Taipei Veterans General Hospital

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Sample Information

Patient Name: 陳永享
Gender: Male
ID No.: Y100138465
History No.: 34491173
Age: 82

Ordering Doctor: DOC3104F 周中偉
Ordering REQ.: 0ARJNFC
Signing in Date: 2020/04/27

Path No.: S109-99389
MP No.: F2014
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S109-11298A
Percentage of tumor cells: 60%
Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

Report Highlights

2 Relevant Biomarkers
1 Therapies Available
14 Clinical Trials

Relevant Non-Small Cell Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	Not detected	NTRK1	Not detected
BRAF	Not detected	NTRK2	Not detected
EGFR	Not detected	NTRK3	Not detected
ERBB2	Not detected	RET	Not detected
KRAS	Not detected	ROS1	Not detected
MET	Not detected		

Relevant Biomarkers

Indicated Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
HRAS p.(G13R) c.37G>C HRas proto-oncogene, GTPase Tier: IIC Allele Frequency: 58.50%	None	cabozantinib	11
MYC amplification MYC proto-oncogene, bHLH transcription factor Tier: IIC	None	None	3

Public data sources included in relevant therapies: FDA[1], 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.

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
HRAS	p.(G13R)	c.37G>C	COSM486	chr11:534286	58.50%	NM_001130442.2	missense	2000
ALK	p.(D1529E)	c.4587C>G	.	chr2:29416366	99.90%	NM_004304.4	missense	1996
ALK	p.(I1461V)	c.4381A>G	.	chr2:29416572	99.85%	NM_004304.4	missense	1999
ALK	p.(=)	c.3375C>A	.	chr2:29445458	99.70%	NM_004304.4	synonymous	1997
FGFR3	p.(=)	c.1953G>A	.	chr4:1807894	99.90%	NM_000142.4	synonymous	1996
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.85%	NM_006206.5	synonymous	1998
KIT	p.(=)	c.1638A>G	.	chr4:55593481	49.35%	NM_000222.2	synonymous	2000
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.75%	NM_213647.2	missense	2000
FGFR4	p.(=)	c.483A>G	.	chr5:176517985	5.05%	NM_213647.2	synonymous	2000
EGFR	p.(=)	c.1491C>T	.	chr7:55228024	22.92%	NM_005228.4	synonymous	1998
RET	p.(=)	c.2307G>T	.	chr10:43613843	76.69%	NM_020975.4	synonymous	1995

Copy Number Variations

Gene	Locus	Copy Number
MYC	chr8:128748885	8.33

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, tipifarnib, a farnesyl transferase inhibitor, has shown clinical activity in preliminary results reported from an ongoing phase II study of HRAS mutant head and neck squamous cell carcinoma and other squamous cell carcinomas[9].

MYC (MYC proto-oncogene, bHLH transcription factor)

Background: The MYC gene encodes the MYC proto-oncogene (c-MYC), a basic helix-loop-helix transcription factor that regulates the expression of numerous genes that control cell cycle progression, apoptosis, metabolic pathways, and cellular transformation[10,11,12,13]. MYC is part of the MYC oncogene family that includes related transcription factors MYCN and MYCL that regulate transcription in 10-15% of promoter regions[14]. MYC functions as a heterodimer in complex with the transcription factor MAX[11,15].

Alterations and prevalence: Recurrent somatic alterations are observed in both solid and hematological cancers. Recurrent somatic mutations in MYC, including codon T58, are infrequent and hypothesized to increase the stability of the MYC protein[16,17]. MYC gene amplification is particularly common in diverse solid tumors. MYC amplification is observed in 30% of serous ovarian cancer, 20% of uterine serous carcinoma, 15% of esophageal and breast cancers, and is common (1-10%) in numerous other cancer types[18,19,20]. MYC is the target of the t(8;14)(q24;32) chromosomal translocation in Burkitt's lymphoma that places MYC coding sequences adjacent to immunoglobulin region regulatory sequences, which results in increased MYC expression[21,22].

Potential relevance: Currently, no therapies are approved for MYC aberrations. Due to the high frequency of somatic MYC alterations in cancer, many approaches are being investigated in clinical trials including strategies to disrupt complex formation with MAX, including inhibition of MYC expression and synthetic lethality associated with MYC overexpression[10,23,24,25].

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

HRAS p.(G13R) c.37G>C

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

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

HRAS p.(G13R) c.37G>C (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ASTX029	✖	✖	✖	✖	● (I/II)
cobimetinib	✖	✖	✖	✖	● (I/II)
mirdametinib, lifirafenib	✖	✖	✖	✖	● (I/II)
belvarafenib + cobimetinib	✖	✖	✖	✖	● (I)
KO-947	✖	✖	✖	✖	● (I)
LXH254	✖	✖	✖	✖	● (I)
LY3214996, midazolam, abemaciclib, chemotherapy, encorafenib, cetuximab	✖	✖	✖	✖	● (I)
RMC-4630	✖	✖	✖	✖	● (I)
RO-5126766, everolimus + RO-5126766	✖	✖	✖	✖	● (I)

MYC amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
VX-970	✖	✖	✖	✖	● (II)
entinostat, nivolumab	✖	✖	✖	✖	● (I/II)
BMS-986158	✖	✖	✖	✖	● (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 ESMO Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated 👎 Not recommended 🛡 Resistance

ESMO information is current as of 2019-11-01. For the most up-to-date information, search www.esmo.org.

HRAS p.(G13R) c.37G>C

○ 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 Thyroid Gland Medullary Carcinoma (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Thyroid Cancer [Annals of Oncology (2019): mdz400, https://doi.org/10.1093/annonc/mdz400]

Signatures

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Pathologist: Yi-Chu Yeh 2020.04.27 13:43:22 +08'00'

References

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