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REVIEW

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Efficacy of immune checkpoint inhibitors in different types of melanoma

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ABSTRACT

Immunotherapy can be used for cutaneous, mucosal, uveal and conjunctival melanoma. Nevertheless, we cannot expect the same benefit from checkpoint inhibitors for all the types of melanoma. The different biological features can explain the variable efficacy. The main results obtained with immune checkpoint inhibitors in the various types of melanoma were reviewed.

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Introduction

In the last years, many improvements have taken place in the therapeutic management of melanoma. The introduction of immune-checkpoint inhibitors (ICIs) have dramatically changed the natural course of the disease. Nevertheless, we cannot expect the same result with immunotherapy for all the types of melanoma: cutaneous, mucosal, uveal and conjunctival.

The incidence of cutaneous melanoma in Europe is about 9/100,000/year with a mortality of 2–3/100,000/year.[1] In the USA, cutaneous melanoma includes about 5% of newly diagnosed tumors for men and 4% for women, representing the second most common tumor for patients less than 40 years of age.[1,2] Regarding the non-cutaneous melanomas, less than 2% of all the cases are represented by mucosal melanoma, which can be detected at different sites such as the oro-pharingeal cavity, gastro-intestinal tract, or genito-urinary system. More than 60% of patients with mucosal melanoma are over 65 years, and the incidence is a slightly women, most likely due to a higher prevalence of mucosal melanomas deriving from the genital system.[2–4] The eye is another possible site of origin for non-cutaneous melanomas. Among ocular tumors, uveal melanoma has an incidence of 0.7 cases/100,000/year among women and 0.5 cases/100,000/year among men, with a peak of incidence between 55 and 65 years.[5] Conjunctmelanoma and lower response presents only about 5% of ocular melanomas with an incidence in Europe and the US of about 0.2–0.7 cases/1,000,000.[6]

ICIs can be used for all the types of melanoma with a variable efficacy depending on the different biological features. We have hereinafter reported the main results obtained with ICIs in cutaneous, mucosal, uveal and conjunctival melanoma (Table 1).

Immune checkpoint inhibitors for cutaneous melanoma

Immune checkpoint inhibitors (ICIs) represent an important breakthrough for the therapy of metastatic cutaneous melanoma, the first neoplasm in which clinical effectiveness of ICIs was demonstrated. Acrolentiginous melanoma is a subtype of cutaneous melanoma, especially common in nonwhite Caucasians differently from sun-exposed cutaneous melanoma. It is characterized by fewer mutation than cutaneous melanoma and lower response rate to ICIs.[7]

ICIs are monoclonal antibodies able to block negative signals for T-cell activation or T-cell effector activity.[8] To date, the most common treatments used for cutaneous melanoma involve the interaction of Programmed Cell Death protein 1 (PD-1) with Programmed Death-Ligand 1 (PD-L1) and Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) with B7-1/B7-2.[9,10]

Anti-CTLA-4

Ipilimumab is a monoclonal antibody (humanized IgG1) targeting CTLA-4.[9] CTLA-4 is a receptor expressed by activated T lymphocytes, which binds B7-1 (CD80) and B7-2 (CD86) of the antigens presenting cells (APCs), inducing a negative signal leading to the anergy of T cells.[10] In the phase 3 study by Hodi, 676 pretreated patients with advanced melanoma were randomized in a 3:1:1 ratio to ipilimumab administered

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Table 1. Studies of immune-checkpoint inhibitors in different types of melanoma.

Primary site	Author (study)	Study design	Setting	N.	ICI	Main results
Cutaneous melanoma	Hodi FS[11,12]	Phase III	Advanced (pretreated patients)	676	Ipi + gp100 vs Ipi vs gp100	OS: 10.1 (Ipi + gp100) vs 10.0 (Ipi) vs 6.4 (gp100) mos. 3-yr survival 25% (Ipi), 15% (Ipi+gp100).
	Robert C[13,14]	Phase III	Advanced (first line)	502	Ipi + Dac vs Dac	OS: 11.2 (Ipi + Dac) vs 9.1 (Dac) mos. 3-yrs OS: 20.8% (Ipi + Dac) vs 12.2%. (Dac). 5-yrs OS: 18.2% (Ipi + Dac) vs 8.8% (Dac).
	Schadendorf D[15]	Pooled analysis	Advanced	1861	Ipi	OS: 11.4 mos. 3-yrs survival: 26% (1st line), 20% (≥2nd line).
	Ascierto PA[16]	Phase III	Advanced	727	Ipi 10 vs 3 mg/kg	OS: 15.7 (10 mg/kg) vs 11.5 (3 mg/kg) mos.
	Margolin K[17]	Phase II	Brain metastases	72	Ipi	DCR: 18% (asymptomatic pts), 5% (symptomatic pts).
	Di Giacomo AM[18]	Phase II	Brain metastases	86	Ipi + Fotemustine	OS: 12.7 mos, 3-yrs OS: 27.8% (asymptomatic pts)
	Robert C (CheckMate 066)[21,22]	Phase III	Advanced (first line)	418	Nivo vs Dac	ORR: 40.0% (Nivo) vs 13.9% (Dac). PFS: 5.1 (Nivo) vs 2.2 (Dac) mos. 1-yr OS: 72.9% (Nivo) vs 42.1% (Dac). 3-yrs OS: 51.2% (Nivo) vs 21.6% (Dac). OS: 37.5 (Nivo) vs 11.2 (Dac) mos
	Weber J (CheckMate 237)[23,24]	Phase III	Advanced (pretreated patients)	405	Nivo vs ICC (Dac, Carboplatin, Paclitaxel)	OS: 16.0 (Nivo) vs 14.0 (ICC) mos. ORR: 27% (Nivo) vs 10% (ICC). DOR: 32.0 (Nivo) vs 13.0 (ICC) mos.
	Robert C (KEYNOTE-006)[25,28,29]	Phase III	Advanced (pretreated patients)	834	Pembro q2 w vs Pembro q3 w vs Ipi	ORR: 33.7% (Pembro q2 w) vs 32.9% (Pembro q3 w) vs 11.9% (Ipi). 2-yr OS: 55% (Pembro) vs 43% (Ipi). OS: 32.7 (Pembro) vs 15.9 (Ipi) mos.
	Goldberg SB[32]	Phase II	Brain metastases	18	Pembro	ORR 22%.
	Larkin J (CheckMate 067)[42,44]	Phase III	Advanced (first line)	945	Nivo + Ipi vs Nivo vs Ipi	PFS: 11.5 (Nivo+Ipi) vs 6.9 (Nivo) vs 2.9 (Ipi) mos. 5-yrs OS: NR (Nivo+Ipi) vs 36.9 (Nivo) vs 19.9 (Ipi) mos.
	Postow MA[40,41]	Phase II	Advanced (first line)	142	Nivo + Ipi vs Ipi	RR: 61% (Nivo+Ipi) vs 11% (Ipi). 2-yrs OS: 63.8% (Nivo+Ipi) vs 53.6% (Ipi). 2-yrs PFS: 51.3% (Nivo+Ipi) vs 12% (Ipi).
	Long GV (ABC)[45]	Phase II	Brain metastases	79	Nivo + Ipi or Nivo (asymptomatic pts or untreated with local therapy); Nivo (symptomatic pts or after local therapy failure)	ORR: 46% (Nivo+Ipi), 20% (Nivo asymptomatic pts); 6% (Nivo symptomatic pts)
	Tawbi HA (CheckMate 204)[46]	Phase II	Brain metastases	94	Nivo + Ipi	ORR: 57% (26% CR, 30% PR)
	Eggermont AM (EORTC 18071)[48–50]	Phase III	Adjuvant	951	Ipi vs PBO	RFS: 26.1 (Ipi) vs 17.1 (PBO) mos. 3-yrs RFS: 46.5% (Ipi) vs 34.8% (PBO). 5-yrs OS: 65.4% (Ipi) vs 54.4% (PBO).
	Weber J (CheckMate 238)[51,52]	Phase III	Adjuvant	906	Ipi vs Nivo	1-yr RFS: 70.5% (Nivo) vs 60.8% (Ipi). 3-yrs RFS: 58% (Nivo) vs 45% (Ipi).
	Eggermont AM (EORTC 1325/Keynote-054)[53]	Phase III	Adjuvant	1019	Pembro vs PBO	1-yr RFS: 75.4% (Pembro) vs 61.0% (PBO).
Mucosal melanoma	D'Angelo SP[68]	Pooled analysis	Advanced	157	Nivo, Nivo + Ipi, Ipi	ORR: 23.3% (Nivo), 37.1% (Nivo+Ipi), 8.3% (Ipi). PFS: 3.0 (Nivo), 5.9 (Nivo+Ipi), 2.7 (Ipi) mos.
	Hamid O[71]	Post-hoc analysis	Advanced	84	Pembro	ORR: 22% (Ipi-naïve pts), 15% (Ipi-treated pts). PFS: 2.8 mos OS: 14.0 (Ipi-naïve pts), 10.2 (Ipi-treated pts) mos.
	Shoushtari AM[34]	Retrospective	Advanced	35	Pembro o Nivo	RR: 23%. mDOR: 12.9 mos. PFS: 3.9 mos. OS: 12.4 mos.
	Weber J (CheckMate 238)[51]	Phase III	Adjuvant	29	Ipi vs Nivo	1-yr RFS 70.5 (Nivo) vs 60.8 (Ipi)
Uveal melanoma	Karidis I[76]	EAP	Advanced (pretreated patients)	25	Pembro	8% PR, 24% SD. PFS: 3.0 mos.
	Algazi AP[77]	Retrospective	Advanced	58	Pembro, Atezolizumab, Nivo	ORR: 3.6%. PFS: 2.6 mos. OS: 7.6 mos.
	Rossi E[78]	Observational	Advanced (first line)	17	Pembro	PFS: 3.8 mos
	Heppt MV[79]	Retrospective	Advanced (pretreated patients)	86	Ipi+anti-PD-1 (Pembro or Nivo)	PFS: 3.0 mos. OS: 16.1 mos.

(*Continued*)

Table 1. (Continued).

Primary site	Author (study)	Study design	Setting	N.	ICI	Main results
Conjunctival melanoma	Finger PT[86]	Case series	Locally advanced and metastatic	5	Pembro Ipi Ipi + Pembro Ipi + Nivo	PR 3 pts CR: 2 pts
	Sagiv O[87]	Case series	Metastatic	5	Nivo Pembro	CR: 4 pts SD: 1 pts

CR = complete response; Dac = Dacarbazine; DCR = disease control rate; DOR = duration of response; EAP = expanded access program; gp100 = glycoprotein 100; HR = hazard ratio; ICC = investigator's choice chemotherapy; ICIs = immune-checkpoint inhibitors; Ipi = Ipilimumab; mos = months; Nivo = Nivolumab; N. = number of patients; NR = not reached; ORR = overall response rate; OS = overall survival; PBO = placebo; PD-L1 = programmed death-ligand 1; Pembro = Pembrolizumab; PFS = progression-free survival; PR = partial response; pts = patients; RFS = relapse-free survival; RR = response rate; SD = stable disease; yr = year.

3-weekly (q3 w) at the dose of 3 mg/kg for 4 cycles + a glycoprotein 100 (gp100) peptide vaccine or ipilimumab alone or gp100 alone.[11] Ipilimumab, both alone and combined with gp100, significantly prolonged the overall survival (OS) (10.1 and 10.0 months, respectively) with respect to gp100 alone (6.4 months). Response rate was 11% with ipilimumab versus 1.5% with gp-100 alone. A re-induction with ipilimumab was possible if patients had a stable disease (SD) for three months or a partial/complete response (PR/CR). After the re-induction, 15 out of 23 patients achieved PR or SD. Sixty percent of patients treated with ipilimumab developed immune-related adverse events (irAEs). Among them, 15% were G3 and G4 (common terminology criteria for adverse events – CTCAE). The most frequent irAE was dermatitis, while diarrhea was the most severe. Seven ipilimumab-related deaths were reported.[11] Survival rates at three years were 25% for patients receiving ipilimumab alone and 15% for patients in ipilimumab plus gp100 arm.[12] Ipilimumab was the first agent improving melanoma long-term survival in a randomized trial with not negligible rate of immune-related adverse events.

In another double-blinded phase III study, 502 treatment-naïve patients with advanced melanoma were treated with dacarbazine (850 mg/mq) + ipilimumab (10 mg/kg) or dacarbazine + placebo q3 w for 4 doses. Subsequently, dacarbazine was administered through week 22. After this induction phase, patients with disease control could receive further administrations of ipilimumab or placebo. The OS was 11.2 months in the ipilimumab + dacarbazine arm, versus 9.1 months in the placebo + dacarbazine group. The OS rate after 3 years was 20.8% and 12.2%, respectively. About 56% of patients in ipilimumab + dacarbazine arm experienced grade 3/4 AEs versus 27.5% of patients receiving dacarbazine + placebo, but no death due to ipilimumab occurred.[13] The survival rate after 5 years was 18.2% in dacarbazine + ipilimumab arm and 8.8% for patients receiving dacarbazine + placebo.[14]

A pooled analysis including 1861 melanoma who had received ipilimumab in 10 prospective and 2 retrospective studies showed a survival plateau of 21% after 3 years.[15] Subsequently, ipilimumab was tested with two different schedules (10 mg/kg and 3 mg/kg) in a randomized phase III study.[16] The patients receiving 10 mg/kg obtained a longer OS (15.7 versus 11.5 months) but experienced a higher toxicity rate, principally represented by diarrhea, colitis, hepatitis and hypophysitis.[16] Furthermore, the efficacy of ipilimumab was confirmed in patients with brain involvement: the disease control rate was 18% and 5% for asymptomatic and symptomatic patients treated with steroids, respectively.[17]In asymptomatic patients with central nervous system (CNS) metastases, the combination of ipilimumab plus fotemustine yielded a 3-yr. OS rate of 27.8%.[18]

Regarding acral melanoma, in a retrospective analysis including 35 patients treated with ipilimumab (34% treatment naïve), the response rate was 11.4%, the PFS 2.5 months and the OS 16.7 months.[19] A 20% of grade 3/4 immune-related adverse was observed.[19]

Anti-PD-1

PD-1, expressed on T cells, B cells and myeloid cells, binds to PD-L1 and B7-DC (PD-L2) ligands which are exhibited by APCs, tumor cells and intratumoral stromal cells. The signals released after this binding induce an immune tolerance.[20] Consequently, tumor growth and progression are promoted.[20] Nivolumab and pembrolizumab are monoclonal antibodies (humanized IgG4) which block PD-1 activating the anti-tumor immune-response.[8]

The CheckMate 066, a randomized phase 3 trial which included 418 patients with advanced melanoma (BRAF wild type) was conducted to compare nivolumab (3 mg/kg every 2 weeks [q2 w]) and dacarbazine (1000 mg/mq q3 w). Nivolumab was superior to dacarbazine for OS with a 1-yr OS rate of 72.9% versus 42.1%, PFS with a mPFS of 5.1 versus 2.2 months, and overall response rate (ORR) (40.0% vs 13.9%; $p < .001$). The survival benefit was independent from the PD-L1 expression. Moreover, nivolumab had a better tolerability, with an incidence of G3 and G4 AEs of 11.7% vs 17.6% with dacarbazine.[21] After a follow up of 38.4 months, the 3-yr. OS rate was 51.2% for nivolumab versus 21.6% for dacarbazine, with a median OS of 37.5 versus 11.2 months.[22]

Weber compared nivolumab (3 mg/kg q2 w) with chemotherapy chosen by investigators (dacarbazine or carboplatin plus paclitaxel) in the CheckMate 037 randomized phase III study. The study enrolled 405 patients previously treated with ipilimumab and an anti-BRAF agent in case of BRAF mutation.[23] OS was 16 months for anti-PD-1 therapy and 14 months for chemotherapy, ORR was 27% versus 10% and median duration of response (DOR) was 32 versus 13 months.[24] G3/G4 AEs were reported in 9% of patients in

nivolumab group versus 31% of patients treated with chemotherapy.[23]

The KEYNOTE-006 phase III study enrolled 834 patients with stage IV and unresectable stage III melanoma who received pembrolizumab 10 mg/kg q2 w or q3 w (until progression or for a maximum of 2 years) or ipilimumab 3 mg/kg q3 w (4 cycles). Only one previous line of systemic treatment was allowed. The study showed a longer PFS and OS of pembrolizumab (both every 3 weeks and every 2 weeks) than ipilimumab. RR was 33.7% and 32.9% for pembrolizumab q2 w and q3 w, respectively, and 11.9% for ipilimumab.[25] Moreover, among the 104 patients who completed 24 months of pembrolizumab, 98% were alive at 9 months with an estimated PFS of 91% (ranging from 95% for CR to 91% for PR and 83% for SD).[26] After 20 months of follow up, PFS was 86%.[27] The 2-yr. OS rate was 55% for pembrolizumab and 43% for ipilimumab.[28] The investigators found a median OS of 32.7 months for pembrolizumab and 15.9 months for patients treated with ipilimumab (median follow up of 57.7 months).[29] Pembrolizumab showed a better safety profile. G3/G4 AEs were 10.1–13.1% for pembrolizumab versus 19.9% for ipilimumab. Treatment interruptions due to toxicity were 4–6.9% versus 9.4% for pembrolizumab and ipilimumab, respectively. The quality of life was better with pembrolizumab than with ipilimumab.[30] No differences between PD-L1 positive and negative patients were observed.[31]

Goldberg reported the results of 18 patients with asymptomatic brain metastases (diameter up to 2 cm) treated with pembrolizumab 10 mg/kg q3 w until progression. Thirty-three percent of the patients were BRAF mutant. Twenty-two percent of the patients obtained an objective response to pembrolizumab, while no response was reported among BRAF mutant patients. After 11 months of median follow up, mOS was not reached.[32]

Overall, both nivolumab and pembrolizumab showed a higher efficacy compared to ipilimumab with a better toxicity profile.

With regards to acral melanoma, in a group of 15 unresectable patients treated with nivolumab, the overall response rate was 33% and PFS 3.96 months.[33] In 25 pretreated patients, PD-1 blockage with nivolumab or pembrolizumab allowed a response rate of 30% and a PFS of 4.1 months.[34] In the Checkmate 172 trial, nivolumab was administered in 55 ipilimumab pretreated patients with acral melanoma: OS was 25.8 months.[35] The largest population of acral melanoma patients treated with an anti-PD-1 agent is reported in the retrospective JAMP trial. Among the 193 acral melanoma patients considered in this study, 74.1% were treatment naïve. The response rate was 16.5% and OS 18.1 months, while the incidence of grade ≥3 immune related adverse events was 14%.[36]

Anti-PD-L1

The monoclonal antibodies anti-PD-L1 can switch off the inhibitory signal for immune response as well as the anti-PD -1 agents. For advanced melanoma, anti-PD-L1 molecules, such as avelumab or BMS 936559, has been tested in monotherapy in phase 1 studies in pretreated patients, showing activity and acceptable toxicity profile.[37,38]

Combination anti-PD-1 plus anti-CTLA-4

After the demonstration of a synergy of CTLA-4 and PD-1 blockage in melanoma preclinical models,[39] this strategy was tested in clinical trials. A higher efficacy of the combination nivolumab + ipilimumab versus the single-agent ipilimumab has been observed in a phase II study which enrolled 142 patients with untreated advanced melanoma: RR was 61% versus 11%, 2-yr. OS 63.8% versus 53.6%, 2-yr. PFS 51.3% versus 12%.[40,41]

In the Checkmate 067 phase 3 study, 945 treatment-naïve patients with stage IV or unresectable stage III were randomly assigned to nivolumab + ipilimumab combination or nivolumab monotherapy or ipilimumab monotherapy. BRAF mutation was detected in 31.1% of the patients. The study aimed to evaluate the superiority of nivolumab + ipilimumab versus ipilimumab and nivolumab versus ipilimumab, but no direct comparison was pre-specified between nivolumab + ipilimumab and nivolumab alone. After a follow up of 36 months, nivolumab + ipilimumab was superior for PFS, OS and RR (57.6% vs 19%) if compared to ipilimumab. The study reported a median PFS of 11.5 months for nivolumab + ipilimumab, 6.9 months for the anti-PD-1 alone and 2.9 months for anti-CTLA-4 alone. Regarding the PD-L1 positive patients, mPFS was 14.0 months both in the combination arm and in the single-agent nivolumab group, but, in the PD-L1 negative patients, mPFS was 11.2 months for nivolumab + ipilimumab and 5.3 months for nivolumab. G3/G4 AEs rate was 55% for the combination cohort, 16.3% for nivolumab alone and 27.3% for single-agent ipilimumab; 36.4% of the patients in the combination group, 7.7% in the nivolumab group and 14.8% in the ipilimumab group interrupted the treatment due to toxicity.[42] After 3 years, 58% of the patients in the combination arm, 52% in the nivolumab arm and 34% in the ipilimumab arm were alive.[43] After 5 years, nivolumab + ipilimumab retained its efficacy, with a mOS that was not reached compared to 36.9 months of nivolumab alone and 19.9 months of ipilimumab alone.[44]

Overall, nivolumab + ipilimumab or nivolumab alone provide an advantage in terms of RR and long-term survival versus single-agent ipilimumab. However, for the combination therapy there is a higher toxicity with a greater number of patients interrupting the treatment. Nevertheless, a prolonged efficacy can be maintained when the treatment is interrupted because of toxicity. Moreover, the predictive role for PD-L1 expression has not been completely elucidated yet nor other predictive factors have been identified.

Although in this study a direct comparison between combined immunotherapy and nivolumab alone was not prespecified, we can infer that anti-PD-1 plus anti-CTLA-4 therapy shows a more impressive efficacy than nivolumab with a less favorable toxicity profile.

Two phase II studies assessed the efficacy of nivolumab + ipilimumab for patients with melanoma metastatic to the brain: the ABC and CheckMate204 trials.[45,46] The ABC trial enrolled treatment naïve patients with melanoma brain metastases. Asymptomatic patients were randomized to nivolumab +

ipilimumab (n = 36: cohort A) or single-agent nivolumab (n = 27: cohort B).) Single-agent nivolumab (n = 16: cohort C) was administered to symptomatic patients, patients previously treated with radiotherapy or patients with leptomeningeal disease. Cohort B was subsequently closed due to an amendment and patients converged into cohort A. Over 50% of the patients were BRAF mutant. After 17 months of median follow up, intracranial responses were 46%, 20% and 6% in cohorts A, B and C, respectively.[45] In the CheckMate 204 study, patients with asymptomatic brain metastases from melanoma (among whom 55% BRAF mutant) were treated with nivolumab + ipilimumab, with an intracranial RR of 57%.[46]

The combination of nivolumab and ipilimumab was tested in 7 naïve patients with advanced acral melanoma in a phase II trial. Three patients (42.9%) achieved an objective response, while median OS and PFS were not reached.[47]

ICIs as adjuvant therapy

After the demonstration of efficacy in metastatic melanoma, ICIs were tested in the adjuvant setting. The EORTC 18071 phase-III trial enrolled 951 patients with stage III melanoma. The study compared ipilimumab 10 mg/kg (q3 w for 4 cycles, followed by a maintenance every 3 months [q3 m] for a maximum of 3 years) with placebo. The median recurrence-free survival (RFS) for ipilimumab was 26.1 months versus 17.1 months for placebo. Three-yr. RFS rate was 46.5% versus 34.8% in the ipilimumab and the placebo group, respectively. However, 52% of the patients receiving ipilimumab did not complete the treatment and 1.1% of the patients died due to toxicity.[48,49] The 5-yr. OS rate was 65.4% and 54.4% for ipilimumab and placebo, respectively.[50]

In the Checkmate 238, double-blind, phase-III trial, patients with stage IIIB-IIIC or IV completely resected (according to AJCC 7th edition) melanoma were randomized to ipilimumab 10 mg/kg (q3 w for 4 doses and then q12 w) or nivolumab 3 mg/kg q2 w, for a maximum of 12 months or until recurrence. The study included 906 patients, among whom about 42% were BRAF mutant. The primary endpoint was RFS. After a median follow up of 18 months, 1-yr RFS rate was 70.5% and 60.8% for nivolumab and ipilimumab, respectively ($p < .001$). Nivolumab showed a better safety profile with 14.4% of G3/G4 AEs versus 45.9% of ipilimumab. The interruption of the treatment due to toxicity occurred in 9.7% of the patients treated with nivolumab versus 42.6% treated with ipilimumab. Two deaths were reported in the ipilimumab cohort.[51] After 36 months of follow up, nivolumab still had a longer RFS than nivolumab (3-yr RFS rates: 58% vs. 45%; $p < .0001$).[52]

In the EORTC 1325/Keynote-54, phase-3 trial, patients with stage IIIA-IIIB-IIIC (AJCC 7th ed) resected melanoma were assigned to pembrolizumab 200 mg q3 w or placebo for maximum 18 doses. The trial included 1019 patients, among whom about 47% were BRAF mutant. After a follow up of 15 months, the 1-yr RFS rate was 75.4% vs 61.0%. Among PD-L1 positive patients, the 1-yr RFS rate was 77.1% vs 62.6% for pembrolizumab and placebo populations, respectively, but the treatment was effective regardless of the PD-L1 expression. AEs G3-G5 were recorded in 14.7% patients receiving pembrolizumab vs 3.4% of patients receiving placebo. Only one death was reported in the pembrolizumab group.[53]

Immune checkpoint inhibitors and anti-BRAF/MEK agents

Preclinical and translational studies have pointed out a synergy between the PD-1/PD-L1 and the BRAF pathways. BRAF/MEK inhibitors are able to modify the tumor microenvironment of melanoma exerting an immunogenic effect such as the increasing of T-cell infiltration, the upregulation of melanoma antigens and the expression of MHC class I/II, opening a new scenario for the combination of target therapy and immunotherapy.[54,55] Some trials have been designed to test safety and efficacy of the combination of target therapy and ICIs.

Poor results (PFS of 3.0 months, disease control rate of 18.6%) were observed in a group of patients receiving pembrolizumab after target therapy.[56] Similarly, in a study of 32 patients receiving target therapy after progression to immunotherapy, ORR was 57%, PFS was 6.7 months and OS 19.6 months. However, in this study, 242 patients were treated with the reverse sequence (immunotherapy after progression to target therapy), obtaining a PFS of 2.7 months and an OS of 5.0 months.[57]

Among the first experiences with dabrafenib + trametinib + pembrolizumab in patients with melanoma and V600 BRAF mutation, 15 patients obtained an ORR of 73%; 40% of patients had a long-term response after over 2 years of follow up. However, the treatment caused G3/G4 AEs in about ¾ of patients (pyrexia and altered liver function the most frequent AEs).[58] In the KEYNOTE-022 phase II trial, 120 patients with BRAF mutation received dabrafenib and trametinib + pembrolizumab or placebo. Despite the difference in median PFS (16.0 months in the target + pembrolizumab group versus 10.3 months of target + placebo group), a statistical significant benefit in terms of PFS was not found. The median duration response was 18.7 for target + pembrolizumab group versus 12.5 months for target alone arm. Moreover, 59.8% of patients in the pembrolizumab + target therapy group responded for over 18 months versus 27.8% of the patients in the placebo + target group.[59]

The combination of atezolizumab + cobimetinib + vemurafenib provided an ORR of 71.8% and a median duration of response of 17.4 months in stage IV BRAF-mutant melanoma patients. About 39.3% of the patients had an ongoing response after 29.9 months of follow up.[60] The combination of atezolizumab + cobimetinib determined a mPFS of 12 months in patients with metastatic melanoma (including also two ocular melanomas) both BRAF wt and BRAF mutant.[61] The phase III trial TRILOGY IMspire 150 (NCT02908672), comparing vemurafenib + cobimetinib with vemurafenib + cobimetinib + atezolizumab, is still ongoing.

Another ongoing phase III study is the COMBI-i (NCT02967692), testing the combination of dabrafenib + trametinib + spartalizumab (an anti-PD-1 agent). The preliminary results of the COMBI-i showed an objective response rate of 75.0% with a 1-yr PFS rate of 65.3% and a 1-yr OS rate of 85.9%.[62]

Immune checkpoint inhibitors for mucosal melanoma

Mucosal melanoma (MM) represents about 1% of all melanoma cases.[2] It has different clinical and biological features compared to cutaneous melanoma. MM is characterized by a high rate of locoregional recurrence and distant metastasis

with a poorer prognosis than cutaneous melanoma. Several MMs are diagnosed at a late stage because of their site of origin. About 50% of mucosal melanomas originate from head and neck (i.e. oral cavity, nasal mucosa), while the majority of the other cases involve anorectal and vulvar or vaginal mucosa, with a prevalence in older women.[63] MM has also a different genetic profile compared to cutaneous melanoma.[64] About 10% of MM are BRAF mutated compared with a 50% BRAF mutation rate in cutaneous melanoma. c-kit gene aberrations are more frequent in MM (16–25%) than in cutaneous melanoma (5–10%).[65,66] The total rate of mutations, including the ultraviolet-related mutations, is lower for MM than cutaneous melanoma. This may explain the inferior efficacy of immunotherapy in mucosal melanoma.[67] PD-L1 expression seems to be lower in patients with mucosal melanoma.[34]

No prospective randomized trials have been carried out to evaluate immunotherapy specifically for MM patients. The majority of the data derive from clinical studies including mostly cutaneous melanoma patients.

The largest pooled analysis regarding advanced MM included patients treated with nivolumab as single agent or combined to ipilimumab in the following clinical trials: CA209-003, CA209-038, CheckMate 066, CheckMate 037, CheckMate 067, CheckMate 069. .[68,21,23,40,43,69,70] MM represented 10% (n. 86) of all the patients treated with nivolumab monotherapy, 9% (n. 35) treated with nivolumab + ipilimumab and 10% (36) treated with ipilimumab alone. The median PFS of the patients with MM was 3.0 months for nivolumab monotherapy, 5.9 months for combination therapy and 2.7 months for ipilimumab monotherapy. The ORR was 23.3%, 37.1% and 8.3% for nivolumab alone, nivolumab + ipilimumab combination and ipilimumab monotherapy, respectively. In cutaneous melanoma treated with the same regimens, the ORR was 40.9% with nivolumab, 60.4% with nivolumab + ipilimumab and 21.2% with ipilimumab. A stronger association between ORR and PD-L1 expression was found in MM than in cutaneous melanoma.[68]

Hamid collected data from 3 trials in which patients had received pembrolizumab: KEYNOTE-001, KEYNOTE-002 and KEYNOTE-006.[71] The patients with mucosal melanoma in the studies considered for the analysis were 84 out 1567.[25,71–73] The majority of patients with MM received ≥2 prior therapies. In patients with MM, ORR was 19% overall, (versus 33% in non-mucosal melanoma), 22% in ipilimumab-naïve (versus 38% in non-mucosal melanoma) and 15% in ipilimumab-treated patients (versus 27% in non-mucosal melanoma). A median PFS of 2.8 months was found for patients with MM. In non-mucosal melanoma, the median PFS was 4.2 months. The median OS was 11.3 months for all patients with mucosal melanoma, 14.0 months for ipilimumab-naive and 10.2 months for patients previously treated with ipilimumab. The median OS in non-mucosal melanoma was 23.5 months, 29.1 months for patients who did not receive ipilimumab and 17.5 months for ipilimumab-treated patients.[71]

In addition to these two pooled analyses, a multi-center retrospective study of 35 patients with advanced MM, treated with either pembrolizumab or nivolumab, demonstrated a response rate of 23% with a median response duration of 12.9 months. PFS was 3.9 months and OS 12.4 months.[34]

Data regarding MM in adjuvant setting are poor. Indeed, only 29/906 patients (3.2%) enrolled in the ChechMate 238 trial had MM.[51]

The limited studies available demonstrated that patients with MM may benefit from anti–PD-1 therapy, although the probability of benefits is lower than in cutaneous melanoma. Immunotherapy in MM can be effective regardless of tumor PD-L1 expression and prior therapies. Moreover, the combination anti-PD-1 plus anti-CTLA-4 therapy may provide a better outcome for these patients.

Immune checkpoint inhibitors for uveal melanoma

Uveal melanoma is the most frequent ocular tumor with a high probability of metastatic diffusion. Liver involvement is frequent in advanced disease.[5,74] The prognosis of metastatic uveal melanoma is poor because of the lack of effective treatments.[75] Ocular melanoma represents a common exclusion criteria for clinical trials testing immunotherapy in melanoma. Nevertheless, the treatments are often the same as those employed for cutaneous melanoma. Indeed, checkpoint inhibitors are considered an option for this disease.

Ipilimumab was tested both in pretreated and naïve patients showing a limited benefit. In the study by Karidis, 8% of partial response and 24% of disease stabilization were reported with pembrolizumab, whereas the PFS was 3 months.[76] The results reported by Algazi regarding pembrolizumab, atezolimab and nivolumab do not differ particulalry.[77]

The efficacy of pembrolizumab was evaluated in a prospective observational study in which the median PFS was 3.8 months. Indeed, the results did not seem different compared with other agents, but an impressive disease control was obtained in responding patients.[78]

Heppt reported the results obtained with the combined use of ipilimumab and PD-1 inhibitor. The median PFS was 3.0 months, while the median OS was estimated to 16.1 months; 39.1% of patients experienced G3/G4 adverse events.[79]

Uveal melanoma is characterized by a lower mutational burden than cutaneous melanoma with few non-synonymuos mutations and no ultraviolet-induced mutational damage.[80,81] A mean mutation rate of 0.46 mutations per megabase has been reported.[81] These genetic characteristics and some immunological features of uveal melanoma can explain the results obtained until now with ICIs.[81,82] Further investigations regarding immunological pathways different from PD-1 or CTLA-4 could allow better results with immunotherapy in uveal melanoma.[80]

Immune checkpoint inhibitors for conjunctival melanoma

No standard treatment for conjunctival melanoma has been defined.[82] The majority of the clinical trials with ICIs exclude both uveal and conjunctival melanoma.[11,21,23,25,32,48,51,53] Few reports regarding the immunological features of this disease are available.[83–88] Cao conducted a study to evaluate the PD-1/PD-L1 pathway in conjunctival melanoma. In sections of 27 human conjunctival melanomas, it has been found that 19% of the melanoma cells and 59% of the stromal cells expressed

PD-L1 (≥5%) on their membrane. Furthermore, the authors pointed out that PD-L1 expression of the tumor cells was related to distant metastases and a shorter cancer specific survival.[89]

Conjunctival melanoma shares genetic features with cutaneous melanoma, whereas it is less comparable to mucosal melanoma and completely different compared to uveal melanoma.[64] Common mutations of uveal melanoma have not been found in conjunctival melanoma, while a typical signature of ultraviolet-induced DNA damage has been reported.[90]

Data regarding immunotherapy for conjunctival melanoma are limited, but some case reports/case series regarding ICIs for recurrent, locally advanced and metastatic conjunctival melanomas have been described. A patient with a relapse of conjunctival melanoma was treated with pembrolizumab 150 mg q3 w for 6 months, followed by surgical removal without residual melanoma cells. Pembrolizumab was continued for further 12 months, without recurrence.[83] Another patient with subcutaneous metastases of conjunctival melanoma received pembrolizumab (200 mg q3 w), with a complete response after the third cycle.[84]

Finger reported the experience regarding 5 patients with ocular residual tumor and metastatic disease, treated with an anti-PD-1 therapy.[86] For patients with local residual tumor, low dose ipilimumab or interferon eye drops were combined with anti-PD-1 treatment. The patients with advanced disease also received ipilimumab: in one case after anti-PD-1 and for the other patient in combination with anti-PD-1. All the patients obtained an objective response.[86] In a further retrospective case series, 5 patients with metastatic conjunctival melanoma received an anti PD-1 agent, reporting 4 complete responses and a disease stabilization. Among them, a patient did not present metastases for 36 months after the end of the treatment.[87]

In the adjuvant setting, ipilimumab was administered to a patient with conjunctival melanoma who did not experience a recurrence for 16 months.[88]

Although the limited data, ICIs can be considered for the treatment of advanced conjunctival melanoma.

Conclusions

ICIs allowed a remarkable advantage in survival and disease control for the most of melanoma patients. Impressive improvements have been obtained for cutaneous melanoma, while for the other types of melanoma ICIs demonstrated less effectiveness. Indeed, a lower proportion of the patients with mucosal melanoma benefited from ICIs. Among the ocular melanomas, ICIs can represent a therapeutic option for conjunctival melanoma, whereas uveal melanoma requires alternative strategies or a better selection of the patients based on the immunological profile.

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