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Letter to the Editor

# BRAF exon 11 mutant melanoma and sensitivity to BRAF/MEK inhibition: Two case reports

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*To the Editor:*

Therapeutic BRAF inhibition is approved for melanoma with a BRAF V600E or V600K mutation (located in exon 15) [1–3]. Infrequent *BRAF* mutations in melanoma, notably the 5% located in exon 11, can be detected by next generation sequencing (NGS) technologies, but the clinical benefit of BRAF/MEK inhibitors in these situations is controversial [4,5]. Here, we report the first two cases of metastatic melanoma with a non-classical BRAF mutation on codon 469 in *BRAF* exon 11 who benefitted from BRAF/MEK inhibition.

## 1. Case report 1

A 42-year-old woman presented with a multimetastatic melanoma with subcutaneous, muscular, lymphatic, pulmonary and brain (n = 3) metastases in January 2018. Mutational analysis based on NGS assay (PGM technology; Thermofisher, Waltham, MA) revealed a p.G469A mutation in exon 11 of *BRAF* associated with a p.L584P mutation in exon 15 of *BRAF*. Initially treated with antiprogrammed cell death 1 (PD1) pembrolizumab in association with stereotactic radiotherapy for three brain metastases, her treatment was switched to ipilimumab when metastatic brain progression was observed but had to be stopped after two infusions because of Common Terminology Criteria for Adverse Events (CTCAE) grade III hepatotoxicity and colitis. When she was admitted to the hospital in July 2018 for impaired general condition (PS 4) and diffuse progression of the disease in the small intestine, cervical vertebrae, brain (9 new lesions) and leptomeningae, the tumour board proposed to test a combination of BRAF and MEK inhibitors (dabrafenib + trametinib) as a salvage therapy. At the first 18F-fluoro-2-deoxy-D-glucose (18FDG) positron-emission tomography (PET)/computed tomography (CT) evaluation, at 3 months, she presented with an excellent clinical response with a decrease of all metastatic sites and a partial response evaluated to 94% according to PET Response Criteria In Solid Tumours. Maintained metabolic response was confirmed at the 6-month re-evaluation by 18FDG-PET/CT. Brain magnetic resonance imaging showed an overall stability except for a 3-mm increase of one of the

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cerebral metastases, which was treated with stereotactic radiotherapy in January 2019 (Fig. 1). The patient's performance status (PS) went from 4 to 0-1, and her lactate dehydrogenase (LDH) level decreased from 573 UI/L to 279 UI/L (N < 159UI/L) between September 2018 and January 2019.

## 2. Case report 2

A 48-year-old patient presented in October 2017 with multiple subcutaneous metastases of a nodular dorsal melanoma harbouring a p.G469S mutation in exon 11 of *BRAF* (c.1406G > S).

After two unsuccessful lines of therapy in two phase I trials evaluating intratumoural ipilimumab with systemic nivolumab (NIVIPIT, NCT 02857569) and nivolumab with castration hormonotherapy (Debiopharm, EUDRACT 2017-001816-12), he presented in October 2018 with a painful epidural metastasis, considerable fatigue (PS 3-4) and weight loss (14 kg in a month). Radiotherapy was performed on his epidural lesion, and dabrafenib and trametinib were initiated 48 h later. One month later, his condition had significantly improved (PS 1), and he had gained 7 kg. His pain was controlled, lymph nodes were clinically reduced in size and LDH levels decreased from 661 UI/L in October 2018 to 360 UI/L (N < 159UI/L) in January 2019. Unfortunately, this impressive clinical response was not durable, and the patient experienced progression in the liver, the lomboaortic and axillary lymph nodes after 3 months. Nevertheless, in spite of the tumour progression, he remained in a relatively good performance status, and he could be enrolled in a phase II clinical trial evaluating the anti-PD1 spartalizumab with an anti-IL1-beta canakinumab (Novartis, NCT 03484923).

## 3. Discussion

This is, to our knowledge, the first report concerning combined anti-BRAF + MEK targeted therapy for patients with metastatic melanoma harbouring a BRAF mutation in exon 11.

Both patients achieved an excellent response associated with a significant improvement in their quality of life for several months. Both patients eventually developed resistance, but they derived a substantial benefit from the targeted therapy with a disease remaining under control for one patient and the possibility to be enrolled in a new clinical trial for the other.

It is noteworthy that baseline characteristics did not predispose them to respond to therapy as they had progressed following immunotherapy and had a

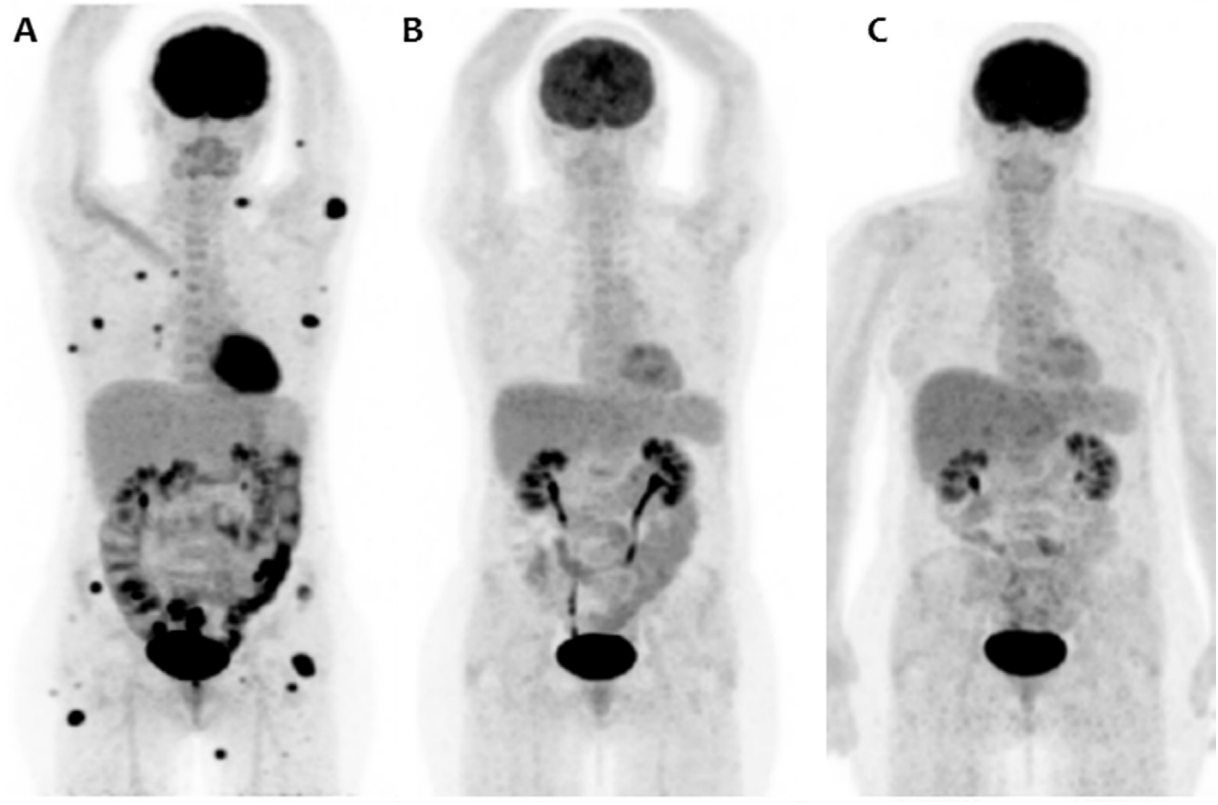


Fig. 1. 18FDG-PET/CT of patient 1 at baseline (A), at week 12 (B) and week 29 (C) of therapy with dabrafenib + trametinib. PET, positron-emission tomography; CT, computed tomography.

very low performance status, multiple metastases and high LDH levels at the time they received targeted therapy.

Because of their low prevalence in melanoma, non-V600 BRAF mutations are not routinely screened, and targeted therapy has not been evaluated in their context. Nevertheless, with the advent of advanced technologies such as NGS, rare *BRAF* mutations can now easily be identified. It is thus critical to explore their theragnostic impact [6–8].

*BRAF* mutations have different functional consequences from low to high kinase activities [9,10]. Class I *BRAF* mutations, such as V600, generate mutant BRAF kinase that strongly activates its downstream effectors MEK and ERK.

In class II mutations, *BRAF* proteins signal as RAS independent dimers; class IIa occur within the activation segment (i.e. L597, K601) and IIb within the glycerin-rich-p-loop. Codon 469 mutations found in our patients, p.G469A (Gly469Ala) and p.G469S (Gly469Ser), belong to the class IIb mutations and are located in the P-loop (464-471) that stabilises ATP and is directly connected to the V600 loop.

Class III mutations induce low kinase activity (G466, D594, Y472) [11].

Class I and IIa are known to be sensitive to combined anti-BRAF and MEK inhibitors [12,13].

For the class IIb mutations, a recently published case report has shown a good clinical efficacy of the combination of dabrafenib + trametinib [14]. This is consistent with *in vitro* and pre-clinical studies demonstrating sensitivity of both G469A and G469S-mutant BRAF to combinations using dabrafenib or encorafenib + anti-MEK [15,16]. However, 'RAF dimer inhibitors' could theoretically be more effective on class IIB mutations because they activate BRAF as a dimer [17].

In our experience, the two variants of the same G469 codon responded well to targeted therapy combining dabrafenib and trametinib.

Mechanisms for secondary resistance are not elucidated yet for this class of BRAF mutations and should be the focus of more research. The *in vitro* effects of dual MAPK inhibitors on G469S seem more subtle, possibly explaining the earlier relapse of one of our patients [16].

For the other patient, the potential theragnostic impact of the additional BRAF mutation that was found in exon 15, p.L584P (Leu584Pro), is currently unknown [18].

Altogether, we think that non-V600 BRAF mutations are important to screen, especially in patients with melanomas who do not respond to immunotherapy as no alternative therapeutic options are available for them.

Finally, this approach should be extended to non-small cell lung cancer (NSCLC) because non-V600 BRAF mutations represent half of *BRAF* mutated tumours [17,19,20].

## Conflict of interest statement

None declared.

## References


[1] Larkin J, Ascierto PA, Dréno B, Atkinson V, Liszkay G, Maio M, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 2014 Nov 13;371(20):1867–76.

[2] Long GV, Hauschild A, Santinami M, Atkinson V, Mandalà M, Chiarion-Sileni V, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. N Engl J Med 2017 09;377(19):1813–23.

[3] Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2018 May;19(5):603–15.

[4] cBioPortal for cancer genomics [Internet]. [cited 2019 Mar 11].

[5] cBioPortal for cancer genomics: BRAF in melanoma (TCGA) [Internet]. [cited 2019 Apr 14].

[6] Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, et al. Mutations of the BRAF gene in human cancer. Nature 2002 Jun 27;417(6892):949–54.

[7] AACR Project GENIE Consortium. AACR project GENIE: powering precision medicine through an international consortium. Cancer Discov 2017;7(8):818–31.

[8] Richtig G, Hoeller C, Kashofer K, Aigelsreiter A, Heinemann A, Kwong LN, et al. Beyond the BRAFV600E hotspot: biology and clinical implications of rare BRAF gene mutations in melanoma patients. Br J Dermatol 2017 Oct;177(4):936–44.

[9] Dhillon AS, Kolch W. Oncogenic B-Raf mutations: crystal clear at last. Cancer Cell 2004 Apr;5(4):303–4.

[10] Dankner M, Rose AAN, Rajkumar S, Siegel PM, Watson IR. Classifying BRAF alterations in cancer: new rational therapeutic strategies for actionable mutations. Oncogene 2018;37(24):3183–99.

[11] Yao Z, Yaeger R, Rodrik-Outmezguine VS, Tao A, Torres NM, Chang MT, et al. Tumours with class 3 BRAF mutants are sensitive to the inhibition of activated RAS. Nature 2017 10;548(7666):234–8.

[12] Bahadoran P, Allegra M, Le Duff F, Long-Mira E, Hofman P, Giacchero D, et al. Major clinical response to a BRAF inhibitor in a patient with a BRAF L597R-mutated melanoma. J Clin Oncol 2013 Jul 1;31(19):e324–6.

[13] Hallmeyer S, Gonzalez R, Lawson DH, Cranmer LD, Linette GP, Puzanov I, et al. Vemurafenib treatment for patients with locally advanced, unresectable stage IIIC or metastatic melanoma and activating exon 15 BRAF mutations other than V600E. Melanoma Res 2017;27(6):585–90.

[14] Reyes R, Mayo-de-Las-Casas C, Teixidó C, Cabrera C, Marín E, Vollmer I, et al. Clinical benefit from BRAF/MEK inhibition in a double non-V600E BRAF mutant lung adenocarcinoma: a case report. Clin Lung Cancer 2019 Mar 4;20(3):e219–23.

[15] Dankner M, Lajoie M, Moldoveanu D, Nguyen T-T, Savage P, Rajkumar S, et al. Dual MAPK inhibition is an effective therapeutic strategy for a subset of class II BRAF mutant melanomas. Clin Cancer Res 2018 Dec 15;24(24):6483–94.

[16] Noeparast A, Teugels E, Giron P, Verschelden G, De Brakeleer S, Decoster L, et al. Non-V600 BRAF mutations recurrently found

in lung cancer predict sensitivity to the combination of Trametinib and Dabrafenib. Oncotarget 2017 Sep 1;8(36):60094–108.

[17] Yaeger R, Corcoran RB. Targeting alterations in the RAF-MEK pathway. Cancer Discov 2019;9(3):329–41.

[18] Bhaumik S, Ahmad F, Das BR. Somatic mutation analysis of KRAS, BRAF, HER2 and PTEN in EGFR mutation-negative non-small cell lung carcinoma: determination of frequency, distribution pattern and identification of novel deletion in HER2 gene from Indian patients. Med Oncol 2016 Oct;33(10):117.

[19] Imielinski M, Berger AH, Hammerman PS, Hernandez B, Pugh TJ, Hodis E, et al. Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing. Cell 2012 Sep 14;150(6):1107.

[20] Lin L, Asthana S, Chan E, Bandyopadhyay S, Martins MM, Olivas V, et al. Mapping the molecular determinants of BRAF oncogene dependence in human lung cancer. Proc Natl Acad Sci USA 2014 Feb 18;111(7):E748–57.