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Evaluation of the efficacy of combined immune checkpoint inhibitors in advanced melanoma treatment - Long term outcomes and emerging therapeutic perspectives: a narrative review

Evaluación de la eficacia de inhibidores combinados de puntos de control inmunológico en el tratamiento avanzado del melanoma - Resultados a largo plazo y perspectivas terapéuticas emergentes: una revisión narrativa

Ana Gabriela Aillón Albán
ana1999aillon@gmail.com
ORCID: https://orcid.org/0009-0005-0984-828
Ministerio de Salud Pública, Ecuador

Fernanda De Las Mercedes López Naveda
ORCID: https://orcid.org/0009-0000-5028-5014
Investigador Independiente, Ecuador

Irina Talia Guzmán Chávez
ORCID: https://orcid.org/0009-0007-8116-1218
Ministerio de Salud Púbica, Ecuador

Andrea Carolina Arregui Ayala
ORCID: https://orcid.org/0009-0008-0740-2121
Investigador Independiente, Ecuador

Clara Noemi Sivisaca Bonifaz
ORCID: https://orcid.org/0009-0001-8882-7787
Ministerio de Salud Púbica, Ecuador

ABSTRACT

Combination therapy with immune checkpoint inhibitors, specifically CTLA-4 and PD-1 blockade, has shown promise in treating advanced melanoma. However, this approach often results in increased toxicity, necessitating a careful evaluation of both efficacy and safety. This review explores clinical outcomes, survival rates, and adverse events associated with these therapies. A systematic review of PubMed, Scopus, and clinical trial databases was conducted for studies published from 2014 to 2024. Studies assessing the combined use of CTLA-4 and PD-1 inhibitors in melanoma patients were included, focusing on overall survival (OS), progression-free survival (PFS), and treatment-related adverse events (AEs). The combination of CTLA-4 and PD-1 inhibitors significantly improved clinical outcomes in advanced melanoma. In trials like CheckMate 067, the five-year overall survival rate reached 52%, with a notable improvement in progression-free survival. However, these benefits came with substantial toxicity, as approximately 55% of patients experienced grade 3 or 4 treatment-related adverse events, including colitis, hepatitis, and pneumonitis. Despite these challenges, combination therapy led to durable responses in a subset of patients, underscoring its efficacy. The review emphasizes the need for balancing efficacy with toxicity management in clinical practice. While CTLA-4 and PD-1 inhibitor combinations improve survival in advanced melanoma, increased toxicity presents challenges. Further research is needed to optimize treatment strategies and enhance patient selection to balance efficacy and safety.

Keywords: advanced melanoma. immune checkpoint inhibitors. CTLA-4. PD-1. combination therapy. survival. toxicity.

RESUMEN

La terapia combinada con inhibidores de puntos de control inmunitarios, específicamente el bloqueo de CTLA-4 y PD-1, se ha mostrado prometedora en el tratamiento del melanoma avanzado. Sin embargo, este enfoque a menudo resulta en una mayor toxicidad, lo que requiere una evaluación cuidadosa tanto de la eficacia como de la seguridad. Esta revisión explora los resultados clínicos, las tasas de supervivencia y los eventos adversos asociados con estas terapias. Se realizó una revisión sistemática de PubMed, Scopus y bases de datos de ensayos clínicos para estudios publicados entre 2014 y 2024. Se incluyeron estudios que evalúan el uso combinado de inhibidores de CTLA-4 y PD-1 en pacientes con melanoma, centrándose en la supervivencia general (SG). supervivencia libre de progresión (SSP) y eventos adversos (EA) relacionados con el tratamiento. La combinación de inhibidores de CTLA-4 y PD-1 mejoró significativamente los resultados clínicos en el melanoma avanzado. En ensayos como CheckMate 067, la tasa de supervivencia general a cinco años alcanzó el 52%, con una mejora notable en la supervivencia libre de progresión. Sin embargo, estos beneficios vinieron acompañados de una toxicidad sustancial, ya que aproximadamente el 55% de los pacientes experimentaron eventos adversos relacionados con el tratamiento de grado 3 o 4, incluidas colitis, hepatitis y neumonitis. A pesar de estos desafíos, la terapia combinada generó respuestas duraderas en un subconjunto de pacientes, lo que subraya su eficacia. La revisión enfatiza la necesidad de equilibrar la eficacia con el manejo de la toxicidad en la práctica clínica. Si bien las combinaciones de inhibidores de CTLA-4 y PD-1 mejoran la supervivencia en el melanoma avanzado, el aumento de la toxicidad presenta desafíos. Se necesita más investigación para optimizar las estrategias de tratamiento y mejorar la selección de pacientes para equilibrar la eficacia y la seguridad.

Palabras clave: melanoma avanzado. inhibidores de puntos de control inmunológico. CTLA-4. PD-1. terapia combinada. supervivencia. toxicidad.

INTRODUCTION

A cancer that develops when melanocytes undergo a malignant change is called melanoma. Neural crest cells give rise to melanocytes. Melanomas may thus grow in other areas where neural crest cells move, such as the brain and gastrointestinal system, even if they originate from the skin (Heistein et al., 2024). Patients with melanoma-in-situ or stage 0 have a 5-year relative survival rate of 97%, whereas those with stage IV cancer have a rate of 30%. The National Cancer Institute (NCI) estimates that between 2014 and 2018, there were 0.9 cases of metastatic melanoma for every 100,000 people (Heistein et al., 2024).

Immunotherapy with immune checkpoint inhibitors (ICIs) has improved the course of treatment for several cancers, including multiple myeloma (MM), in recent years. An essential component of anti-tumor immunity, tumor-specific T cells are suppressed from attacking by immunological checkpoint molecules. Certain immune checkpoint inhibitors (ICIs) impede the communication between T cells' PD-1 (programmed cell death-1) and the cancer cells' and myeloid cells' PD-L1 ligand (Pradeep et al., 2022). Additional immune checkpoint inhibitors (ICIs) target cytotoxic T-lymphocyte antigen-4 (CTLA-4), which depletes regulatory T cells and inhibits negative signals during T-cell contact with antigen-presenting cells, therefore improving and restoring T-cell reactivity (Romano et al., 2015).

Clinical studies comparing PD-1 inhibitors to CTLA-4 inhibitors have shown a distinct survival benefit for the former, as seen by three-year OS rates over 50% in KEYNOTE-006 (Robert et al., 2019)and CheckMate-067 (Wolchok et al., 2017a). ipilimumab and nivolumab together showed a slight but statistically insignificant three-year survival improvement over nivolumab monotherapy (58% vs. 52%) in the CheckMate-067 study. In assessments conducted at five and 6.5 years into the long term, this advantage was still present (Larkin et al., 2019).

For some patient groups, including as those with asymptomatic central nervous system (CNS) metastases, BRAF mutations, and increased blood LDH levels, combination treatment has emerged as the accepted standard of care (Switzer et al., 2022). Approximately 33% of patients with stage IV melanoma are now receiving this combo treatment. As opposed to 21% on monotherapy, 59% of patients have grade 3–4 immune-related adverse events (irAEs) with this treatment option (Wolchok et al., 2017b). The increased toxicity has been confirmed by further research and clinical experience (Gunturu et al., 2022). Its whole range of toxicity is also still poorly understood, and novel adverse effects are constantly being reported (Schneider et al., 2021).

The aim of this narrative review is to evaluate the long-term efficacy and safety of combined immune checkpoint inhibitors, specifically CTLA-4 and PD-1 inhibitors, in the treatment of advanced melanoma. The review explores pre-clinical evidence, clinical outcomes, resistance mechanisms, and toxicity profiles, while highlighting emerging therapeutic perspectives and strategies for optimizing treatment responses. Through this analysis, the review seeks to provide insights into the potential benefits and challenges of combination immunotherapy, guiding future research and clinical practice for improving patient outcomes in advanced melanoma.

METHODOLOGY

This narrative review employed a structured approach to systematically gather and assess relevant literature regarding the long-term outcomes and emerging therapeutic perspectives of combined immune checkpoint inhibitors (ICIs) in advanced melanoma treatment. The methodology was designed to comprehensively cover pre-clinical and clinical evidence, along with the efficacy of combination therapies, focusing on the integration of CTLA-4 and PD-1 blockade. Established review protocols were followed to ensure a thorough examination of the subject matter. Primary academic databases, including PubMed, Scopus, and Google Scholar, were searched for pertinent studies. Key search terms such as "immune checkpoint inhibitors," "CTLA-4 and PD-1 combination therapy," "advanced melanoma treatment," and "nivolumab and ipilimumab outcomes" were utilized to identify the most relevant literature.

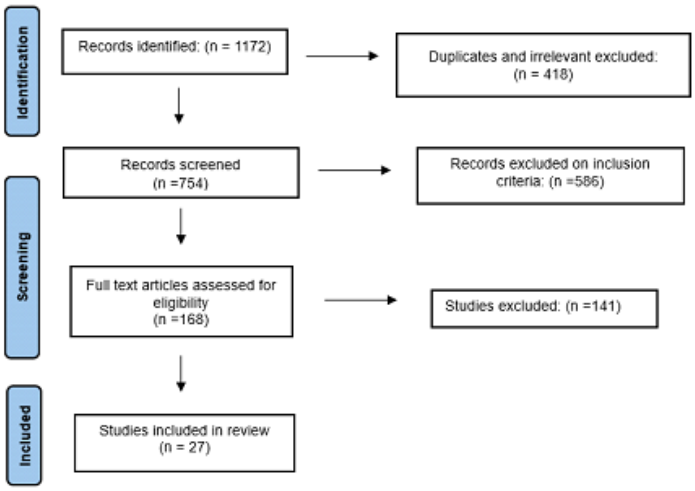
Inclusion and Exclusion Criteria

To ensure that the review reflects current advancements and long-term treatment outcomes, only studies published in English between 2010 and 2024 were included. Eligible studies had to focus on human subjects with advanced or metastatic melanoma and provide substantial evidence regarding the efficacy, toxicity, survival rates, and mechanistic insights of combined ICI therapy (e.g., nivolumab and ipilimumab). Both clinical trial data and pre-clinical studies were included to provide a holistic understanding of the topic. Studies that did not address the combination of ICIs or lacked robust clinical evidence were excluded. A thorough review of abstracts and titles was performed to assess the relevance of each article.

Categorization and Analysis

The collected literature was categorized based on the pre-clinical rationale for combination therapies, clinical trial outcomes, toxicity profiles, and emerging perspectives on biomarkers for treatment stratification. This approach facilitated a detailed analysis of how CTLA-4 and PD-1 inhibition interact to enhance T-cell reactivity, reduce immune resistance, and improve survival rates in patients with advanced melanoma. Special attention was given to comparative studies assessing monotherapy versus combination therapy, with a focus on progression-free survival (PFS), overall survival (OS), and treatment-related adverse events. By synthesizing findings from a wide range of studies, this review aimed to provide insights into the mechanisms and clinical effectiveness of combined immune checkpoint blockade, offering valuable information for oncologists in optimizing treatment strategies for advanced melanoma.

Figure 1: Prisma flow diagram



source: the authors.

RESULTS

Rationale for Checkpoint Blockade Combination Therapy Use

Checkpoint inhibitor monotherapy mostly improves subgroups of patients. CTLA-4 and PD-1 generate T-eff at distinct times and sites (Wei et al., 2017). Combination therapy may be complementary or synergistic. Resistance mechanisms also affect checkpoint blockade therapy. Primary resistance to anti-CTLA-4 inhibition is linked to decreased IFN-γ signaling genes in vitro and clinically in individuals with poor ipilimumab responses. PD-L1 expression on circulating CD4+ T CD8+ T cells may predict anti-CTLA-4 resistance in patients, supporting the use of PD-1/PD-L1 blocking therapy (Jacquelot et al., 2017). In murine models and patients receiving anti-PD-1 treatment, infiltrating myeloid cells and their signaling pathways and upregulation of alternative immune checkpoints like T cell immunoglobulin mucin-3 (TIM-3) is also linked to checkpoint resistance (Koyama et al., 2016). Monotherapy with checkpoint inhibitors activates compensatory T cell-associated checkpoints. Combination treatment may inhibit tumor development by blocking many pathways, including PD-1, LAG-3, and CTLA-4 (Huang et al., 2017). Mouse studies showed that anti-CTLA-4 and anti-PD-1 antibodies enhanced B16 melanoma cell rejection (Curran et al., 2010). Results show that combination therapy is twice as effective as monotherapy in B16 melanoma rejection, with increased T cell infiltration, T-eff presence, and increased IFN-γ and pro-inflammatory cytokines, resulting in an inflammatory rather than immunosuppressive TME. More pre-clinical investigations revealed that anti-CTLA-4 and anti-PD-1 treatments may work together to increase TILs, reduce T-reg, and slow tumor progression (Spranger et al., 2014). Older patients, who have less T-regs, react better to anti-PD-1 drugs (Kugel et al., 2018). These results and studies showing that anti-CTLA-4 therapy reduces CTLA-4-expressing T-regs may support stratifying patients for combination treatments (Simpson et al., 2013) (Romano et al., 2015).

Since CTLA-4 and PD-1 inhibitors have distinct anti-tumor actions, combining them may improve therapy. Additionally, blocking one route boosted activity and upregulated other inhibitory pathways, which may be countered by combination treatment. Evidence justified the creation of combination blockade regimens and accelerated research into other blockade targets (Khair et al., 2019). In combination therapy, toxicity profiles, particularly those related with CTLA-4 blocking usage, may be a concern, yet pre-clinical and clinical data in melanoma revealed promising outcomes.

Clinical Evidences of Combined CTLA-4 and PD-1 mAb Therapies

53 patients with melanoma received concurrent treatment with nivolumab and ipilimumab in the first clinical study examining the safety and effectiveness of combination checkpoint blocking antibodies, which was reported in 2013 (Wolchok et al., 2013). Thirty-three patients got just ipilimumab. The ORR for combination treatment in the double therapy group was 40%, whereas the ORR for monotherapy was 20%. However, the combination treatment group had a greater rate of drug-related toxicity; 53% of patients had grade 3 or 4 adverse events (AEs), compared to 18% in the monotherapy group. Medication was used to treat certain drug-related symptoms.

945 previously untreated patients were assigned to nivolumab, ipilimumab, or the two combination medicines in the registration phase III Checkmate 067 study. The results showed median progression-free survival (PFS) of 6.9 months, 2.9 months, and 11.5 months, as well as 3-year overall survival (OS) rates of 52, 34, and 58%, respectively (Wolchok et al., 2017b). The results of this large-scale, well-powered trial demonstrated that combination therapy and nivolumab monotherapy were more effective than ipilimumab monotherapy. Patients receiving preparations that included nivolumab showed consistently longer progression-free survival (PFS), with subgroups classified by metastasis stage and PD-L1 or BRAF mutation status (Larkin et al., 2015). PFS was 11.7 months for individuals with BRAF mutations and 11.2 months for people with wild-type BRAF. Patients with positive PD-L1 status performed better, with a median PFS of 14 months in the combined treatment and nivolumab monotherapy groups, compared to 3.9 months for those on ipilimumab alone. Additionally, Checkmate 067 found that individuals receiving a combination regimen had greater rates of complete response (11.5%) than those receiving nivolumab alone (8.9%) or ipilimumab alone (2.2%). The combination group's tumor burden change (−51.9%) was considerably larger than that of the nivolumab alone and ipilimumab alone groups, which are respectively −34.5% and 5.9%. This metric may be used to predict the response to therapy.

Moreover, toxicity rates linked to combination therapy were higher (96% vs. 86% in both monotherapy regimens) and resulted in treatment discontinuation more frequently in the combined group than in either monotherapy group, according to treatment-related adverse events reported in the Checkmate 067 trial comparing ipilimumab, nivolumab, and the two combined. Compared to 21 and 28% of patients receiving nivolumab or ipilimumab alone, respectively, 59% of patients receiving combined treatment had grade 3 or 4 adverse events (AEs). The majority of these AEs were gastrointestinal in character. When patients stopped their therapy, 67% of them survived for three years after treatment, and side effects were often eliminated in three to four weeks when handled according to known safety recommendations (Wolchok et al., 2017b). These show that the benefits of dual therapy persisted even after treatment was stopped and that combination treatment provoked greater rates of toxicity than either monotherapy. For individuals with PD-L1-positive tumors, the combination and nivolumab alone groups had similar median survival rates. This might be a result of ipilimumab-enhanced T cell infiltration, which favors a TME that would respond well to anti-PD-1 drug activity (Hodi et al., 2016).

According to earlier research on anti-PD-1 monotherapies, individuals whose tumors expressed PD-L1 at levels ≥5% seemed to have more effectiveness than those whose cancers expressed less of the protein (Hodi et al., 2016). However, a different research showed that PFS was longer in the combination group (11.2 months) than in the nivolumab alone group (5.3 months) in patients who were PD-L1-negative (Larkin et al., 2015). These combination therapy seem to help patients with low PD-L1 tumor expression, according to the overall trials conducted to far.

Additionally, studies using combination checkpoint blockade regimens, in which the two antibodies were given one after the other, have been beneficial in treating melanoma. In a phase III research, nivolumab was administered as maintenance treatment for both groups until toxicity or disease progression (Weber et al., 2016). The patients in both groups had unresectable stage III or IV melanoma and were either treated with nivolumab then ipilimumab (n = 68) or vice versa (n = 70). The groups' levels of toxicity were similar, but the nivolumab/ipilimumab group had a higher 12-month survival rate (76%) than the individuals in its counterpart cohort who got the medications in reverse.

Lower rates of combined treatment toxicity have been seen when ipilimumab doses in conjunction with PD-1 aimed therapy have been reduced. Certain countries have authorized the use of nivolumab in conjunction with low-dose ipilimumab to treat renal cell carcinoma. It has been shown that this combination therapy has less toxicity than other regimens that use larger doses of ipilimumab (Motzer et al., 2018). Pembrolizumab has been proposed by research as a substitute for nivolumab when used in conjunction with ipilimumab. A phase I research that looked at the safety of combining low-dose (1 mg/kg, down from 3 mg/kg) ipilimumab with standard-dose (2 mg/kg) pembrolizumab was not powered to look at effectiveness, however it did show a degree of efficacy similar to that of a combination of nivolumab and ipilimumab (Long et al., 2017). On the other hand, the pembrolizumab formulation showed a more controllable toxicity profile.

Nivolumab Plus Ipilimumab Combination Therapy for Unresectable Melanoma

For metastatic melanoma, combined treatment with nivolumab + ipilimumab is advised as the first line of

immunotherapy (Swetter et al., 2021)(Nakamura, Asai, et al., 2020). Since nivolumab + ipilimumab combination treatment has a higher ORR than nivolumab monotherapy (57.6% (95% CI 52.0–63.2%) vs. 43.7% (95% CI 38.1–49.3%)), they are preferred in combination therapy. Despite its high frequency of severe or major adverse effects (SAEs) (Fujimura et al., 2020), this combination therapy is commonly utilized for the treatment of metastatic melanoma with or without BRAF mutations (Larkin et al., 2015). Notably, nivolumab + ipilimumab combination treatment did not substantially outperform anti-PD1 Ab monotherapy in patients with acral melanoma (palm and sole melanoma) in the Japanese population [19]. In fact, in the nivolumab + ipilimumab groups, the OS was not met ($p = 0.55$), the PFS was 3.2 months ($p = 0.74$), and the ORR was 31% (Nakamura et al., 2022). However, in the same retrospective analysis, the ORR to nivolumab + ipilimumab was considerably greater than that of anti-PD1 Ab monotherapy (61% vs. 10%; $p < 0.001$) in non-acral melanoma in the Japanese population. All things considered, the effectiveness of nivolumab + ipilimumab combination treatment is dictated, at least in part, by the clinical subtype of melanoma, much like anti-PD1 Abs (Nakamura, Namikawa, et al., 2020).

The effectiveness of anti-PD1 Ab monotherapy and nivolumab + ipilimumab combination treatment is influenced by a number of serological variables (Yoshida et al., 2020). Lactate dehydrogenase (LDH) is one of the regular blood tests that may be the most significant serological component for predicting the clinical outcomes of combination treatment with nivolumab + ipilimumab (Larkin et al., 2019). Nivolumab + ipilimumab combination treatment had a significantly higher 5-year OS rate and PFS rate in patients with increased LDH levels (38%, 28%) than did nivolumab monotherapy (28%, 18%). Additional serological factors for predicting the therapeutic benefits of nivolumab, with or without ipilimumab treatment, including C reactive protein (CRP) and IL-6. Indeed, in patients with metastatic melanoma receiving ICIs, greater levels of CRP and IL-6 are linked to prognostic variables with shorter OS (Laino et al., 2020)(Yoshida et al., 2020). The use of ipilimumab in combination therapy with nivolumab in the neoadjuvant setting was found to significantly expand tumor-resident T cell clones capable of directly eliminating melanoma at primary tumor sites (Blank et al., 2018). This finding suggests that ipilimumab is a crucial treatment option for advanced melanoma with high tumor burden and elevated LDH levels. In a real-world situation, nivolumab + ipilimumab combination treatment was efficacious for late-stage malignant melanoma with seven metastasized organs (Fujimura et al., 2019).

Nivolumab Plus Ipilimumab Combination Therapy for Melanoma with Brain Metastasis

Because patients with brain metastases from melanoma are often excluded from clinical trials, the effectiveness of nivolumab + ipilimumab for treating this kind of patient remains debatable (Larkin et al., 2015)(Robert et al., 2015). The following is the effectiveness of nivolumab with ipilimumab for melanoma with brain metastases: In patients with asymptomatic melanoma with brain metastases who had not previously received local therapy, the 1-year survival rate for nivolumab plus ipilimumab combination therapy was 81.5%; the median OS achieved with this combination therapy was not reached (median follow-up, 14 months)(Tawbi et al., 2018). However, in a multicenter, open-label phase II trial, the effectiveness of dabrafenib plus trametinib combination therapy (COMBI-MB) was evaluated for melanoma with brain metastasis. The results showed that the median OS for the BRAFV600E group, which was asymptomatic with no prior local therapy group, was 10.8 months (95% CI, 8.7–19.6 months); for the BRAFV600E group, which was asymptomatic with prior local therapy group, the median OS was 24.3 months (95% CI, 7.9–unreached months); in the BRAFV600E group, asymptomatic with prior local therapy group, 10.1 months (95% CI, 4.6–17.6 months); and for the BRAFV600D/K/R group, asymptomatic with or without prior local therapy group, it was 11.5 months (95% CI, 6.8–22.4 months) (Davies et al., 2017).

DISCUSSION

The efficacy of combination therapy also varies depending on the melanoma subtype. For instance, in the Japanese population, the combination therapy did not significantly outperform anti-PD-1 monotherapy in patients with acral melanoma, suggesting that clinical subtypes and genetic differences may influence treatment response (Nakamura, Asai, et al., 2020). In contrast, patients with non-acral melanoma responded significantly better to the combination therapy, with an objective response rate (ORR) of 61%, compared to 10% for those receiving monotherapy.

Patients with melanoma brain metastasis have historically been excluded from many clinical trials, leading to limited data on treatment efficacy in this subgroup. However, emerging evidence suggests that combination therapy can offer substantial benefits. A study in patients with asymptomatic melanoma brain metastasis reported a 1-year survival rate of 81.5% with combination therapy, with the median OS not yet reached (Tawbi et al., 2018). This is a remarkable improvement compared to alternative treatments, such as dabrafenib and trametinib combination therapy, which showed a median OS of 10.8 months in patients with BRAFV600E mutations (Davies et al., 2017).

As combination therapies evolve, the focus has shifted toward identifying biomarkers that predict response and

minimize toxicity. Elevated LDH, C-reactive protein (CRP), and IL-6 levels have been associated with poorer outcomes in patients receiving ICIs, but they may also serve as indicators for tailoring therapy (Laino et al., 2020)(Yoshida et al., 2020). The identification of such biomarkers could optimize treatment strategies, allowing for a more personalized approach and minimizing unnecessary exposure to severe toxicities.

Immune checkpoint inhibitors (ICIs) in combination, especially nivolumab and ipilimumab, have transformed the way metastatic melanoma is treated, providing significant increases in overall response rates and long-term survival. The combination of PD-1 and CTLA-4 inhibition has shown significant therapeutic advantages when compared to monotherapy; however, these improvements are associated with a higher risk of toxicity, including grade 3 or 4 adverse events (AEs) (Wolchok et al., 2017b).

Overall survival (OS) and progression-free survival (PFS) have shown improved results with nivolumab and ipilimumab combination treatment, particularly in patients with greater tumor burdens and raised lactate dehydrogenase (LDH) levels. Research indicates that individuals with increased LDH levels had a 5-year OS rate of 38%, whereas those on nivolumab monotherapy had a rate of 28% (Larkin et al., 2019). Furthermore, patients with lower PD-L1 expression showed better response to combination treatment, with a median PFS of 11.2 months against 5.3 months for nivolumab monotherapy (Larkin et al., 2015). This suggests that combination therapy may be able to overcome some resistance mechanisms.

Fascinatingly, in the neoadjuvant context, the combination treatment has also been shown to increase tumor-resident T cell clones, providing direct tumor eradication at primary locations (Blank et al., 2018). This implies that combination treatment is an essential strategy for individuals with a high tumor burden since ipilimumab is essential in boosting the immune response in these patients.

Although there is no questioning the effectiveness of combination treatment, there is a big problem with the increased frequency of serious adverse events (AEs), especially gastrointestinal toxicities. In the Checkmate 067 study, grade 3 or 4 adverse events (AEs) were reported by 59% of patients receiving combination treatment, whereas the corresponding numbers for the nivolumab and ipilimumab monotherapy groups were 21% and 28% (Wolchok et al., 2017a). Although 67% of patients who stopped owing to toxicity lived for three years, highlighting the long-term advantages of the medication even after cessation, the combination group saw more frequent treatment discontinuations as a result of the greater risk of adverse events.

One tactic to lessen these effects has been to reduce the dosage of ipilimumab. For example, it has been shown that ipilimumab at lower dosages combined with nivolumab may maintain effectiveness while lowering toxicity profiles, particularly in patients with renal cell carcinoma (Motzer et al., 2018). A comparable strategy that combined low-dose ipilimumab with pembrolizumab in place of nivolumab similarly showed a controllable toxicity profile while retaining effectiveness (Long et al., 2017).

The melanoma subtype affects combination treatment effectiveness as well. For example, in patients with acral melanoma in the Japanese population, combination therapy did not substantially outperform anti-PD-1 monotherapy, indicating that treatment efficacy may be influenced by clinical subtypes and genetic variations (Nakamura, Asai, et al., 2020). On the other hand, non-acral melanoma patients reacted far better to combination treatment, with an objective response rate (ORR) of 61%, as opposed to 10% for monotherapy patients.

Due to their past exclusion from several clinical studies, patients with brain metastases from melanoma have traditionally had little information on the effectiveness of treatments for them. On the other hand, new research indicates that combination treatment may provide significant advantages. Combination treatment resulted in a 1-year survival rate of 81.5% for patients with asymptomatic melanoma brain metastases; the median OS was not yet achieved (Tawbi et al., 2018). When compared to other therapies, such as combination therapy consisting of dabrafenib and trametinib, patients with BRAFV600E mutations had a median overall survival of 10.8 months (Davies et al., 2017).

As combination therapies evolve, the focus has shifted toward identifying biomarkers that predict response and minimize toxicity. Elevated LDH, C-reactive protein (CRP), and IL-6 levels have been associated with poorer outcomes in patients receiving ICIs, but they may also serve as indicators for tailoring therapy (Laino et al., 2020)(Yoshida et al., 2020). The identification of such biomarkers could optimize treatment strategies, allowing for a more personalized approach and minimizing unnecessary exposure to severe toxicities.

CONCLUSION

When compared to monotherapy, the use of combination immune checkpoint inhibitors—specifically, CTLA-4 and PD-1 blockade—has completely changed the way advanced melanoma is treated, improving both overall and progression-

free survival. Clinical studies have shown that by boosting anti-tumor immune responses, combination treatment, such as nivolumab and ipilimumab, offers many patients significant long-term advantages. But more toxicity also means greater effectiveness, thus patient selection and treatment must be done carefully. Notwithstanding the difficulties, this therapeutic approach is a noteworthy development in the treatment of melanoma and has the potential to change the way that advanced illness is treated.

Although the combination of PD-1 and CTLA-4 inhibitors has shown great potential, it is important to recognize that there are a number of drawbacks. One of the key concerns is the increased likelihood of severe immune-related side effects, which often need early therapy termination. Furthermore, the capacity to tailor medication and lower toxicity is restricted by the absence of proven biomarkers for predicting response to therapy. The majority of research has been on short- to medium-term results, with long-term data still being collected. Patient selection criteria may further limit the generalizability of trial outcomes, because many trials exclude patients with comorbidities or low performance status, which may underrepresent real-world populations.

Anticipating response to combination immune checkpoint treatment, the development of trustworthy biomarkers will be essential for maximizing patient selection and reducing harm. To increase effectiveness while lowering side effects, further research should look at combination regimens that include other drugs, such as new immunomodulators or targeted therapies. To provide a better knowledge of the longevity of treatment responses and survival advantages, longer-term follow-up studies are required. Furthermore, increasing the diversity of patient groups in clinical trials will be crucial to assuring fair access to potentially game-changing therapies and enhancing the generalizability of the results.

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