short review

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Immunotherapy for metastatic melanoma—from little benefit to first-line treatment

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Summary At the turn of the past century, unresectable metastatic melanoma was primarily treated with different chemotherapeutic agents, such as dacarbazine, with only poor efficacy. Immunotherapeutic agents, such as interleukin-2 or adjuvant interferon alpha, were used with modest results but frequent side effects. In the last 10 years, modern immunotherapy using checkpoint inhibition has dramatically changed the treatment landscape of metastatic melanoma and is now considered the first-line treatment for stage IV melanoma. Consequently, median overall survival has increased from 9.1 months with dacarbazine to up to 72.1 months using the current gold standard ipilimumab + nivolumab first-line. In 2023, in Europe, the anti-PD1 antibodies nivolumab and pembrolizumab are licensed in the adjuvant and metastatic setting and the combination therapies ipilimumab + nivolumab and relatlimab + nivolumab are approved in the metastatic setting. Nevertheless, despite tremendous progress in the last two decades, at least 50% of our patients with stage IV melanoma still die. Currently, research focuses on combining checkpoint inhibition with other drugs such as cancer vaccines, BRAF/MEK inhibition, other tyrosine kinase inhibitors or histone deacetylase inhibitors.

Keywords Checkpoint inhibition · Ipilimumab · Nivolumab · Pembrolizumab · Relatlimab · Review

Introduction

At the turn of the past century, different chemotherapeutic agents were used for the treatment of stage IV melanoma. Efficacy was poor, e.g., dacarbazine showed a 3-year overall survival (OS) of 12.2% and a median OS of 9.1 months [1]. Fortunately, a lot has changed in the last two decades. Today, immunotherapy and targeted therapies are essential therapeutic mainstays and chemotherapy is only rarely used as a last-line treatment. Consequently, median OS has increased from 9.1 months with dacarbazine to up to 72.1 months using the immunotherapeutic combination of ipilimumab and nivolumab first-line [1, 2]. In 2023, based on data from the DREAMSEQ and SECOMBIT trials [3, 4], immunotherapy with checkpoint inhibitors is the recommended first-line treatment for stage IV melanoma patients [5].

Take home message

Immunotherapy is recommended as the first-line treatment for stage IV melanoma.

This short review aims to present the exciting journey of immunotherapy for malignant melanoma, from adjuvant and barely effective interferon treatment to potent combined checkpoint inhibition.

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Interferon alpha

Modern immunotherapy started with the use of interferons. From 1997–2018, Interferon alpha (IFN-α) was the only approved drug in Europe for adjuvant treatment of patients with totally resected melanoma [6, 7]. The results of pivotal studies were statistically significant, which led to approval, but efficacy was relatively modest. For example, the difference in event-free survival at 5 and 10 years was 3.5% and 2.7%, respectively, and IFN-α increased OS only marginally from 2.8% to 3.0% [8]. However, adverse events, especially influenza-like symptoms, were frequent. In one study, using intermediate-dose IFN-α, therapy was stopped or interrupted because of side effects in up to 20% of the patients [9].

Interleukin-2

In 1998, high-dose intravenous bolus interleukin-2 (IL-2) was approved by the US Food and Drug Administration (FDA) for treating patients with metastatic melanoma based on the results of eight clinical trials of IL-2 showing an overall response rate (ORR) of 16% (complete remission [CR] 6%, partial remission [PR] 10%) [10]. Interestingly, disease did not progress in any patient responding for more than 30 months. Toxicities, although severe, generally reversed rapidly after therapy was completed; however, 6 patients (2%) died from adverse events, all related to sepsis [10].

Anti-CTLA-4 antibody ipilimumab

In 2011, a new era in the treatment of unresectable or metastatic melanoma started in Europe with European Medicines Agency (EMA) approval of ipilimumab, the first immune checkpoint inhibitor. Immune checkpoints are regulatory pathways of the immune system, which can act in inhibitory or stimulatory manners. Unfortunately, some cancers can protect themselves from attack, e.g., by stimulating inhibitory pathways. Immune checkpoint inhibitors are immunotherapeutic drugs which work by blocking these regulatory pathways, thus, interfering with immune regulation. The antibody ipilimumab blocks cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), a crucial negative regulator of T cells. Consequently, the anti-CTLA-4 antibody ipilimumab augments antitumoral T-cell immunity.

Two pivotal studies—CheckMate 020 and CheckMate 024—led to approval. In CheckMate 020, ipilimumab (3 mg/kg) with or without a glycoprotein 100 (gp100) peptide vaccine compared with gp100 alone was administered in a 3:1:1 ratio in 676 patients with previously treated unresectable stage III or IV melanoma. Ipilimumab increased median OS to 10.0 months in the combination and 10.1 months in the monotherapy cohort compared to 6.4 months in patients receiving only gp100, indicating a survival benefit with ipilimumab [11]. Checkmate 024 investigated 502 patients with previously untreated metastatic melanoma. Patients were randomized to the standard chemotherapeutic agent dacarbazine plus ipilimumab or placebo in a 1:1 ratio. Dacarbazine (850 mg per square meter of body surface area) and ipilimumab (10 mg/kg) or placebo were given at weeks 1, 4, 7, and 10, followed by dacarbazine monotherapy every 3 weeks through week 22. Ipilimumab increased the median OS from 9.1 to 11.2 months, and survival rates were higher in the ipilimumab–dacarbazine group (e.g., 20.8% vs. 12.2% at 3 years, hazard ratio 0.72) [1]. Notably, dacarbazine did not add to the effect of ipilimumab.

Furthermore, a pooled analysis of long-term survival data from phase II and III trials of ipilimumab in unresectable or metastatic melanoma ($n = 1861$) estimated a 3-year survival rate of 22% [12]. However, most interestingly, survival curves reached a plateau around the third year after treatment and a prolonged benefit was observed for up to 10 years in some patients [12]. Despite the fact that ipilimumab 10 mg/kg showed improved survival in comparison to ipilimumab 3 mg/kg [13, 14], a dose reduction from 10 mg/kg to 3 mg/kg significantly reduced severe adverse events from 35.9% to 17.3% [15]. Therefore, in Europe, ipilimumab is used in-label with 3 mg/kg.

Anti-PD-1 antibodies pembrolizumab and nivolumab

Since 2013, clinical studies have investigated the efficacy of the anti-programmed death-1 (PD-1) antibodies pembrolizumab and nivolumab in metastatic melanoma, leading to EMA approval of these drugs in 2015 [16, 17]. The blockage of the interaction of PD-1 on T cells with PD-L1 and PD-L2 on tumor cells using these antibodies represented the next milestone in checkpoint inhibition, effective in various cancer entities, not only melanoma. PD-1 is one in a group of inhibitory receptors upregulated upon CD8-positive T-cell exhaustion during cancer, and PD-1 blockade can reactivate T-cell immunity [18].

Pembrolizumab was approved based on the phase III study KEYNOTE-006, which investigated pembrolizumab (10 mg/kg) every 2 or 3 weeks or four doses of ipilimumab (3 mg/kg) every 3 weeks in a 1:1:1 ratio. The response rates of pembrolizumab every 2 and 3 weeks were 33.7% and 32.9%, compared to 11.9% with ipilimumab treatment, and pembrolizumab prolonged progression-free survival (PFS) and OS compared to ipilimumab [19].

Nivolumab showed similar effects on PFS and OS as well as similar toxicity in the phase III trial CheckMate 037, in which patients after CTLA-4 failure received either nivolumab (3 mg/kg every 2 weeks) or chemotherapy (dacarbazine 1000 mg/m^2 every 3 weeks or carboplatin area under the curve 6 plus paclitaxel 175 mg/m^2 every 3 weeks). The nivolumab

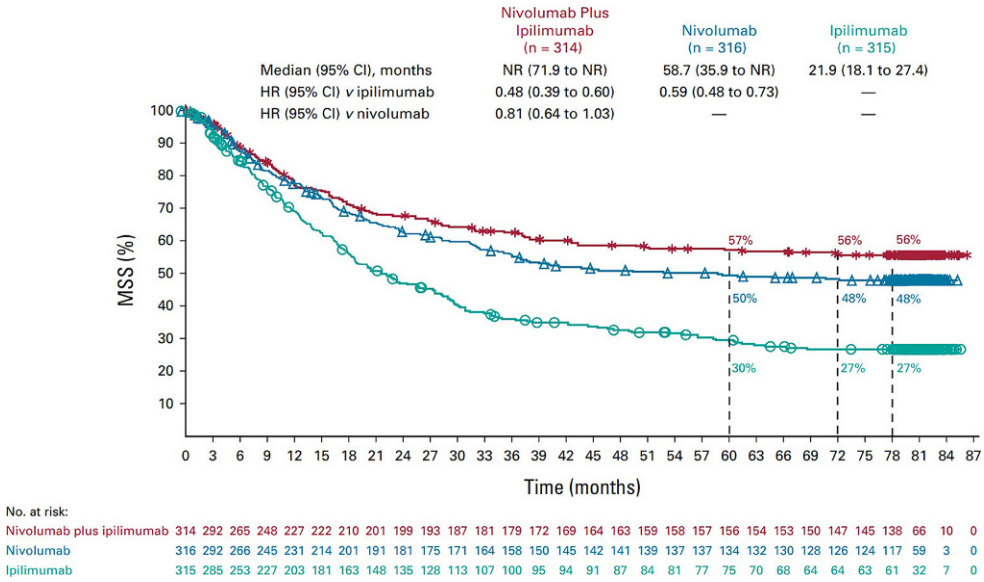

Fig. 1 In this descriptive post hoc analysis, an event was defined as death as a result of melanoma. *HR* hazard ratio, *MSS* melanoma-specific survival, *NR* not reached, *95% CI* 95% confidence interval. Figure from Wolchok JD et al. [2]

group achieved objective responses in 31.7% compared to 10.6% using chemotherapy [20]. Similar efficacy of nivolumab in previously untreated patients was also observed in the monotherapy arm of CheckMate 067 (see below).

Currently, PD1 inhibition is the standard immunotherapeutic treatment for metastatic melanoma and the backbone of most current and future combination therapies.

Take home message

The anti-PD1 antibodies nivolumab and pembrolizumab are the backbones of most current and future combination therapies.

Inspired by the results in the metastatic disease, the PD1 antibodies nivolumab and pembrolizumab were also investigated in adjuvant settings. Nivolumab (3 mg/kg every 2 weeks) compared to ipilimumab (10 mg/kg every 3 weeks for four doses and then every 12 weeks) was investigated in the CheckMate 238 trial for up to 1 year in patients after complete resection of stage IIIB/C or stage IV melanoma. In comparison, pembrolizumab (200 mg every 3 weeks for 1 year) was compared to placebo in completely resected stage IIIA–C melanoma in the KEYNOTE-054 study. CheckMate 238 showed a 12-month recurrence-free survival (RFS) rate of 70.5% in the nivolumab group compared to 60.8% in the ipilimumab arm [21]. Similarly, KEYTNOTE-054 revealed a 1-year RFS of 75.4% using pembrolizumab compared to 61.0% in the placebo group [22]. Since late 2022, pembrolizumab is also licensed for adjuvant treatment of melanoma stage IIB/C, and approval of nivolumab for this indication in Europe is expected in 2023. Treatment-related adverse events grade 3 or higher using PD1 antibodies have been reported in about 14.4 to 17% [21, 23–25].

Combined inhibition of CTLA-4 and PD-1: ipilimumab plus nivolumab

With the question whether one plus one is better, it was logical to explore combined checkpoint inhibition. The phase III trial CheckMate 067 (leading to EMA approval in 2016) investigated previously untreated patients with unresectable stage III or IV melanoma. Participants were randomized 1:1:1 to either A) nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) every 3 weeks (four doses) followed by nivolumab (3 mg/kg) every 2 weeks, B) nivolumab (3 mg/kg) every 2 weeks, or C) four doses of ipilimumab (3 mg/kg) every 3 weeks.

Similarly, the phase II study Checkmate 069 compared four doses of nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) followed by nivolumab monotherapy to ipilimumab (3 mg/kg) plus placebo followed by placebo in a 2:1 ratio in patients with previously untreated, unresectable stage III or IV melanoma [26].

CheckMate 069 showed a 2-year OS of 63.8% in the combination vs. 53.6% in the nivolumab monotherapy arm [26], and a recently published long-term efficacy analysis of CheckMate 067 demonstrated prolonged and durable clinical benefit of combined therapy (Fig. 1). With a minimum follow-up of 6.5 years, the median OS was 72.1 months in the combination group compared to 36.9 and 19.9 months in the nivolumab and ipilimumab group, respectively [2]. Median melanoma-specific survival was not reached in the combination group compared to 58.7 and 21.9 months in the nivolumab and ipilimumab group, respectively [2]. Interestingly, after 6.5 years, most patients were recurrence-free despite treatment discontinuation, indicating long-term benefit of checkpoint inhibition.

Take home message

Ipilimumab + nivolumab is currently the gold standard for the treatment of stage IV melanoma.

However, the enhanced efficacy of combined immunotherapy is accompanied by increased toxicity. Treatment-related adverse events grade ≥3 occurred in 48% of the ipilimumab + nivolumab combination group, leading to treatment discontinuation in 27.5% of patients [27].

Combined inhibition of LAG-3 and PD-1: relatlimab plus nivolumab

The newest checkpoint inhibitor approved in 2022 is relatlimab in combination with nivolumab. Relatlimab targets the lymphocyte-activation gene 3 (LAG-3) found on cytotoxic and regulatory T cells, controlling T cell activation and growth. The approval study RELATIVITY-047 showed positive results in previously untreated advanced metastatic melanoma: combination of relatlimab plus nivolumab compared to nivolumab monotherapy improved median PFS from 4.6 months to 10.1 months [28]. Nevertheless, PFS was not higher in absolute numbers. There was no significant difference in PFS between combination and monotherapy in PD-L1-positive patients and a difference was only seen in PD-L1-negative patients (using a cut-off level of 1%): a subgroup analysis showed that median PFS was higher in PD-L1-negative (<1%) than in PD-L1-positive (≥1%) patients (6.4 months and 2.9 months, hazard ratio 0.68 and 0.96, respectively) [28]. In addition, in either group, the benefit was not statistically significant regarding ORR or OS [28].

In Europe, based on the PD-L1 expression subgroup analysis, the combination of relatlimab and nivolumab was only approved for the subgroup of PD-L1-negative (<1%) patients. This decision changes the need for PD-L1 testing for the treatment of metastatic melanoma. Until 2022, PD-L1 expression determination was not mandatory and was only rarely considered for therapeutic decisions in daily practice because PD-L1 expression in melanoma had never showed a significant discriminatory effect between PD-1 antibodies and other available treatments, in contrary to other tumor types such as urothelial carcinoma. However, PD-L1 expression testing is now necessary if administration of relatlimab and nivolumab is considered. Regarding tolerability, severe adverse events grade ≥3 were reported in 18.9% using the combination of relatlimab plus nivolumab [28], which is only slightly higher than with PD-1 monotherapy but considerably lower than with ipilimumab combined with nivolumab.

Future

The last two decades were exciting for physicians treating patients with metastatic melanoma; however, at least 50% of our patients with stage IV melanoma still die. How could efficacy be increased? Most current studies focus on combining well-known checkpoint inhibitors, mainly anti-PD1 antibodies, with other drugs such as histone deacetylase inhibitors, BRAF/MEK inhibition, other tyrosine kinase inhibitors or cancer vaccines. Furthermore, biomarkers are urgently needed (and are being investigated) to identify patients who will benefit from available therapies.

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References

1. Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. 2011;364(26):2517–26.
2. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Long-term outcomes with nivolumab plus Ipilimumab or nivolumab alone versus Ipilimumab in patients with advanced melanoma. J Clin Oncol. 2022;40(2):127–37.
3. Atkins MB, Lee SJ, Chmielowski B, Tarhini AA, Cohen GI, Truong TG, et al. Combination dabrafenib and trametinib versus combination nivolumab and ipilimumab for patients with advanced BRAF-mutant melanoma: the DREAMseq trial-ECOG-ACRIN EA6134. J Clin Oncol. 2023;41(2):186–97.
4. Ascierto PA, Mandalà M, Ferrucci PF, Guidoboni M, Rutkowski P, Ferraresi V, et al. Sequencing of Ipilimumab plus nivolumab and encorafenib plus binimetinib for untreated BRAF-mutated metastatic melanoma (SECOMBIT):

a randomized, three-arm, open-label phase II trial. J Clin Oncol. 2023;41(2):212–21.
5. Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Basset-Seguin N, et al. European consensus-based interdisciplinary guideline for melanoma. Part 2: treatment—update 2022. Eur J Cancer. 2022;170:256–84.
6. Petrella T, Verma S, Spithoff K, Quirt I, McCready D. Adjuvant interferon therapy for patients at high risk for recurrent melanoma: an updated systematic review and practice guideline. Clin Oncol. 2012;24(6):413–23.
7. Davar D, Kirkwood JM. Adjuvant therapy of melanoma. Cancer Treat Res. 2016;167:181–208.
8. Ives NJ, Suciu S, Eggermont AMM, Kirkwood J, Lorigan P, Markovic SN, et al. Adjuvant interferon-α for the treatment of high-risk melanoma: an individual patient data meta-analysis. Eur J Cancer. 2017;82:171–83.
9. Eggermont AM, Suciu S, MacKie R, Ruka W, Testori A, Kruit W, et al. Post-surgery adjuvant therapy with intermediate doses of interferon alfa 2b versus observation in patients with stage IIb/III melanoma (EORTC 18952): randomised controlled trial. Lancet. 2005;366(9492):1189–96.
10. Atkins MB, Lotze MT, Dutcher JP, Fisher RI, Weiss G, Margolin K, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol. 1999;17(7):2105–16.
11. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711–23.
12. Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, Hamid O, et al. Pooled analysis of long-term survival data from phase II and phase III trials of Ipilimumab in unresectable or metastatic melanoma. J Clin Oncol. 2015;33(17):1889–94.
13. Ascierto PA, Del Vecchio M, Robert C, Mackiewicz A, Chiarion-Sileni V, Arance A, et al. Ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2017;18(5):611–22.
14. Ascierto PA, Del Vecchio M, Mackiewicz A, Robert C, Chiarion-Sileni V, Arance A, et al. Overall survival at 5 years of follow-up in a phase III trial comparing ipilimumab 10 mg/kg with 3 mg/kg in patients with advanced melanoma. J Immunother Cancer. 2020;8(1):e391.
15. Guo CY, Jiang SC, Kuang YK, Hu H. Incidence of Ipilimumab-related serious adverse events in patients with advanced cancer: a meta-analysis. J Cancer. 2019;10(1):120–30.
16. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med. 2013;369(2):122–33.
17. Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O, Kefford R, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet. 2014;384(9948):1109–17.
18. Ando S, Araki K. CD8 T-cell heterogeneity during T-cell exhaustion and PD-1-targeted immunotherapy. Int Immunol. 2022;34(11):571–7.
19. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015;372(26):2521–32.
20. Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2015;16(4):375–84.
21. Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, et al. Adjuvant nivolumab versus Ipilimumab in resected stage III or IV melanoma. N Engl J Med. 2017;377(19):1824–35.
22. Eggermont AMM, Blank CU, Mandala M, Long GV, Atkinson VG, Dalle S, et al. Prognostic and predictive value of AJCC-8 staging in the phase III EORTC1325/KEYNOTE-054 trial of pembrolizumab vs placebo in resected high-risk stage III melanoma. Eur J Cancer. 2019;116:148–57.
23. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and Ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015;373(1):23–34.
24. Robert C, Ribas A, Schachter J, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol. 2019;20(9):1239–51.
25. Eggermont AMM, Blank CU, Mandala M, Long GV, Atkinson VG, Dalle S, et al. Longer follow-up confirms recurrence-free survival benefit of adjuvant pembrolizumab in high-risk stage III melanoma: updated results from the EORTC 1325-MG/KEYNOTE-054 trial. J Clin Oncol. 2020;38(33):3925–36.
26. Hodi FS, Chesney J, Pavlick AC, Robert C, Grossmann KF, McDermott DF, et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol. 2016;17(11):1558–68.
27. Lebbé C, Meyer N, Mortier L, Marquez-Rodas I, Robert C, Rutkowski P, et al. Evaluation of two dosing regimens for nivolumab in combination with Ipilimumab in patients with advanced melanoma: results from the phase IIIb/IV checkmate 511 trial. J Clin Oncol. 2019;37(11):867–75.
28. Tawbi HA, Schadendorf D, Lipson EJ, Ascierto PA, Matamala L, Castillo Gutiérrez E, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. N Engl J Med. 2022;386(1):24–34.