Programmed cell death 1 checkpoint inhibitors in the treatment of patients with advanced melanoma

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The treatment landscape of advanced melanoma has changed significantly following the discovery and marketing authorisation of immune checkpoints inhibitors. Ipilimumab (anti-CTLA-4) was the first one to be approved, and it. demonstrated long-term survival in about 20% of patients. Subsequently, anti-programmed cell death-1 (a-PD-1) antibodies (pembrolizuamb, nivolumab), inhibitors of PD-1/programmed cell death-1 ligand (PD1-L) synapse, showed higher clinical efficacy with lower toxicity comparing to ipilimumab. The highest clinical benefit in patients was observed when nivolumab and ipiliumumab were combined. However, the above strategy, due to very high toxicity, has limitations for use in all patients with advanced melanoma. Notwithstanding, patients treated with anti-PD1 beyond disease progression benefit from treatment continuation; further studies are warranted in this indication. Furthermore, patients responding to treatment with anti-PD1 will benefit from the therapy after its discontinuation. Immune checkpoint inhibitors are clinically effective regardless of *BRAF* mutation. Currently there is no recommendation regarding which treatment option should be selected for the treatment of the population – immunotherapy or targeted therapy with BRAF and MEK inhibitors. Randomised trials are ongoing comparing these two treatment strategies in patients with BRAF mutation. Encouraging results were observed in early phase trials in patients receiving the combination of immune and targeted therapy. Phase 3 studies are underway. Patients with elevated serum lactate dehydrogenase present poor prognosis regardless of the systemic treatment used. novel treatment strategies should probably be developed for these patients.

Key words: melanoma, immunotherapy, anti-PD1.

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Introduction

The treatment landscape of advanced melanoma has been changing significantly with the approval of new medicinal products. Until the year 2010, patients with advanced melanoma were treated mainly with chemical agents. Some responses with cytotoxic drugs were observed; however, the benefit in overall survival (OS) has never been proven [1]. From year 2010 seven new drugs and three combination strategies of the medicines have been approved for the treatment of advanced measurable melanoma (unresectable or metastatic). The first immune check-point inhibitor approved for the treatment of advanced melanoma was ipilimumab (anti CTLA-4, cytotoxic T-lymphocyte antigen-4), which demonstrated long-term survival in about 20% of patients. In 10-year follow-up the probability survival curve began to plateau at approximately year three [2, 3]. Next, more effective immunotherapy strategies, such as anti-programmed cell death receptor-1 (PD-1) antibodies (nivolumab, pembrolizumab), were developed [4–6]. The highest clinical efficacy was observed when nivolumab was combined with ipilimumab; however, this strategy was accompanied with very high toxicity [4]. On the other hand, in a population limited to patients with *BRAF*-mutated melanoma, a combination treatment strategy with BRAF (dabrafenib, vemurafenib) and MEK inhibitor (trametinib, cobimetinib) could be applied. Recently an oncolytic DNA vaccine (T-VEC, talimogene laherparepvec), a strategy based on intra-tumour administration, has been approved in patients with metastases limited to skin and lymph nodes. However, its position on the advanced melanoma therapy market is still not evaluable [7].

Nivolumab

Nivolumab is an IgG4, anti-PD-1 monoclonal antibody evaluated in a number of clinical trials in patients with melanoma. Two phase 3 studies were carried out in patients with unresectable, locally advanced (stage III), or metastatic (stage IV) melanoma. The first study was CheckMate 037 in *BRAF*-mutant and *BRAF*-wild type (*BRAF*-wt) patients, who progressed after ipilimumab therapy. Patients with *BRAF* mutation after progression following BRAF inhibitor were eligible to enter the study. In one study arm patients received nivolumab (3 mg/kg every two weeks), and in the comparator arm patients were treated with chemotherapy of the investigator's choice. Patients treated with nivolumab demonstrated higher response rate compared to the chemotherapy group – 32% vs. 11% [8]. However, there was no statistical difference in

median OS between the study arm – 15.7 months (nivolumab) vs. the comparator group – 14.4 months (chemotherapy); $p = 0.71$. The lack of the clinical benefit of nivolumab could be related to the fact that control group patients (40%) received pembrolizumab, when progressed during chemotherapy. Furthermore, the number of patients with elevated LDH levels and brain metastases was imbalanced, favouring the chemotherapy arm [9].

In another phase 3 study (CheckMate 066) the efficacy of nivolumab 3 mg/kg administered every two weeks was compared with chemotherapy in the first-line treatment in patients with BRAF-wt advanced melanoma. The response rate was higher in patients treated with nivolumab than with chemotherapy – 40% vs. 13.9% [10]. The median OS of patients treated with nivolumab was not reached at data analysis; however, the two-year OS was higher in this group of study patients – 57.7% vs. control – 26.7% [11]. Currently, the longest follow-up of patients treated with anti-PD1 was observed in a phase 1 study (CheckMate 003) carried out in 107 patients receiving various doses of nivolumab (0.3–10 mg/kg). The five-year OS was observed in 34% of patients, and OS rates appeared to plateau at around 48 months, which was indicative of long-term benefit in some patients. The median OS in all treated patients was 17.3 months, and 20.3 months in patients treated with the approved 3 mg/kg dose of nivolumab [12].

Adverse events are less frequent in patients treated with nivolumab than in those treated with ipilimumab or chemotherapy [4, 10]. A safety profile was evaluated in a pooled analysis including 576 advanced melanoma patients receiving approved 3 mg/kg dose of nivolumab in two phase 1 studies (CheckMate-003, CheckMate-038) and two phase 3 studies (CheckMate 037, CheckMate 066). The most frequently observed adverse events (AEs) included fatigue, pruritus, diarrhoea, rash, and nausea. Any grade AEs were seen in 71% of patients (grade 3/4 – 10%). The most commonly observed immune-related adverse events (irAEs) were pruritus, rash, diarrhoea, vitiligo, hypothyroidism, and elevated aminotransferases. Any grade irAEs were observed in 49%, bit grade 3 and 4 only in 3.6% of patients [13].

Pembrolizumab

Pembrolizumab is a humanised IgG4 monoclonal antibody anti-PD-1. Pembrolizumab is approved for the treatment of advanced melanoma in a dose of 2 mg/kg every three weeks. Pembrolizumab in various doses was evaluated in a phase 1 study (KEYNOTE 001), which enrolled 655 patients with advanced melanoma. The median OS was 23.5, 22.9, and 25.9 months in patients receiving 2 mg/kg every three weeks, 10 mg/kg every two weeks, and 10 mg/kg every there weeks, respectively. Across all studied doses the median OS was 20 months in patients previously treated with ipilimuamb and 28 months in ipilimumab naïve patients. The three-year OS was identical regardless of earlier ipilimumab treatment, at 41%. The best results were obtained in the treatment naïve patients – median OS was 32 months (three-year OS – 45%) [14]. In a phase 2 study (KEYNOTE 002) pembrolizumab was evaluated in doses of 2 mg/kg and 10 mg/kg every three weeks, comparing to chemotherapy in advanced BRAF-mutant and BRAF-wt advanced melanoma patients after progression following ipilimumab. Enrolled patients with BRAF mutation were required to have received earlier BRAF and/or MEK inhibitor (25%) treatment. Almost half of the patients received earlier chemotherapy (48%). In the final analysis the response rate was significantly higher in patients receiving pembrolizumab (22.2% – 2 mg/kg; 27.6% – 10 mg/kg) compared to the chemotherapy arm (4.5%). There was no difference in median PFS between studied groups (2.9 vs. 3 vs. 2.8 months). However, there was a difference in two-year PFS (progression-free survival) between the study arms: pembrolizumab 2 mg/kg vs. chemotherapy – 16% vs. 0.6% ($p < 0.0001$; HR = 0.58) and pembrolizumab 10 mg/kg vs. chemotherapy – 21.9% vs. 0.6% ($p < 0.0001$; HR = 0.47). A significant improvement in median OS was seen only in patients treated with pembrolizumab 10 mg/kg compared to the chemotherapy group – 14.7 vs. 11 months ($p = 0.01$; HR = 0.74). In the group treated with the pembrolizumab (2 mg/kg) there was only a trend towards longer median OS comparined to the chemotherapy arm – 13.4 vs. 11 months ($p = 0.1$) [15].

In one phase 3 trial (KEYNOTE 006) pembrolizumab in a dose of 10 mg/kg was evaluated in two different schedules (every two or three weeks) compared to ipilimumab in patients with advanced *BRAF*-mutant of *BRAF*-wt melanoma. Patients were treated in the first or second line. In patients with *BRAF* mutation earlier treatment with *BRAF* inhibitor was not obligatory. The response rate observed in patients receiving pembrolizumab every three or two weeks, or ipilimumab was 37%, 36% and 13%, respectively. The two-year OS in both pembrolizumab arms was 55% compared to 43% in the ipilimumab group – the difference between the pembrolizumab arms and ipilimumab was statistically significant. Median OS in the pembrolizumab groups was not reached at the time of study analysis. In patients treated with ipilimumab the median OS was 16 months [6].

Adverse events are less frequently observed in patients treated with pembrolizumab than with ipilimumab or chemotherapy [6, 15]. The pooled analysis from KEYNOTE-001 and KEYNOTE-002 conducted in 1012 patients demonstrated similar toxicity across all evaluated dosing schemes of pembrolizumab (2 mg/kg every three weeks, 10 mg/kg every two, and 10 mg/kg every three weeks). Treatment-related adverse events (AE) were observed in 75–83% of patients; however, most of them were grade 1 or 2. The most frequent AEs included fatigue, pruritus, rash, arthritis, diarrhoea, and nausea. Grade 3 and 4 AEs were noted in 13.5% of patients. The most frequently observed immune-related irAEs were hypothyroidism (7.4%), pneumonitis (2.6%), and hyperthyroidism (2.4%). Other irAEs like colitis, hypophysitis, nephritis, and hepatitis occurred in less than 2% of patients [16].

Treatment with anti-PD1 beyond disease progression

In a pooled analysis (CheckMate 066 and 067) conducted in 526 patients treated with nivolumab, progression of the disease was observed in over half of the patients ($n = 306$).

Continuation of the treatment beyond progression was performed in 85 (28%) patients, while 221 (72%) patients discontinued nivolumab therapy. CR and PR was observed in 24 (28%) patients treated beyond progression, while SD with tumour regression was noted in 14 patients (16%). Of those patients developing CR and PR after progression, 45% of patients are still on treatment and 87% of patients are still alive at the time of study analysis. Patients who were selected by the investigator to be treated beyond progression were healthier than those who were not selected, based on ECOG (Eastern Cooperative Oncology Group) performance status, M-stage, and LDH (lactate dehydrogenase). The results of the above retrospective analysis suggest that some patients treated with nivolumab beyond RECIST-defined (response evaluation criteria in solid tumors) progression may clinically benefit [17].

Nivolumab plus ipilimumab

The efficacy of first-line nivolumab combined with ipilimumab was evaluated in two randomised studies in patients with *BRAF*-mutant and *BRAF*-wt advanced melanoma. In the phase 2 study (CheckMate 069), 140 patients received nivolumab 1 mg/kg plus ipilimumab 3 mg/kg or ipilimumab 3 mg/kg plus placebo, every three weeks for four doses. Subsequently, patients assigned to nivolumab plus ipilimumab received nivolumab 3 mg/kg every two weeks until disease progression or unacceptable toxicity, whereas patients allocated to ipilimumab alone received placebo every two weeks during this phase. The objective clinical response rate was higher in patients treated with nivolumab plus ipilimumab – 59% vs. 11%. The two-year OS was 63.8% in patients assigned to nivolumab plus ipilimumab and 53.6% for those assigned to ipilimumab alone. Median OS has not been reached in either group at the time of study analysis [5].

In a phase 3 study (CheckMate 067), 945 patients were enrolled into one of three study arms: nivolumab plus ipilimumab (scheme and dosing analogous to the CheckMate 067 study), nivolumab 3 mg/kg every two weeks till disease progression or unacceptable toxicity and ipilimumab 3 mg/kg every three weeks (four doses). The objective response rate was 57.6%, 43.7%, and 19% in patients treated with nivolumab plus ipilimumab, nivolumab, or ipilimumab, respectively. The median PFS was 11.5, 6.9, and 2.9 months in patients receiving nivolumab plus ipilimumab, nivolumab, or ipilimumab, respectively. In patients with tumours positive for the PD-1 ligand (PD-L1) (PD-L1 expression in ≥ 5% cells), the median PFS was 14.0 months in the nivolumab plus ipilimumab group and in the nivolumab group, but in patients with PD-L1-negative tumours (PD-L1 expression in < 5% cells), PFS was longer with the combination therapy than with nivolumab alone (11.2 months vs. 5.3 months). The OS data from this study are not yet available [4]. Based on these results nivolumab combined with ipilimumab was approved in Europe in advanced melanoma patients with low PD-L1 expression.

In the pooled analyses from 3 CheckMate studies 066, 067, and 069 (n = 832) the frequency of patients with PD-L1 expression ≥ 5% was 28% and did not differ based on the site of biopsy collection, or between primary and metastatic lesions. The remaining patients did not present PD-L1 expression (<5%). In patients with PD-L1-negative tumours the median PFS in the group receiving nivolumab plus ipilimumab comparing to nivolumab alone was significantly longer – 11.1 vs. 4.9 months (p = 0.0014). However, in patients with PD-L1-positive tumours the median PFS in the group treated with nivolumab plus ipilimumab was not reached, while in patients receiving nivolumab monotherapy was 22 months (p = 0.94). Furthermore, higher response rates in patients treated with nivolumab plus ipilimumab compared to nivolumab alone were observed regardless of PD-L1 expression. However, in patients with tumours positive for PD-L1 numerically higher response rates comparing to PD-L1-negative tumours were observed – PD-L1 ≥ 5%: 68.5% (nivolumab + ipilimumab) vs. 59% (nivolumab) and PD-L1 < 5%: 54.9% (nivolumab + ipilimumab) vs. 39.7% (nivolumab) [18]. In conclusion, information gained from PD-L1 testing to better understand the risk-benefit of different treatment options should be used with caution, and in consideration of all available clinical information.

Treatment with combination of nivolumab and ipilimumab is linked with very high frequency of AEs compared to nivolumab or ipilimumab alone. The PD-L1 expression did not display any influence on the frequency of AEs in patients treated with nivolumab plus ipilimumab or nivolumab monotherapy. Any grade AEs in patients treated with the combination occurred in 95.5% (grade 3/4 – 55%), while in patients receiving nivolumab alone in 82.1% (grade 3/4 – 16.3%) and ipilimumab alone in 86.2% (grade 3/4 – 27.3%) [4]. In a pooled analysis from three studies (CA209-004, CheckMate 067, and 069) 448 advanced melanoma patients were treated with the combination of nivolumab and ipilimumab. Treatment-related AEs were seen in 95% of patients, while grade 3 and 4 treatment-related AEs were noted in 55%. The most frequently observed any grade AEs were diarrhoea (44%), fatigue (37%), rash (35%), pruritus (35%), nausea (25%), pyrexia (19%), increased alanine aminotransferase (18%), increase aspartate aminotransferase (17%), hypothyroidism (15%), and decreased appetite (15%). The most commonly noted grade 3 and 4 AEs included diarrhoea (10%), colitis (9%), increased alanine aminotransferase (9%), elevated lipase (9%), increase aspartate aminotransferase (6%), and endocrine disorders (5%). Most treatment-related select AEs resolved, except endocrinopathies that required long-term hormone replacement therapy. Treatment discontinuation due to toxicity was noted in 40% of patients [19].

Long-term response after treatment discontinuation

Treatment with the currently approved anti-PD1 antibodies should be continued until disease progression or unacceptable toxicity in patients with melanoma, lung cancer, kidney cancer, head and neck cancer, or Hodgkin lymphoma [20, 21]. In a group of patients developing long-term response without significant toxicity these drugs might be administered for many years, which is cost ef-

fective. In a phase 1 study (Keynote 001) evaluating pembrolizumab, according to the protocol patients developing CR and receiving treatment for two years stopped pembrolizumab administration for observation. This applied to 10% of patients (n = 61). The median time of treatment was 10 months. Only two patients developed progression of the disease while off treatment. At the time of analysis, in 97% (n = 59) of patients the responses maintained [14]. In a pooled analysis (CheckMate 067 and 069) 176 patients treated with nivolumab plus ipilimumab discontinued treatment due to AEs. The median PFS was longer in patients in which the treatment was terminated due to AEs compared to patients with AEs where treatment discontinuation was not necessary – 16.7 vs. 10.8 months (p < 0.04) [22]. These results demonstrate that patients developing CR or AEs leading to treatment discontinuation benefit from the treatment while being off treatment.

Elevated LDH as poor prognostic factor

It has been shown that melanoma patients with elevated serum LDH present poor prognosis regardless of the systemic treatment used [23–25]. In a pooled analysis (CheckMate 066, 067, and 069) performed in 1270 advanced melanoma patients, elevated LDH was noted in 455 patients, with the elevation over twice the upper laboratory norm (ULN) in 132 patients. The response rate and median PFS was higher in patients with normal LDH compared to elevated LDH (Table 1) [26].

Conclusions

The treatment efficacy observed in melanoma patients receiving nivolumab or pembrolizumab is very similar. Moreover, these two drugs display similar toxicity profiles. However, there are more data from randomised phase 3 studies of the approved doses' efficacy of nivolumab than pembrolizumab. Nevertheless, experts in the field of melanoma state that these two drugs can be used interchangeably. A high proportion of patients did not respond to anti-PD1 therapy. The identification of efficacy biomarkers for the selection of patients that will benefit from immunotherapy is warranted. It seems that patients treated with anti-PD1 and developing response benefit from the therapy after treatment discontinuation. However, these data need confirmation in randomised studies. There are some issues that have to be established in clinical trials.

Table 1. Response rate (RR) and progression-free survival (PFS) in patients with normal and elevated serum lactate dehydrogenase (LDH) in patients treated in CheckMate 066, 067, 069 studies

	Nivolumab + ipilimumab	Nivolumab	Ipilimumab
RR			
LDH ≤ ULN	65%	51%	23%
LDH > ULN	45%	31%	10%
LDH > 2 × ULN	33%	17%	0%
PFS			
LDH ≤ ULN	NR	11.3 months	4.1 months
LDH > ULN	5.2 months	2.7 months	2.6 months
LDH > 2 × ULN	2.6 months	2.1 months	2.3 months

Currently it is unknown which is the best treatment option in patients with *BRAF*-mutant advanced melanoma. Randomised trials comparing the efficacy of immunotherapy and targeted therapy in the first- and second-line treatment in this group of patients are currently on-going [27, 28]. Much attention has been paid to the combination of immunotherapy and targeted therapy lately [24]. Very encouraging results have been presented in a phase 1 study in *BRAF*-mutant advanced melanoma patients receiving atezolizumab (anti PD-L1) combined with vemurafenib and cobimetinib, with a response rate of 83%; currently a phase 3 study is on-going [29, 30]. Also the combination of atezolizumab with trametinib in patients with *BRAF*-wt melanoma demonstrated encouraging results in an early phase study – a phase 3 study is planned [31]. Patients with advanced melanoma and high serum LDH present very poor prognosis, regardless of the systemic treatment used [23–26]. Current research should be focused on understanding the relationship between high LDH and the lack of treatment efficacy with immunotherapy and targeted therapy. Probably novel treatment strategies should be developed in this patient population.

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