Taipei Veterans General Hospital

Department of Pathology and Laboratory Medicine
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11217, R.O.C.
Tel: 02-2875-7449

Sample Information

Patient Name: 吳德卿
Gender: Male
ID No.: F101709768
History No.: 47876255
Age: 68

Ordering Doctor: DOC5390F 高冠鈞
Ordering REQ.: 0BPRKQX
Signing in Date: 2021/12/17

Path No.: S110-94848
MP No.: F21107
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S110-36096A
Percentage of tumor cells: 20%

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

Note:

Sample Cancer Type: Other Solid Tumor

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Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*HRAS p.(G13D) c.38G>A* HRas proto-oncogene, GTPase Allele Frequency: 5.55% **Prognostic significance:** None **Diagnostic significance:** None	None	cabozantinib	1

Public data sources included in relevant therapies: FDA1, NCCN, **EMA**2, ESMO
Public data sources included in prognostic and diagnostic significance: NCCN, 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.

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2021.11(003).The content of this report has not been evaluated or approved by the FDA or other regulatory agencies.

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
HRAS	p.(G13D)	c.38G>A	COSM490	chr11:534285	5.55%	NM_001130442.2	missense	2000

Biomarker Descriptions

HRAS (HRas proto-oncogene, GTPase)

Background: The HRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes KRAS and NRAS. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways that control the regulation of cell division, differentiation, and survival[1,2,3]. RAS proteins require the covalent attachment of a hydrophobic group to their C-terminus (prenylation) for membrane localization and downstream signaling[4]. Whereas KRAS and NRAS are subject to prenylation by farnesyl transferase or geranylgeranyl transferase, HRAS is completely dependent on farnesylation.

Alterations and prevalence: Recurrent mutations in RAS oncogenes cause constitutive activation and are found in 20-30% of cancers. HRAS mutations are observed in 4-10% of pheochromocytoma and paraganglioma, thymoma, bladder, and head and neck cancers[5,6]. The majority of HRAS mutations consist of point mutations at G12, G13, and Q61[5,7,8].

Potential relevance: Currently, no therapies are approved for HRAS aberrations. However, the farnesyl transferase inhibitor, tipifarnib[9,10], was granted fast-track (2019) and breakthrough therapy (2021) designation by the FDA for the treatment of HRAS mutant head and neck squamous cell carcinomas (HNSCC) after disease progression on platinum chemotherapy.

Relevant Therapy Summary

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

HRAS p.(G13D) c.38G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
cabozantinib	✖	✖	✖	○	✖
tipifarnib	✖	✖	✖	✖	○ (II)

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

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Relevant Therapy Details

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 2021-10-01. For the most up-to-date information, search www.esmo.org.

HRAS p.(G13D) c.38G>A

○ cabozantinib

Cancer type: Thyroid Gland Medullary Carcinoma **Variant class:** RAS mutation

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

Population segment (Line of therapy):
- Metastatic (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Thyroid Cancer [Annals of Oncology 30: 1856–1883, 2019 doi:10.1093/annonc/mdz400]

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Clinical Trials in Taiwan region:

Clinical Trials Summary

HRAS p.(G13D) c.38G>A

NCT ID	Title	Phase
NCT03719690	A Two Cohort, Non-comparative, Pivotal Study Evaluating the Efficacy of Tipifarnib in Patients with Head and Neck Squamous Cell Carcinoma (HNSCC) With HRAS Mutations (AIM-HN) and the Impact of HRAS Mutations on Response to First Line Systemic Therapies for HNSCC (SEQ-HN).	II

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2021-10-13. For the most up-to-date information, search www.fda.gov.

HRAS p.(G13D) c.38G>A

tipifarnib

Cancer type: Head and Neck Cancer **Variant class:** HRAS mutation

Supporting Statement:
The FDA has granted Breakthrough Therapy Designation to the small molecule inhibitor, tipifarnib, for HRAS mutations with variant allele frequency ≥ 20% in head and neck squamous cell carcinomas (HNSCC) after disease progression on platinum-based chemotherapy

Reference:

https://ir.kuraoncology.com/news-releases/news-release-details/kura-oncology-receives-fda-breakthrough-therapy-designation

tipifarnib

Cancer type: Head and Neck Cancer **Variant class:** HRAS mutation

Supporting Statement:
The FDA has granted Fast Track Designation to the farnesyltransferase inhibitor, tipifarnib, for HRAS mutant recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) after disease progression on platinum-based chemotherapy.

Reference:

https://ir.kuraoncology.com/news-releases/news-release-details/kura-oncology-receives-fast-track-designation-tipifarnib-hras

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Signatures

Testing Personnel:

2021.12.20
08:32:37 +08'00'

Laboratory Supervisor:

2021.12.20
08:32:50 +08'00'

Pathologist:

2021.12.20
08:33:03 +08'00'

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References

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8. Moura et al. High prevalence of RAS mutations in RET-negative sporadic medullary thyroid carcinomas. J. Clin. Endocrinol. Metab. 2011 May;96(5):E863-8. PMID: 21325462
9. https://ir.kuraoncology.com/news-releases/news-release-details/kura-oncology-receives-fda-breakthrough-therapy-designation
10. https://ir.kuraoncology.com/news-releases/news-release-details/kura-oncology-receives-fast-track-designation-tipifarnib-hras

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