Letter to the Editor

DOI: 10.5582/ddt.2022.01072

A Japanese case of melanoma of unknown origin with a rare *BRAF*^{V600R} mutation was successfully treated with BRAF/MEK inhibitors

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SUMMARY Combination therapy with BRAF and MEK inhibitors (BRAF/MEKi) has shown significantly prolonged progression-free survival (PFS) and overall survival (OS) for *BRAF* mutated melanoma. Over 90% of the activating mutations are *BRAF*^{V600E} or *BRAF*^{V600K} changes. There are no reports of *BRAF*^{V600R} in Japanese patients with melanoma. The third most common *BRAF* mutation is *BRAF*^{V600R}. In this case, we detected the *BRAF*^{V600R} mutation with FoundationOne CDx in a Japanese patient with melanoma.. The patient was treated with BRAF/MEKi and maintained stable disease status for 1 year.

Keywords BRAF, V600R, melanoma, FoundationOne CDx

Letter to the Editor,

Combination therapy with BRAF and MEK inhibitors (BRAF/MEKi) has shown significantly prolonged progression-free survival (PFS) and overall survival (OS) for *BRAF*^{V600E}- and *BRAF*^{V600K}-mutated melanoma (*1*). Mutations in amino acid 600 of the *BRAF* gene account for approximately 50% and 30% of cases of melanomas in Caucasian and Japanese patients, respectively (*2*). Over 90% of the activating mutations are valine (V) to glutamic acid (E) (*BRAF*^{V600E}) or valine (V) to lysine acid (K) (*BRAF*^{V600K}) changes (*3*). The third most common *BRAF* mutation is from valine (V) to arginine (R) (*BRAF*^{V600R}), which accounts for 1-4% of cases (*3*). There are no reports of *BRAF*^{V600R} in Japanese patients with melanoma. Here, we report a case of melanoma with *BRAF*^{V600R} that was successfully treated with BRAF/MEKi.

A 67-year-old Japanese man presented to our hospital with axial lymph node swelling and subcutaneous nodules. Fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) revealed metastatic lesions in the lungs, liver, duodenum, bone, and lymph nodes (Figure 1A). As no primary melanoma lesion was identified, a diagnosis of melanoma of unknown primary origin was made based on a biopsy of the subcutaneous nodule. Companion diagnostic tests (Cobas 4800 BRAF V600 Mutation Test; Roche Molecular Diagnostics, Pleasanton, CA, USA) did not show *BRAF*^{V600E} or ^{V600K} mutations. Therefore, combination therapy with anti-cytotoxic-T-lymphocyte-associated antigen 4 (anti-CTLA-4) and anti-programmed cell death-1 (anti-PD-1) antibodies was initiated. After the second course, hepatitis was diagnosed as an immune-related adverse event (irAE). The patient was treated with prednisolone (2 mg/kg/day), and hepatitis improved after 4 weeks. On a CT scan after irAE resolution, disease progression (PD; RECIST 1.1) was observed. Then, a cancer genome profiling test (FoundationOne CDx, which detects base substitutions, insertions, deletions, copy number abnormalities, and rearrangements in 324 genes) was performed. As shown in Figure 1B, the *BRAF*^{V600R} mutation was evident. The patient was treated with BRAF/MEKi and maintained stable disease status for 1 year (Figure 1C).

BRAF^{V600R} has been reported to increase the ability to activate MEK by increasing ERK phosphorylation as well as BRAF^{V600E} and BRAF^{V600K} (*4*). Some patients in Australia responded to BRAF/MEKi (*5*). However, clinical practice has shown that non-V600E/K BRAF mutations cannot be detected with the current companion diagnostic tests. Therefore, some patients with melanoma may have missed treatment opportunities, although the probability is low.

In this case, we detected the *BRAF*^{V600R} mutation with

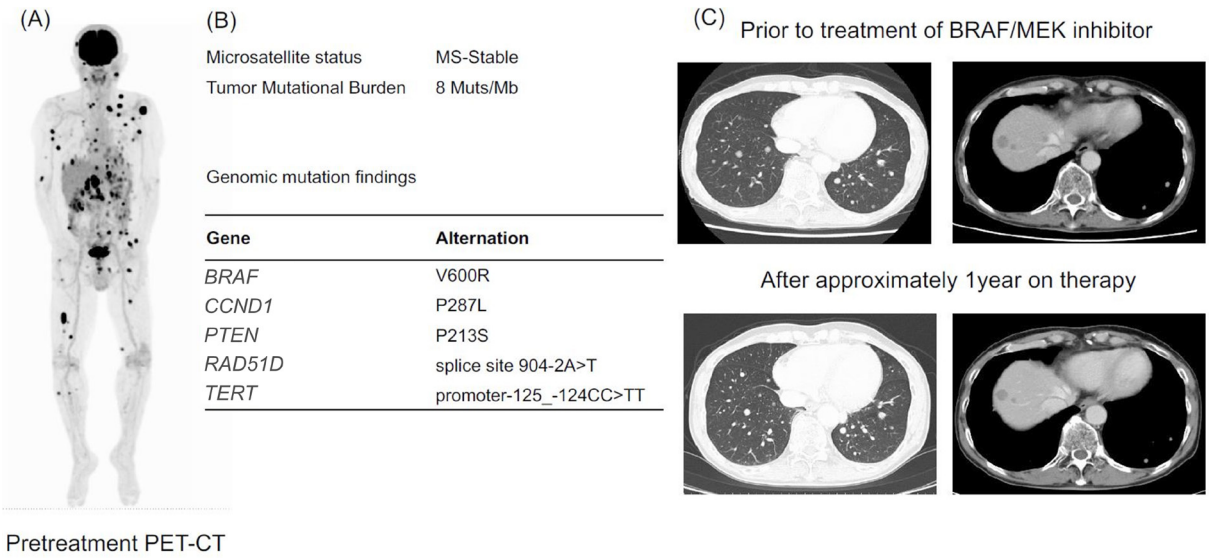

Figure 1. (a) FDG-PET/CT performed before treatment. (b) Gene alterations detected with the Foundation One CDx, a next-generation sequencing test. (c) CT performed before (above) and after (below) BRAF/MEK inhibitor therapy.

FoundationOne CDx and treated the patient with BRAF/MEKi. Multi-gene panel testing, such as FoundationOne CDx, is useful for detecting rare gene mutations. However, this method is expensive and time-consuming. A cheaper and faster method should be developed that can detect non-*BRAF*^{V600E} and -*BRAF*^{V600K} mutations such as *BRAF*^{V600R} by utilizing a melanoma-specific gene panel.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received September 1, 2022; Revised October 19, 2022; Accepted October 20, 2022.

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Released online in J-STAGE as advance publication October 23, 2022.