# Immunotherapy in advanced cutaneous melanoma patients

## *Immunoterapia chorych na zaawansowanego czerniaka skóry*

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### Summary

The incidence of cancer has been increasing worldwide. Melanoma is known to be one of the most immunogenic malignancies in humans. In recent years innovative and promising therapeutic strategies that modulate the immune response or target various intracellular pathways in melanoma have been developed. Recently new drugs which improved overall survival in phase III regulatory studies namely, ipilimumab (anti-CTLA-4 antibody) and vemurafenib (BRAF inhibitor) have been approved in Europe and the USA, and so has a combination of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) in the USA for the treatment of metastatic melanoma. A number of novel immunotherapy strategies including anti-PD-1, anti-PD-1L or cancer vaccines show a durable high response rate in advanced melanoma patients, however efficacy of these drugs needs to be confirmed in phase III studies. Results from preclinical studies and early clinical trials indicate a high potential for combining immunotherapy with other treatment strategies – currently many new drug combinations are being evaluated in phase I or II in patients with metastatic melanoma.

**Key words:** melanoma, immunotherapy, cancer vaccines, anti-CTLA-4, anti-PD-1.

### Streszczenie

Zachorowalność na czerniaka na świecie wzrasta. Czerniak jest jednym z najbardziej immunogennych nowotworów u ludzi. W ostatnich latach opracowano różne innowacyjne i obiecujące strategie terapeutyczne w czerniaku, które modulują odpowiedź immunologiczną lub docelowe różne wewnątrzkomórkowe szlaki. W badaniach III fazy, oceniających skuteczność nowych leków, wykazano korzyść w zakresie wydłużenia przeżycia chorych leczonych ipilimumabem (przeciwciało anty-CTLA-4) oraz wemurafenibem (inhibitor BRAF). Leki te zostały zarejestrowane w Europie i USA; również dabrafenib (inhibitor BRAF) i trametynib (inhibitor MEK) dopuszczono do obrotu w USA do leczenia przerzutowego czerniaka. Liczne nowe immunoterapeutyki, takie jak anty-PD-1, anty-PD-1L czy szczepionki rakowe, wykazują wysoki odsetek trwałych odpowiedzi po zastosowanym leczeniu u chorych na zaawansowanego czerniaka, jednak ich skuteczność musi zostać potwierdzona w badaniach III fazy. Wyniki pochodzące z badań przedklinicznych i klinicznych wczesnej fazy wskazują na wysoki potencjał immunoterapii skojarzonej z innymi lekami – obecnie wiele nowych terapii skojarzonych ocenianych jest w badaniach I lub II fazy u chorych na czerniaka z przerzutami.

**Słowa kluczowe:** czerniak, immunoterapia, szczepionki przeciwnowotworowe, anty-CTLA-4, anty-PD-1.

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## Introduction

The incidence of cancer has been increasing worldwide [1]. Skin melanoma is a rare malignancy, however the morbidity has risen several times in the past years [2, 3]. Early diagnosis of the disease and surgical treatment is associated with high rates of cure of melanoma. 93-97% of melanoma patients survive 5 years after resection of a thin primary lesion (Breslow equal or below 1 mm). However, mortality increases when melanoma starts to metastasize [4].

In the past forty years no treatment of metastatic melanoma was available. Until 2010 only dacarbazine (DTIC) in Europe and the USA and interleukin-2 (IL-2) in the USA were approved for the treatment of metastatic melanoma, however, none of these drugs extended overall survival (OS) of treated patients. Multidrug chemotherapy was associated with a higher response rate but did not demonstrate extension of OS in randomised phase III studies as compared to DTIC alone. Results of trials evaluating other cytotoxic agents alone or in combination with biotherapy were also disappointing [5-7]. Meta-analysis of 42 clinical trials, which included 2100 metastatic melanoma patients demonstrated 6.2-month median OS, and 1-year survival of 25.5% of patients [8].

## The new era of metastatic melanoma treatment

Renal cell carcinoma and melanoma are acknowledged to be the most immunogenic malignancy in humans. In the case of melanoma it may clinically manifest as spontaneous regression of primary lesion (approximately in 7% of cases) and mounting immune response against melanoma cells in some patients [9, 10]. Better understanding of the molecular and cellular mechanisms that control the immune system has enabled the development of a number of innovative and promising therapeutic strategies that modulate the immune response in melanoma patients.

Recently new drugs have improved OS in phase III regulatory studies leading to the approval of ipilimumab and vemurafenib in Europe and the USA as well as dabrafenib and trametinib in the USA for the treatment of metastatic melanoma. Currently various immunomodulatory therapies such as monoclonal antibodies directed against CTLA-4, PD-1, PD-1L or cancer vaccines alone or in combination are being tested in clinical trials.

### *Anti-CTLA-4*

Two very similar monoclonal antibodies (mAb), ipilimumab and tremelimumab, directed against cytotoxic T-lymphocyte antigen-4 (CTLA-4) have been evaluated in phase III studies. CTLA-4 is an immune check-point molecule that is up-regulated on activated T-cells. The interaction of CD80/86 molecule presented on antigen presenting cells (APC) with CTLA-4 up-regulated on activated T-cells leads to the suppression of specific CD4+ and CD8+ T-cells. Anti-CTLA-4 inhibits binding of CTLA-4 with CD80/86, thus it switches off the mechanism of immune suppression and enables continuous unrestrained stimulation of T-cells by dendritic cells (DCs) [11]. Ipilimumab is currently approved in Europe and the USA in patients with unresected or metastatic melanoma after failure of chemotherapy. Additionally U.S. Food and Drug Administration (FDA) accepted ipilimumab in the first-line treatment of advanced melanoma. The approval was based on the results of a phase III trial, which included 676 patients receiving ipilimumab with a peptide vaccine (gp100), ipilimumab alone or gp100 in monotherapy. 3 mg/kg of ipilimumab were infused 4 times every 3 weeks. The highest objective response rate (CR – complete response, PR – partial response) was observed in patients treated with ipilimumab alone (11%) comparing to therapy with ipilimumab plus gp100 (5.7%) or gp100 (1.5%). Patients treated with ipilimumab alone and in combination with gp100 demonstrated almost identical median OS which was 10 and 10.1 months, respectively, while patients receiving gp100 alone demonstrated 6.4 months ($p < 0.001$). Treatment with ipilimumab resulted in 23% of patients surviving 5 years, while 14% of patients of the control arm [12]. Ipilimumab was also evaluated in a phase III study in untreated patients with advanced melanoma. In one study arm patients received 10 mg/kg ipilimumab with DTIC, while in the second arm DTIC alone. Median OS was slightly longer in patients treated with ipilimumab – 11.2 vs. 9.1 months (HR = 0.72; $p = 0.0009$). Two and three-year OS of patients receiving ipilimumab with DTIC was 28.5% and 17.9%, respectively comparing to 20.8% and 12.2% of patients treated with chemotherapy [13]. Updated results from two phase II studies evaluating 10 mg/kg ipilimumab in advanced melanoma patients showed a 2-year survival of 24%-30% and a 3-year survival of 24-25% of patients [14, 15]. Results from many Expanded Access Programs (EAP) or Patients Assistance Programs (PAP) evaluating ipilimumab were similar to those observed in the phase II and III studies [16]. Margolin et al. presented a U.S. multisite retrospective chart review demonstrating effectiveness of first-line 3 mg/kg ipilimumab therapy in advanced melanoma patients. The analysis included 120 patients, most with stage M1c (55%). The median OS was 14.3 months [17]. Treatment with ipilimumab was related to a specific toxicity profile. Immune-related adverse events (irAEs) occurred in 80% of treated patients, while grade 3-4 irAEs were noted in 7-39% of patients. The most frequently observed irAE were diarrhoea, colitis, dermatitis, hepatitis and endocrinopathies [18-21].

Another mAb targeting CTLA-4 and evaluated in a phase III study is tremelimumab. The study included

655 patients with unresected stage IIIC and IV melanoma. Enrolled patients received tremelimumab or DTIC/TMZ (temozolomide) in the first-line treatment. Patients in the study group presented longer progression free survival (PFS) compared to the control arm – 35.8 vs. 13.7 months ($p$ = 0.0011). However, the study failed to demonstrate advantage of tremelimumab over chemotherapy in terms of OS elongation (tremelimumab: 12.5 months vs. chemotherapy: 10.7 months, $p$ = 0.127). Diarrhoea, pruritus, and rash were the most common treatment-related adverse events in the tremelimumab arm; 7.4% had endocrine toxicities. The authors explain that the differences between the results of phase III studies evaluating tremelimumab and ipilimumab might be caused by different patients selection (tremelimumab study excluded patients with LDH > 2 × ULN) or dosing of the study drug. Moreover, 16% or more progressing of patients after chemotherapy received ipilimumab as the compassionate use [22].

### Anti-PD1 and anti-PD-1L

Within the immune system, multiple pathways exist to regulate the antigen-specific T-cell response. Among them, programmed death 1 (PD-1) and its ligand – programmed death 1 ligand 1 (PD-L1), display critical roles in regulating the balance between T-cell activation and tolerance. PD-1 is a transmembrane coinhibitory receptor upregulated on activated T cells [23]. PD-1L is selectively expressed on malignant cells and on cells within the tumour microenvironment in response to inflammatory stimuli [24-27]. PD-1 binding to PD-L1, can block T-cell proliferation, cytokine production, cytolytic function, and can lead to impaired T-cell survival [23]. Blockade of the interaction between PD-1 and PD-L1 can enhance T-cell response *in vitro* and mediate preclinical antitumor activity [24, 25].

BMS-936558 (nivolumab) and BMS-936559 are fully human antibodies directed against PD-1 and PD-L1, respectively [28-30]. In phase I/II study nivolumab was evaluated in 296 patients with advanced cancer (94 patients with metastatic melanoma) who failed earlier systemic treatment. Nivolumab was administered in a dose range of 0.1-10 mg/kg depending on the study cohort. The cumulative response rate (all doses) was 28%. Responses were durable and in 20 of 31 patients lasted over 1 year. Grade 3 or 4 toxicity was observed in 14% of patients. However, irAEs were noted less frequently than during ipilimumab treatment. Expression of PD-L1 in patients' tumours might be a predictive factor, because objective response after nivolumab treatment was observed in 36% of patients with PD-L1-positive tumours and in none of those with PD-L1-negative [28]. A phase II study evaluating 2 mg/kg nivolumab was conducted in Japan in 35 advanced melanoma patients who failed treatment with DTIC. PR was observed in 23% and SD in 48% of patients, while CRs were not noted. The median PFS was 172 days. Grade 3/4 irAEs were not observed [29].

Anti-PD-L1 (BMS-936559) was tested in a phase I study in 207 patients with advanced cancer. Fifty-two of 55 metastatic melanoma patients were evaluable for tumour assessment. The doses varied depending on the study cohort (0.3-10 mg/kg). Objective response was observed in 17% of patients. Grade 3 and 4 drug-related AE occurred in 9% of all treated patients. SD lasting over 6 months was noted in 27% of patients [30].

### Cancer vaccines

Therapeutic cancer vaccines are active specific immunotherapy strategies, which encompass cell- and non-cell-based products. Cell-based vaccines comprise: cancer cell lysates, whole cancer cells with adjuvants, gene-modified whole cancer cells, DCs pulsed with DNA, RNA, peptides, proteins or cell lysates, pulsed DCs modified with immune stimulators, fused cancer cells with DCs cells or B-lymphocytes. Non-cell-based vaccines include DNA vaccines (naked, plasmid), peptide vaccines, protein vaccines, viral-vector vaccines, anti-idiotypic antibody vaccines and particle-based vaccines [31, 32].

Many cancer vaccines have been studied in phase III trials, however to date none of these strategies has improved OS of melanoma patients. One example is Cancervax – allogeneic polyvalent cancer vaccine consisting of three established melanoma cell lines and BCG as an adjuvant [33]. Very promising results of a phase II trial were not confirmed in a phase III study [34, 35]. Also Melacine, a melanoma tumor cell lysate vaccine consisting of two allogeneic melanoma cell lines (MSM-M-1 and MSM-M-2) combined with Detox® adjuvant failed to show advantage over comparator in melanoma patients [36]. Although, in a retrospective analysis patients who matched with at least two of five human leukocyte antigens (HLA) present on vaccine cells had a longer RFS (recurrence free survival) and OS after Melacine treatment [37]. During the European Cancer Congress 2013 held in Amsterdam, results of two interesting melanoma vaccine strategies were presented: AGI-101H and talimogene laherparepvec (T-VEC). AGI-101H consists of two human melanoma cell lines modified with molecular adjuvant Hyper-IL-6 (H6) cDNA. Secreted H6 at the site of vaccine injection provides co-stimulatory signals to the immune system by inhibiting T regulatory (FoxP3 +) cells formation, activation of maturation and presentation of cryptic antigens by dendritic cells, activation of T CD8+ and NK cells. Moreover, H6 during the manufacturing culture stimulates vaccine cells via binding gp130 subunit of IL-6-type cytokines receptor complex. It leads to activation of JAK-kinase and chronic phosphorylation of STAT3 and results in altering vaccine cells towards melanoma stem cells (MSCs)-like

phenotype. Up to 92% of AGI-101H cells have ALDH activity – a MSCs marker and loose differentiation antigen SSEA-1. Non-selected 77 and 35 patients with unresectable stage IIIB, IIIC or IV melanoma were enrolled into trial 2 and 4, respectively. Median length of follow-up in trial 2 and 4 was equal to 139.3 and 94.9 months, respectively. Among the 112 enrolled patients, 6.3% had IIIB, 22.3% – IIIC and 22% – IV-M1a, 5% – IV-M1b and 43% – IV-M1c. CR and PR was observed in 18.7% and 8.9% of patients, respectively. Disease control rate (CR, PR, or SD – stable disease) was noted in 52.6% of patients. The observed median OS was equal to 17.3 and 10.5 months in trial 2 and 4, respectively. Patients with WHO 0-1 performance status presented 20,3 and 53,8 months median OS observed in trial 2 and 4, respectively. No grade 3/4 adverse events were observed [38]. Talimogene laherparepvec (T-VEC) is a oncolytic vaccine derived from herpes simplex virus type-1 producing GM-CSF. T-VEC was evaluated in a phase III study in patients with metastatic melanoma. Enrolled patients received T-VEC intralesionally or GM-CSF subcutaneously. Among 436 patients, 8% had IIIB, 22% – IIIC, 27% – IV-M1a, 21% – IV-M1b and 22% presented stage IV-M1c. Objective response was higher in patients treated with T-VEC – 26.4% vs. 5.7%. Patients receiving T-VEC developed longer median overall survival (23.3 vs. 19 months), however the difference was not statistically significant ($p$ = 0.07). T-VEC was well tolerated, grade 3/4 AEs occurred in 2.1% of patients [39].

### *Combined treatment*

Results from preclinical studies and early clinical trials indicate a high potential for combining immunotherapy with other treatment modalities [40].

A peptide vaccine (gp100) combined with IL-2 was evaluated in a phase III study in patients with unresectable stage III or IV cutaneous melanoma. The study included 185 HLA*A0201-positive patients. The study group treated with gp100 plus IL-2 presented a higher response rate (16% vs. 6%; $p$ = 0.03) comparing to patients receiving IL-2 alone. Also median PFS was longer in patients in the study group – 2.2 vs. 1.6 months; $p$ = 0.008. Patients receiving vaccine with IL-2 developed longer median OS (17.8 vs. 11.1 months) however, the difference between the two groups was of borderline statistical significance ($p$ = 0.06) [41]. Recently, results of a phase I study evaluating combined nivolumab and ipilimumab in patients with advanced melanoma were presented. Fifty-three and 33 patients received nivolumab concurrently with ipilimumab and sequential nivolumab and ipilimumab, respectively. The objective response rate (ORR) in patients treated in the concurrent cohorts was 40%, however grade 3-4 toxicity occurred in 54% of patients. The most frequently observed AE was lipase, ALT, AST elevation. ORR in the group receiving sequential nivolumab and ipilimumab was 20%, while grade 3 and 4 toxicity was observed in 18% of patients. Lipase elevation was the most frequently observed AE. Currently, a phase 3 study is open to investigate the efficacy of concurrent nivolumab plus ipilimumab vs. ipilimumab vs. nivolumab in patients with advanced melanoma (NCT01844505) [42]. Nivolumab was also administered with a multipeptide vaccine (MART-1/gp100/NY-ESO-1 peptides with Montanide ISA51 adjuvant) in advanced melanoma patients participating in a phase I trial. In all study cohorts patients responded to the treatment (1/3/10 mg/kg – 2PR/5PR/2PR and 1 SD) [43]. Another interesting drug combination was tested in a phase I study evaluating concurrent ipilimumab and vemurafenib (BRAF inhibitor) in patients with advanced *BRAF*-mutant melanoma. The trial stopped accruing patients due to hepatotoxicity (elevated aminotransferase levels). These unexpected AEs limit the use of ipilimumab and vemurafenib concurrently and further investigation should focus on the optimal sequencing of these agents [44].

Currently combined strategies including anti-CTLA-4, anti-PD-1, anti-PD-1L, vaccines, cytokines, kinase inhibitors or cytotoxic drugs are under investigation in early phase trials in patients with metastatic melanoma [45-50].

## Future directions

In recent years a very significant progress has been made in the treatment of advanced melanoma patients. In light of recently approved drugs, further studies to understand the most beneficial treatment option and schedule for patients with metastatic melanoma are warranted. The ongoing clinical studies should further improve our understanding how to use immunomodulatory and immunostimulatory agents for optimization of melanoma treatment. Moreover, further personalization of the treatment is needed what requires identification of novel predictive and prognostic markers. Recent studies demonstrate that combinational therapy offers a very durable, high response rate in advanced melanoma patients, however these strategies need confirmation in randomised phase III studies.

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