Case Reports in Oncology

Case Rep Oncol 2024;17:161–168
DOI: 10.1159/000535902
Received: August 30, 2023
Accepted: December 13, 2023
Published online: January 29, 2024



**Case Report**

# A Dramatic Response to Second-Line Nivolumab and Ipilimumab in BRAF-V600-Mutated Metastatic Melanoma

Dahlia Fedele[a] Stefano Moroso[a] Angelo Turoldo[b] Gabriele Bazzocchi[c] Claudio Conforti[d] Iris Zalaudek[e] Alessandra Guglielmi[a]

[a]Department of Medical Oncology, ASUGI, Maggiore Hospital, Trieste, Italy; [b]University Department of Clinical Surgery, ASUGI, Cattinara Hospital, Trieste, Italy; [c]Department of Diagnostic Imaging, ASUGI, Maggiore Hospital, Trieste, Italy; [d]IDI-IRCCS, Dermatological Research Hospital, Rome, Italy; [e]University Department of Clinical Dermatology, ASUGI, Maggiore Hospital, Trieste, Italy

**Keywords**
Metastatic melanoma · Immune checkpoint inhibitor · BRAF/MEK inhibitor

**Abstract**
***Introduction:*** Current treatment options for BRAF V600-mutated unresectable stage III/IV melanoma include anti-PD-1 monotherapy or combination with anti-CTLA-4 or anti-LAG-3 agents, BRAF/MEK inhibitors, and clinical trials. The strategy of combination immunotherapy with nivolumab and ipilimumab has shown promising results, achieving higher response rates, longer duration of response, improved progression-free survival, and enhanced overall survival. The optimal sequence of treatments remains a topic of interest, with preliminary data suggesting a greater effectiveness of immunotherapy as the first-line approach. Preclinical trials have indicated that the efficacy of this sequence may be due to the modification of the immune environment by BRAF kinase inhibitors, leading to immune escape by tumor cells and resistance to immune checkpoint inhibitors. ***Case Presentation:*** We present a case of a 72-year-old woman with high-burden metastatic melanoma who failed to respond to prior targeted therapy with BRAF/MEK inhibitors and exhibited a successful response to the second-line treatment with ipilimumab and nivolumab. We discuss the potential reasons for this positive outcome contributing to the current debate concerning treatment sequences, resistance mechanisms, and biomarkers predictive of response to immune checkpoint inhibitors in metastatic melanoma. ***Conclusion:*** We believe that in few years the therapeutic algorithms in BRAF V600-mutated unresectable stage III/IV melanoma will be more complex since they will

Correspondence to:
Dahlia Fedele, dahlia.fed@tiscali.it

Case Rep Oncol 2024;17:161–168
DOI: 10.1159/000535902




define clearly the correct therapeutic sequences with the inclusion of new immune checkpoint inhibitor drugs and multiple predictive biomarkers of response to better select patients eligible to immunotherapy.



## Introduction

Current first-line treatments for unresectable stage III/IV BRAF mutated melanoma include anti-PD-1 monotherapy or in combination with anti-CTLA-4 or anti-LAG3 agents, BRAF/MEK inhibitors, and clinical trials. The CheckMate 067 study assessed the benefits of adding ipilimumab to nivolumab. This combination arm showed numerically superior response rates, duration of response, time to subsequent therapies, progression-free survival (PFS), and overall survival, with these benefits persisting at a 6.5-year follow-up [1]. Italian regulatory indications (AIFA) reserve the use of ipilimumab and nivolumab combination for patients with programmed death-ligand 1 (PDL1; clone SP 263) levels <1% or those with asymptomatic brain metastasis in stage IV disease, consistent with literature data [1, 2]. Another promising option, the combination of nivolumab and relatlimab (not currently available in Italy), continues to show significant PFS benefits over nivolumab alone in unresectable or metastatic melanoma after a median follow-up of 25.3 months with an improving trend in melanoma-specific survival, although not statistically significant at the moment [3, 4].

The optimal sequence of treatments for melanoma harboring the BRAF-V600 E mutation, whether target therapy followed by immunotherapy or vice versa, has been the subject of prospective clinical trials, suggesting a trend favoring immunotherapy as a first-line treatment [5, 6]. However, patient-specific factors such as tumor load, LDH level, metastasis site, and individual preferences must be considered in clinical decision-making.

A current focus in solid cancer treatment is to identify molecular biomarkers predictive of response to immune checkpoint inhibitors (ICIs). These biomarkers can be categorized as tumor-intrinsic (e.g., PDL1, tumor mutational burden), tumor microenvironment (e.g., tumor-infiltrating lymphocytes [TILs]), and systemic biomarkers (e.g., circulating factors, microbiota) [7]. PDL1 is a widely recognized biomarker in various solid tumors, including cutaneous melanoma. However, its dynamic and transient expression, along with potential intrapatient and intratumor heterogeneity, limits its reliability as a therapeutic response indicator to ICI [8]. Tumor mutational burden is an index summarizing a tumor's mutational load and shows a linear correlation with ICI efficacy [9] although consensus on the cutoff for its expression level is lacking.

TILs are an heterogeneous population comprising various cell subtypes, including effector and regulatory T-lymphocytes, natural killer cells, dendritic cells, and macrophages [10]. The role of these subpopulations in immunotherapy response is a subject of ongoing research, necessitating further studies to delineate the anti-tumor effects of each subtype.

## Case Report

A 72-year-old woman underwent surgical excision for a pT1 melanoma on her right shoulder in 2008. In June 2020, she had a cutaneous relapse on the right chest wall along the middle axillary line. The histological exam confirmed a metastasis of an amelanotic malignant

melanoma BRAF-V600 E mutated. After radical resection of the lesion and negative staging obtained with CT scan, assuming a pathological stage IV disease with no absolute contraindications, the woman underwent monthly adjuvant nivolumab (480 mg) from September 2020 to August 2021 without any evidence of relapse at the end of the planned period of treatment. The tolerance was good except for mild cutaneous adverse effects not requiring discontinuation of treatment.

In August 2021, the woman experienced episodes of angina and underwent coronary angioplasty. In October 2021, she became symptomatic for severe anemia but endoscopic exams did not reveal any pathological gastrointestinal conditions. A PET/CT scan identified a 2 cm nodule in the right lung and a mild spot on a jejunal loop which was further investigated through an enteral videocapsule that detected an ulcerated and bleeding lesion in the small intestine.

At the end of November 2021, the patient underwent exploratory laparotomy with small bowel resection achieving excellent palliation of anemia. The histological exam confirmed a transmural localization of amelanotic melanoma with pathological mesenteric lymph nodes. Molecular biology assessment showed a BRAF-V600 E mutation and PDL1 (clone SP 263) 0% MEL score 0. The patient then began dabrafenib + trametinib in January 2022 after performing a baseline CT scan that detected a rapidly progressive disease in the right lung and the appearance of peritoneal carcinomatosis. A CT scan after 3 months showed a clear progression of abdominal carcinomatosis (as shown in Fig. 1), consistent with the rapid worsening of clinical conditions.

In May 2022, despite the short interval from the end of adjuvant immunotherapy to the occurrence of distant relapse (2 months) and given the failure of BRAF/MEK inhibitor, we decided to start nivolumab 1 mg/kg + ipilimumab 3 mg/kg as the second-line treatment to pursue symptom palliation. The baseline performance status was very poor due to abdominal swelling, chronic constipation, and pain. After only 1 cycle, the patient experienced a progressive clinical benefit and the CT scan performed in July 2022 demonstrated a partial response >90% both at the pulmonary and abdominal levels, as shown in Figure 2.

In August 2022, the woman started monthly nivolumab (480 mg) as maintenance therapy, which is still ongoing, with further objective response at each subsequent instrumental assessment. The patient is currently in excellent clinical condition and the last CT evaluation in March 2023 showed a complete pulmonary response, as well as further dimensional reduction of the peritoneal nodules, as shown in Figure 3.

## Discussion and Conclusions

This case demonstrates a dramatically response to ipilimumab/nivolumab in a woman with high tumor burden metastatic melanoma BRAF-V600 E mutated recurred at the end of adjuvant anti-PD1 and rapidly progressing during BRAF/MEK inhibitor. The best treatment sequencing to achieve higher benefit in overall response rate (ORR), PFS, and overall survival in patients with BRAF mutation was investigated in prospective trials [5, 6]. In Secombit trial, the ORR of ipilimumab plus nivolumab was numerically higher when given first in the sequence 45% versus 25% [5] and the same finding was showed in retrospective analysis of KEYNOTE-001, KEYNOTE-002, and KEYNOTE-006 where the ORR of pembrolizumab among patients previously treated with BRAF inhibitor (with or without anti-MEK) was 28.4% compared with 44.2% who were BRAF inhibitor-naïve [11]. Similarly, reduced ORR for the second-line combo-immunotherapy after BRAF/MEK inhibitor were also reported in DREAMseq where ORR for ipilimumab plus nivolumab as the first-line and second-line treatments were 46% and 30%, similar to what it has observed in arms A and B of Secombit trial [6].

Case Rep Oncol 2024;17:161–168
DOI: 10.1159/000535902



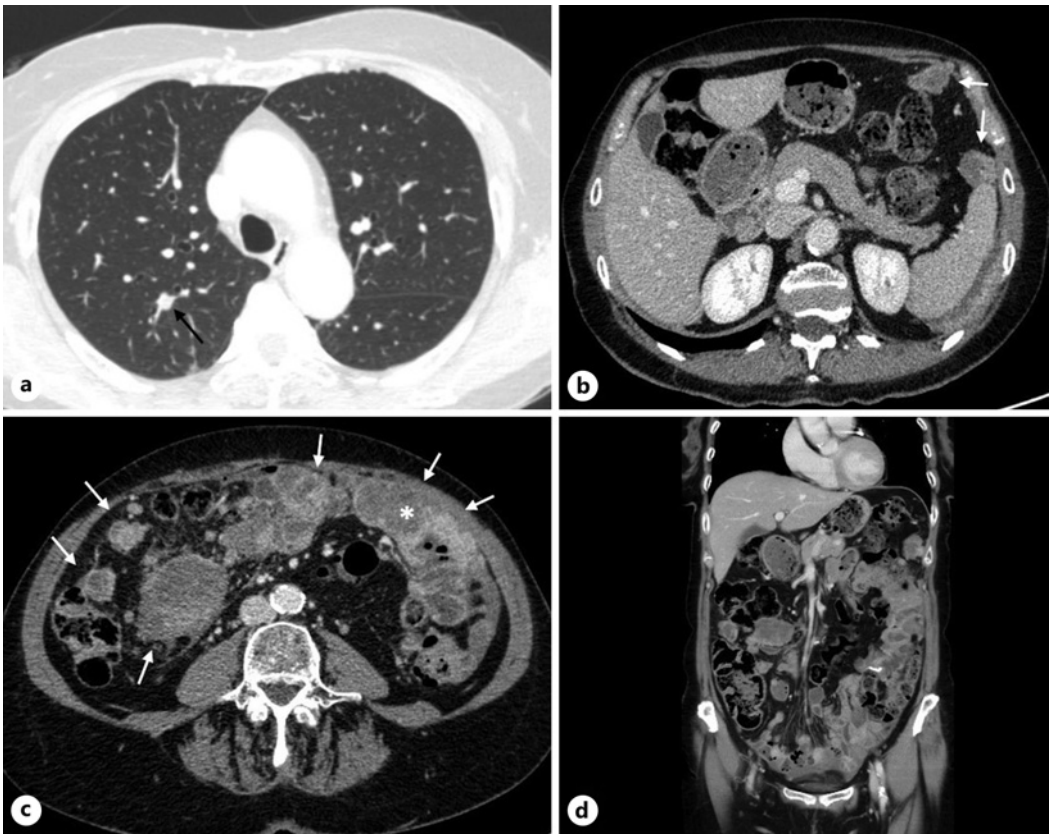


**Fig. 1.** Baseline evaluation after target therapy. Volumetric CT MPR images in the axial (**a**–**c**) and coronal (**d**) planes after intravenous contrast media administration. **a** There is a metastasis (black arrow) in the posterior segment of the upper lobe of the right lung. Multiple metastatic implants on the peritoneal surface (white arrows) ranging in size from a few millimeters to masses (**b**, **c**). The omentum, located anteriorly and to the left of the midline, appears stranded and bulky from confluent nodules (asterisk). Coronal image (**d**) shows confluent metastatic sites at the level of the omentum (left abdominal quadrants) and a small amount of peritoneal effusion in the pelvis.

Furthermore, a recent study highlighted a deleterious impact of target therapy in case of relapse treatment with ICI. These observations are related to the modification of the immune environment by BRAF inhibitor, specifically the acquired resistance to anti-MAPK-targeted therapy contributes to an immune-evasive tumor microenvironment and resistance to immunotherapy. Such resistance was related to a decrease in CD3+ and CD8+ T-cell infiltration and CD103+ dendritic cell depletion in targeted therapy-resistant tumors when compared to target therapy naive melanoma patients [12].

The peculiarity of our clinical case was the lack of objective response to BRAF/MEK inhibitor (normally expected in 65–70% of treated patients) and an unexpected clear and rapid clinical-radiological response to combo-immunotherapy after a disease relapse within 6 months of the end of adjuvant anti-PD1. Post-combo-target therapeutic choices, in a context of such rapid evolution of disease, could have been chemotherapy, immunotherapy (ipilimumab alone or ipilimumab/nivolumab), or best supportive care. The decision to start nivolumab again, with the reinforcement of ipilimumab, was made considering the ORR of 58% and the DOR at 6.5 years not yet reached found in Checkmate 067 trial even if the patients enrolled were previously untreated [1]. However, because of different mechanisms of action, ipilimumab may have overcome the resistance to PD-1/PD-L1 inhibitors by promoting tumor-specific CD8+

Case Rep Oncol 2024;17:161–168
DOI: 10.1159/000535902




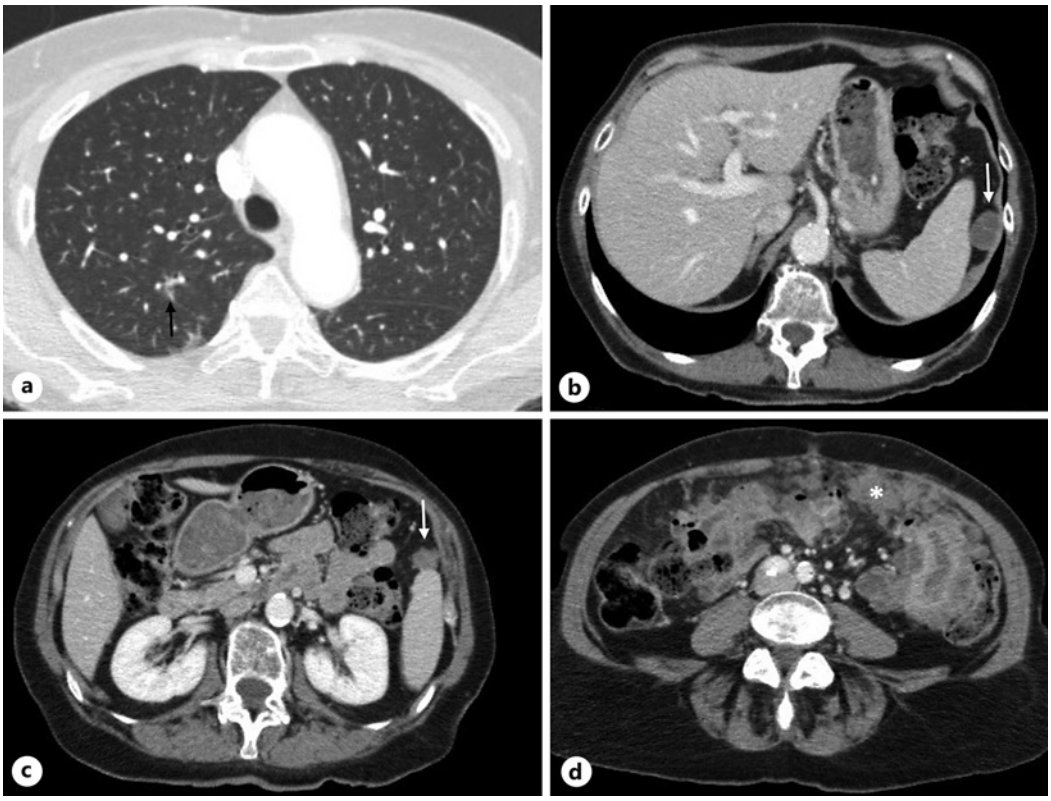


**Fig. 2.** First CT control 2 months after the start of immunotherapy. Volumetric CT MPR images in the axial (**a**–**d**) planes after intravenous contrast media administration. **a** Reduction in size of lung metastasis appearing as a ground-glass band (black arrow) in the posterior segment of the upper lobe of the right lung. **b**–**d** Reduction in size and density of peritoneal nodules (white arrows) and omental masses with initial restoration of fat density between confluent nodules (asterisk).

T-cell proliferation [13] and depleting CTLA-4-positive regulatory T cells through antibody-dependent cell-mediated cytotoxicity. Therefore, the anti-CTLA-4 may have resensitized tumor cells to nivolumab by promoting T-cell priming and reducing T regulatory cells [14].

Furthermore, we can also assume that the activation of the immune system of the woman has already occurred in the adjuvant setting so as to have guaranteed a coverage from re-currences during the year of therapy and the coronary disease could have contributed to a depression of immune system then worsened by ileal resection resulting in faster disease progression; we can also speculate that the duration of the combo-target therapy (3 months only) was too short, due to a primary resistance of the tumor cells, to be able to determine a cross-resistance.

Limitations of this clinical case are certainly the lack of tissue collection for tumor microenvironment analysis in order to support all the above considerations, second to have not tested other predictive biomarkers in addition to PDL1, this one mandatory for the combo-immunotherapy administration. We, however, believe that this case could contribute for a debate regarding still unresolved issues in metastatic melanoma topic: which right therapeutic sequence, which patients to enroll to combo-immunotherapy, when to re-introduce immunotherapy for metastatic disease after adjuvant immunotherapy, which predictive biomarkers of response can be considered in clinical practice?

The availability of predictive biomarkers for immunotherapy could help clinicians choose the best therapeutic strategy for melanoma patients. To date reliable biomarkers able to

Case Rep Oncol 2024;17:161–168
DOI: 10.1159/000535902



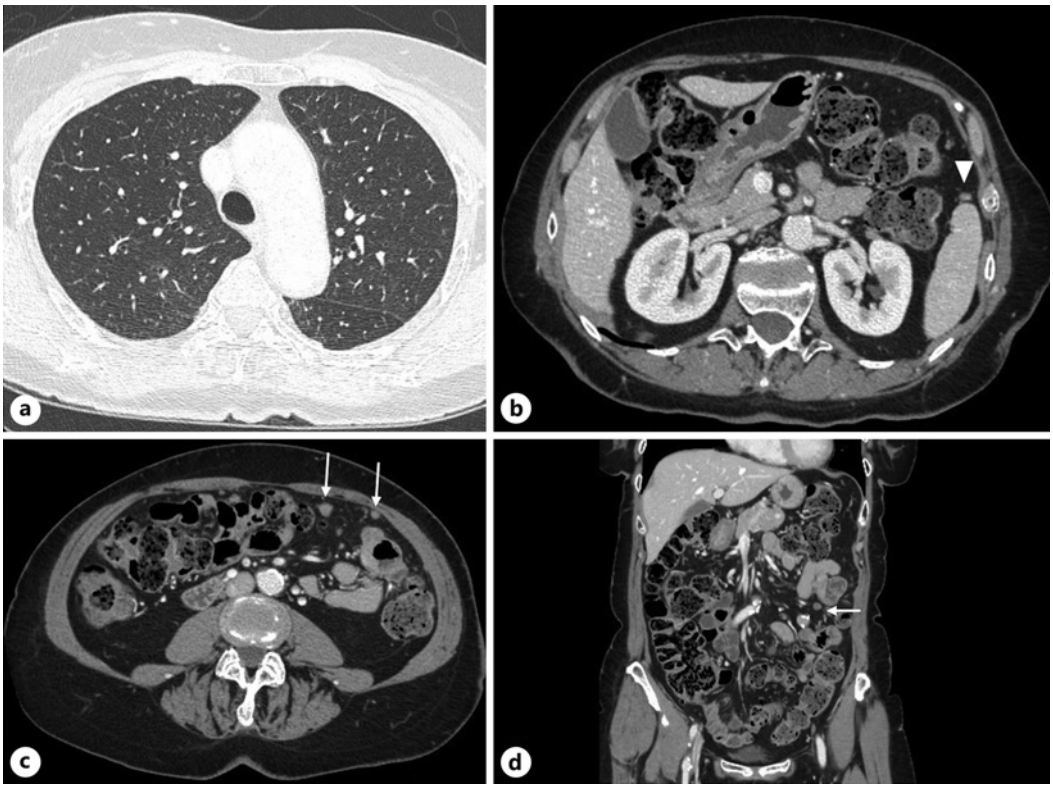


**Fig. 3.** Third CT control 10 months after the start of immunotherapy. Volumetric CT MPR images in the axial (**a**–**c**) and coronal (**d**) planes after intravenous contrast media administration. **a** The pulmonary metastasis is no longer visible in the posterior segment of the upper lobe of the right lung. **b**–**d** Further reduction in size of peritoneal nodules (arrowhead) and omental masses are no longer present but only small and isolated nodules (white arrows) with restoration of omental and mesenteric fat density.

predict ICI efficacy in melanoma are lacking and despite several of them it has been proposed (e.g., PDL 1, tumor mutational burden, TILs, and systemic biomarkers), it seems that single factor could not summarize the entire complexity of cancer [7]. The hypothesis that multiple biomarkers could predict the efficacy of immunotherapy led to the concept of "a cancer immunogram" [15] and in line with this concept some predictive tools have been developed but they should be tested prospectively to assess their use in clinical practice [7].

We believe that the future landscape of metastatic melanoma therapy will define clearly the correct therapeutic sequences providing in addition new immune-ICI drugs and the inclusion of multiple predictive biomarkers of response to better select patients suitable to immunotherapy. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535902).

## Statement of Ethics

Ethical approval is not required for this report in accordance with local and national guidelines. The patient gave her written informed consent to publish her case (including publication of diagnostic images).

## Conflict of Interest Statement

The authors disclose any possible conflicts of interest.

## Funding Sources

This article is not a research work but a case report. No funds were requested for the evaluation of this clinical case and for the drafting of the case report.

## Author Contributions

Dahlia Fedele, Stefano Moroso, Angelo Turoldo, Gabriele Bazzocchi, Claudio Conforti, Iris Zalaudek, and Alessandra Guglielmi participated in drafting the work and reviewing it critically for specific content (dermatological, oncological, surgical and radiological evaluation), have given their final approval to the version to be published and agree to be responsible for all aspects of the work ensuring the veracity of the data exposed, and gave substantial contributions to the conception and design of the work, G. Bazzocchi also for interpretation of radiologic parts.

## Data Availability Statement

The patient's clinical data relating to this case report are not publicly available for legal (privacy) reasons. If necessary, further inquiries can be directed to the corresponding author. Online supplementary materials include 3 figures and legends. The image files are available in the original DICOM file if required.

## References

1 Wolchok JD, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Long-Term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. J Clin Oncol. 2022;40(2):127–37.
2 Tawbi HA, Forsyth PA, Hodi FS, Algazi AP, Hamid O, Lao CD, et al. Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (CheckMate 204): final results of an open-label, multicentre, phase 2 study. Lancet Oncol. 2021;22(12):1692–704.
3 Tawbi HAMD, Schadendorf D, Lipson EJ, Ascierto PA, Matamala L, Castillo Gutiérrez E, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. N Engl J Med. 2022;386(1):24–34.
4 Long GV, Stephen Hodi F, Lipson EJ, Schadendorf D, Ascierto PA, Matamala L, et al. Overall survival and response with nivolumab and relatlimab in advanced melanoma. NEJM Evid. 2023;2(4).
5 Ascierto PA, Mandalà M, Ferrucci PF, Guidoboni M, Rutkowski P, Ferraresi V, et al. Sequencing of ipilimumab plus nivolumab and encorafenib plus binimetinib for untreated BRAF-mutated metastatic melanoma (SECOMBIT): a randomized, three-arm, open-label phase II trial. J Clin Oncol. 2023;41(2):212–21.
6 Atkins MB, Lee SJ, Chmielowski B, Tarhini AA, Cohen GI, Truong TG, et al. Combination Dabrafenib and Trametinib versus combination nivolumab and ipilimumab for patients with advanced BRAF-mutant melanoma: the DREAMseq trial-ECOG-ACRIN EA6134. J Clin Oncol. 2023;41(2):186–97.
7 Garutti M, Bonin S, Buriolla S, Bertoli E, Pizzichetta MA, Zalaudek I, et al. Find the flame: predictive biomarkers for immunotherapy in melanoma. Cancer. 2021;13(8):1819.
8 Gibney GT, Weiner LM, Atkins MB. Predictive biomarkers for checkpoint inhibitor-based immunotherapy. Lancet Oncol. 2016;17(12):e542–e551.
9 Vokes NI, Liu D, Ricciuti B, Jimenez-Aguilar E, Rizvi H, Dietlein F, et al. Harmonization of tumor mutational burden quantification and association with response to immune checkpoint blockade in non–small-cell lung cancer. JCO Precis Oncol. 2019(3):1–12.

Case Rep Oncol 2024;17:161–168
DOI: 10.1159/000535902




10 Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nat. 2008;454(7203):436–44.
11 Puzanov I, Ribas A, Robert C, Schachter J, Nyakas M, Daud A, et al. Association of BRAF V600E/K mutation status and prior BRAF/MEK inhibition with pembrolizumab outcomes in advanced melanoma: pooled analysis of 3 clinical trials. JAMA Oncol. 2020;6(8):1256–64.
12 Haas L, Elewaut A, Gerard CL, Umkehrer C, Leiendecker L, Pedersen M, et al. Acquired resistance to anti-MAPK targeted therapy confers an immune- evasive tumor microenvironment and cross-resistance to immunotherapy in melanoma. Nat Cancer. 2021;2(7):693–708.
13 Pitt JM, Vétizou M, Daillère R, Roberti MP, Yamazaki T, Routy B, et al. Resistance mechanisms to immune-checkpoint blockade in cancer: tumor-intrinsic and -extrinsic factors. Immunity. 2016;44(6):1255–69.
14 Arce Vargas F, Furness AJS, Litchfield K, Joshi K, Rosenthal R, Ghorani E, et al. Fc effector function contributes to the activity of human anti-CTLA-4 antibodies. Cancer Cell. 2018;33(4):649–63.e4.
15 Blank CU, Haanen JB, Ribas A, Schumacher TN. CANCER IMMUNOLOGY "the cancer immunogram". Science. 2016;352(6286):658–60.