Taipei Veterans General Hospital

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Sample Information

Patient Name: 葉永華
Gender: Male
ID No.: Y120259732
History No.: 49338638
Age: 55

Ordering Doctor: DOC4222D_陳天華
Ordering REQ.: 0CJXBDM
Signing in Date: 2023/04/27

Path No.: M112-00081
MP No.: F23021
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S112-16070A
Percentage of tumor cells: 70%

Reporting Doctor: DOC5466K 葉奕成 (Phone: 8#5466)

Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

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Relevant Non-Small Cell Lung Cancer Variants

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	***BRAF p.(T599dup) c.1797_1798insACA***	NTRK2	None detected
EGFR	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	None detected
MET	None detected		

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*BRAF p.(T599dup) c.1797_1798insACA* B-Raf proto-oncogene, serine/threonine kinase Allele Frequency: 13.33%	None	bevacizumab + chemotherapy ipilimumab + nivolumab trametinib	2

Public data sources included in relevant therapies: FDA1, NCCN, **EMA**2, ESMO
Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

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.(T599dup)	c.1797_1798insACA	COSM144982	chr7:140453137	13.33%	NM_004333.6	nonframeshift Insertion	1988

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[1,2]. 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[3]. Class 3 mutants are RAS dependent as the kinase domain function is impaired or dead[3,4,5].

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)[6,7,8,9,10]. Mutations at V600 belong to class 1 and include V600E, the most recurrent somatic BRAF mutation across diverse cancer types[4,11]. Class 2 mutations include K601E/N/T, L597Q/V, G469A/V/R/, G464V/E/, and BRAF fusions[4]. Class 3 mutations include D287H, V459L, G466V/E/A, S467L, G469E, and N581S/I[4]. BRAF V600E is universally present in hairy cell leukemia, mature B-cell cancer, and prevalent in histiocytic neoplasms[12,13,14]. 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[11]. In primary cancers, BRAF amplification is observed in 8% of ovarian cancer and about 1% of breast cancer[7,10]. 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[15,16,17,18,19]. Part of the oncogenic mechanism of BRAF gene fusions is the removal of the N-terminal auto-inhibitory domain leading to constitutive kinase activation[5,15,17].

Potential relevance: Vemurafenib[20] (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[4]. BRAF kinase inhibitors including dabrafenib[21] (2013) and encorafenib[22] (2018) are also approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E/K mutations. Encorafenib[22] is approved in combination with cetuximab[23] (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[4]. Trametinib[24] (2013) and binimetinib[25] (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[26] (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[27], has also been approved in combination with cobimetinib and vemurafenib for BRAF V600 mutation-positive unresectable or metastatic melanoma. In 2018, binimetinib[28] was also granted breakthrough designation in combination with cetuximab and encorafenib for BRAF V600E mutant metastatic colorectal cancer. The pan-RAF kinase inhibitor, tovorafenib (DAY-101), was granted breakthrough therapy designation (2020) by the FDA for pediatric patients with advanced low-grade glioma harboring activating RAF alterations[29]. The ERK inhibitor ulixertinib[30] was also granted a

Biomarker Descriptions (continued)

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[31], 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[32]. 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)[33,34,35,36,37,38,39]. Clinical responses to sorafenib and trametinib in limited case studies of patients with BRAF fusions have been reported[19].

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

BRAF p.(T599dup) c.1797_1798insACA

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trametinib	✖	○	✖	✖	✖
bevacizumab + CAPOX	✖	✖	✖	○	✖
bevacizumab + FOLFOX	✖	✖	✖	○	✖
ipilimumab + nivolumab	✖	✖	✖	○	✖
belvarafenib	✖	✖	✖	✖	● (II)
KIN-2787, binimetinib	✖	✖	✖	✖	● (I)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Relevant Therapy Details

Current NCCN Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

NCCN information is current as of 2023-03-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

BRAF p.(T599dup) c.1797_1798insACA

○ trametinib

Cancer type: Cutaneous Melanoma

Variant class: BRAF mutation

Other criteria: BRAF V600 negative

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 1.2023]

Current ESMO Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

ESMO information is current as of 2023-03-01. For the most up-to-date information, search www.esmo.org.

BRAF p.(T599dup) c.1797_1798insACA

○ bevacizumab + CAPOX

Cancer type: Colorectal Cancer **Variant class:** BRAF mutation

ESMO Level of Evidence/Grade of Recommendation: I / B

Population segment (Line of therapy):
- Stage IV; Unresectable (First-line therapy); ESMO-MCBS v1.1 score: 1

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2022); https://doi.org/10.1016/j.annonc.2022.10.003 (In press)]

○ bevacizumab + FOLFOX

Cancer type: Colorectal Cancer **Variant class:** BRAF mutation

ESMO Level of Evidence/Grade of Recommendation: I / B

Population segment (Line of therapy):
- Stage IV; Unresectable (First-line therapy); ESMO-MCBS v1.1 score: 1

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2022); https://doi.org/10.1016/j.annonc.2022.10.003 (In press)]

○ ipilimumab + nivolumab

Cancer type: Melanoma **Variant class:** BRAF mutation

ESMO Level of Evidence/Grade of Recommendation: II / B

Population segment (Line of therapy):
- Asymptomatic, Brain Metastases (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-EANO-ESMO Brain Metastasis from Solid Tumours [Ann Oncol (2021), https://doi.org/10.1016/j.annonc.2021.07.016]

Clinical Trials in Taiwan region:

Clinical Trials Summary

BRAF p.(T599dup) c.1797_1798insACA

NCT ID	Title	Phase
NCT04589845	Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial	II
NCT04913285	A Phase I/I b Open-label, Multicenter Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of KIN-2787 in Participants With BRAF and/or NRAS Mutation-positive Solid Tumors.	I

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2023-03-15. For the most up-to-date information, search www.fda.gov.

BRAF p.(T599dup) c.1797_1798insACA

KIN-2787

Cancer type: Melanoma **Variant class:** BRAF Class II

Supporting Statement:

The FDA has granted Fast Track Designation to the pan-RAF inhibitor, KIN-2787, for the treatment of BRAF Class II or III alterteration-positive and/or NRAS mutation-positive stage IIb to IV malignant melanoma that is metastatic or unresectable.

Reference:

https://investors.kinnate.com/news-releases/news-release-details/kinnate-biopharma-inc-receives-fast-track-designation-us-food

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