily recognized by the immune system, making it uniquely immunogenic. Tumor antigens are divided into two groups: tumor-associated antigens (TAA), which are also found in normal cells, and tumor-specific antigens (TSA), which are present only in tumor cells [10]. As a result of an impaired immune response, leading to tumor tolerance, the disease can progress. Immunotherapy effectively breaks down this barrier of immunosuppression, which has been crucial in the treatment of melanoma for the past decade and led to the approval of immune checkpoint inhibitors. This innovative therapy has opened a new era of cancer treatment based on immunology and specific tumor mutations [10].

Immune checkpoint inhibitors

Immune checkpoints are an important mechanism regulating the immune response to maintain tolerance to one's own tissues and prevent autoimmune damage. Cancer cells can use this mechanism to evade attacks from the immune system, especially T cells. In melanoma, two major checkpoints stand out: CTLA-4 and PD-1 [27]. CTLA-4 (cytotoxic T-lymphocyte antigen 4) is one of the main inhibitors of the immune response, blocking T-lymphocyte activation at the central level. PD-1 (programmed cell death protein 1), on the other hand, is an inhibitory receptor present on activated T lymphocytes, as well as on B and NK lymphocytes during the effector response. Like CTLA-4, PD-1 is also highly expressed on Treg lymphocytes, which promotes their proliferation, so blocking PD-1 can reduce their number and activity, enhancing the anti-tumor response. Chronic activation, a hallmark of cancer, can lead to sustained PD-1 expression, resulting in depletion of NK and T lymphocytes, limiting their ability to effectively eliminate cancer cells [20]. Ipilimumab (a humanized monoclonal antibody) is the first and only anti-CTLA-4 drug approved in July 2011 by the Food and Drug Administration, FDA for the treatment of advanced melanoma. It inhibits the binding of the CTLA-4 antigen of T lymphocytes to the ligand. It exploits the body's natural ability to eliminate the tumor with the help of the immune system, by increasing the production of pro-inflammatory cytokines, clonal T-cell expansion and tumor infiltration [32].

Ipilimumab

CTLA-4 is a protein belonging to the CD28:B7 immunoglobulin family that is present on the surface of regulatory T cells (Treg) [27,33]. As an immune checkpoint inhibitor, CTLA-4 controls T cell effector functions, preventing autoimmunity and enabling tolerance to one's own antigens [18,34]. Overexpression of CTLA-4 on tumor cells is one of the mechanisms by which tumors can suppress the immune response. Monoclonal antibodies such as ipilimumab and tremelimumab (CP-675206) block CTLA-4, allowing CD28 to bind to B7-1 receptors, leading to T-cell activation and proliferation [19]. Ipilimumab is a humanized monoclonal antibody of the IgG1 class that blocks CTLA-4, enabling more complete activation of T cells against tumor cells. It was approved by the FDA in 2011 as the first immune checkpoint inhibitor for the treatment of advanced melanoma [35]. Results from a landmark Phase III trial showed that ipilimumab significantly prolongs overall survival in patients with inoperable or metastatic melanoma, with a median OS (overall survival) of 10.1 months compared to 6.4 months in the control group [34]. Although a response to ipilimumab occurs in only a fraction of patients (about 10-15%), it can be long-lasting, even several years, in responders. Sustained survival of up to 10 years has been observed in 20% of patients with stage IV melanoma [10]. The discovery of ipilimumab was considered a breakthrough; it was the first drug to improve survival rates in advanced, metastatic melanoma [7]. Despite ipilimumab's enhancement of immune activity and antitumor response, it can also break immune tolerance to its own antigens and cause multiple, autoimmune side effects (irAEs). irAEs occur in 72% of ipilimumab-treated patients, with high-grade adverse events accounting for 24% [34]. Grade 3 and 4 irAEs include gastrointestinal toxicities (16% - inflammatory bowel disease, colitis, hepatitis), endocrine system (8.5%), dermatitis and pituitary inflammation (1.5%) [7,18,28]. In addition, fatigue (6.9%), dyspnea (3.9%), anemia (3.1%), decreased appetite (1.5%) and rash (0.8%) [7]. Approximately 1 in 10 patients may develop severe immune-mediated, life-threatening toxicity, requiring treatment with systemic corticosteroids and/or other immunosuppressive drugs [5,7]. Treatment discontinuation during the study due to adverse events occurred in 52% of ipilimumab-treated patients, while death occurred in 1% of patients [7]. In clinical practice, ipilimumab is now sometimes used alone or, more often, in combination with a PD-1 inhibitor (e.g., nivolumab), leading to a synergistic increase in treatment efficacy. Combination therapy improves response rates and survival, although it also increases the risk of toxicity [36].

Nivolumab

Programmed cell death receptor-1 (PD-1, CD279) is a member of the CD28/CTLA-4 family of receptors and is present on the surface of activated CD8+ T lymphocytes, CD4+ T lymphocytes, B lymphocytes, monocytes and NK cells [7,19]. PD-1 is an inhibitor of T lymphocyte activation. Its main ligands are PD-L1 and PD-L2, which can be presented by tumor cells and other cells in the tumor microenvironment. The interaction of PD-1 with the ligand results in inhibition of the T-cell response, leading to the so-called "exhaustion" of effector cells and allowing the tumor to evade immune surveillance [37]. High PD-L1 expression is associated with a worse prognosis [7]. Blocking PD-1 receptors has become an important therapeutic target for the treatment of melanoma, which has led to the development of new immune inhibitors

such as anti-PD1 antibodies. PD-1 blocking therapy has shown promising treatment results, and drugs such as Nivolumab, Pembrolizumab and Atezolizumab have been approved for melanoma therapy [27]. Within a few years of phase I-III trials, nivolumab and pembrolizumab gained rapid FDA approval for the treatment of advanced melanoma, and later for many other cancers [39]. Nivolumab is an IgG4 anti-PD-1 monoclonal antibody approved by the FDA in 2014 for the treatment of patients with inoperable or metastatic melanoma and disease progression after ipilimumab and a BRAF inhibitor (if the BRAF V600 mutation is positive)[7]. In the CheckMate 067 trial, patients with previously untreated melanoma received nivolumab, ipilimumab or a combination of both drugs. The 5-year overall survival rate was 44% for nivolumab in monotherapy, and 52% for combination therapy with ipilimumab [38].

Pembrolizumab

Pembrolizumab (MK3475/Lambrolizumab) is the first humanized IgG4 anti-PD-1 antibody approved by the FDA in 2015 [38]. In the KEYNOTE-006 clinical trial, pembrolizumab was shown to significantly improve overall survival (OS) and progression-free survival (PFS) compared to the CTLA-4 inhibitor ipilimumab. The 2-year survival rate was 55% in the pembrolizumab-treated group, compared to 43% in the ipilimumab group [39]. Pembrolizumab is also used for adjuvant treatment after resection of stage III melanoma. The KEYNOTE-054 trial showed that therapy with this drug reduces the risk of relapse compared to placebo in patients after complete resection [40].

Immuno-Related Adverse Events

The frequency of irAEs depends on the type of inhibitor used. Anti-CTLA-4 drugs, such as ipilimumab, are associated with a higher risk of severe complications compared to PD-1 inhibitors. In clinical trials, ipilimumab induced grade 3-4 irAEs in 10-27% of patients, compared to nivolumab and pembrolizumab in 5-10% [41]. Typical side effects include: cutaneous inflammatory changes - rash, pruritus, colitis - diarrhea, abdominal pain (more common with ipilimumab, endocrine disorders - thyroiditis, adrenal insufficiency, pituitary inflammation, pneumonitis - significant especially with anti-PD-1, often asymptomatic in the early phase [42].

Conclusions

Melanoma is a skin neoplasm with a poor prognosis, especially in the metastatic stage, which requires effective treatments. Traditional therapies, such as chemotherapy, radiotherapy and targeted therapies, do not yield satisfactory results in metastatic patients, highlighting the need to search for new therapeutic strategies. Immunotherapy of melanoma using immune checkpoint inhibitors represents a breakthrough in the treatment of this cancer, especially in its advanced stages. Drugs such as ipilimumab (anti-CTLA-4), nivolumab and pembrolizumab (anti-PD-1) significantly prolong patients' survival and increase long-term response rates compared to previous approaches such as chemotherapy. Blockade of CTLA-4 and PD-1 receptors allows restoration of anti-tumor T-cell activity and eliminates immune tolerance mechanisms exploited by tumor cells. Although immunotherapy may be associated with immune-mediated side effects, its overall benefit profile. However, the efficacy of immunotherapy is not universal, and some patients do not respond to treatment or develop resistance. In addition, there are new challenges, such as the risk of immune-related adverse effects (irAEs). Despite exciting advances in the treatment of advanced melanoma, prevention and early detection remain the primary goals of the war against this cancer. Impact on education, public awareness, student education and consequences as a result of the use of melanoma morbidity and mortality.

All authors have read and agreed with the published version of the manuscript.

Funding Statement: The study did not receive special funding.

Conflict of Interest Statement: The authors report no conflict of interests

Funding sources: There are no sources of funding to declare.

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