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Immunotherapy of Melanoma – Current State of Knowledge and Future Perspectives

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ABSTRACT

Introduction: In recent years, understanding how the immune system responds to cancer cells have greatly shaped in development of new therapies for ontological diseases, including advanced melanoma. Notably, immune checkpoint inhibitors (ICIs) like a CTLA-4 inhibitor ipilimumab and the PD-1 inhibitors pembrolizumab and nivolumab have emerged as key therapeutic option. Numerous clinical trials have shown that their use promotes a significant improvement of overall survival (OS), progression-free survival (PFS), and quality of life of patients. However, a significant limitation of immunotherapy is the occurrence of adverse events, which in many cases prevent the continuation of treatment. Methods: We reviewed the selected literature available in the PubMed database, encompassing publications from the past decade. Prospective and retrospective clinical trials, systematic reviews, and meta-analyses on melanoma immunotherapy, we considered for this review. Results: After analyzing the available studies, it shown that immunotherapy in the form of ICIs significantly prolongs OS and PFS in patients with advanced melanoma. The efficacy of the therapy was observed in both anti-CTLA-4 and anti-PD-1 monotherapy and in combination regimens, although these are associated with a higher incidence of adverse events. Conclusion: The introduction of checkpoint inhibitors into everyday clinical practice has significantly improved the prognosis of patients with advanced melanoma and changed the standard of care in this group. A combination therapy of anti-CTLA-4 and anti-PD-1 produces the best results, but severe adverse effects limit its routine use. Therefore, researchers intensively investigate resistance mechanisms and strategies for patient personalization.

Keywords: immunothetapy, melanoma, immune checkpoint inhibitors (ICIs)

1. INTRODUCTION

Melanoma is one of the fastest growing cancers. The tumor originates from melanocytes, characterized by a high potential for metastasis (Hodi et al., 2021). Although it accounts for only about 1% of all diagnosed skin cancers, it is considered one of the most deadly (Siegel et al., 2018). Over the past 30 years, the incidence of melanoma has doubled, reflecting, among other things, an aging population, increased exposure to UV radiation, and improved awareness and detection of the disease (Guy et al., 2015). Advances in oncological diagnostics and surgery over the years do not correlate with a better prognosis for melanoma patients. However, immunotherapy has revolutionised treatment, enabling new

treatment options for patients with advanced forms of the disease (Hodi et al., 2021). Immunotherapy uses the immune system's ability to recognize and eliminate cancer cells. Immune checkpoint inhibitors (ICIs), such as anti-CTLA-4 antibodies (ipilimumab) and anti-PD-1 antibodies (nivolumab and pembrolizumab), state a significant role in the treatment of melanoma. They block the immunosuppression mechanisms used by cancer cells (Postow et al., 2020). Clinical trials have shown that the use of the above ICIs leads to a significant improvement in overall survival (OS) and prolonged progression-free survival (PFS) (Hodi et al., 2021; Robert et al., 2023). Despite its successes, immunotherapy is not effective in all patients—some do not respond to the new treatment method, and some develop secondary resistance (Eggermont et al., 2020a). The use of ICIs is also associated with the possibility of creating many autoimmune-related adverse effects, which limits its use in some patients (Postow et al., 2020). Strategies for the use of immunotherapy continue to be the subject of numerous clinical trials and aim to optimize treatment (Larkin et al., 2022).

2. REVIEW METHODS

A literature review was conducted in PubMed databases, covering English-language publications from 2015 to 2025. Our review included clinical trials, systematic reviews, and meta-analyses of immunotherapy in the form of ICIs in patients with advanced melanoma. Exclusion criteria: lack of full text, publications in languages other than English, and descriptive studies without data on the efficacy of the therapy. During the selection we made based on titles, abstracts, and full texts. The results we grouped according to the type of therapy. The article screening process followed the PRISMA guidelines (Figure 1).

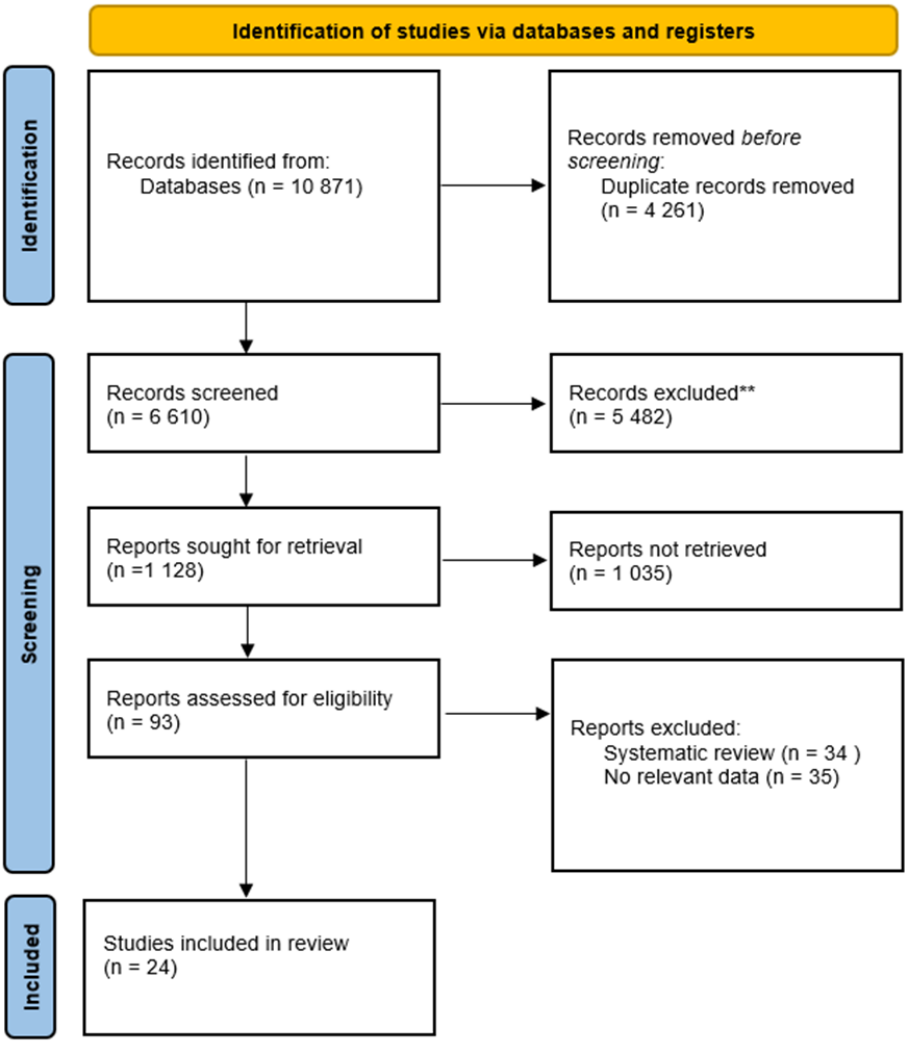

Figure 1. PRISMA flow diagram.

3. RESULTS AND DISCUSSION

CTLA-4 blockade

Ipilimumab – a human IgG1 monoclonal antibody, one of the leading representatives of ICIs, which acts by blocking the CTLA-4 (Cytotoxic T-Lymphocyte-Associated Protein 4) receptor present on the surface of T lymphocytes. CTLA-4 is an inhibitor of the immune response by competing with the CD28 receptor for binding to the costimulatory molecules B7-1 and B7-2 on antigen-presenting cells, inhibiting T cell activity. By blocking CTLA-4, ipilimumab reverses this inhibition, allowing for morę potent T cell activity against tumor cells (Schandendorf et al., 2015). One of the first clinical trials to evaluate the efficacy and safety of ipilimumab as an adjuvant treatment for advanced melanoma was the EORTC 18071 trial. This trial involved 951 patients after radical removal of stage III melanoma, who were randomly assigned to receive ipilimumab at a dose of 10 mg/kg or placebo. Researchers assessed relapse-free survival (RFS), which was significantly longer compared to placebo — the median RFS was 26.1 months vs. 17.1 months, while 3-year RFS was 46.5% vs. 34.8% (HR 0.75; p = 0.0013), respectively. However, treatment was associated with high toxicity, severe adverse events were observed in 54% of patients treated with ipilimumab, and 1% died due to treatment (Eggermont et al., 2015). Five years later, another randomized study (E1609) was conducted with ipilimumab to evaluate its efficacy and tolerability at two doses – 3 mg/kg (ipi3) and 10 mg/kg (ipi10) – compared with classic high-dose alpha-2b interferon therapy (High-Dose Interferon, HDI). The study included 1,670 patients with stage III (IIIB–C) or IV (M1a–b) melanoma after radical surgical treatment. These patients randomly received the ipi3, ipi10, and HDI groups.

The analysis showed that the use of ipilimumab (3mg/kg dose) statistically significant improvement in OS compared to HDI (HR 0.78; p = 0.044). The difference in RFS did not reach statistical significance (HR 0.85; p = 0.065), but they observed a favorable trend in favor of ipilimumab. In contrast, a higher dose of the drug (ipi10) did not improve either OS or RFS and it was associated with significantly more severe adverse events, with 54% of patients requiring early discontinuation of treatment. E1609 is the first study to demonstrate the superiority of adjuvant immunotherapy with a CTLA-4 inhibitor over traditional interferon alfa treatment in terms of OS. A dose of 3 mg/kg was considered optimal due to its best efficacy-toxicity ratio. The study results have contributed to a change in the standard of adjuvant treatment for patients with melanoma at high risk of recurrence (Tarhini et al., 2020). Table 1 compares the results of clinical trials on the use of anti-CTLA-1 drugs.

Table 1 Comparison of clinical trial results for anti-CTLA-4 drugs.

Study	Number of patients	Advancement of the disease	Drug, dosage	Result
EORTC 18071	951	Stage III, after resection	Ipilimumab 10mg/kg vs placebo	Median RFS: 26.1 vs 17.1 months; 3-0-year RFS: 46.5% vs 34.8% (HR 0.75)
E1609	1670	Stages III and IV (M1a-b), after resection	Ipilimumab 3mg/kg (ipi3) vs ipilimumab 10mg/kg (ipi10) vs HDI	OS - improvement in ipi3 vs HDI (HR 0.78; p = 0.044); ipi10 - no benefit, greater toxicity than ipi3 and HDI

PD-1 blockade

Anti-PD-1 immunotherapy is currently the standard treatment for advanced melanoma, with nivolumab and pembrolizumab being the prominent representatives. The mechanism of action involves blocking the PD-1-PD-L1/2 interaction, which prevents the activation of SHP-1/SHP-2 and the dephosphorylation of TCR pathway components, increasing T cell proliferation and the expression of specific genes that prolong the survival of these cells (Robert et al., 2019). In a randomized, double-masked study (EORTC 1325/KEYNOTE-054), researchers evaluated the efficacy of adjuvant immunotherapy with pembrolizumab in patients with radically resected melanoma. The study enrolled 1,019 adult patients with histopathologically confirmed stage IIIA to IIIC melanoma who were randomly assigned in equal proportions (1:1) to receive pembrolizumab or placebo. Patients received pembrolizumab intravenously at a dose of 200 mg every three weeks for up to one year (maximum 18 cycles). Analysis of the population of patients who started therapy showed a clear

clinical benefit: relapse-free survival (RFS) was significantly longer in the pembrolizumab-treated group compared with placebo (HR 0.56; 98.4% CI: 0.43–0.74).

The researchers noticed this effect in all subgroups analyzed, regardless of age, gender, or disease stage. Based on the results of the study, pembrolizumab was approved as an adjuvant treatment for stage III melanoma by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), becoming the new standard of care for patients at high risk of recurrence (Eggermont et al., 2020b). The objective of the subsequent randomized, double-masked Phase III KEYNOTE-716 study was to evaluate the efficacy of pembrolizumab as adjuvant therapy in patients with radically excised stage IIB/IIC melanoma. Researchers randomly assigned 976 patients to receive pembrolizumab (200 mg every 3 weeks, 17 cycles) or placebo. The primary endpoint was RFS. In the first interim analysis (median follow-up 14 months), significantly lower RFS researchers observed in the pembrolizumab group (HR 0.65; p = 0.0066). In a subsequent analysis after 21 months, the beneficial effect persisted (HR 0.61), and the 18-month RFS was 86% in the pembrolizumab group compared to 77% in the placebo group. In the Phase II KEYNOTE-022 study, pembrolizumab was combined with dabrafenib and trametinib to evaluate the efficacy of this combination in patients with advanced melanoma with BRAF V600E/K. Results after 36.6 months showed that triple therapy significantly prolonged PFS compared to dual therapy (dabrafenib + trametinib + placebo): 16.9 vs. 10.7 months (HR 0.53; 95% CI: 0.34-0.83), and the duration of response (DOR) was more than twice as long: 25.1 vs 12.1 months. Median OS was not reached in the pembrolizumab group, while in the control group it was 26.3 months. The 24-month OS was 63% and 52%, respectively. However, researchers noticed, that combination therapy causes significantly higher risk of adverse events (58% vs. 25%), mainly immune-related (Ferrucci et al., 2020).

An article by Weide et al., (2016) described an attempt to identify baseline factors that predict the efficacy of pembrolizumab treatment in patients with advanced melanoma. The study included 616 patients with stage III/IV disease treated in various clinical trials. It shown that low lactate dehydrogenase (LDH) levels, no metastases outside soft tissue and lungs, a high lymphocyte percentage >17.5%, and a high eosinophil percentage >1.5% correlated independently with OS. The combination of these four parameters allows for a preliminary prognosis – patients with all of the above factors had an annual survival rate of 84%, while patients without any of the above factors had a survival rate of – 15%. The authors emphasize that the study is prognostic and should not be used to make treatment decisions at this time. However, the results of the study are an essential step towards the individualization of immunotherapy treatment and may contribute to better selection of patients for pembrolizumab therapy. Table 2 compares the results of clinical trials on the use of anti-PD-1 drugs in melanoma therapy.

Table 2. Comparison of clinical trial results for anti-PD-1 drugs.

Study	Number of patients	Advancement of the disease	Drug, dosage	Result
KEYNOTE-054	1019	Stage IIIA-C, after resection	Pembrolizumab 200mg for one year vs placebo	HR 0.56 (for RFS), benefit in all subgroups
KEYNOTE-716	976	Stage IIB/IIC, after resection	Pembrolizumab 200 mg – 17 cycles vs. placebo	HR 0.65 (for RFS); 18-month RFS: 86% vs 77%; reduction in distant metastases: 6% vs 12%
KEYNOTE-022, faza 2	-	BRAF V600E/K (+)	Pembrolizumab + dabrafenib + trametinib vs the same combo excluding pembrolizumab	PFS: 16.9 vs 10.7 months (HR 0.53); DOR: 25.1 vs 12.1 months

CTLA-4 blockade vs PD1 blockade

Both CTLA-4 and PD-1 blocking drugs are types of ICIs and are effective against melanoma. However, the studies below demonstrate the superiority of pembrolizumab/nivolumab over ipilimumab. Table 3 shows differences in their mechanisms of action and clinical presentations.

Table 3. Differences in the mechanisms of action among drug groups used in melanoma immunotherapy.

Group	Representative	Mechanism of action	Clinical effect
CTLA-4 blockade	Ipilimumab	Blocks the inhibition of CD28-B7-1/2 costimulation, resulting in increased T-cell activation	An increase in the number of activated T cells capable of recognizing melanoma tumor cells. "Massive boost" effect and longer persistence of immune memory
PD-1 blockade	Pembrolizumab/nivolumab	Block of PD-1 binding to PD-L1/2, resulting in a lack of SHP-1/2 activation and TCR pathway activation	Unblocking of effector T cells present in the tumor (reactivation). Increase in proliferation and cytotoxicity, prolonging the survival of T cells in the tumor environment.

The Phase III KEYNOTE-006 study compared pembrolizumab and ipilimumab in patients with advanced, unresectable melanoma to assess their efficacy. The study involved 834 patients, and the follow-up period was 10 years. The median OS was 32.7 months for pembrolizumab and 15.9 months for ipilimumab (HR 0.71). Researchers noticed, the median PFS was 9.4 vs. 3.8 months (HR 0.64), respectively. After 10 years, PFS was 22% of patients in the pembrolizumab group and 12.8% in the ipilimumab group, OS was 34.0% vs. 23.6%, respectively. The results show the pembrolizumab has a clear advantage in treating advanced melanoma (Long et al., 2024). Another randomized study comparing the use of combination therapy (nivolumab+ipilimumab) with monotherapy (nivolumab or ipilimumab) was the CheckMate 067 study. After 6.5 years of follow-up, combination therapy shown to provide the longest OS – median 72.1 months, compared to monotherapy: nivolumab – 36.9 months, ipilimumab – 19.9 months. This study also presented data on melanoma-specific survival (MSS), i.e., survival time taking into account only deaths caused by melanoma. The median MSS for the combination therapy group was not reached, while in the nivolumab group it was 58.7 months, and for ipilimumab, 21.9 months (Wolchok et al., 2022). A meta-analysis published in 2022, including 12 randomized clinical trials, showed the superiority of PD-1 inhibitor monotherapy over ipilimumab in terms of OS – the risk of death was 31% lower (HR = 0.69; 95% CI: 0.62-0.76) and PFS, with a 42% reduction in the risk of progression (HR = 0.58; 95% CI: 0.52-0.66). The objective response rate (ORR) for anti-PD-1 was 40.4% vs 13.9% for ipilimumab (OR = 4.51; 95% CI: 3.58-5.68). The authors suggest the use of PD-1 inhibitors as first-line treatment in patients with advanced melanoma (Lima et al., 2017).

CTLA4 blockade + PD1 blockade

Many clinical trials conducted to date suggest that combination therapy with anti-CTLA4 + anti-PD-1 in patients with advanced melanoma is much more effective than monotherapy with these antibodies. A higher OS rate and long-term responses have been confirmed (Larkin et al., 2019). A retrospective study evaluated the efficacy and safety of combination therapy with ipilimumab and a PD-1 inhibitor (pembrolizumab or nivolumab) in patients with metastatic melanoma who had previously been resistant to anti-PD-1 therapy. The analysis included 355 patients - 193 received combination therapy and 162 received ipilimumab monotherapy. The results showed a clear advantage of combination therapy. The ORR was 31% in this group, compared with 13% in monotherapy ($p < 0.0001$). Median OS was also significantly longer - 20.4 months for combination therapy versus 8.8 months in the ipilimumab group (HR 0.50; $p < 0.0001$). Similar results researchers observed for median PFS. One-year OS was 58% in the combination therapy group and 38% in monotherapy. The benefits of combination therapy persisted in all subgroups analyzed, except for patients with BRAF mutations (Pires da Silva et al., 2021). The IMMUNED randomized, double-blind clinical trial evaluated the efficacy of adjuvant immunotherapy in patients with completely resected stage IV melanoma with no evidence of disease (NED). The study enrolled 167 patients and randomly assigned them to one of three groups: nivolumab with ipilimumab, nivolumab monotherapy, or placebo. After 28.4 months of follow-up, the median recurrence-free survival (RFS) was not reached in the combination therapy group, while it was 12.4 months

for nivolumab and 6.4 months for placebo. Compared with placebo, the risk of recurrence or death was significantly lower in both the nivolumab plus ipilimumab group (HR 0.23; p<0.0001) and the nivolumab monotherapy group (HR 0.56; p = 0.011). Treatment effects were consistent across all subgroups (Zimmer et al., 2020).

One prospective study evaluated the efficacy of pembrolizumab in combination with low-dose ipilimumab in patients with advanced melanoma who had progressed on prior PD-1 or PD-L1 inhibitor monotherapy. The treatment regimen consisted of four cycles of treatment followed by continuation of pembrolizumab monotherapy. According to the irRECIST criteria, the treatment response rate was 29%, including 7% complete responses and 21% partial responses. The median progression-free survival (PFS) was 5 months, and the median OS was 24.7 months. The results suggest that the combination of pembrolizumab with low-dose ipilimumab may be an effective and relatively well-tolerated treatment option for patients who have failed prior anti-PD-1/PD-L1 immunotherapy (Olson et al., 2021). The 2024 NADINA study evaluated the efficacy of neoadjuvant immunotherapy (ipilimumab + nivolumab) in patients with resectable stage III melanoma. The study enrolled 423 patients and randomly assigned them to a neoadjuvant combination immunotherapy group (n = 212) and a group in which patients underwent surgery followed by nivolumab for 12 months as standard adjuvant treatment. After a median follow-up of 9.9 months, 12-month event-free survival (EFS) was 83.7% in the neoadjuvant group, compared to 57.2% in the adjuvant group. High pathological response (PR) rates researchers achieved in the neoadjuvant group: 59% of patients had a deep pathological response, and only 26.4% showed no response. In patients with a deep response, the 12-month RFS was as high as 95.1%. In another cohort study, researchers evaluated the efficacy of combination therapy with ipilimumab and nivolumab in 709 patients with advanced melanoma. The median age of patients was 61 years, and the above combination therapy was the first-line treatment between 2015 and 2021. The median OS was 28.7 months (95% CI: 20.7-42.2), and the median PFS was 6.6 months (95% CI: 5.3-8.7). Two years after the start of treatment, 51% of patients were alive, and after four years, 43% were alive.

Researchers divided the patients into several subgroups. Patients with normal LDH levels and without brain metastases, had the highest OS (van Zeijl et al., 2023). One of the aforementioned meta-analyses showed that combination therapy with nivolumab + ipilimumab has even higher clinical efficacy than anti-PD-1 monotherapy – ORR 58.4% vs 43.6%, respectively, but this does not always correlate with an improvement in OS. However, combination therapy was also associated with the highest risk of toxicity: grade 3-4 adverse events occurred in 55.9% of patients, compared with 14.1% in the PD-1 monotherapy group, and in the ipilimumab group – 26.2% (Lima et al., 2017).

4. CONCLUSION

The introduction of immunotherapy, mainly as adjuvant treatment in the form of checkpoint inhibitors, has led to a significant improvement in the prognosis of patients with melanoma. Both PD-1 inhibitors (nivolumab, pembrolizumab) and CTLA-4 inhibitors (ipilimumab) have shown considerable efficacy in this disease have shown considerable efficacy in patients with melanoma. Many studies conducted to date show that their use significantly prolongs OS and PFS. These results have led to the approval of this therapy by regulatory authorities and its inclusion in international guidelines. Ipilimumab is considerably less effective than PD-1 inhibitors, while combination therapy produces the best therapeutic (anti-CTLA-4 + anti-PD1), but its high toxicity is a limitation. Therefore, at this time, adjuvant treatment for melanoma consists of PD-1 inhibitors, except for specific groups of patients who selected for combination therapy. Despite many successes and scientific reports, further research into the mechanisms of resistance to ICIs is necessary, as approximately half of patients do not respond to immunotherapy treatment.

Abbreviations:

ICIs – Immune Checkpoint Inhibitors
CTLA-4 - Cytotoxic T-Lymphocyte-Associated Protein 4
PD-1 – Programmed Cell Death Protein 1
OS – Overall Survival
HR – Hazard Ratio
RFS – Relapse-Free Survival
CI – Confidence Interval
EMA – European Medicines Agency
FDA – Food and Drug Administration

PFS – Progressive Free Survival
DOR – Duration of Response
NED – No Evidence of Disease
MSS – Melanoma Specific Survival
ORR – Objective Response Rate
EFS – Event Free Survival
PR – Pathologic Response
HDI – High Dose Interferon

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Informed consent
Not applicable.

Ethical approval
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Conflict of interest
The authors declare that they have no conflicts of interests, competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data and materials availability
All data associated with this study will be available based on reasonable request to the Corresponding Author.

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