

# Metastatic melanoma response to combination therapy with ipilimumab and vemurafenib

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## Abstract

Combination therapies for the treatment of metastatic melanoma are a matter of debate nowadays. We report on a stage IV metastatic melanoma patient with the BRAF V600 mutation and a large tumor burden initially treated with two cycles of ipilimumab. Due to dramatic disease progression, demonstrated on interim <sup>18</sup>F-FDG PET/CT, vemurafenib was added in the patient's therapeutical scheme. After completion of the concurrent ipilimumab and vemurafenib administration, a third <sup>18</sup>F-FDG PET/CT showed an impressive metabolic remission of the metastatic disease, reflecting the potential role of the modality in treatment response evaluation of melanoma patients receiving combination therapies.

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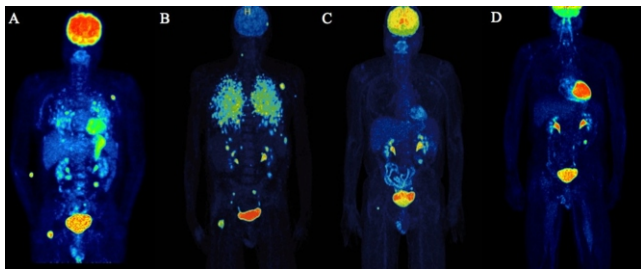
## Introduction

Although until recently the median overall survival of metastatic melanoma was less than 12 months, the management of this highly aggressive tumor entity has been revolutionized in the last few years with the introduction of immune checkpoint inhibitors and targeted agents [1, 2]. These additions in the therapeutic arsenal of melanoma have, however, raised the issue of appropriate treatment response evaluation, since the mechanism of action of immune checkpoint inhibitors, is markedly different than that of cytotoxic chemotherapy. Fluorine-18-FDG PET/CT is an imaging modality with proven very high sensitivity and specificity in metastatic disease detection, whereas its performance in treatment response assessment has also been highlighted by few studies [3, 4, 5, 6, 7]. Nevertheless, the data regarding the use of <sup>18</sup>F-FDG PET/CT in therapy evaluation of patients receiving a combination of targeted therapy with immunotherapy are limited. Herein, we report on a 61 years old metastatic melanoma patient who received combination treatment with the anti-CTLA4 antibody ipilimumab and the BRAF inhibitor vemurafenib and underwent <sup>18</sup>F-FDG PET/CT monitoring during the course of treatment.

## Case Report

A 61 years old male patient with unresectable, stage IV, metastatic melanoma with initial localization in the spine, scheduled for treatment with the immune checkpoint inhibitor ipilimumab was referred to the nuclear medicine department for baseline <sup>18</sup>F-FDG PET/CT before the onset of treatment. The baseline PET/CT scan demonstrated multiple metastatic lesions in the lungs, liver, femur, descending colon as well metastatic involvement of an axillary lymph node (Figure 1A). After completion of two cycles of ipilimumab administration (3mg/kg q3 weekly) the patient underwent a second PET/CT for early treatment response evaluation. Positron emission tomography/CT exhibited a dramatic disease progression with multiple new lung metastases accompanied by a bronchopulmonary infection, as well as new lesions in the liver, spleen, osseous structures (os ilium, 5<sup>th</sup> rib) and soft tissues (Figure 1B). Moreover, the pre-existing metastatic lesions demonstrated an increase in size and intensity of <sup>18</sup>F-FDG accumulation. Due to rapid disease progression, vemurafenib was offered and added in the patient's therapeutical sche-

me (960mg per os q12hr) as an individual treatment decision. After completion of the combined treatment of vemurafenib and four cycles of ipilimumab, a third PET/CT was performed for late treatment response evaluation. With the exception of the metastatic sites in the right femoral head and the descending colon, which, also significantly subsided in size and metabolism, PET/CT exhibited complete metabolic remission of the metastatic disease in all previously involved sites (Figure 1C, Figure 2). Overall, the combination therapy was well tolerated. After completion of the four ipilimumab cycles, the patient continued the vemurafenib treatment on a daily basis. Twelve months after maintenance therapy with vemurafenib, a follow-up PET/CT showed complete remission of the previous lesions and at the same time a new lesion in the small intestine (Figure 1D). Fifteen months after initiation of vemurafenib, the patient also received 4 cycles of the PD-1 inhibitor pembrolizumab due to transient disease progression. Thirty seven months after the initial diagnosis of unresectable melanoma the patient is still alive, undergoing regular imaging monitoring with  $^{18}\text{F}$ -FDG PET/CT and brain MRI, and having exceeded by far the expected survival for the disease.



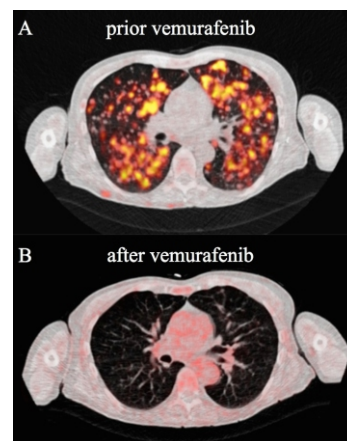
**Figure 1.** Maximum intensity projection (MIP)  $^{18}\text{F}$ -FDG PET/CT images of the 61 years old metastatic melanoma patient shortly before onset of ipilimumab (A), after two cycles of ipilimumab and before the addition of vemurafenib (B), shortly after the end of the combined ipilimumab-vemurafenib treatment (C), as well as 12 months after maintenance therapy with vemurafenib (D).

The baseline PET/CT scan demonstrated multiple metastatic lesions in the lungs, liver, femur, descending colon and axilla (A). After completion of two cycles of ipilimumab the second PET/CT showed multiple new lung, liver, spleen, bone and soft tissues metastases, as well as progression of the preexisting lesions (B). Shortly after completion of the combined treatment of vemurafenib and four cycles of ipilimumab, the third PET/CT showed complete metabolic remission of the metastatic disease in all previously involved sites with the exception of the metastatic sites in the right femoral head and the descending colon, which, partially subsided (C). Twelve months after maintenance therapy with vemurafenib, a follow-up PET/CT showed complete remission of the previous lesions and at the same time a new lesion in the small intestine (D).

## Discussion

The recent introduction of immune checkpoint inhibitors

and targeted agents has revolutionized advanced melanoma therapy. The anti-CTLA4 antibody ipilimumab and the BRAF inhibitor vemurafenib have led to improved survival rates and have been the first agents to achieve FDA approval in this new era of melanoma therapy [1, 2, 8]. The two agents have, however, marked differences regarding their therapeutic potential, with ipilimumab demonstrating a durable survival benefit but requiring time to achieve it, and vemurafenib exhibiting a rapid but not durable response due to development of tumor resistance to BRAF inhibition [1, 2, 9, 10, 11, 12]. These contrasting advantages and disadvantages have provided rationale for the onset of debate regarding combination and/or sequencing therapies that can carry the potential benefits of both immunotherapy and targeted therapy [13, 14].



**Figure 2.** Transaxial  $^{18}\text{F}$ -FDG PET/CT images at the level of the lungs after administration of two cycles of ipilimumab and prior to vemurafenib (A), and after completion of the combined therapy of ipilimumab and vemurafenib (B). Despite the initially extended metastatic infiltration of both lungs after two ipilimumab cycles demonstrated both on  $^{18}\text{F}$ -FDG PET and underlying CT (A), the patient demonstrated complete metabolic remission of the lung disease after administration of combined therapy of vemurafenib and ipilimumab (B).

The data regarding combination therapy of ipilimumab and vemurafenib are still rather limited. Ribas et al. (2013) conducted a phase I trial for evaluation of the concurrent administration of ipilimumab and vemurafenib in BRAF-mutated metastatic melanoma patients, which was, however, early stopped due to the observed hepatotoxicity of the combined treatment [15]. On the other hand, in an own case series involving patients with a high tumor load, symptomatic disease and a high frequency of brain metastases, the combination of the two agents was well tolerated and the median progression free survival (PFS) was higher than expected for monotherapy [16]. Further, a recently published phase II study showed that vemurafenib followed by ipilimumab had a manageable safety profile, ipilimumab had efficacy after treatment with vemurafenib in patients with BRAF-mutated melanoma and that tumors remained sensitive to vemurafenib retreatment after progressing on ipilimumab<sup>8</sup>. In the present case, the combined administration of ipilimumab and vemurafenib in a patient with disseminated metastatic disease, led to a rapid and also durable clinical be-

nefit lasting 15 months.

Treatment response evaluation of tumor immunotherapy is a matter of debate, since the mechanism of action of these agents is very different from that of cytotoxic chemotherapy. Immunotherapeutic agents can lead to atypical response patterns and are often accompanied by new immune-related adverse events [17]. Due to its ability in detecting metabolic changes before anatomic alterations take place, PET/CT can be a powerful tool in personalized treatment management [18]. Although data regarding application of  $^{18}\text{F}$ -FDG PET/CT in combination treatment response evaluation are mainly anecdotal, the published studies concerning use of  $^{18}\text{F}$ -FDG PET/CT in evaluation of the effect immunotherapeutic and targeted agents applied separately, encourage the application of the modality in biological response assessment of combined therapies [19, 20, 21, 22, 23]. In our case, PET/CT played a significant role in patient monitoring and prediction of treatment response; not only did the modality reveal disease progression after the first two ipilimumab cycles, leading to the addition of vemurafenib in the therapeutic scheme, but it was also predictive of the durable clinical benefit the patient demonstrated, by revealing a metabolic status remission shortly after the combined ipilimumab /vemurafenib therapy.

*In conclusion*, the here presented case provides additional data regarding efficacy of combined therapies in advanced melanoma, as well as further evidence in the direction of establishment of  $^{18}\text{F}$ -FDG PET/CT as a useful biomarker in the complex field of melanoma combined therapy evaluation.

*The authors of this study declare no conflicts of interest*

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