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Hanna Koseła-Paterczyk[1], Maja Wasylecka-Morawiec[1], Katarzyna Kozak[1], Beata Jagielska[2], Tomasz Świtaj[1], Piotr Rutkowski[1]

[1]Department of Soft Tissue, Bone Sarcoma and Melanoma, Memorial Cancer Centre and Institute of Oncology, Warsaw
[2]Department of Oncology and Internal Medicine, Memorial Cancer Centre and Institute of Oncology, Warsaw

The efficacy and safety of ipilimumab in patients with advanced cutaneous or mucosal melanoma

Address for correspondence:
Dr n. med. Hanna Koseła-Paterczyk
Department of Soft Tissue, Bone Sarcoma and Melanoma
Memorial Cancer Centre and Institute of Oncology
Roentgena 5, 02–781 Warsaw
Phone: +48 (22) 546 20 31
e-mail: hanna.kosela@gmail.com

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ABSTRACT

Introduction. Ipilimumab is a monoclonal antibody registered for the treatment of patients with unresectable or metastatic melanoma. Studies have shown prolongation of overall survival in patients treated with ipilimumab. Adverse events related to excessive stimulation of the immune system may occur during treatment. The aim of this paper was to analyse the results of treatment with the use of ipilimumab, which were achieved in one institution in the frame of a therapeutic program established in Poland.

Materials and methods. Forty-seven patients (27 men, 20 women) were treated from April 2014 to February 2015 with ipilimumab in a dose of 3 mg/kg of body weight after failure of one previous systemic line of treatment. Median age at the beginning of the treatment was 54 years (range 18–73). Nineteen patients (40%) had *BRAF* mutation. Thirty patients received chemotherapy as first-line treatment prior to ipilimumab, 14 patients were given vemurafenib, and three patients were treated in clinical trials. Performance status 0 or 1 was found in 15 patients and 32 patients, respectively. Five patients (10.6%) had asymptomatic brain metastases. Twenty-four (51%) patients had metastatic disease with three or less organs involved, whereas 23 (49%) patients had metastases in more than three organs. Lactate dehydrogenase (LDH) activity and neutrophil count was elevated at the beginning of treatment in 40% and 30% of patients, respectively.

Results. Thirty-five patients (74%) completed four doses of treatment. Four patients (8.5%) had partial response to the treatment, 12 patients (25.5%) had stable disease (SD) for three or more months, and 31 (66%) had progressive disease. Sixteen patients (34%) had clinical benefit from the treatment (PR + SD). Median progression-free survival (PFS) time was two months. Median overall survival (OS) time was 7.5 months. Increased LDH activity at the beginning of treatment and elevated neutrophil count significantly influenced overall survival of patients ($p = 0.005$ and $p = 0.01$, respectively). After progression on ipilimumab 25 patients (53%) received further lines of systemic treatment.

Conclusions. This analysis confirms the efficacy of ipilimumab in some patients with advanced melanoma in second-line systemic therapy. A limited proportion of patients obtain long lasting control of the disease after use of ipilimumab with good tolerance to the treatment. There is a need to determine predictive factors of response to treatment for better selection of patients.

Key words: melanoma, ipilimumab, survival, toxicity

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Introduction

Melanoma is an aggressive skin cancer, characterised by a high risk of metastatic spread. The incidence of melanoma is increasing and also raises the percentage of patients diagnosed with metastatic disease, whose prognosis remains poor. Survival outcomes for patients with advanced melanoma have historically been

poor, with the five-year survival rate for patients with stage IV disease not higher than 5–10%, and median overall survival (OS) of 6–9 months [1, 2]. In the year 2010 in Poland the number of new patients diagnosed with melanoma was 1200 men and 1350 women, and 1200 died because of distant melanoma spread (more than 600 men and 570 women) [3]. Until recently, the only option for the palliative treatment of patients with a diagnosis of metastatic melanoma was chemotherapy based on dacarbazine, the efficacy of which was low (no impact on overall survival). In recent years the results of a series of clinical trials for new molecules have been published, some of which have already been registered and are used in practice. This has translated into a survival advantage in this group of patients with poor-prognosis [4, 5].

One of the new drugs is ipilimumab, which is a human monoclonal antibody blocking the antigen CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4) on the surface of T lymphocytes. The blockade of CTLA-4 increases the activity of lymphocytes and removes the mechanisms of immune tolerance; it causes enhanced activation of cytotoxic lymphocytes and decreases the control by the suppressor cells [6]. In the year 2010 the results of a multicentre randomised trial were published on the efficacy of ipilimumab in patients diagnosed with metastatic melanoma, who had failed prior treatment. It showed improved OS, for the first time for a systemic therapy for melanoma. Median OS in the group receiving ipilimumab treatment (at a dose of 3 mg/kg body weight) was 10 months, compared to 6.4 months in the control group (patients receiving the vaccine gp100); this difference was statistically significant. Among patients treated with ipilimumab the objective response rate was rather low (10.9%), but the two-year survival in patients receiving immunotherapy reached about 20%. In the group of patients treated with ipilimumab 10–15% had side effects of treatment in grade 3 or 4 according to the CTC (Common Toxicity Criteria) [7]. The efficacy of the drug was confirmed in the following clinical study. This time the trial was conducted in previously untreated patients. Median OS in the group treated with the combination of ipilimumab and dacarbazine was 11.2 months, compared to 9.1 months in patients receiving dacarbazine alone, one-year survival rate was 47.3% vs. 36.3%, and two-year survival was 28.5% to 17.9% (HR 0.72, $p < 0.001$). In this study, ipilimumab was administered at a dose of 10 mg/kg body weight [8].

The results of these studies were the basis for the registration of ipilimumab in the European Union for the treatment of patients diagnosed with skin and mucosal melanoma in local unresectable stage or metastatic disease. In the year 2011 the drug was initially registered in the second-line of treatment, in 2013 this registration was extended also to the first line of treatment.

In Poland, the drug has been available as part of the drug program of the National Health Fund (NFZ) since March 2014 for the second-line treatment of patients diagnosed with melanoma of the skin or mucous membranes in stage III (unresectable) or IV. The program has been implemented in nineteen oncology centres in the country, and more than 200 patients have been treated so far.

The aim of the study was to analyse the results of efficacy and safety of ipilimumab in patients treated in the Department of Soft Tissue, Bone Sarcoma, and Melanoma (KNTMKiCz) of the Memorial Cancer Centre and Institute of Oncology in Warsaw as part of the therapeutic program of the National Health Fund.

Materials and methods

To this retrospective analysis were included 47 patients (20 female, 27 male). All patients were treated with palliative ipilimumab in KNTMKiCz because of melanoma of the skin or mucous membranes in stage III (inoperative) or IV (distant spread of the disease) in the period from April 2014 to February 2015. All patients received ipilimumab in the second line of treatment. The median age at treatment was 54 years (range 18–73 years). Detailed characteristics of patients are shown in Table 1.

Ipilimumab was administered in a 1.5-hour infusion at a dose of 3 mg/kg of body weight in four cycles every 21 days. Response to treatment was assessed according to the criteria of the immune response using — among others — with computed tomography 12 weeks after the start of treatment or after administration of the last dose of the entire treatment.

Statistical analysis was performed using the software package Statistica Version 7 (StatSoft). For the survival curves, the median survival time was estimated by the Kaplan-Meier method. Overall survival was calculated from the date of initiation of treatment with ipilimumab to the date of last follow-up or death. Time of progression-free survival (PFS) was calculated from the date of initiation of treatment with ipilimumab to the date of last follow-up or radiologically proven progression of the disease. The median follow-up time was seven months. Side effects of the treatment were evaluated according to the CTC criteria (version 4).

Results

Efficacy

Thirty-five patients (74%) received the full four treatment doses. Among the 12 patients who did not

Table 1. Patient characteristics

Patient characteristics (n = 47)	Number	%
Sex		
Female	20	42
Men	27	58
ECOG performance status		
0	15	32
1	32	68
Localisation of the primary lesion		
Skin	38	80
Unknown	6	12.7
Mucous membranes	3	6.3
First-line treatment		
Chemotherapy	30	64
Vemurafenib	14	30
Clinical trial	3	6
BRAF mutation		
Yes	19	40
No	28	60
Spread of the disease:		
Spread to ≤ 3 organs	24	51
Spread to > 3 organs	23	49
Metastases in the central nervous system		
Yes	5	10.6
No	42	89.3
Baseline albumin level		
Normal	28	60
Below normal	19	40
Baseline lactate dehydrogenase (LDH) level		
Normal	28	60
Below normal	19	40
Baseline neutrophil count		
Normal	33	70
Below normal	14	30

complete the planned treatment, in nine the reason for discontinuation was progression of cancer, in three patients it was the toxicity of treatment. None of the patients achieved complete response to therapy (CR); four patients (8.5%) had a partial response to treatment (PR) (Figure 1). Disease stabilisation (SD) lasting three months or longer was found in 12 (25.5%) of the treated, and 31 (66%) patients had progressive disease (PD). In sixteen (34%) patients a clinical benefit of the treatment (PR + SD) could be observed. The phenomenon of pseudo progression of the cancer did not occur in the observed group.

The median PFS was two months (Figure 2). The median PFS was six months in the group of patients who achieved control of the disease after ipilimumab treatment. Performance status, the presence of metastatic lesions in the CNS, the spread of the disease or baseline albumin, LDH level, and neutrophil count had no statistically significant impact on the PFS. Median OS was 7.5 months (Figure 3). In the group of patients who achieved control of the disease, median OS was not reached. An important difference with respect to OS was, according to the initial activity of LDH ($p = 0.005$) (Figure 4), elevated baseline count of neutrophils had also a negative impact on survival ($p = 0.01$) (Figure 5). No statistically significant impact on overall survival could be seen in the groups of patients with worst general condition, with the presence of metastatic lesions in the CNS, metastatic spread to more than three organs, or decreased baseline albumin level. At the time of the analysis, there were 26 patients who had died. After disease progression on ipilimumab 25 patients (53%) received further systemic therapy (3 — chemotherapy, 21 — pembrolizumab, 1 — dabrafenib).

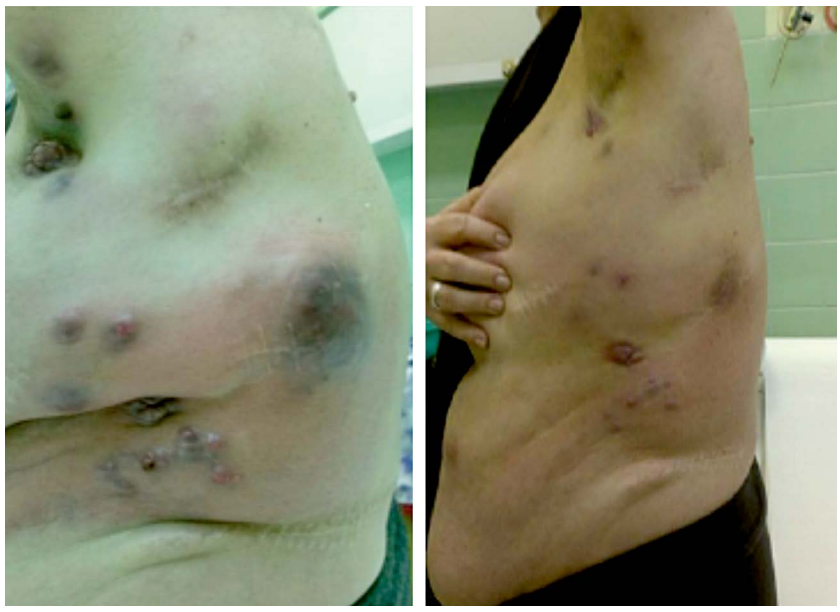

Figure 1. Partial regression of the disease after four doses of treatment

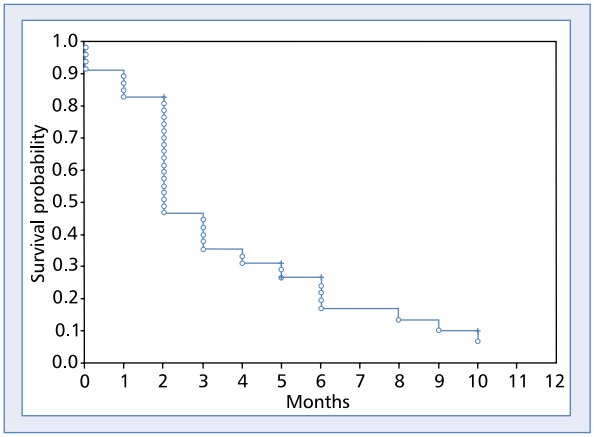

Figure 2. Progression-free survival (PFS)

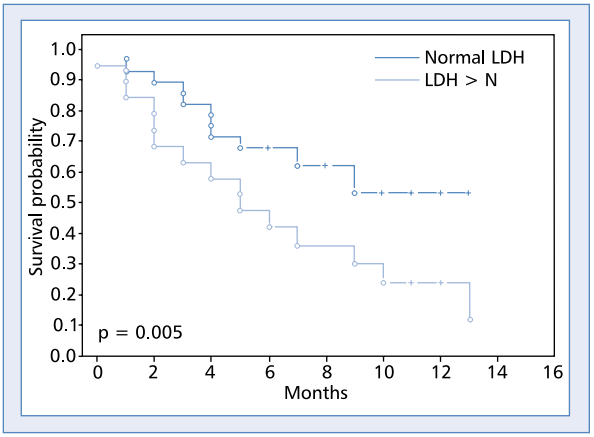

Figure 4. Overall survival (OS) according to baseline LDH level

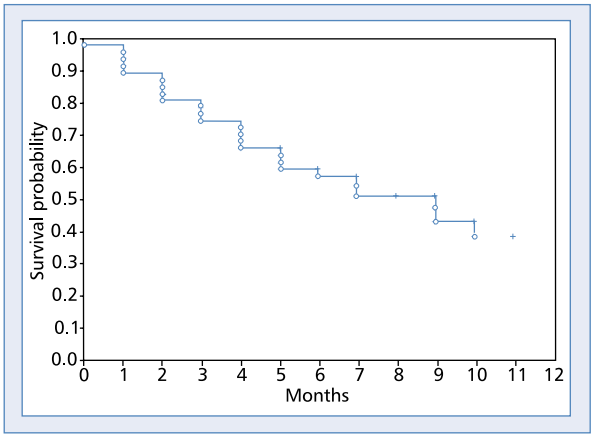

Figure 3. Overall survival (OS)

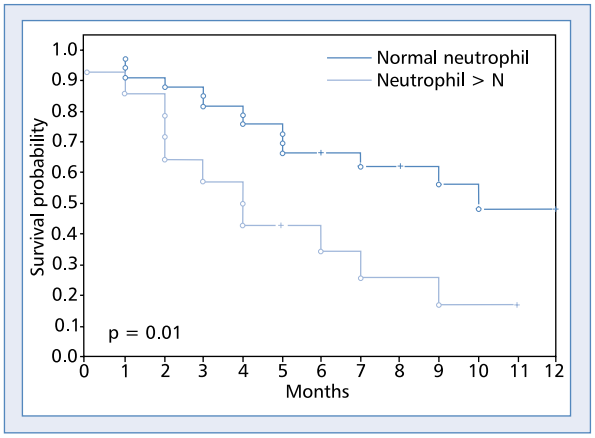

Figure 5. Overall survival (OS) according to baseline neutrophil count

Adverse events

The treatment was rather well tolerated. Eighteen patients (38%) had side effects of treatment. Only three patients discontinued the therapy due to toxicity. There were no deaths due to toxicity of treatment. Seven patients had a thyroid dysfunction in stage 1 of the CTC (asymptomatic variations in hormone levels). Four patients experienced skin rash degree CTC 1 or 2, which decreased without additional treatment (Figure 6). One patient had transaminase elevations in stage 1 of the CTC. Six patients (12.7%) had adverse reactions in a higher degree requiring the use of high doses of corticosteroids in accordance with the recommended algorithms [9]. Five patients had grade 3 diarrhoea by CTC (more than seven bowel movements daily), and one patient experienced inflammation of the pituitary Grade 3. None of these patients required use of immunosuppressive therapy recommended in the algorithms other than corticosteroids (e.g. Infliximab used for patients who developed severe autoimmune inflammatory bowel disease).

Discussion

Ipilimumab is a drug that has been thoroughly investigated in clinical trials. Especially interesting — in the context of the current work — are the analyses on the efficacy and safety of treatment derived from the so-called expanded access programs, to which patients were included before the official registration of the drug. The results of these studies are usually slightly different from comming from clinical studies, where the inclusion criteria are quite rigorous and many patients commonly seen in everyday clinical practice are less represented (e.g. after failure of a number of prior lines of therapy). It is worth mentioning the results of the Polish expanded access program, published in 2013. Fifty patients from five cancer centres were treated. The results are reasonably consistent with those obtained in the present analysis: 70% of patients received the full four doses of treatment. Although the median PFS was longer (three months), the median OS was similar (eight months). A factor significantly affecting the prognosis of patients was performance status at the treatment start

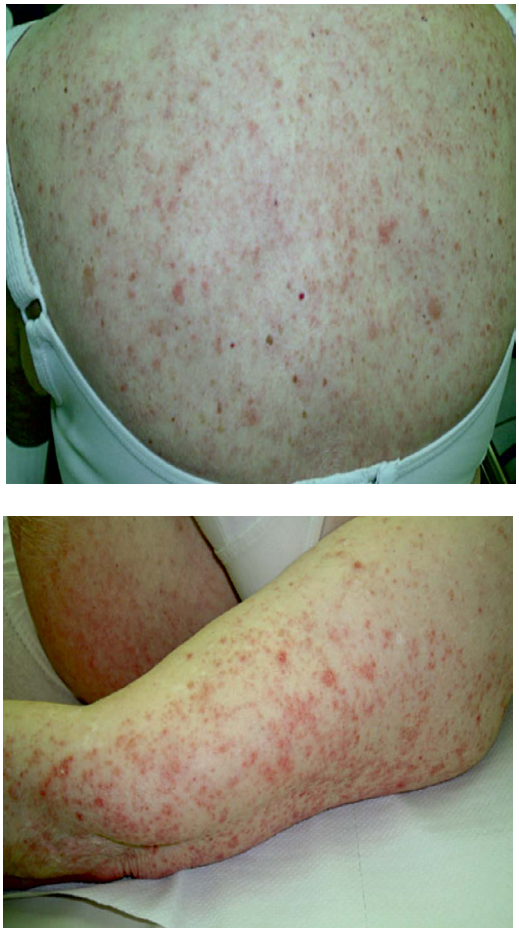

Figure 6. Skin rash grade 2 CTC in a patient after two doses of treatment

[10]. Further data are presented from Spanish centres, where the results come from 153 patients enrolled in the program, of which 61% received the full four doses of treatment. Complete response was observed in 1.3% of patients, a partial response was observed in 9.6% of patients, and stable disease in 14.5%. Median OS was 6.5 months. Negative prognostic factors for survival proved to be an increased lymphocyte count and increased LDH activity [11]. In the UK 193 patients were included in the expanded access program, including 20% with a diagnosis of metastatic lesions to the CNS. Only 53% of patients received the full four doses of the drug; among those who did not complete the treatment the main cause was progression of the disease. The median PFS was 2.8 months, and median OS reached 6.1 months. The objective response rate to treatment was 14% [12]. A significant number of patients treated with ipilimumab (196) were included in the recently published analysis from Czech centres. A full course of treatment was received by 66.8% of patients. Median OS was — similarly to our group — 7.5 months, and it was much longer in those who achieved response to treatment (42.3 months in the Czech Republic; in the following analysis the median OS in this group was not reached) [13].

There are currently attempts to assess predictive factors of response to ipilimumab. Response to immunotherapy has a different dynamic than that observed when using targeted therapy or classical systemic therapy. The expected positive response to ipilimumab is stabilisation of the disease or slow decrease in tumour lesions rather than rapid regression of the tumour. Patients with rapidly extending malignancies and/or high tumour burden in most cases do not benefit from immunotherapy. The delayed response to treatment (weeks or even months after its start) justifies carrying out the first radiological evaluation of efficacy after the administration of all (four) drug doses [14]. Therefore, there are relatively high percentages of patients failing to end the full course of treatment due to disease progression. Less benefit from treatment with ipilimumab in patients with high levels of disease was shown, among other results, in a randomised study of patients diagnosed with metastatic melanoma to the CNS. The study enrolled asymptomatic patients who did not require the use of corticosteroids and those whose symptoms of the disease required use of stable doses of corticosteroids. Median PFS and OS in asymptomatic patients were twice as long as in patients in need of treatment against oedema [15].

One of the indicators of high activity of cancer is increased LDH level. LDH level exceeding the upper normal limit has for years been known as a poor prognostic factor in melanoma patients [16, 17]. Poor prognosis for melanoma patients diagnosed with elevated LDH levels also applies to those treated with ipilimumab. In a large analysis of predictive factors of patients treated with ipilimumab conducted in the UK and the Netherlands, elevated LDH levels was the strongest negative factor among those examined. The study conclusion was that patients with a baseline LDH activity exceeding the upper normal limit by a factor of two are unlikely to benefit from treatment with ipilimumabem [18]. Also, in our analysed group of patients who at baseline had elevated LDH levels, significantly shorter OS was seen compared with those in whom the level was within normal limits. Another factor with a negative predictor of outcome in the analysed group was elevated baseline neutrophil count. Both indicators (baseline LDH level and neutrophil count) were also singled out as strong and independent prognostic factors among patients treated with ipilimumab in the nomogram proposed this year aiming to help in the inclusion of patients for treatment [19].

During ipilimumab treatment rather unique toxicity can occur, previously not commonly found in the systemic treatment of cancer. This toxicity is associated

with overstimulation of the immune system. Algorithms have been developed in the case of these adverse effects, the use of which strongly reduces the risk of toxic accumulation; in the treatment of ipilimumab adverse events are used immunosuppressive drugs (primarily corticosteroids) [9, 20]. In the registration study, side effects of treatment were observed in 60% of patients treated with ipilimumab, with toxicity of grade 3 or 4 in 10–15% of patients, wherein 14 patients (2.1%) died due to treatment toxicity [7]. In the past, drug toxicity among patients treated in routine clinical practice seems to be slightly higher. This may be due to the often less stringent control and less frequent visits to the treating centre than among patients participating in clinical trials. With the already quoted analysis of data from the expanded access program in the UK, toxicity of treatment was observed in 70% of patients, and 30% of patients had adverse reactions Grade 3 or higher (usually diarrhoea). In 10% of patients of this group, the treatment was discontinued because of toxicity [12]. In the analysed group, the percentage of adverse events was not high — side effects of treatment were observed in 38% of patients, and grade 3 toxicity occurred in 12.7% of patients, with no treatment-related deaths. Due to the specific profile of adverse drug reactions, the treatment of which requires experience and multidisciplinary facilities (e.g. endoscopy), ipilimumab treatment should be carried out in major cancer centres with relevant experience. Patients should be thoroughly informed about the possible side effects of the drug and should be instructed to react quickly and contact the care provider centre if they occur [21].

Conclusions

The presented results confirm the efficacy and safety of ipilimumab treatment in patients diagnosed with advanced melanoma, after failure of prior lines of therapy. In the analysed group prognosis is similar to that presented in previous publications. A limitation of the above analysis is certainly the relatively short observation period, which does not allow a full assessment of the duration of response and overall survival. It is also recommended to repeat the analyses after obtaining data from a larger number of patients from other centres in Poland.

Ipilimumab is not a drug that leads to a high percentage of objective response to treatment, but some of the treated patients manage to achieve long-term control of the with good tolerability. It is advisable to carefully select patients for treatment, due to the specific kinetics of response. The slow time of onset of the response (as opposed to the rapid response seen e.g. when using BRAF inhibitors) restricts the use of ipilimumab in patients with dynamic course of the disease accompanied by a rapid deterioration of general condition. The rule of eligibility is often difficult in such clinical situations as disseminated malignancy and the need to propose patients access to the latest therapies. It should also be considered whether the drug's availability in Poland only in the second-line treatment does not limit its therapeutic possibilities. Often patients after failure of first-line systemic therapy already have majorly advanced disease with progressing rapidly deterioration of general condition, thus being poor candidates for ipilimumab use. Thiese limitations do not change the fact that ipilimumab is an effective drug that gives hope for long-term survival to very poor-prognosis patients. Moreover, the results of this work can be the starting point for changing current strategy for immunotherapy of melanoma in the case of detection of inoperable metastases in the treatment of anti-PD-1 (nivolumab or pembrolizumab), which are more effective, with a median overall survival of up to two years and better tolerance [22, 23], or implementation of a combined therapy with anti-CTLA-4 and anti-PD-1 (with a greater toxicity and cost of the combination drug) [24].

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