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A patient with metastatic malignant melanoma treated with nivolumab: case report

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ABSTRACT

This is a case report of a 41-year-old female patient diagnosed in 2012 with malignant melanoma of the right cheek. She was treated surgically. In 2013 right-sided cervical lymphadenectomy was performed due to melanoma metastases. Subsequently, new metastases were found in the lungs, liver, and bones. She was treated with nivolumab. A partial remission of the disease was noted and response is currently ongoing.

Key words: malignant melanoma, nivolumab, immunotherapy

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Case report

This is the case of a 41-year-old woman who in 2012 noticed a distressing pigmented lesion in a right cheek. In April 2012 the lesion was surgically removed. Histological examination revealed a nodular melanoma, with ulceration, Breslow thickness of the lesion 5 mm, and mitotic index of 11/mm². In May 2012 the scar was removed and no melanoma cells were revealed in histology. Pathological stage was assessed as pT4b. After surgery the patient remained under observation, without any adjuvant treatment.

In June 2013 the patient detected enlarged lymph nodes on the cervical right side, and during physical examination local recurrence in the right cheek area was suspected. On 4th July 2013 the patient underwent radical removal of the right-sided lymphatic system and removal of melanoma local recurrence with covering of the lesion with a free skin flap. Histological examination confirmed local recurrence; metastatic melanoma cells were found in five out of 11 dissected lymph nodes. Due to numerous lymph nodes involved and the high risk of spreading of disease, on 5th August 2013 a *BRAF V600* mutation test

was performed with negative result. On 16th September 2013, CT scans of the chest, abdomen, and pelvis with contrast medium were performed (Figures 1, 2). Metastases to the lungs, bones (L2 vertebra, left hip bone, and sacrum), and liver were found. Lactate dehydrogenase (LDH) level was 423 IU/L (normal range up to 265). The patient had pain in the spine, requiring oxycodone therapy. Clinical disease stage was assessed as T4bN3M1c.

In September 2013 the patient was recruited into the BMS CA-209 066 multicentre, randomised, blinded trial comparing nivolumab to dacarbazine. This clinical study involved patients with locally advanced or metastatic melanoma without *BRAF V600* mutation. Nivolumab was administered at the dose of 3 mg/kg every two weeks and dacarbazine at the dose of 1000 mg/m² every three weeks. The patient had no chronic concomitant diseases at the time of entry into the study, and performance status (PS) was 1 according to the ECOG scale.

In the first radiological assessment after three months of treatment the disease stabilisation was detected according to RECIST 1.1 criteria. ECOG PS improved to 0, pain in the spine entirely subsided, and

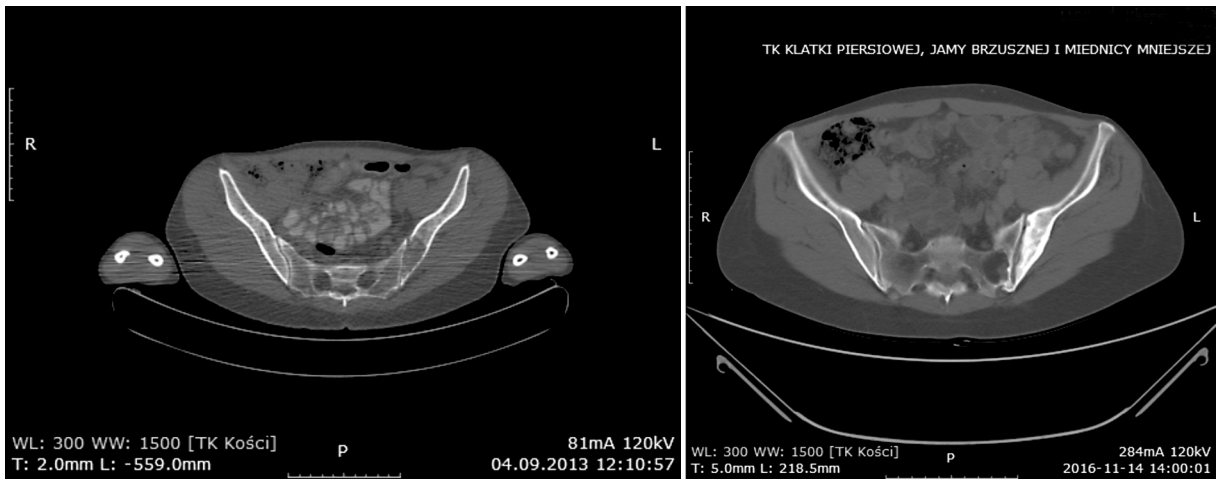


Figure 1. Pelvic CT scan from September 2013 (left) and November 2016 (right). Calcification of metastatic lesion in the left iliac

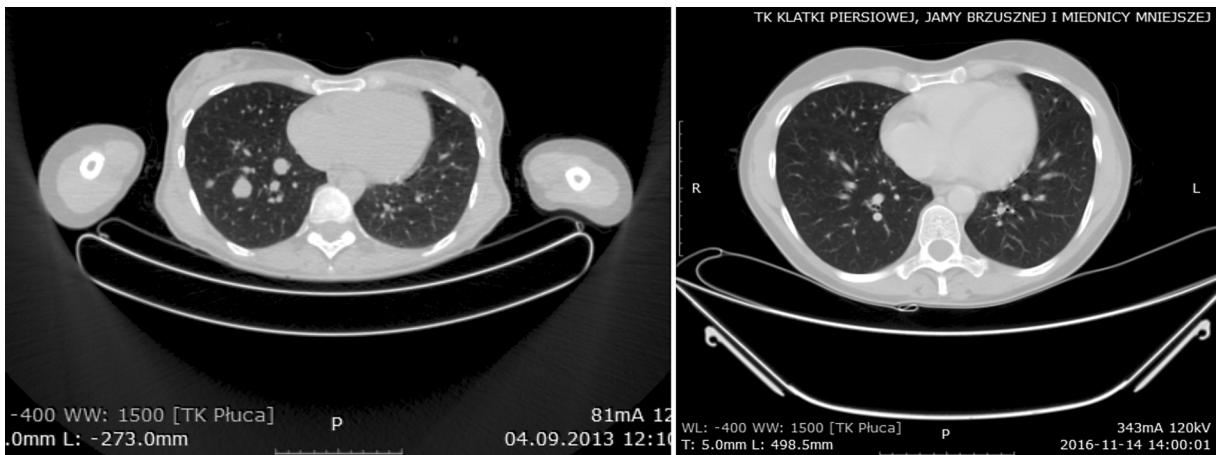


Figure 2. Chest CT scan from September 2013 (left) and November 2016 (right). Remission of the lung lesions

the treatment with analgesics was discontinued. Two consecutive radiological evaluations performed every three months showed persistent disease stabilisation according to the RECIST 1.1 criteria. In the radiological assessment after 12 months, a partial remission was observed according to RECIST 1.1.

After trial unblinding it was revealed that the patient was receiving nivolumab. No side effects have been reported. Currently the patient remains in good condition (ECOG = 0).

The patient's most recent clinical visit was on 8th August 2017, after almost four years of treatment with nivolumab.

Discussion

Currently, immunotherapy is a cornerstone of treatment of patients with advanced melanoma without

BRAF V600 mutation. One of the available drugs that affect the immune system is nivolumab, an anti-PD1 monoclonal antibody. In the CheckMate-066 pivotal study the drug was compared to the earlier gold-standard chemotherapy, e.g. dacarbazine. The study included previously untreated patients without *BRAF V600* mutation (based on a later CheckMate-067 study, nivolumab is known to be active in patients with *BRAF* mutations).

Originally the study was blinded. After interim analysis performed in June 2014 a significant difference in overall survival (OS) was found in favour of nivolumab. The study was unblinded and patients taking dacarbazine were offered treatment with nivolumab. Median PFS was 5.1 months for nivolumab and 2.2 months for dacarbazine ($p < 0.001$). In the dacarbazine arm median OS was 10.8 months; however, in the nivolumab group median OS was not achieved.

There was a statistically significant improvement in OS in the nivolumab group compared to the dacarbazine

group — relative risk for death was 0.42 ($p < 0.001$). Objective response rate (ORR) in the nivolumab and dacarbazine group was 40.0% and 13.9%, respectively ($p < 0.001$). Nivolumab was well tolerated; the most common side effects included fatigue (19.9% of patients), pruritus (17%), and nausea (16.5%). Treatment-emergent grade 3/4 adverse events occurred in 11.7% of patients treated with nivolumab.

The lack of treatment-predictive factors is still an unresolved problem. Based on clinical and laboratory criteria, the patient was classified to the highest risk group — symptomatic disease, metastatic location (liver and bones as unfavourable locations), and elevated LDH level at treatment initiation. Despite this, the patient achieved a good and long-lasting treatment effect with partial remission (according to RECIST 1.1) of metastatic lesions and pain improvement.

Summary

A patient diagnosed with right cheek melanoma at disseminated stage has been treated with nivolumab for almost four years. This treatment is effective and well tolerated.

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