



Sample Information

Patient Name: 劉慧美  
Gender: Female  
ID No.: B200260608  
History No.: 14039522  
Age: 75

Ordering Doctor: DOC4205A 柯博伸  
Ordering REQ.: OCMVQWC  
Signing in Date: 2023/07/06

Path No.: M112-00169  
MP No.: MY23037  
Assay: Oncomine Myeloid Assay  
Sample Type: Bone Marrow  
Bone Marrow Aspirating Date: 2023/06/29

Reporting Doctor: DOC5444B 楊靜芬 (Phone: 8#5444)

Note:

Sample Cancer Type: Large B-Cell Lymphoma

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Relevant Biomarkers

No clinically significant biomarkers found in this sample.

Prevalent cancer biomarkers without relevant evidence based on included data sources

BRAF p.(G469A) c.1406G>C

Variants (Exclude variant in Taiwan BioBank with >1% allele frequency)

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
BRAF	p.(G469A)	c.1406G>C	COSM460	chr7:140481402	19.21%	NM_004333.6	missense	1999

## Biomarker Descriptions

### BRAF (B-Raf proto-oncogene, serine/threonine kinase)

**Background:** The BRAF gene encodes the B-Raf proto-oncogene serine/threonine kinase, a member of the RAF family of serine/threonine protein kinases which also includes ARAF and RAF1 (CRAF). BRAF is among the most commonly mutated kinases in cancer. Activation of the MAPK pathway occurs through BRAF mutations and leads to an increase in cell division, dedifferentiation, and survival<sup>1,2</sup>. BRAF mutations are categorized into three distinct functional classes namely, class 1, 2, and 3, and are defined by the dependency on the RAS pathway. Class 1 and 2 BRAF mutants are RAS-independent in that they signal as active monomers (Class 1) or dimers (Class 2) and become uncoupled from RAS GTPase signaling, resulting in constitutive activation of BRAF<sup>3</sup>. Class 3 mutants are RAS dependent as the kinase domain function is impaired or dead<sup>3,4,5</sup>.

**Alterations and prevalence:** Recurrent somatic mutations in BRAF are observed in 40-60% of melanoma and thyroid cancer, approximately 10% of colorectal cancer, and about 2% of non-small cell lung cancer (NSCLC)<sup>6,7,8,9,10</sup>. Mutations at V600 belong to class 1 and include V600E, the most recurrent somatic BRAF mutation across diverse cancer types<sup>4,11</sup>. Class 2 mutations include K601E/N/T, L597Q/V, G469A/V/R/, G464V/E/, and BRAF fusions<sup>4</sup>. Class 3 mutations include D287H, V459L, G466V/E/A, S467L, G469E, and N581S/I<sup>4</sup>. BRAF V600E is universally present in hairy cell leukemia, mature B-cell cancer, and prevalent in histiocytic neoplasms<sup>12,13,14</sup>. Other recurrent BRAF somatic mutations cluster in the glycine-rich phosphate-binding loop at codons 464-469 in exon 11 as well as additional codons flanking V600 in the activation loop<sup>11</sup>. In primary cancers, BRAF amplification is observed in 8% of ovarian cancer and about 1% of breast cancer<sup>7,10</sup>. BRAF fusions are mutually exclusive to BRAF V600 mutations and have been described in melanoma, thyroid cancer, pilocytic astrocytoma, NSCLC, and several other cancer types<sup>15,16,17,18,19</sup>. Part of the oncogenic mechanism of BRAF gene fusions is the removal of the N-terminal auto-inhibitory domain leading to constitutive kinase activation<sup>5,15,17</sup>.

**Potential relevance:** Vemurafenib<sup>20</sup> (2011) was the first targeted therapy approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E mutation. BRAF class 1 mutations, including V600E, are sensitive to vemurafenib, whereas class 2 and 3 mutations are insensitive<sup>4</sup>. BRAF kinase inhibitors including dabrafenib<sup>21</sup> (2013) and encorafenib<sup>22</sup> (2018) are also approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E/K mutations. Encorafenib<sup>22</sup> is approved in combination with cetuximab<sup>23</sup> (2020) for the treatment of BRAF V600E mutated colorectal cancer. Due to the tight coupling of RAF and MEK signaling, several MEK inhibitors have been approved for patients harboring BRAF alterations<sup>4</sup>. Trametinib<sup>24</sup> (2013) and binimetinib<sup>25</sup> (2018) were approved for the treatment of metastatic melanoma with BRAF V600E/K mutations. Combination therapies of BRAF plus MEK inhibitors have been approved in melanoma and NSCLC. The combinations of dabrafenib/trametinib (2015) and vemurafenib/cobimetinib<sup>26</sup> (2015) were approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E/K mutation. Subsequently, the combination of dabrafenib and trametinib was approved for metastatic NSCLC (2017) with a BRAF V600E mutation. The PD-L1 antibody, atezolizumab<sup>27</sup>, has also been approved in combination with cobimetinib and vemurafenib for BRAF V600 mutation-positive unresectable or metastatic melanoma. In 2018, binimetinib<sup>28</sup> was also granted breakthrough designation in combination with cetuximab and encorafenib for BRAF V600E mutant metastatic colorectal cancer. The ERK inhibitor ulixertinib<sup>29</sup> was granted fast track designation in 2020 for the treatment of patients with non-colorectal solid tumors harboring BRAF mutations G469A/V, L485W, or L597Q. The FDA granted fast track designation (2022) to the pan-RAF inhibitor, KIN-2787<sup>30</sup>, for the treatment of BRAF class II or III alteration-positive malignant or unresectable melanoma. BRAF fusion is a suggested mechanism of resistance to BRAF targeted therapy in melanoma<sup>31</sup>. Additional mechanisms of resistance to BRAF targeted therapy include BRAF amplification and alternative splice transcripts as well as activation of PI3K signaling and activating mutations in KRAS, NRAS, and MAP2K1/2 (MEK1/2)<sup>32,33,34,35,36,37,38</sup>. Clinical responses to sorafenib and trametinib in limited case studies of patients with BRAF fusions have been reported<sup>19</sup>.

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