VIA MEDICA

REVIEW ARTICLE

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Nivolumab — perspectives in cancer treatment

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ABSTRACT

Blockade of the immune checkpoint PD-1 is a new and promising strategy for the treatment of advanced cancers. The introduction of nivolumab has improved prognosis in a large group of cancer patients. Currently, it is possible to obtain results of treatment that have not previously been observed in cancer immunotherapy. It seems that nivolumab has less treatment toxicity than many conventional chemo-therapeutics or ipilimumab. Nivolumab is currently registered in oncology patients with advanced melanoma, kidney cancer, and non-small cell lung cancer. In the near future the scope of registration of the drug will probably expand to other indications in malignant tumours. More details on the activity of the drug used in a variety of schemes and various types of cancer, as well as predictive factors of therapy, will be available after the announcement of further results of ongoing numerous clinical studies using nivolumab.

Key words: immunotherapy, PD-1 inhibitor, drug combinations, toxicity of immunotherapy

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Introduction

Recent years have proven to be a breakthrough for the development of cancer immunotherapy, which resulted in the registration of a range of particles for oncological treatment. One of them is nivolumab, a fully humanised monoclonal antibody that specifically binds to the receptor of programmed cell death (PD-1, programmed cell death protein-1) and blocks its function [1]. Receptor of programmed cell death is a checkpoint receptor that prevents excessive stimulation of the immune response and contributes to the maintenance of immune tolerance to self-antigens. The main ligands of PD-1 are PD-L1 and PD-L2, expression of which is present on cells of the immune system, and can also be induced in many other tissues in response to antigen recognition. Activation of lymphocytes T results in PD-1 expression on their surface and production of interferons, which in turn stimulates the formation of PD-L1 on the cell surface of various tissues, including cancer. When PD1 receptors on T cells bind with PD-L1 or PD-L2, lymphocytes receive signals of inhibition and do not start an efficient immune response [2, 3]. Continuous activation of PD-1 receptors on the surface of T cells is specific for the cells exhausting their effector functions. Such phenotype of the cells with a reduced activity was observed in tumour-infiltrating lymphocytes (TIL) in a number of malignancies. This phenomenon is associated with a worse prognosis and an increased risk of relapse. Tzhe strong evidence from preclinical research on the role of PD-1/PD-L1 pathway in tumour immunology, clinical studies on particles blocking its function have been initiated.

The first phase I study with nivolumab included 39 patients with advanced melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and prostate and colorectal cancer. No dose-limiting toxicity was identified and the maximum tolerated dose was not defined. In addition, antitumor activity of the drug was demonstrated. One durable, complete response to therapy (kidney cancer) was reported, and two partial responses (RCC and melanoma). Moreover, two patients (diagnosed with melanoma and NSCLC) had a significant regression of tumour size, which did not

meet the criteria for partial response to treatment [6]. In view of these promising results, a larger phase I study was initiated with a similar treatment scheme.

Another phase I study, this time very large, was carried out. It enrolled 296 patients with kidney cancer, lung cancer, and melanoma. The majority of study participants showed progression after previous, often multiple lines of systemic therapy (in 47% of patients at least three lines of treatment were previously used). Toxicity of therapy in grade 3 or 4 according to the Common Terminology Criteria for Adverse Events (CTCAE) occurred in 14% of patients, and three people died because of pulmonary toxicity. The maximum tolerated dose has not been determined. Objective response (complete or partial) was observed in patients diagnosed with melanoma, NSCLC, and RCC. In total, responses were found in 18% of patients diagnosed with NSCLC (14/76 patients), in 28% of melanoma patients (26/94 patients), and in 27% diagnosed with RCC (9/33). The duration of responses was long — in 20 patients lasted more than a year [7].

The results of these studies initiated a series of research protocols for the evaluation of the efficacy and safety of nivolumab in patients with melanoma, RCC, and NSCLC, and resulted in subsequent registrations of the drug. This paper presents the results of the most important of them. It also outlines future directions of exploration of data on the drug.

Renal cell cancer

Monotherapy

The first phase I study dedicated to patients with a diagnosis of RCC enrolled 34 patients with dissemination of the disease. As usual in studies of this phase, participants were patients who had failed multiple prior lines of therapy, with 44% previously exposed to three or more systemic therapies (74% of patients were treated previously with antiangiogenic drugs, and 59% had immunotherapy). Patients were randomised into two groups receiving doses of 1 mg or 10 mg/kg b.w. intravenously in cycles of two weeks. Treatment could take up to two years. A total of 29% of patients responded to treatment, and the median duration of response was 12.9 months. Of the five patients with confirmed response, who discontinued treatment, three patients had benefits that lasted more than 45 weeks. In addition, nine patients (27%) had long-term (> 24 weeks) stable disease. The median overall survival (OS) was 22 months, which was a big achievement, considering the fact that they were patients after failure of prior lines of systemic therapy. 71% of patients lived a year, and 44% survived for 3 years after starting treatment. Toxicity grade 3 or 4 was found in 18% of patients, but in all it was reversible [8].

Another study — phase II — included 168 patients with a diagnosis of metastatic clear-cell kidney cancer. Most patients (70%) received prior systemic therapy, and 33% previously used three or more lines of treatment. Unfavourable prognosis by the Memorial Sloan Kettering Cancer Centre (MSKCC) score was found in 25% of patients. Patients were randomised in the ratio 1:1:1 into one of three groups receiving one of three doses of nivolumab 0.3 mg, 2 mg, or 10 mg/kg b.w. every 3 weeks. The primary endpoint was progression-free survival (PFS), and secondary endpoints were objective response to treatment (ORR), OS, and safety. The median PFS was 2.7 months in the dose of 0.3 mg/kg b.w., 4 months for 2 mg/kg b.w., and 5.5 months for a dose of 10 mg/kg b.w.; differences showed no statistical significance ($p = 0.9$). Rates of ORR were very similar in all groups and amounted about 20%. Response to treatment was observed after approximately three months of therapy. The median duration of response was the longest in the group treated with 10 mg/kg b.w. only (22.3 months). Benefits in terms of OS were significantly higher than one would predict based on achieved PFS, which may be associated with the mechanism of action of the drug boosting the immune system. Median OS was 18.2 months for the dose of 0.3 mg/kg b.w., 25.5 months for the dose of 2 mg/kg b.w., and 24.7 months for the 10 mg/kg b.w. Hazard ratio (HR) for death in the group receiving 2 mg/kg b.w. and 10 mg/kg b.w. compared with the group treated with 0.3 mg/kg b.w. was, respectively, 0.8 [80% confidence interval (CI) 0.6–1.1] and 0.9 (80% CI 0.6–1.2).

Nineteen patients experienced side effects of treatment in grade 3 or 4, fatigue being the most common (22–35%) [9]. The results of this study and the previously cited phase I study [7] became the basis for commencement of a phase III study with a definitively fixed dose of the drug at 3 mg/kg b.w. every 2 weeks.

The phase III study (CheckMate 025) was a large multicentre randomised clinical study, which enrolled 821 patients with a diagnosis of clear-cell kidney cancer after failure of no more than two lines of prior therapy with anti-angiogenic drugs. Patients were randomly allocated (ratio 1:1) to receive nivolumab at a dose of 3 mg/kg b.w. administered intravenously every 2 weeks or for the group receiving oral inhibitor of the mTOR pathway — everolimus 10 mg once daily. The primary endpoint was OS. Median OS in the group treated with nivolumab was 25 months (95% CI 21.8–not attained), and for those receiving everolimus it was 19.6 months (95% CI 17.6–23.1). Relative risk reduction for death in the group receiving nivolumab relative to patients treated with everolimus amounted to 27% (98.5% CI 0.57–0.93; $p = 0.002$). Benefit in OS was observed in all groups of patients, regardless of the number of prior

treatments or points obtained by patients according to MSKCC prognostic scale. The percentage of ORR was also higher among patients receiving nivolumab than in those receiving everolimus (25% *vs.* 5%, $p < 0.001$). Partial response (PR) was observed in 24% of patients in the group receiving nivolumab and in 5% of patients treated with everolimus. Complete remission (CR) was observed in 4 patients treated with nivolumab and in 2 — with everolimus. The median time to response in case of nivolumab was 3.5 months (range 1.4–24.8 months) and 3.7 months (range 1.5–11.2 months) for everolimus. The median duration of response was similar for both agents (up to 1 year). The median PFS for both drugs was similar: 4.6 months for nivolumab and 4.4 for everolimus (95% CI 0.75–1.03; $p = 0.11$).

Any side effects associated with treatment occurred in 79% of subjects receiving nivolumab and 88% receiving everolimus. The most common nivolumab adverse events were fatigue (33%), nausea (14%) and pruritus (14%) and for everolimus they were fatigue (34%), stomatitis (29%), and anaemia (24%). Adverse events grade 3 or 4 occurred in 19% receiving nivolumab and the most common was fatigue; among 34% of patients receiving everolimus the most common serious toxicity was anaemia (Tab. 1) [10].

The results of the study were corroborated with the presentation at the American Society of Clinical Oncology (ASCO) Genitourinary Cancer Symposium in 2016 of new data on overall survival in individual subgroups of patients. Thus, in the case of patients previously treated with sunitinib, who were the majority in the study (63%), median OS in patients receiving nivolumab was 23.6 months, and in those treated with everolimus it was 19.8 months (HR 0.81; 95% CI 0.64–1.04). In patients previously treated with pazopanib the median OS among patients receiving nivolumab has not been reached, while in those treated with everolimus it was 17.6 months (HR 0.6; 95% CI 0.42–0.84). It was also shown that, although the benefit in terms of OS was seen in patients from all prognostic groups according to MSKCC, in the group of patients with the worst prognosis the difference in median OS was, in those treated with nivolumab, almost two-fold higher than in those receiving everolimus, amounting to 15.3 *vs.* 7.9 months (HR 0.48; 95% CI 0.32–0.7) [11].

The results of this study became the basis of registration of nivolumab by the United States Agency for Food and Drug Administration (FDA) in November 2015 for use in patients with advanced RCC after failure of prior anti-angiogenic therapy [12].

Drug combinations

The results of studies on the use of nivolumab in drug combination in patients diagnosed with advanced RCC are also interesting. For now, data are available from small phase I studies.

First study used nivolumab in combination with standard tyrosine kinase inhibitors (sunitinib and pazopanib). The study enrolled patients after failure of at least one line of systemic therapy. Patients received nivolumab at dose of 2 mg/kg b.w. (the dose was increased to 5 mg/kg b.w. every 3 weeks — the maximum dose) in combination with sunitinib and pazopanib dosed in a standard fashion. Finally, 33 patients received nivolumab and sunitinib in this arm. The maximum tolerated dose of combination has not been determined. Twenty patients received nivolumab with pazopanib, and the arm has been closed due to the occurrence of dose-limiting hepatotoxicity and fatigue (with nivolumab administered at a dose of 2 mg/kg b.w.). Generally, the toxicity of the drug combination proved to be quite high — side effects of grade 3 or 4 occurred in 73% of patients in the sunitinib arm and 60% in the pazopanib arm. Among patients treated with sunitinib most common severe toxicities was an increase in transaminases (18%), hypertension and hyponatremia (15%). Among those treated with the combination with pazopanib an increase in transaminases (20%) and fatigue (15%) were observed. Grade 3 or 4 led to the treatment discontinuation in approximately 20% of patients in each arm. Response rates were quite high and amounted to 52% for combination of nivolumab with sunitinib and 45% for combination of nivolumab with pazopanib. An objective response to treatment generally occurred at the first assessment and were long lasting. Stable disease (SD) was found in both arms in about 30% of patients. Progression-free survival after 6 months of treatment was 78% for patients treated with nivolumab in combination with sunitinib and 55% for those receiving nivolumab and pazopanib [13].

In another study, nivolumab was administered in combination with ipilimumab (ipilimumab monotherapy showed some activity in patients with advanced RCC [14]). Patients were included in three groups. In group 1 ipilimumab was administered at 3 mg/kg b.w. every 3 weeks in combination with nivolumab 1 mg/kg b.w. Four administrations of the combination were employed followed by nivolumab alone was continued every 2 weeks at 3 mg/kg b.w. until PD or unacceptable toxicity. In group 2, ipilimumab was administered at a dose of 1 mg/kg b.w. every 3 weeks in combination with nivolumab at a dose of 3 mg/kg b.w. Both drugs were given in combination 4 times, and then administration of nivolumab was continued at the same dose as monotherapy until PD or unacceptable toxicity was detected. The third arm of the study, in which both drugs were dosed at 3 mg/kg b.w., was closed after including 6 patients due to significant toxicity. Each of the remaining groups included 47 patients. In both groups patients treated with first-line accounted for about half. The side

Table 1. Summary of treatment toxicity of nivolumab reported in phase III trials

	RCC [10]		NSCLC-squamous [25]		NSCLC-not squamous [26]		Melanoma [37]			
							Monotherapy		Plus ipilimumab	
	All (%)	Grade 3 or 4 (%)	All (%)	Grade 3 or 4 (%)	All (%)	Grade 3 or 4 (%)	All (%)	Grade 3 or 4 (%)	All (%)	Grade 3 or 4 (%)
All	79	19	58	7	69	10	82.1	16.3	95.5	55
Diarrhoea	12	1	8	0	16	1	19.2	2.2	44.1	9.3
Fatigue	33	2	16	1	32	3	34.2	1.3	35.1	4.2
Itching	14	0	4	0	11	0	18.8	0	33.2	1.9
Skin rash	10	< 1	4	0	13	< 1	25.9	0.6	40.3	4.8
Nausea	14	< 1	9	0	22	2	13.1	0	25.9	2.2
Fever	UNK	UNK	5	0	12	< 1	5.8	0	18.5	0.6
Decreased appetite	12	< 1	11	1	29	2	10.9	0	17.9	1.3
Increase in ALT	UNK	UNK	2	2	6	< 1	3.8	1.3	17.6	8.3
Vomiting	UNK	UNK	3	0	13	< 1	6.4	0.3	15.3	2.6
Increase in AST	UNK	UNK	2	2	UNK	UNK	3.8	1	15.3	6.1
Hypothyroidism	UNK	UNK	1	0	7	0	8.6	0	15	0.3
Colitis	UNK	UNK	1	1	UNK	UNK	1.3	0.6	11.8	7.7
Arthralgia	UNK	UNK	5	0	16	1	7.7	0	10.5	0.3
Headaches	UNK	UNK	UNK	UNK	10	1	7.3	0	10.2	0.3
Dyspnoea	7	1	UNK	UNK	23	5	4.5	0.3	10.2	0.6
Pneumonia	4	1	5	0	6	3	UNK	UNK	10.6	2.1
Adverse events leading to discontinuation of treatment	8	UNK	3	UNK	5	UNK	7.7	5.1	36.4	29.4

RCC — renal cell carcinoma; NSCLC — non-small cell lung cancer; ALT — alanine aminotransferase; AST — aspartate aminotransferase; UNK — no data

effects associated with treatment were seen in 88% of patients. Treatment was discontinued due to toxicity in 16% of patients. In group 1 toxicity grade 3 or 4 was observed in 64% of patients, and in group 2 — in 34% of patients. The most common severe side effects were gastrointestinal tract and liver toxic reactions. The OR to treatment was quite high: in group 1 it was 43% and in group 2 — 38%; the percentage of SD in both groups was about 40%; PFS at 6 months in group 1 was 64% in group 2 — 53% [15].

In summary, nivolumab is an effective drug in the treatment of patients with kidney cancer and already has a solid role in the management of patients wirh RCC. The effectiveness of nivolumab in patients diagnosed with RCC is currently under research, both when used in advanced disease as first-line therapy or in drug combinations, and in patients with high risk of relapse following local treatment of the disease [16, 17]. There are also descriptions of cases proving the high effectiveness of the therapy in patients diagnosed with kidney cancer of less frequent subtypes without a clear cell component (such as papillary RCC). Such patients were not enrolled in the large clinical trials cited above [18].

Non-small cell lung cancer

Results of clinical studies on the efficacy and safety of the immune checkpoint inhibitors of CTLA-4 in patients diagnosed with advanced NSCLC are available. Use of both ipilimumab and tremelimumab failed to reach statistically significant survival improvement. Further studies are underway [19]. By contrast, the expression of PD-L1 is widespread in NSCLC cells — it was found in approximately 50% of both the subtype squamous and adenocarcinoma. Such expression may be associated with a worse prognosis [20]. The results of many studies have been published, including large phase III trials, on PD-1 inhibitors in patients with NSCLC. They successfully demonstrated prolonged overall survival in this poor-prognosis patients which has resulted in registrations of pembrolizumab and nivolumab [21, 22].

Monotherapy

The first data on the effectiveness of nivolumab were noted in large phase I study. The study involved 129 patients diagnosed with NSCLC after failure of prior lines of systemic therapy. The drug was administered at a dose of 1.3 and 10 mg/kg b.w. in 2-week cycles up to 2 years. The median OS for all patients in this group was 9.9 months. Rates of 1-, 2-, and 3-year survival among all patients were, respectively, 42%, 24%, and 18%, and in receiving the dose of 3 mg/kg b.w. (finally selected for subsequent study), these percentages were, respectively, 56%, 42%, and 27%. Median OS at this dose of the drug was 14.9 months (95% CI 7.3–30.3). The median PFS for all patients was 2.3 months (95% CI 1.8–3.7), while ORR was 17%. Among the patients with noted response to treatment, the median duration of response was 17 months. In addition, 10% of patients showed disease stabilisation lasting more than half a year. The response was similar in patients with both subtypes: squamous and non-squamous cell lung cancer. In half of the patients who discontinued treatment for reasons other than PD the 9 months' duration of response was found. Interestingly, a retrospective analysis was carried out in the proportion of participants who showed a higher response rate among patients with a history of smoking (at least 5 pack-years) (30% *vs.* 0%). Toxicity of grade 3 or 4 occurred in 14% of patients. Three patients (2%) died due to treatment-induced pulmonary inflammation [23].

In the next (CheckMate 063), single-arm phase II study 117 NSCLC patients participated from 27 centres. It included patients with advanced squamous cell lung cancer after failure of at least two prior lines of systemic therapy (65% of patients had previously been given three or more lines of therapy). Nivolumab was administered at 3 mg/kg b.w. every 2 weeks, and the treatment was continued until disease progression or unacceptable toxicity. The objective response to treatment was 14.5% (95% CI 8.7–22.2), median time to treatment response was 3.3 months, and median duration of response has not been reached. In addition, 26% patients had SD with a median duration of half a year. The median PFS was 1.9 months; after 6 months 25.9% of patients had no disease progression, and after a year — 20%. Median OS was 8.2 months; after a year 40.8% of patients were still alive. Almost 3/4 of those treated reported the occurrence of toxicity of treatment, which mostly included fatigue, poor appetite, and nausea. Adverse reactions to the treatment of grade 3 or 4 were seen in 17% of patients (including fatigue, pneumonia, and diarrhoea) [24].

The results of these studies have justified the initiation of phase III randomised trials. The results of these studies were published in 2015 in the "New England Journal of Medicine". Both trials demonstrated prolongation of OS in patients with NSCLC treated with nivolumab when compared to docetaxel (standard second-line treatment).

The first study (CheckMate 017) was addressed to patients diagnosed with squamous-cell carcinoma after failure of one line of systemic therapy (Polish patients participated in the study). In total 272 patients were treated. Participants were randomised into one of two arms. In the first arm nivolumab was administered at a dose of 3 mg/kg b.w. every 2 weeks, and in the second — docetaxel 75 mg/m^2 body surface every 21 days. Treatment

was continued until disease progression or unacceptable toxicity. All patients had previously been treated with platinum-based chemotherapy; 34% of patients previously also received paclitaxel. The primary endpoint was OS. Median OS for patients receiving nivolumab was 9.2 months (95% CI 7.3–13.3) *vs.* 6 months for those treated with docetaxel (95% CI 5.1–7.3). The risk of death in the group receiving nivolumab was 41% lower when compared to the docetaxel group (HR 0.59, 95% CI 0.44–0.79; $p < 0.001$). After a year 42% of patients in the arm with nivolumab were still alive and 24% in the docetaxel arm. The benefit in terms of OS was observed across all prognostic groups, except for patients over the age of 75 years. The objective response rate to treatment was 20% for patients receiving nivolumab and 9% in patients treated with chemotherapy ($p = 0.008$). Median time to response to treatment in both arms was about 2 months, and the median duration of response to treatment was 8.4 months in the docetaxel arm, but this has not been achieved in the group receiving nivolumab. In addition, in both arms approximately 30% of patients achieved SD. Significantly better among patients receiving nivolumab was also PFS, which was among them was 3.5 months compared with 2.8 months in docetaxel-treated ($p < 0.001$). In the arm with nivolumab side effects of any degree were observed in 58% of patients, and 7% reported toxicity of grade 3 or 4 (Tab. 1). The toxicity of chemotherapy was higher — 55% of patients experienced adverse events grade 3 or 4 (predominantly haematological toxicity) [25].

The design of subsequent trial (CheckMate 057) was quite similar. It included 582 patients diagnosed with NSCLC of weaving other than squamous cell. Patients were randomised in a 1:1 ratio into arms with nivolumab or docetaxel. The treatment regimen and dosing were described in the previous study. In both arms, almost 90% of patients received only one prior line of systemic therapy. Overall survival was significantly better among patients receiving immunotherapy. Median OS was 12.2 months for patients receiving nivolumab (95% CI 9.7–15) and 9.4 months in patients treated with docetaxel (95% CI 8.1–10.7). Relative risk reduction of death reached 27% ($p = 0.002$). After a year 51% of patients receiving nivolumab were still alive, and 39% of those treated with docetaxel; after 18 months the rates were 39% and 23%. Hazard ratio in the analysis of OS pointed to the advantage of nivolumab across all groups of patients apart from a small group treated in the third line, patients with the presence of central nervous system metastases, those never smoking tobacco, and those who had had mutations in the receptor for epidermal growth factor (EGFR). The objective response to treatment among those treated with nivolumab was 19%, and in docetaxel — 12% ($p = 0.02$). The median duration of response was 17.2 months in the patients treated with immunotherapy and 5.6 months in patients receiving chemotherapy. Although the median PFS for patients treated with nivolumab was shorter than that achieved in patients treated with docetaxel (2.3 months *vs.* 4.2 months), after a year more patients were free from progression in the arm with immunotherapy than with docetaxel (19% *vs.* 8%). Significantly better prognosis among those treated with nivolumab was observed in the group of patients with tumours that expressed PD-L1 (see below). The side effects of treatment in grade 3 or 4 were again more frequently reported in patients receiving chemotherapy (54%) than immunotherapy (10%) (Tab. 1) [26].

At the ASCO congress in 2015 the results of a phase I study in which nivolumab was used as first-line treatment in NSCLC patients were presented — the results of this study were promising with a median survival of up to approximately 2 years [27].

Drug combinations

There are interesting results available from two phase I studies on the use of nivolumab in combination with drugs commonly used in the treatment of advanced NSCLC.

The first study included 21 patients previously untreated with chemotherapy or after progression (one patient) with prior treatment with EGFR tyrosine kinase inhibitors (erlotinib). Patients received nivolumab at a dose of 3 mg/kg b.w. in combination with erlotinib at 150 mg/day. The side effects associated with treatment occurred in all patients participating in the study. In four patients grade 3 or 4 toxicity was observed — increase in the level of liver transaminases in blood serum, weight loss, and diarrhoea. The objective response rate to treatment was 19%, and 45% of patients had SD. PFS at six months was 47%. After a year 73% of patients were still alive [28].

In the next study participated 56 patients. The treatment was administered in the first line. Patients were randomized to four arms, each of them received nivolumab at a dose of 10 mg/kg b.w. and a platinum derivative with gemcitabine, pemetrexed, or paclitaxel. Chemotherapy was administered for 4 cycles, and nivolumab was administered to the occurrence of PD or unacceptable toxicity. Grade 3 or 4 side effects of treatment occurred in 45% of patients (least — 23% — in arm with gemcitabine and cisplatin, the most — 73% — in arm with paclitaxel and carboplatin). The most commonly reported toxicities were fatigue, nausea, and loss of appetite. The objective response to treatment ranged from 33% in the arm with gemcitabine and cisplatin to 47% in combination with pemetrexed and paclitaxel. The 1-year OS was 50% in the gemcitabine arm and 87% in the pemetrexed arm [29].

Melanoma

Metastatic melanoma is the only malignant disease for which ipilimumab — the older generation checkpoint inhibitor (anti-CTLA-4) — induced prolongation of OS, both alone and in combination with chemotherapy [30, 31]. The widespread use of this drug helped to increase knowledge among physicians about immunotherapy, as well as the specific toxicity of treatment and the ways to deal with it. Currently, patients diagnosed with melanoma are a very important group of participants in studies on inhibitors of control points of the new generation, such as pembrolizumab or nivolumab, which resulted in further drug registrations for this indication.

Monotherapy

The most important large study evaluating the efficacy of nivolumab in monotherapy in patients with locally advanced unresectable or metastatic melanoma was the CheckMate 066 study, which included also patients treated in Polish centres. The study enrolled 418 patients previously untreated, without *BRAF* mutation. The study was blinded and subjects were randomly assigned to an arm with nivolumab administered at a dose of 3 mg/kg b.w. every 2 weeks and placebo or to an arm with dacarbazine at a dose of 1000 mg/m^2 body surface, and placebo. Treatment continued until disease progression or unacceptable toxicity. The primary endpoint was OS. After a year of receiving nivolumab 72.9% of patients were still alive (95% CI 65.5–78.9), while among patients receiving dacarbazine — 42.1% (95% CI 33–50.9); the relative reduction in the risk of death was 58% ($p < 0.001$). The benefit in terms of OS was achieved in all patients treated with nivolumab, regardless of affiliation to different prognostic subgroups. The median PFS was 5.1 months for nivolumab and 2.2 months for dacarbazine (HR 0.43; 95% CI 0.34–0.56; $p < 0.001$). The percentage of ORR was 40% for those treated with immunotherapy and 13.9% for chemotherapy. Common side effects among patients treated with nivolumab were fatigue, pruritus, and nausea. Grade 3 or 4 toxicity occurred in 11.7% of patients in the arm with nivolumab, and in 17.6% of the patients in the dacarbazine arm. The majority of grade 3 or 4 adverse events disappeared shortly after the discontinuation of therapy and with the use of corticosteroids. After obtaining these results the study was unblinded and patients treated with dacarbazine were able to receive nivolumab after progression. After progression, further treatment was given to 40% of patients from the arm with nivolumab and 64% of patients treated with dacarbazine [32].

Also, the results of the next multi-centre study are interesting — a randomised, un-blinded, phase III study (CheckMate 037) tested nivolumab monotherapy. The study included patients who had failed previous treatment with ipilimumab, and — in the case of BRAF mutation — after progression during BRAF inhibitor. Patients were randomised 2:1 to an arm receiving nivolumab at a dose of 3 mg/kg b.w. every 2 weeks or (at the discretion of the treating physician) dacarbazine or paclitaxel with carboplatin in due doses. Treatment continued until disease progression or unacceptable toxicity. The groups were well balanced in terms of patient characteristics, with the exception of the starting elevated levels of lactate dehydrogenase and the presence of metastases to the central nervous system — there were more patients with these poor prognostic factors in the arm treated with nivolumab. Half of the patients in the study previously received at least two lines of systemic therapy. The study enrolled 405 patients. The ORR rate was 31.7% (95% CI 23.5–40.8) for nivolumab and 10.6% for those treated with chemotherapy (95% CI 3.5–23.1). Median duration of nivolumab treatment was 5.3 months in comparison with two months of chemotherapy. In the chemotherapy arm 82% of patients ended treatment (mostly due to PD), while in the arm with nivolumab it was 52%. The proportion of patients without disease progression after half year was 48% for those treated with nivolumab and 34% for those treated with chemotherapy. Data on the OS in this study are not yet available. Serious toxicity of treatment in grade 3 or 4 occurred in 5% of patients in the arm with nivolumab and in 9% in the arm with chemotherapy. The toxicity of therapy was the cause of the interruption in 3% of patients with nivolumab and 7% with chemotherapy. There is no correlation between the toxicity of nivolumab and earlier onset of adverse effects of ipilimumab [33].

A retrospective analysis of the treatment with nivolumab in patients from four clinical trials evaluated the results in two groups of patients with different status of *BRAF* mutations in melanoma cells. Nivolumab in the majority of patients (83%) was administered at a dose of 3 mg/kg b.w. every 2 weeks. The results in both groups were similar. Of the 440 analysed patients, 106 had detected *BRAF* mutations, whereas in 334 this mutation was not shown. The ORR rate was 34.6% (95% CI 28.3–41.3) for patients without the mutation and 29.7% (95% CI 19.7–41.5) in patients with *BRAF* mutations receiving nivolumab. Previous treatment with BRAF inhibitors or ipilimumab did not affect ORR in a statistically significant way, as well as the status of PD-L1 in tumour (see below). The median duration of response to treatment with nivolumab was 14.8 months for patients without the *BRAF* mutation and 11.2 months for patients with the *BRAF* mutation. The percentage of side effects in both groups were also similar. The data from this analysis suggest that the nivolumab is effective regardless of the status of *BRAF* mutation. Importantly,

in patients with mutated *BRAF*, whether or not a patient has previously been treated with BRAF inhibitors has no effect on activity of therapy [34].

Drug combinations

In 2013, the results of a fairly large phase I study were published, in which patients diagnosed with advanced melanoma received concomitant nivolumab in combination with ipilimumab. The effectiveness has proven to be very good, also in the case of patients with highly advanced cancer, who usually are not considered as good candidates for treatment with ipilimumab. The risk of side effects is high for this combination [35]. The study results justified the initiation of two other large, randomised trials.

The first study enrolled 142 previously untreated patients. The majority of patients (77%) had *BRAF* mutation. The study was double-blind. Patients were randomised in a 2:1 ratio into two arms. Patients received ipilimumab at a dose 3 mg/kg b.w. — 4 cycles every 21 days and nivolumab 1 mg/kg b.w. every 21 days or placebo. Then, in the maintenance phase, patients continued to receive nivolumab at a dose of 3 mg/kg b.w. or placebo every 2 weeks. Treatment was maintained until disease progression or unacceptable toxicity. The primary endpoint was ORR. In patients without the *BRAF* mutation ORR was 61% in the arm treated with the combination of drugs as compared to 11% in the same ipilimumab ($p < 0.001$). A complete response was observed in 22% of patients receiving two drugs and none in the arm with ipilimumab alone. Response to treatment achieved on immunotherapy is long, and the median duration of response has not been reached in any of the arms. The median PFS for patients taking a combination of drugs has not been reached, and in patients undergoing monotherapy it was 4.4 months ($p < 0.001$). Similar results were obtained in patients with confirmed mutated *BRAF* in melanoma cells. Benefits in terms of ORR were found in all patients treated with the combination drug, regardless of current prognostic factors, as well as among patients in disease stage M1c and elevated lactate dehydrogenase. Toxicity of patients in the study was quite high, especially in the group treated with two drugs. In the group receiving the combination of drugs 59% of the patients received at least 4 nivolumab doses, and 57% at least four doses of ipilimumab. In the ipilimumab arm 70% of patients received the full treatment cycle. The incidence of grade 3 or 4 adverse events was 54% among those treated with two drugs and 24% in the monotherapy arm. Considerably more adverse events occurred at the time when the two drugs were administered than in the maintenance phase of treatment with nivolumab alone. The most common serious side effects in the group receiving the combination of drugs were colitis (17%), diarrhoea (11%), and elevated serum alanine aminotransferase (11%); among patients receiving ipilimumab alone it was diarrhoea (11%). Most of these side effects subsided under the influence of immunomodulatory therapy [36].

Another phase III trial (CheckMate 067) was very large for this disease entity. A total of 945 previously untreated patients were systemically enrolled. In this double-blind, placebo-controlled trial were included, including Polish patients. The subjects were enrolled in a ratio 1:1:1 into three arms: nivolumab plus ipilimumab, nivolumab plus placebo, and ipilimumab plus placebo. The median PFS was 6.9 months (95% CI 4.3–9.5) in patients with nivolumab alone, 11.5 months (95% CI 8.9–16.7) in the nivolumab plus ipilimumab arm, and 2.9 months (95% CI 2.8–3.4) in the group with only ipilimumab. Significantly longer PFS was observed in the group receiving the combination of drugs than in the group receiving ipilimumab alone (HR of progression 0.42; 99.5% CI 0.31–0.57; $p < 0.001$), and in the group using nivolumab alone than in the group receiving ipilimumab (HR 0.57; 95% CI 0.43–0.76; $p < 0.001$). Longer PFS was also observed in patients treated with the combination of ipilimumab and nivolumab than in patients receiving nivolumab alone (HR 0.74; 95% CI 0.60–0.92). Objective responses were seen in 43.7% (95% CI 38.1–49.3) of patients in the group with nivolumab alone, 57.6% (95% CI 52.0–63.2) in the group with nivolumab in combination with ipilimumab, and 19.0% (95% CI 14.9–23.8) in the group with only ipilimumab. The percentage of patients who had a complete response was higher in the group receiving ipilimumab plus nivolumab (11.5%) than in the group of patients receiving nivolumab (8.9%) or ipilimumab alone (2.2%). The times to achieve an objective response to treatment were similar in all three groups, and the median duration of response to treatment was not achieved in any of the arms. The results of median OS in this study are still not published. Again, drug combination was the most toxic. Adverse events related to treatment occurred in 82.1% of patients in the arm with only nivolumab, with 95.5% of people in the group receiving ipilimumab and nivolumab and in 86.2% of patients in the group using only ipilimumab. The most common adverse events in the group receiving the combination drug were diarrhoea (44.1%), fatigue (35.1%), and pruritus (33.2%). The incidence of adverse events grade 3 or 4 was also higher in the group receiving the two drugs (55.0%) than in the arm with nivolumab (16.3%) and ipilimumab (27.3%). Adverse events of any grade that led to the study drug discontinuation occurred in 7.7% of patients in arm with nivolumab, up to 36.4% treated with the combination, and in 14.8% of people in the group using ipilimumab. The most common such toxicities were diarrhoea and colitis (Tab. 1) [37].

Table 2. Results of treatment with nivolumab in patients with advanced melanoma

	Nivolumab in doses 0.1–10 mg/kg b.w. Phase I	Nivolumab at a dose 3 mg/kg b.w. every 2 weeks after previous treatment Phase III	Nivolumab BRAF/–/ Phase III (actualized)	Ipilimumab + nivolumab Phase III
Author	Topalian 2014 [45]	Weber 2015 [33]	Robert 2015 [32]	Wolchok 2015 [35]
N (% I line)	107 (0%)	272 (0%)	210 (100%)	314 (100%)
%M1c	Majority (exact data unknown)	75%	61.0%	57.6%
Mutation in *BRAF*	UNK	24%	0%	32.2%
ORR	31%	38%	40% (42.9%)	57.6%
PFS (median in months)	3.7	4.7	5.1 (5.4)	11.5
1-year OS	62%	UNK	72.9% (70.7%) (2-year OS 57.7%)	UNK

ORR — objective response rate; PFS — progression-free survival; OS — overall survival; UNK— no data

In summary, nivolumab is a drug with high efficiency among patients with advanced melanoma (Tab. 2). The drug has already been registered in both the United States and in Europe. The drug is already available, since 1 July 2016, for Polish patients in the drug program of the National Health Fund. Studies on the efficacy of nivolumab used in drug combinations are being continued, as well as in groups of patients at high risk of dissemination after local treatment, and in patients with a diagnosis of ocular melanoma [38]. Evidence from studies indicates greater efficacy and safety of treatment with nivolumab than with ipilimumab. This raises the question: what is the future of ipilimumab in the treatment of advanced melanoma? And will the use of this drug be limited to administration in selected patients in a drug combination with nivolumab. An interesting issue is also the possibility of combining immunotherapy with treatment targeted BRAF or MEK inhibitors. In preclinical studies, it seems that a combination could have synergistic antitumor promoting activity [39], although there is a fear of its high potential for toxicity. A phase I study of the vemurafenib in combination with ipilimumab was interrupted due to high liver toxicity of the co-administered drugs [40]. It seems that the toxicity is lower of the combination of ipilimumab with dabrafenib, but the data are from small phase I studies only [41]. Further studies on the use of nivolumab combined with BRAF and MEK inhibitors are under way (research: NCT01940809, NCT02224781) [38].

Expression of PD-L1

As with any other therapy, the predictors of response to treatment are being investigated for nivolumab. In the studies of PD-1 inhibitors it was tested whether the level of PD-L1 expression on tumor cells could be such a predictive factor. In most cases, it turned out that it could not be considered as a good predictor to select patients before starting treatment.

In many clinical trials, the expression of PD-L1 was associated with higher response rates to treatment. Usually it did not translate into an effect on prognosis, and treatment results were good even among patients without expression of PD-L1, so it is not appropriate to exclude this group of patients from therapy [1]. The only diagnosis where the case of the PD-L1 expression appears to have a significant effect on prognosis of treated patients is NSCLC non-squamous type. In the above-cited phase III study, the expression of PD-L1 was a predictor of benefit from nivolumab treatment, from the lowest level of this expression (1%) for PFS, and from 5% for OS. Median OS was two-fold higher in patients receiving nivolumab compared with patients treated with docetaxel, in patients with the expression of PD-L1. In patients with PD-L1 expression of more than 5%, median OS among receiving nivolumab was 19.4 months, and in those receiving docetaxel — 8 months. Whereas, there were no differences in OS between the arms of the study when the tumour showed no expression of PD-L1. The ORR rate was almost three-fold greater in those expressing PD-L1 [26]. Accordingly, although the FDA approved the drug for all patients diagnosed with NSCLC with non-squamous type in second-line therapy, assessment of PD-L1 expression prior to treatment is recommended in these patients [22].

Interesting data have come from studies with nivolumab in advanced melanoma. In the three-armed study, CheckMate 067, among patients diagnosed with PD-L1 expression in tumour cells, the median PFS in both nivolumab for monotherapy and for nivolumab in combination with ipilimumab was 14 months. However, among patients in whom such expression was not found

treated with only nivolumab PFS was only 5.3 months, and for receiving the combination of drugs 11.2 months. This of course requires further analysis, but it can attest to the fact that in the group of patients in whom expression of PD-L1 is present in the tumour cells, a single agent nivolumab may be considered, since it gives as good results as a combination of drugs at much lower toxicity [37].

Toxicity

Treatment with nivolumab may be associated with quite unique toxicity, that is unusual for anti-cancer treatment (conventional chemotherapy and molecularly targeted therapies). The side effects are due to overstimulation of the immune system. As in the case of ipilimumab, algorithms have been developed in case of side effects, the use of which significantly reduces the risk of accumulation of toxicity. Immunosuppressant drugs are administered in treatment, mainly corticosteroids [42, 43].

Last year, at the ASCO Anual Meeting, the results of a retrospective analysis of the safety of treatment with nivolumab were presented — the analysis was based on findings from 576 patients diagnosed with advanced melanoma and treated in clinical trials. Half of them had previously been treated with ipilimumab. The most common side effects of therapy — in each stage of severity — were: fatigue (25%), pruritus (17%), diarrhoea, and rash (13%). Grade 3 or 4 adverse events occurred in 10% of patients in the whole group and in 8% of patients previously treated with ipilimumab. In the analysed group there were no cases of death due to the toxicity of therapy. The side effects resulting from excessive stimulation of the immune system usually concerned skin (34%), gastrointestinal tract (13%), endocrine system (8%), and liver (4%). Such side effects, of grade 3 or 4, occurred in 4% of patients. Median time to onset of toxicity was five weeks for dermal toxicity, and up to 15 weeks in case of nephrotoxicity. Immunomodulatory treatment (in the vast majority corticosteroids) were used in 35% of patients. The median time to resolution of toxicity under the influence of treatment was 3 weeks for hepatotoxicity and 29 weeks for dermal toxicity (in patients who had skin toxicity, topical corticosteroids were administered in the vast majority). The use of immunomodulatory therapy for the treatment of toxicity does not affect the response to anticancer treatment [44].

Table 1 summarises the adverse reactions occurring in the above-described phase III trials.

Summary

Blockade of the immune checkpoint PD-1 is a new and promising strategy for therapy of advanced cancers. The introduction of nivolumab has improved prognosis in a large group of cancer patients. The results of immunotherapy are better than those achieved before. Nivolumab seems to be better tolerated than many standard chemotherapy or ipilimumab, due to its relatively low toxicity. More information on the activity of nivolumab used in different schemes and different types of cancer, as well as more data on the predictors of treatment, will be available along with the subsequent publication of results of ongoing multiple clinical trials using this drug. Currently, nivolumab is registered in the European Union, alone or in combination with ipilimumab, to treat advanced melanoma (unresectable or metastatic) in adult patients and in the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults. Additionally, this drug is approved for the treatment of patients with metastatic RCC after failure of anti-angiogenic therapy.

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