Immunochemotherapy - A Missed Opportunity for Metastasized Malignant Melanoma? Reporting a Therapeutic Success with Checkpoint Inhibitor Rechallenge after Cytotoxic Immuno-Primming in a Heavily Pretreated Patient

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**Keywords**
Melanoma · Immunogenetic cell death · Immunochemotherapy · Double checkpoint inhibition

**Abstract**
Treatment of metastasized malignant melanoma still has very limited therapeutic options. After exhaustion of immuno-checkpoint inhibition (ICI) and potentially targeted therapy, no promising alternatives are currently available. We report on an 83-year-old patient suffering from disseminated metastatic melanoma who showed an almost complete response to ICI following chemotherapy, after repeated failure of different regimens including two nonresponsive regimens of ICI. The presented outcome suggests a cytotoxic immuno-priming, facilitating a response to prior nonresponsive ICI. As this concept has not been established until now for malignant melanoma, in contrast to multiple other cancer entities, our case report corroborates previous evidence and therefore suggests a new treatment option, which should be researched further.
**Introduction**

Current guidelines for metastatic melanoma recommend the use of immuno-checkpoint inhibitors (ICI) in the absence of therapeutically targetable gene mutations [1]. ICI have shown remarkable benefits in overall survival in comparison to chemotherapy, but despite these considerable improvements, a significant number of patients do not benefit from these new therapies.

At the same time, therapy regimens combining ICI and chemotherapy are successfully established for multiple cancer entities. The underlying mechanism providing better outcome is most likely also an improved response to ICI by immunogenic cell death caused by chemotherapy [2, 3]; apoptosis caused by chemotherapy increases antigen presentation and release of costimulatory signals creates a proinflammatory environment, by this overriding tumor resistance to immunotherapy.

**Case Presentation**

The 83-year-old patient (male, Caucasian) presented himself in our emergency room in July 2016 because of an ulcerated skin lesion and was admitted with the diagnosis of malignant melanoma. Primary location was on the right lower leg, at time of diagnosis with no further cutaneous manifestations.

The patient underwent primary tumor excision with a 2 cm safety margin. Histological exam of tumor and sentinel lymph node confirmed the diagnosis of malignant melanoma and showed one lymphatic metastasis. The tumor was therefore classified as stage IIIC according to AJCC (8th edition) with a tumor thickness of 3.6 mm (TNM pT3b pN1 (sn) cM0). Molecular analysis did not reveal any BRAF or c-kit mutations, but a mutation in the NRAS gene, Codon 61. PD-L1 status was negative. In August 2016, the patient underwent a radical lymphadenectomy in the right inguinal region. Histological exam showed two micrometastases. Operation was followed by adjuvant radiotherapy in the right inguinal region.

In January 2017, cutaneous satellite metastases around the original postoperative scar appeared and palliative therapy was initiated, as shown in Table 1. In regards to the course of treatment, some steps should be outlined in more detail. The only effective systemic treatment until the last course has been the MEK inhibitor trametinib. Given the NRAS-mutation off-label application was based on current literature, showing disease control in about 50% of patients [4]. Treatment was initiated twice, showing a good partial response. It had to be discontinued the first time because of cutaneous toxicity. Tolerability was better the second time on a reduced dose, but progression was recorded after 5 months. Most importantly, in our case, the patient received ICI twice without any clinical response. The first PD1 inhibitor, pembrolizumab, was initiated in March 2017. A year later, in March 2018, CTLA4 inhibitor ipilimumab was employed. For both treatments, the patient did not notice any side effects at all. Due to age and comorbidities, double ICI (ipilimumab and nivolumab) was discarded then.

Running out of treatment options, we decided to apply palliative chemotherapy with dacarbazine (DTIC), as the patient was still in relatively good condition and insisted on continuation. Being well aware of the limited effectiveness of DTIC, rationale for its use was the potential induction of an immunogenic cell death. Accordingly, we prescheduled the subsequent introduction of ICI in case of a response to the chemotherapy. Treatment was well-tolerated and follow-up after 3 cycles showed a partial response, but clinical reevaluation after the 6 cycles of DTIC clearly indicated again disease progression with nodular cutaneous metastases and pronounced edematous swelling. We swiftly started double ICI with nivolumab...
and ipilimumab in May 2020. The decision was based on the fact that the previous mono-
therapies had been well-tolerated, albeit showing no clinical effect.

Once again therapy was well-tolerated with the only documented side effect being a
pruritus with an accompanying exanthem on the trunk. After 4 cycles we saw an exceptional
clinical response that was confirmed through imaging as well. In particular, we observed an
almost complete regression of all skin metastases (Fig. 1, 2) and no detectable signs of
cerebral metastases. A maintenance therapy was initiated, maintaining the complete response
for 8 months, until in March 2021 new skin metastasis appeared, marking the beginning of
recurrent diseases. The patient died 2 months later.

**Discussion/Conclusion**

Even though ICI is an effective and established treatment for metastasized malignant
melanoma, about half of patients do show no response [5]. In the absence of targetable genetic
aberrations, the only systemic treatment left is DTIC, which only shows a response rate of
about 30% [6]. Hence, a large proportion of patients is still left without effective treatment or
runs out of options very fast. In this context, the case presented suggests rethinking current
treatment standards.

Therapy of history with repetitive nonresponsiveness to mono ICI suggests an immuno-
priming by prior cytotoxic therapy. Temporary response to DTIC may have induced immuno-
genic cell death, which subsequently triggered an improved response to ICI, as has been shown
by Grimaldi et al. [3] in the case of lung cancers. According results were published by Vera
Aguilera et al. [7] evaluating retrospective 60 melanoma patients. Those treated after ICI failure
with ICI with chemotherapy versus ICI or chemotherapy alone had an almost doubled overall
survival (3.5 vs. 1.8 years). A similar observation was published by Kan et al. [8], reporting a
case series of 4 melanoma patients showing substantial response to pembrolizumab following
DTIC after primary treatment failure to nivolumab. This outcome raises the question if current
treatment standards have to be reconsidered. Taken the ultimate success of the regimen
combining ICI and chemotherapy, similar approaches might be promising for melanoma as well
and should be investigated. Which sequence (DTIC followed by ICI, DTIC, and ICI combined, or
ICI interrupted by interval DTIC) has to be the subject of future studies? As a side note, the first
reports imply a possible incompatibility of concurrent DTIC and ipilimumab [9].

| Treatment                      | Period       | Response  |  |
|-------------------------------|--------------|-----------|---|
| Radiation location with highest tumor burden | Jan–Mar 2017 | 3 months  | PR (local) |
| Pembrolizumab (PD-L1)         | Mar–Aug 2017 | 6 months  | PD |
| Trametinib                    | Sept 2017–Feb 2018 | 6 months | moderate PR > ADR |
| Ipilimumab (CTLA4)            | Mar–Jun 2018 | 4 months  | PD |
| Trametinib (red.)             | Jun 2018–Nov 2019 | 5 months | moderate PR > PD |
| Stereotactic radiation        | Jan 2020    | *         | PR (brain) |
| DTIC                          | Dec 2019–Apr 2020 | 5 months | PR |
| Nivolumab and ipilimumab (PD-L1 + CTLA4) | May–Aug 2020 | 4 months | CR |
| Nivolumab (PD-L1)             | Aug 2020–Mar 2021 | 8 months | CR > PD > Death |

ADR, Adverse Drug Reaction; CR, Complete Response; PD, Progressive Disease; PR, Partial Remission; red, reduced dose.
As the patient received radiotherapy prior to double ICI, a possible abscopal effect should be mentioned. The effect is described in literature as an observed objective response to radiotherapy outside the radiation field. The course of action, far from being completely understood, is thought to be immune mediated, similar to what has been described for chemotherapy. An increased antigen presentation and a proinflammatory environment are thought to drive these responses [10–15]. Also, other local interventions have been shown to have the potential to induce systemic anticancer immune responses [16]. Still, radiation has most likely no correlation to the described treatment response because of the time gap of about 4 months between radiation and ICI administration. Also, first time use of double ICI with ipilimumab and nivolumab has to be mentioned, as double ICI does show higher response rates,
PFS, and OS, compared to mono ICI [17]. However, previous expositions to ICI, including PD1 and CTLA4 inhibition, did not show any effect at all in our case, and we therefore consider this effect less relevant in explaining this therapeutic success.

In conclusion, our case corroborates the available literature in suggesting a complementary effect of the chemotherapy on the immune-mediated antitumor reaction of ICI also for malignant melanoma. These findings could justify clinical studies testing the hypothesis of effective combination therapies, as has been shown for other tumors. This is especially important given the fact that therapeutic options are limited for those melanoma patients who are not responding to ICI.

**Statement of Ethics**

Written informed consent was obtained from the patient at lifetime and from patient’s next of kin for publication of the details of his medical case and any accompanying images. The presented research was conducted in accordance with the World Medical Association Declaration of Helsinki. Ethical approval is not required for this study in accordance with local and national guidelines.

**Conflict of Interest Statement**

The authors declare no conflict of interest to declare.

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**Author Contributions**

Friedemann Jobst, Nicola Delmastro, and Til R. Kiderlen provided the data. Friedemann Jobst, Nicola Delmastro, and Til R. Kiderlen did the write up. Maike de Wit and Til R. Kiderlen did review the article and provided professional input.

**Data Availability Statement**

All data that support the findings of this study are included in this article. Further inquiries can be directed to the corresponding author.

**References**

1 Michielin O, van Aldooi ACJ, Ascieto PA, Dummer R, Keilholz U. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up †. Ann Oncol. 2019 Dec 1;30(12):1884–901.

2 Bonaventura P, Shekarian T, Alcazer V, Valladeau-Guilemond J, Valsesia-Wittmann S, Amigorena S, et al. Cold tumors: a therapeutic challenge for immunotherapy. Front Immunol. 2019 Feb 8;10:168.

3 Grimaldi A, Cammarata I, Martire C, Focaccetti C, Piconese S, Buccilli M, et al. Combination of chemotherapy and PD-1 blockade induces T cell responses to tumor non-mutated neoantigens. Commun Biol. 2020 Dec;3(1):85.
4. Dummer R, Schadendorf D, Ascierto PA, Arance A, Dutriaux C, Di Giacomo AM, et al. Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2017 Apr 1;18(4):435–45.

5. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015 Jul 2;373(1):23–34.

6. Robert C, Thomas L, Bondarenko I, O’Day S, Weber J, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med*. 2011 Jun 30;364(26):2517–26.

7. Vera Aguilera J, Paludo J, McWilliams RR, Zhang H, Li Y, Kumar AB, et al. Chemo-immunotherapy combination after PD-1 inhibitor failure improves clinical outcomes in metastatic melanoma patients. *Melanoma Res*. 2020 Aug;30(4):364–75.

8. Kan T, Takahagi S, Kawai M, Matsuhashi D, Tanaka A, Hide M. Rechallenge of programmed cell death 1 inhibitor after an interval with dacarbazine treatment may be effective for advanced malignant melanoma. *J Dermatol*. 2020 Aug;47(8):907–10.

9. Yamazaki N, Ubara H, Fukushima S, Uchi H, Shibagaki N, Kiyohara Y, et al. Phase II study of the immune-checkpoint inhibitor ipilimumab plus dacarbazine in Japanese patients with previously untreated, unresectable or metastatic melanoma. *Cancer Chemother Pharmacol*. 2015 Nov;76(5):969–75.

10. Liu Y, Dong Y, Kong L, Shi F, Zhu H, Yu J. Abscopal effect of radiotherapy combined with immune checkpoint inhibitors. *J Hematol Oncol*. 2018 Dec;11(1):104.

11. Gui C, Kleinberg LR, Lim M, Redmond KJ. Extracranial abscopal responses after radiation therapy for intracranial metastases: a review of the clinical literature and commentary on mechanism. *Cureus*. 2019;11(3):e4207.

12. Esposito A, Criscitiello C, Curigliano G. Immune checkpoint inhibitors with radiotherapy and locoregional treatment: synergism and potential clinical implications. *Curr Opin Oncol*. 2015 Nov;27(6):445–51.

13. Ko EC, Formenti SC. Radiotherapy and checkpoint inhibitors: a winning new combination? *Ther Adv Med Oncol*. 2018 Jan;11:10.

14. Brooks ED, Schoenhals JE, Tang C, Micevic G, Gomez DR, Chang JY, et al. Stereotactic ablative radiation therapy combined with immunotherapy for solid tumors. *Cancer*. 2016;22(4):257–66.

15. Postow MA, Callahan CA, Barker S, Yamada M, Yuan AA, Kitano RA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. *N Engl J Med*. 2012;366:925.

16. Falk H, Lamba S, Johannesen HH, Wooler G, Venzo A, Gehl J. Electrochemotherapy and calcium electroporation inducing a systemic immune response with local and distant remission of tumors in a patient with malignant melanoma: a case report. *Acta Oncol*. 2017 Aug;56(8):1126–31.

17. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2017 Oct 5;377(14):1345–56.