# Potential immune-related adverse events during dabrafenib and trametinib treatment: A case series of patients with BRAF V600E melanoma

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Received April 7, 2022; Accepted July 27, 2022

DOI: 10.3892/mco.2022.2598

**Abstract.** In recent years, BRAF inhibitors (BRAFi) and MEK inhibitors (MEKi), together with immune checkpoint inhibitors (ICIs), have changed the therapeutic strategy of cutaneous melanoma, both in adjuvant and metastatic settings. These inhibitors have significantly improved the clinical outcome for patients with melanoma, including in both BRAF-mutated and BRAF-wild type disease. Some preclinical and clinical studies have revealed that BRAFi and MEKi are able to influence T- and B-cell activation, and to modulate immune system activation within the tumor microenvironment. Dabrafenib and trametinib have been shown to enhance the expression of melanoma antigens on BRAF-mutated cells, and to favor both a cytotoxic and immune response against melanoma cells. Thereby, the present study described a case series of five women treated with BRAFi and MEKi, in both adjuvant and metastatic settings, that experienced potential immune-related adverse events. In particular, these patients exhibited sarcoidosis, mesenteric panniculitis, lymphocytic colitis and neuropathy of phrenic nerve. Considering that T and B cells are responsible for immune-related adverse events, as observed in patients treated with ICIs, the present study suggested a possible role of BRAFi and MEKi as triggers of immune system activation and subsequent immune-related toxicities.

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*Abbreviations:* BRAFi, BRAF inhibitors; EBUS-TBNA, EndoBronchial UltraSound-guided TransBronchial Needle Aspiration; FFPE, formalin-fixed paraffin-embedded; ICIs, immune checkpoint inhibitors; MDA, melanocyte differentiation antigens; MEKi, MEK inhibitors; PCR, polymerase chain reaction; SLN, sentinel lymph node; TILs, tumor infiltrating lymphocytes; WB, whole body

*Key words:* immune-related adverse events, target therapy, melanoma

## Introduction

Target therapy in adjuvant and metastatic settings represents an unprecedented novelty in the history of cutaneous melanoma treatment. In the last few years, the introduction of immune checkpoint inhibitors (ICIs) and target therapy significantly improved clinical outcome of metastatic melanoma patients, leading to 5-years survival rates of 30% (1,2). This benefit has been reached both in BRAF-mutated and BRAF-wild type disease.

Dabrafenib (BRAF inhibitor, BRAFi) and trametinib (MEK inhibitor, MEKi) have dramatically reduced risk of relapse and disease progression in BRAF-mutated cutaneous melanoma and they have been recently approved in adjuvant therapy for stage III melanoma. In addition to specific molecular mutations targeting, an influence on antitumor immunity and immune surveillance has been described. In particular, several preclinical studies showed that target therapy may modify tumor immune microenvironment, T cell infiltration and T cell activity (3). BRAFi and MEKi's adverse events include cutaneous side-effects, asthenia, nausea, pyrexia, arthralgia, cardiovascular events, such as QT-prolongation or decreased left ventricular ejection fraction and eye complications are the most frequent (4).

We report here five cases of adult women affected by stage III or IV melanoma, treated with BRAFi and MEKi. All patients were admitted to our Hospital (Oncology Clinic, AOU Ospedali Riuniti di Ancona, Ancona, Italy) and provided written informed consent for the publication of their data. They experienced rare adverse events, from which an immune-related etiopathogenesis can be assumed.

## Case report

*Case 1*. A forty-nine years-old woman was diagnosed with a right back melanoma. In April 2019 she underwent surgery: a local excision of the primary tumor was performed. Histological report showed superficial spreading melanoma, Breslow thickness was 4.8 mm and 15 mitoses mmq were found; neither ulceration nor regression signs were described. Genomic DNA was isolated from formalin-fixed paraffin-embedded (FFPE) tumor tissue and tumor molecular characterization detected by Real-Time PCR (polymerase chain reaction) showed a BRAF mutated melanoma (exon 15, V600E). In May 2019 the patient underwent a whole body (WB) CT-scan that did not reveal distant metastases. A safety margins re-excision was performed together with right axillary and inguinal sentinel lymph node (SLN) biopsy: the latter was positive for melanoma metastasis. Furthermore, a right inguinal-iliac-obturator dissection was carried out, but no metastases were found. Finally, as part of an expanded access program active at our Hospital, in June 2019 she started an adjuvant therapy combining BRAFi/MEKi dabrafenib and trametinib. In February 2020 a WB CT-scan found out mediastinal lymphadenopathies (Fig. 1). A bronchoscopy and fine needle aspiration were thus performed and the pathological report revealed sarcoidosis. No medical treatment was made and target therapy was continued without interruption. A CT-scan in September 2020 did not show disease recurrence or signs of sarcoidosis in mediastinal lymph nodes. She completed one year-lasting adjuvant treatment in May 2020. To date, she is still disease free.

*Case 2*. A fifty-nine years old woman was diagnosed with a melanoma of the back and she underwent surgery in December 2020. Histological diagnosis showed superficial spreading melanoma: ulceration was present, Breslow thickness was 2.8 mm, and 20 mitoses/mq were found. No regression was detected and Tumor Infiltrating lymphocytes (TILs) 'non brisk'; surgical margins were tumor-free. Genomic DNA was isolated from FFPE tumor tissue and tumor molecular characterization detected by PCR displayed a BRAF mutated melanoma (exon 15, V600E). A WB CT-scan showed no distant metastases. In February 2021 she underwent surgical margins radicalization, showing no residual disease. Bilateral axillary sentinel lymph nodes were removed showing a 1.1 mm metastatic focus in the right axilla and a 1.3 mm focus of infiltration in the left axilla. Stage of disease, according to AJCC VIII edition, was pT3b pN2a cM0 (IIIC). In April 2021 the patient started adjuvant therapy with dabrafenib and trametinib. Since the beginning of treatment, she experienced dyspnea. She performed a chest X-Ray highlighting an elevation of diaphragm, that was bilateral but more evident on the right side. An electromyography showed a right chronic phrenic nerve neuropathy. A diagnosis of neuritis caused by BRAFi/MEKi was made and in December 2021 she completed one-year adjuvant therapy with dabrafenib and trametinib, without reporting further side effects. Subsequent CT scans showed unchanged images about diaphragm elevation.

*Case 3*. In July 2019 a 65 years old woman underwent surgery for a pigmented lesion on the sole of the right foot with histological diagnosis of acral lentiginous melanoma, with vertical growth phase, V Clark level, 5.2 mm Breslow thickness, 18 mitoses/mmq, no TILs, with neoplastic vascular and endolymphatic invasion. A sentinel lymph node was removed and showed multiple melanoma microfoci in the subcapsular area, with the largest one of 0.1 mm. Molecular investigation (using the Real Time PCR method) on FFPE tumor tissue further revealed a mutation of *BRAF* gene (V600E). WB CT scan showed no distant metastases. According to AJCC VIII edition, stage of disease was pT4b pN1a cM0 (IIIA). History revealed that the patient was a strong smoker, suffering from arterial hypertension receiving medical therapy. Her family history included diagnosis of acral melanoma in a first-degree family member.

After surgery, in November 2019, the patient started an adjuvant therapy with BRAFi/MEKi combination (dabrafenib plus trametinib). A CT scan performed in July 2020 highlighted conglobate lymphadenopathies with partial necrotic contextual aspects mainly in the right middle mediastinum, in the paratracheal area involving the Barety loggia and up to the right tracheo-bronchial corner with a maximum diameter of 2.5 cm. The case was discussed in a multidisciplinary meeting. An EndoBronchial UltraSound-guided TransBronchial Needle Aspiration (EBUS-TBNA) was performed and histological examination of mediastinal lymphadenopathies showed granulomatous lymphadenitis. At that time the patient did not complain of cough or dyspnea.

Therefore the patient resumed treatment with dabrafenib and trametinib and no steroid or medical therapy was performed. She completed one year of adjuvant therapy in November 2020 and did not report any other toxicity. Chest CT-scan performed in February and May 2021 showed a progressive reduction of mediastinal lymphadenopathies.

*Case 4*. In November 2014, a 74-years old woman experienced a painful swelling on the right axilla hollow. In December 2014 she underwent agobiopsy with histological diagnosis of metastasis from melanoma. A CT-scan showed subcutaneous metastases and lymphadenopathies on axillary, supraclavicular and mediastinal regions. Because of non-suspicious cutaneous lesion identified by Dermatologist and the presence of V600E BRAF mutation on histologic sample (detected with PCR and pyrosequencing on FFPE tumor tissue), the patient began a target therapy with dabrafenib and trametinib from February 2015 (within an expanded access program active at our Hospital). In June 2015 and May 2017 the patient was subjected to gamma-knife radiosurgery on cerebral lesions, located in the right insular region and right deep parietal region.

CT-scan controls performed during treatment reported a stable disease. In January 2019, the patient reported episodes of diarrhea that required hospitalization in a Medicine Department because of dehydration. Creatinine clearance was 12.76 ml/min upon admission and gastrointestinal symptoms were associated with electrolyte and acid-base disorders, leading to a clinical diagnosis of prerenal acute kidney injury. Fecal cultures resulted negative for *Salmonella*, *Shigella* and *Yersinia*, as well as parasitological exams. Campylobacter antigens were detected in fecal samples. A colonoscopy revealed no macroscopic lesions on intestinal mucosa and

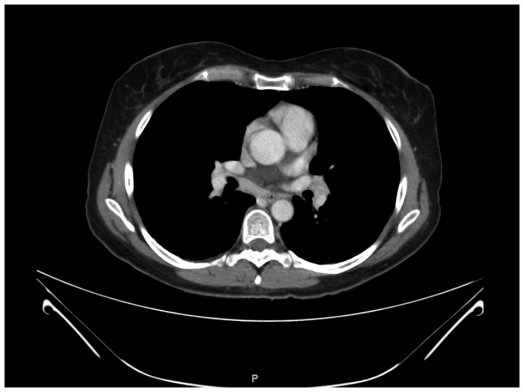

Figure 1. Case number 1. Thoracic CT-scan of February 2020 found out mediastinal lymphadenopathies.

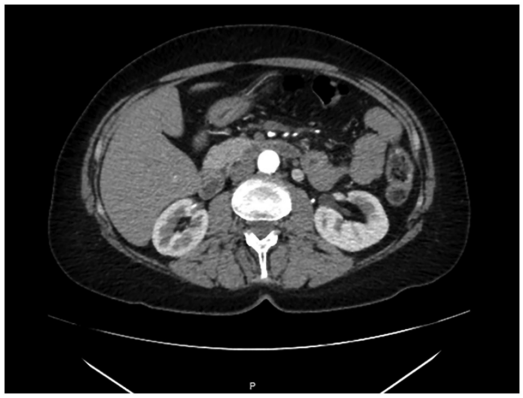

Figure 2. Case number 5. CT-scan of October 2018 showed thickening of mesenteric adipose tissue, suggesting a condition of mesenteric fibrosis.

random biopsies were performed. The histologic examination showed microscopic features of lymphocytic colitis.

A treatment with metronidazole was administered, along with mesalazine and probiotics. Campylobacter infection has been demonstrated to be correlated with lymphocytic colitis, and the patient required both antibiotic and anti-inflammatory therapy. Therapy with dabrafenib and trametinib was interrupted at the beginning of gastrointestinal symptomatology, since January 2019. Clinical conditions gradually improved during the hospitalization and the patient was dismissed after renal function recovery.

In March 2019, the patient went to the Emergency Department for recurrence of diarrhea and sickness: hematological exams showed increase of creatininemia, hypocalcemia and hypokalemia, associated with metabolic acidosis. Abdomen ultrasound described diffuse distension of the loops of the small and large intestine with hypermotility. Coproculture and *Clostridium difficile* antigens research were negative, while urine culture showed presence of colonies of Klebsiella pneumoniae and Escherichia coli ESBL negative. Antibiotic therapy was administered, along with fluid. In March 2019, the patient started anti-inflammatory treatment with oral mesalazine and budesonide. Therapy with dabrafenib and trametinib was suspended from January 2019 until recovery from acute symptoms, and it was resumed from Aprile 2019 at reduced dosage (dabrafenib 75 mg 1 capsule twice daily instead of 2 capsules twice daily; trametinib 2 mg daily).

Since April 2019, the patient has not experienced severe gastrointestinal symptoms and dabrafenib and trametinib were administered at full dose along with anti-inflammatory treatment. Budesonide was stopped in September 2019, while mesalazine was administered for several months. The ongoing need to prolong anti-inflammatory therapy (both steroidal and non-steroidal drugs) leads to suppose that the infectious origin has not been the only cause of the symptoms.

Radiological exams from the beginning of antitumoral therapy showed stable disease on all metastatic lesions and dabrafenib and trametinib treatment is currently ongoing at full dose with no further toxicities.

*Case 5*. A 51-year old female patient underwent an excision of cutaneous lesion on the left arm in 2010. Histological exam revealed the presence of cutaneous melanoma, with the following features: Clark level III invasion, 0.85 mm Breslow index, 2 mitoses/10 HPF, medium TILs (non-brisk), absence of neoplastic vascular invasion (stage at diagnosis pT1b pN0 cM0). Furthermore, V600E BRAF mutation involving the exon 15 was identified, by using direct sequencing of PCR on FFPE tumor tissue. According to the clinical guidelines, she started a clinical and radiological follow up. After two years from diagnosis, CT-scan showed pathological lymph nodes on the left axillary region, so a left axillary lymphadenectomy was performed. The histological examination was positive for metastasis of melanoma in 16 out of 25 lymph nodes. No other pathological localizations were detected and a new follow up based on the alternation between CT scan and PET examination was started. In 2013 another left axillary lymphadenectomy was performed based on 18-FDG PET-CT results and the histological examination was positive for melanoma relapse in 2 out of 6 lymph nodes.

CT-scan performed in May 2015 revealed pathological lymphadenopathies on right axillary and left inguinal regions. No visceral or cerebral disease was identified. The histological examination confirmed relapse of melanoma in the lymph nodes detected at the CT-scan.

Since June 2015, the patient started a first line treatment with the combination of BRAFi and MEKi (dabrafenib plus trametinib), resulting in a partial response of the disease during the CT-scan control of October 2015 and reporting no disturbances.

A CT-scan performed in October 2018 showed thickening of mesenteric adipose tissue with some lymph nodes suggesting a condition of mesenteric fibrosis (Fig. 2). At the clinical exam of December 2018, the patient reported mild abdominal pain for which she performed abdominal ultrasound that confirmed the mesenteric panniculitis shown in the previous CT-scan investigation. The patient reported to assume occasional anti-inflammatory therapy independently and continued treatment with dabrafenib and trametinib without interruptions. In June 2022, the patient was still assuming target therapy with optimal tolerance and radiological evidence of stable disease.

## Discussion

In this manuscript we reported a case series of melanoma patients receiving BRAFi and MEKi, who experienced

Table I. Clinical features of patients with melanoma receiving dabrafenib and trametinib, that experienced potential immune-related adverse events.

| Case | Primary site | Stage at onset of disease | Toxicity | Toxicity treatment |
|---|---|---|---|---|
| 1 | Right back | IIIB | Sarcoidosis | No medical treatment |
| 2 | Back | IIIC | Neuropathy of phrenic nerve | Corticosteroids |
| 3 | Right foot | IIIA | Granulomatous lymphadenitis | No medical treatment |
| 4 | Unknown | IV | Lymphocytic colitis | Metronidazole, mesalazine, budesonide and probiotics |
| 5 | Left arm | IIIC | Mesenteric panniculitis | Occasional anti-inflammatory treatment |

rare adverse events not usually related to target therapy. Specifically, in our clinical practice we have treated five adult women experiencing one of the following conditions during treatment: sarcoidosis, mesenteric panniculitis, lymphocytic colitis and neuropathy of phrenic nerve (Table I). Only two of five patients received a specific anti-inflammatory treatment, with steroid and/or non-steroid medications. In the other cases, symptoms or instrumental findings resolved by themselves.

To our knowledge, other Authors presented single case reports of sarcoid-like reaction in melanoma patients treated with a combination of BRAFi and MEKi. Lheure *et al* (5) described for the first time five cases of sarcoidosis in melanoma patients treated with vemurafenib. In other two reports (6,7), mediastinal lymphadenopathies coherent with sarcoidosis localization occurred in a metastatic patient receiving dabrafenib and trametinib or vemurafenib and cobimetinib. In another case, a young female treated with adjuvant target therapy received diagnosis of granulomatous synechizing uveitis and cutaneous sarcoidosis located near a tattoo (8).

Ben-Betzalel *et al* (9) previously described 10 patients treated with vemurafenib or vemurafenib and cobimetinib, who experienced suspicious immune related events, including vitiligo, uveitis, erythema nodosum and keratitis sicca. The Authors reported an association between those toxicities and PFS (progression free survival), revealing a more durable response to target therapy in the described patients. The side effects we have encountered, with the exception of sarcoidosis, are not yet described in literature and represent novel toxicities due to BRAFi and MEKi treatment.

Clinical, radiological and histological findings of our case series led us to hypothesize an immune-related etiopathogenetic cause of target therapy toxicities. It is interesting to note that all the cases we described concern women: autoimmune diseases are notoriously more frequent in women and this is explained by very different immunological responses between women and men. Regardless of age, women are characterized by a higher numbers of CD4+ T cells and CD4+/CD8+ T cell ratios, compared to men, while androgens seem to have immunosuppressive effects (10). In literature, there are inconclusive results about the incidence of immune-related events between women and men receiving ICIs, with some of these studies showing no sex difference (11-13).

Sarcoidosis, mesenteric panniculitis and lymphocytic colitis are caused by pro-inflammatory molecular mechanisms (14-16) and seem to be all related to an underlying chronic inflammatory process.

Native and adaptive immune cells are potentially involved in triggering BRAFi and MEKi toxicities. Indeed, preclinical and clinical evidence showed that target therapies can influence T-cells activation and modulate the immune system activation within the tumor microenvironment.

Looking at the immune microenvironment of BRAF-mutant melanoma cells, it has been demonstrated by Wang *et al* (17) that CD4+ tumor-infiltrating lymphocytes is more represented in BRAF-mutant tumors, in comparison to BRAF-wild type ones, both in primary and metastatic sites. BRAF-mutant melanoma metastases showed an increased enrichment of CD4+ T cells and B cells, while have a decrease in CD8+ cells, when compared to BRAF-wild type tumor tissues. So, the presence of BRAF-mutation in melanoma cells characterized a distinct tumor and immune microenvironment, that differs from BRAF-wild type melanoma.

In BRAF-mutant tumor cells, an upregulation of MAPK signaling pathway that results in an ineffective immune response and creates a microenvironment inhibitory to T cell functions is known. Thus, BRAF-tumors are able to escape immune surveillance (3). It has been further demonstrated that BRAFi can increase IFNgamma expression of intratumoral CD4+ TILs and decrease proportions of Treg and MDSCs in BRAF-mutated melanoma mouse models (18,19). An enhanced antitumor activity of T cells caused by BRAFi has been revealed along with an up-regulation of melanocyte differentiation antigens (MDA) and MHC expression on cancer cells, which makes cells more susceptible to lymphocyte recognition (20). In addition BRAFi upregulate MHC class I and CD70 molecules on APCs and increase CD8+ T cell infiltration into tumor microenvironment (3,21), enhancing T-cells cytotoxicity in BRAF-mutant and wild type melanoma (22). Wilmott *et al* (23) further reported an increase of CD4+ and CD8+ T-cell infiltrate in tumors of patients with BRAF-mutated metastatic melanoma.

On the other hand, MEKi increase the expression of HLA class I and II on BRAF-mutated and BRAF-wild type melanoma cells (24) and, as reported by Vella *et al* (25), promotes maturation of moDCs, through the inhibition of ERK phosphorylation. In *in vivo* murine models, trametinib decreases a subset of immunosuppression factors and increases CD4+ TILs levels. If combined with anti-PD1 antibodies, it also increases CD8+ cells.

Ultimately, Kuske *et al* (3) affirmed that BRAFi and MEKi exert their activity against melanoma cells also through modulation of native and adaptive immune cells and can restore the immune stimulatory microenvironment.

Both *in vitro* and *in vivo*, an increased expression of melanoma differentiation antigens on BRAF-mutated cells is stimulated by BRAFi (25), along with an enhanced expression of melanoma antigens during the first week of treatment in melanoma patients (26). MEKi suppress PD-L1 expression on melanoma cells, which resulted more susceptible to immune destruction (27). From these results, it can be deduced that the synergy of dabrafenib and trametinib improves antigen-specific T-cell recognition, results in a pro-immunogenic effect on melanoma cells and potentially strengthens immune response against cancer cells.

Whereas the activity of CD4+ and CD8+ lymphocytes is responsible for immune-related adverse events in patients receiving ICIs and there are growing evidences of the influence of dabrafenib and trametinib on these cells, these drugs are likely to be involved in the onset of such toxicities.

Moreover, investigations on exploratory biomarker analyses on tissue samples of patients enrolled in COMBI-AD trial (28) demonstrated that a subgroup of BRAF-mutated melanoma patients characterized by an immune gene signature experienced a very long relapse-free survival. This benefit occurs both in the group receiving dabrafenib plus trametinib as adjuvant therapy and in the group receiving placebo. The immune gene signature corresponds to the high IFNgamma signature subgroup, characterized by specific gene expression of IFNG, CXCL9, CXCL10, CXCL11 and GBP1. Authors confirmed a prognostic role of this immune gene signature in BRAF V600E stage III melanoma patients, conferring them a relatively good clinical outcome and establishing a link between BRAF mutation and immune microenvironment.

Ultimately, we assumed that not only the long-term efficacy but also the adverse events of BRAFi and MEKi might be related to an immunomodulatory activity. In this perspective, sarcoidosis, mesenteric panniculitis and lymphocytic colitis may be interpreted as paradoxical effects caused by excessive stimulation of the immune system by BRAFi and MEKi.

In conclusion, our study suggests that adverse events reported by melanoma patients treated with target therapies should not be underestimated, because of a possible role of immune system activation in triggering onset of toxicities. Rare and unexpected rare events, such as those we have described, can occur and early recognition, appropriate diagnosis and specific medical treatment allow a safe continuation of the therapy. Further preclinical and clinical studies are needed to shed light on the molecular mechanisms and intercellular interactions inside melanoma and immune cells in patients treated with BRAFi and MEKi.

**Acknowledgements**

To analyze BRAF mutational status, tumor molecular characterizations have been carried out on FFPE tumor samples by commercial laboratories: In particular, Laboratory of Pathological Anatomy, 'Ospedale C. e G. Mazzoni', (Ascoli Piceno, Italy) for cases 1 and 2; Laboratory of Pathological Anatomy, 'Ospedali Riuniti di Ancona-Università Politecnica delle Marche' (Ancona, Italy) for cases 3 and 4; Laboratory of Pathological Anatomy, 'Fondazione IRCCS Istituto Tumori di Milano' (Milano, Italy) for case 5.

**Funding**

No funding was received.

**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Authors' contributions**

FM conceived the present study, contributed to data collection and analysis, and critically reviewed the manuscript. VC, LS, NR, VL, AM and FT contributed to data collection and wrote the manuscript. FM and VC contributed to interpretation of data and confirm the authenticity of all the raw data. RB contributed to conception of the manuscript and critically reviewed the data collected. All authors read and approved the final version of the manuscript.

**Ethics approval and consent to participate**

All patients provided their written informed consent for participation to this work.

**Patient consent for publication**

All patients provided their written consent for the publication of their data and associated images.

**Competing interests**

RB is a consultant/advisory board member for Astra Zeneca, Boehringer Ingelheim, Novartis, MSD, Otsuka, Eli-Lilly, Roche. The other authors have no conflicts of interest to declare. FM is a consultant/advisory board member for Novartis.

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