

Neoadjuvant immunotherapy with combined ipilimumab and nivolumab in patients with melanoma with primary or in transit disease

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Summary

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The introduction of new therapeutic agents has revolutionized the treatment of metastatic melanoma. The approval of adjuvant anti-programmed death-1 monotherapy with nivolumab or pembrolizumab, and dabrafenib plus trametinib has recently set a new landmark in the treatment of stage III melanoma. Now, clinical trials have shown that immune checkpoint blockade can be performed in a neoadjuvant setting, an approach established as a standard therapeutic approach for other tumour entities such as breast cancer. Recent studies suggest that a pathological response achieved by neoadjuvant immunotherapy is associated with long-term tumour control and that short neoadjuvant application of checkpoint inhibitors may be superior to adjuvant therapy. Most recently, neoadjuvant ipilimumab plus nivolumab in stage III melanoma was reported. With two courses of dose-optimized ipilimumab (1 mg kg⁻¹) combined with nivolumab (3 mg kg⁻¹), pathological responses were observed in 77% of patients, while only 20% of patients experienced grade 3 or 4 adverse events. However, the neoadjuvant trials employing combined immune checkpoint blockade conducted so far have excluded patients with in transit metastases, a common finding in stage III melanoma. Here we report four patients with in transit metastases or an advanced primary tumour who have been treated with neoadjuvant ipilimumab plus nivolumab according to the OpACIN-neo trial scheme (arm B). All patients achieved radiological disease control and a pathological response. None of the patients has relapsed so far.

What's already known about this topic?

- Neoadjuvant immunotherapy is used in resectable stage III melanoma with lymph node involvement.
- Neoadjuvant ipilimumab plus nivolumab is associated with a high pathological complete response (pCR) rate.
- Pathological response data can be used as a surrogate outcome marker, as pCR and relapse-free survival appear to correlate.
- Patients with melanoma with in transit metastases were excluded from prospective clinical trials employing neoadjuvant ipilimumab plus nivolumab.

What does this study add?

- Neoadjuvant immunotherapy was performed in three patients with lymph node and satellite or in transit metastases, and in one patient with an advanced primary and lymph node metastases.
- All patients achieved a radiological objective response and a pathological response (partial or complete) in all metastatic sites and in the advanced primary.
- To date, none of the patients has relapsed.

The prognosis of patients with stage III melanoma with macroscopic lymph node metastases is poor, with a 5-year melanoma-specific survival of 69% (stage IIIC) or 32% (stage IIID).¹ The approval of adjuvant programmed death-1 blockade with nivolumab or pembrolizumab, and BRAF/mitogen-activated protein kinase kinase inhibition with dabrafenib plus trametinib, will most likely improve outcomes in patients with stage III melanoma.^{2–4} However, the latest trials have focused on a neoadjuvant treatment regimen with combined immunotherapy, with promising results.^{5,6} The OpACIN-neo study showed a high pathological response rate of up to 80% in patients with melanoma receiving neoadjuvant treatment. Furthermore, none of the patients with a pathological response has relapsed so far. Treatment with ipilimumab (1 mg kg⁻¹) and nivolumab (3 mg kg⁻¹) appears to be the best-tolerated dosing scheme, with only a 20% rate of grade 3 or 4 immune-related adverse events (irAEs), while still inducing a high pathological response rate (77%) in patients with stage III melanoma.^{5,6}

Although their results are very promising, both OpACIN and OpACIN-neo excluded patients with in transit metastases,^{5,6} a frequent clinical finding in stage III melanoma, affecting 5–10% of patients.⁷ For this reason, patients with melanoma with in transit disease represent a clinical situation in which treatment with neoadjuvant ipilimumab plus nivolumab could be considered but efficacy data are lacking. Here we report a case series of four patients with resectable stage III melanoma treated with neoadjuvant immunotherapy according to the OpACIN-neo scheme (arm B) since November 2018.⁵ All patients presented with at least one macroscopic locoregional lymph node metastasis. Furthermore, three patients had additional in transit metastases and one patient showed an advanced primary tumour.

Case report

Patient 1 was a 51-year-old woman who presented with a subcutaneous in transit metastasis at the left upper arm. A computed tomography (CT) scan of the chest and abdomen showed one suspect axillary lymph node without signs for further metastases. The second patient was a 62-year-old man who was diagnosed with axillary lymph node metastases and multiple in transit and satellite metastases on the upper back.

Patient 3, a 60-year-old man, had experienced one thoracic in transit metastasis and two axillary lymph node metastases discovered during routine follow-up. Patient 4 was a 75-year-old man with a locally advanced primary melanoma on the right thigh and multiple inguinal and iliac lymph node metastases. The patients' clinicopathological characteristics are shown in Table 1. All cases were discussed in a grand round, and neoadjuvant immunotherapy was recommended according to the OpACIN-neo scheme (arm B).⁵ Alternative treatment options (e.g. regional lymph node dissection or tumour resection followed by adjuvant therapy) were offered to all patients.

Tumour assessment was performed with CT of the chest and abdomen in all four patients prior to neoadjuvant therapy. Additionally, two patients underwent pretreatment biopsy of the cutaneous metastases or of the primary tumour. Staging was completed with magnetic resonance imaging (MRI) of the brain in two of the four patients. Patient 3 interrupted imaging because of claustrophobia and in patient 4 an MRI of the brain was not performed prior to treatment due to logistic reasons. The visible tumour manifestations were recorded by photography. All patients received two courses of ipilimumab (1 mg kg⁻¹) and nivolumab (3 mg kg⁻¹) every 3 weeks before surgery (weeks 0 and 3). In week 6 tumour assessment by thoracic and abdominal CT scan and MRI scan of the brain was performed again (Fig. 1).

Clinical examination of the visible metastases showed a significant effect with reduced tumour burden in all four patients (Fig. 1). The thoracic in transit metastasis in patient 3 was no longer detectable by palpation or ultrasound. Three patients achieved a partial response, and the fourth achieved stable disease according to RECIST 1.1 by CT evaluation at week 6. Within 1 week after assessment, complete regional lymph node dissections and resections of the in transit or satellite metastases and the advanced primary were performed. Pathological assessment was based on the International Neoadjuvant Melanoma Consortium scoring system.⁸ Two patients (patients 1 and 2) achieved a pathological complete response (pCR) not only in the lymph nodes but also in the in transit or satellite metastases. Patient 3 achieved a pathological partial response (pPR; > 10% but ≤ 50% viable tumour cells) in lymph nodes of the left axilla, while the former in transit metastasis could not be evaluated as it was no longer clinically detectable.

Table 1 Patient characteristics and treatment outcomes

Patient	1	2	3	4
Age (years)	51	62	60	75
Sex	Female	Male	Male	Male
Stage (AJCC 2017)	IIIC	IIIC	IIIC	IV ^a
Metastatic sites	Regional lymph nodes, in transit	Regional lymph nodes, in transit	Regional lymph nodes, in transit	Regional lymph nodes, advanced primary tumour
Pretreatment biopsy	In transit metastasis	Not performed	Not performed	Primary tumour
Pathological response				
Primary tumour	NA	NA	NA	pCR
In transit/satellite	pCR	pCR	cCR	NA
Lymph node	pCR	pCR	pPR	pPR
Radiological response (RECIST 1.1)	PR	PR	PR	SD
irAEs				
Grade 1 or 2	Yes	Yes	Yes	No
Grade 3 or 4	No	No	No	No
Follow-up since surgery (months)	8.2	6.9	6.3	3.6
Relapse during follow-up	No	No	No	No

AJCC, American Joint Committee on Cancer; NA, not applicable; pCR, pathological complete response (absence of any viable tumour cells); cCR, clinically complete response; pPR, pathological partial response (> 10% but ≤ 50% viable tumour cells); PR, partial response; SD, stable disease; irAE, immune-related adverse event. ^aFor logistic reasons magnetic resonance imaging of the brain was performed for the first time after neoadjuvant treatment and showed a suspect lesion in the right cerebral hemisphere.

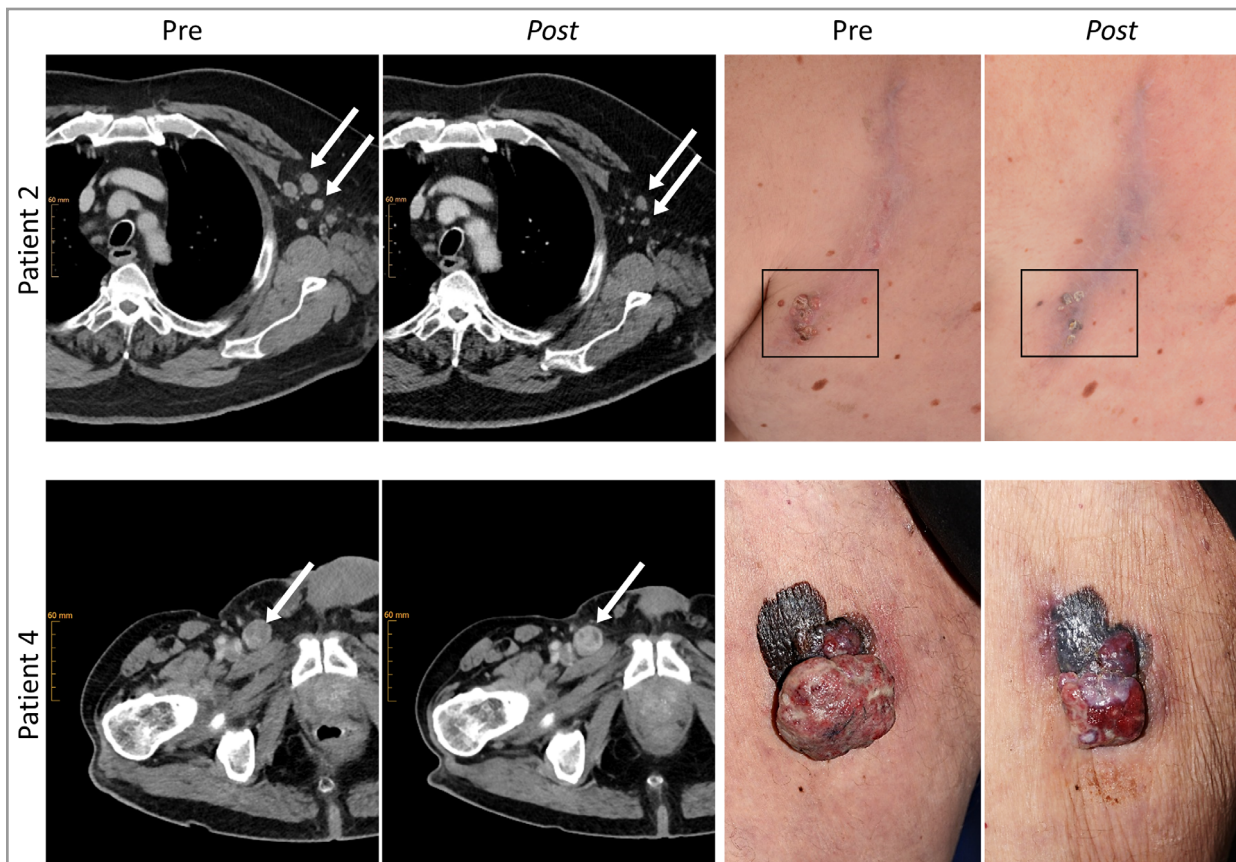


Figure 1 Representative computed tomography scans and clinical photographs of two patients obtained prior to (pre) and after (post) neoadjuvant therapy. The upper row shows patient 2. After neoadjuvant therapy, cutaneous and lymph node metastases (left axilla) showed a partial response. In the lower row, patient 4 is illustrated. While the primary melanoma showed clinical signs of remission, the iliac lymph node metastasis slightly increased in size. Metastases are indicated by white arrows; the black box marks the area affected by cutaneous metastases in patient 2.

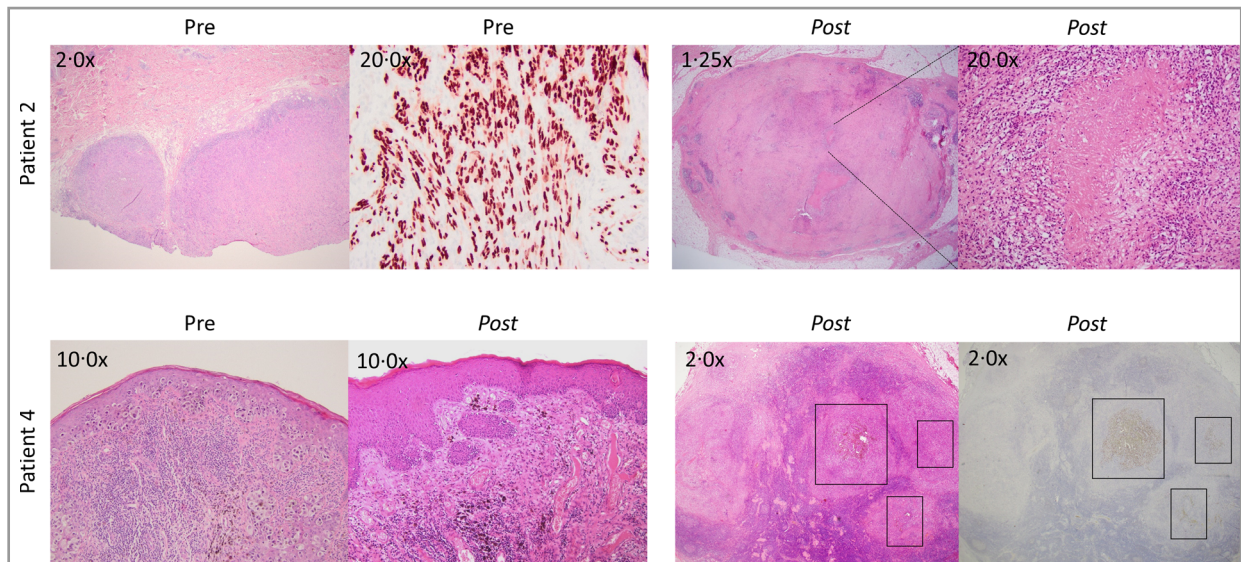


Figure 2 Pathological assessments. In patient 2, a pathological complete response was observed (top row). The images on the left show viable tumour cells in a biopsy taken from the in transit metastasis. Sox10 immunohistochemistry (IHC) is shown at higher magnification. After neoadjuvant therapy, no viable tumour cells were visible anymore; a necrosis with surrounding histiocytes is shown in higher magnification on the right. IHC was negative for Sox10, MART-1 and HMB-45. In patient 4, a pathological partial response (lymph nodes) and a pathological complete response (primary melanoma) were reached (bottom row). On the left, haematoxylin and eosin (H&E) stainings of the primary melanoma are shown. After neoadjuvant therapy, only an inflammatory infiltrate and melanophages were apparent. On the right, postneoadjuvant histologies from a representative lymph node are shown. In the H&E stains, the rectangles indicate areas where vital melanoma cells were suspected. In these areas, IHC for Sox10 showed positive reactions, confirming the presence of vital tumour cells in these areas. Representative slides from both patients are shown.

Patient 4 achieved a pCR of the advanced primary tumour and a pPR in the resected lymph node metastases (Fig. 2). Table 1 summarizes the clinical and pathological evaluations.

Treatment-related irAEs of grade 1 or 2 (according to the Common Toxicity Criteria of Adverse Events, CTCAE) were observed in three of the four patients. Two patients developed an exanthema (grade 1 according to CTCAE), which completely resolved upon treatment with topical corticosteroids within a few days. Two patients presented with vitiligo after approximately 8 and 16 weeks of treatment, respectively. One patient had grade 1 diarrhoea that resolved without specific treatment. Two patients developed hyperthyroidism (grade 1 and 2). The patient with grade 2 hyperthyroidism was treated with thiamazole. We did not observe any grade 3 or 4 irAEs. All patients underwent surgery at the preplanned time point. Surgery was tolerated well; however, three patients developed a limited postoperative wound infection.

Based on the individual pathological response (pCR vs. pPR) further treatments were initiated. We refrained from adjuvant immunotherapy with nivolumab in patients 1 and 2 due to the pCR. They were referred to clinical and serological (S100) follow-up every 6 weeks, with additional sonography of the locoregional lymph nodes every 3 months, and abdominal and thoracic CT scan and MRI scan of the brain every 6 months, according to the German melanoma guideline.⁹ Patients 3 and 4 (with no pCR) started adjuvant therapy with nivolumab (3 mg kg^{-1}) after recovering from surgery.

Discussion

Combined immunotherapy using ipilimumab and nivolumab is known for its high toxicity rates and often leads to treatment discontinuation in patients with stage IV melanoma.¹⁰ However, response rates to combined ipilimumab plus nivolumab are higher than those observed upon anti-programmed death-1 monotherapy, in both palliative and neoadjuvant settings.^{6,10–12} Therefore, the OpACIN-neo trial compared three different dosing schedules of ipilimumab plus nivolumab to identify a better-tolerated regimen.^{5,6} Our case report confirms that treatment with ipilimumab (1 mg kg^{-1}) and nivolumab (3 mg kg^{-1}) is a safe therapy regimen without occurrence of any grade 3 or 4 toxicities as reported for OpACIN-neo and CheckMate 511.^{5,13}

Neoadjuvant immunotherapy with subsequent tumour resection allows examination of early on-treatment tumour tissue, providing an opportunity to understand the mechanisms of response and resistance towards immune checkpoint blockade.⁸ Moreover, pathological examination enables measurement of response to therapy in every individual patient and therefore provides important information for further treatment decisions. Identification of high-risk patients (without pathological response to therapy) might allow an early switch to a more effective treatment, if available. According to data from previous studies, pCR appears to correlate with disease-free survival.^{5,6} None of the patients in the clinical

trials relapsed, as for our patients. However, a longer follow-up is required.

To our knowledge, neoadjuvant immunotherapy in patients with satellite or in transit metastases has not yet been reported. All of our patients achieved a pathological response in all metastatic sites, as well as in the advanced primary. In this context it is notable that radiological tumour assessment seems to underestimate pathological response, which is important not only in the neoadjuvant but also in the palliative setting.^{5,6} Furthermore, continuous (photographic) documentation of satellite or in transit metastases before and during neoadjuvant therapy is advisable to ensure that the lesions can be located exactly for surgery.

Altogether, our results provide evidence that neoadjuvant treatment by immune checkpoint blockade is effective also for satellite and in transit metastases. Additional investigations with a larger number of patients and a longer follow-up will be needed to validate these findings.

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