Taipei Veterans General Hospital

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## Sample Information

**Patient Name:** 藍嘉齊
**Gender:** Male
**ID No.:** G121456429
**History No.:** 43719411
**Age:** 38

**Ordering Doctor:** DOC8340G 劉品均
**Ordering REQ.:** 0AQWDXP
**Signing in Date:** 2020/04/09

**Path No.:** S109-99340
**MP No.:** F2009
**Assay:** Oncomine Focus Assay
**Sample Type:** FFPE
**Block No.:** S109-75857A
**Percentage of tumor cells:** 90%
**Note:**

## Sample Cancer Type: Non-Small Cell Lung Cancer

| Table of Contents | Page |
|---|---|


### Report Highlights

1 Clinically Significant Biomarkers
0 Therapies Available
6 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 | | |

## Clinically Significant Biomarkers

Indicated Contraindicated

| Genomic Alteration | Relevant Therapies (In this cancer type) | Relevant Therapies (In other cancer type) | Clinical Trials |
|---|---|---|---|
| *CDK4 amplification*<br>cyclin dependent kinase 4<br>Tier: IIC | None | None | 6 |

**Sources included in relevant therapies:** FDA1, NCCN, EMA2, ESMO

**Prevalent cancer biomarkers without clinical significance based on included data sources**
CTNNB1 p.(D32H) c.94G>C

## Tier Criteria Met

| Genomic Alteration | Tier Classification for Non-Small Cell Lung Cancer |
|---|---|
| *CDK4 amplification*<br>Tier: IIC | IIC: Biomarker is an inclusion criteria for clinical trials |

**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 |
|---|---|---|---|---|---|---|---|---|
| CTNNB1 | p.(D32H) | c.94G>C | COSM5668 | chr3:41266097 | 15.71% | NM_001904.3 | missense | 1999 |
| JAK1 | p.(=) | c.2199A>G | . | chr1:65310489 | 99.09% | NM_002227.3 | synonymous | 1983 |
| ALK | p.(D1529E) | c.4587C>G | . | chr2:29416366 | 100.00% | NM_004304.4 | missense | 1998 |
| ALK | p.(I1461V) | c.4381A>G | . | chr2:29416572 | 99.95% | NM_004304.4 | missense | 1998 |
| ALK | p.(=) | c.3375C>A | . | chr2:29445458 | 100.00% | NM_004304.4 | synonymous | 1998 |
| FGFR3 | p.(=) | c.1953G>A | . | chr4:1807894 | 99.90% | NM_000142.4 | synonymous | 1999 |
| PDGFRA | p.(=) | c.1701A>G | . | chr4:55141055 | 99.95% | NM_006206.5 | synonymous | 1998 |
| PDGFRA | p.(=) | c.2472C>T | . | chr4:55152040 | 38.20% | NM_006206.5 | synonymous | 2000 |
| FGFR4 | p.(P136L) | c.407C>T | . | chr5:176517797 | 99.45% | NM_213647.2 | missense | 1999 |
| EGFR | p.(H773fs) | c.2317_2318insC | . | chr7:55249014 | 5.44% | NM_005228.4 | frameshift Insertion | 1968 |
| FGFR1 | p.(=) | c.2178T>G | . | chr8:38271771 | 8.57% | NM_001174067.1 | synonymous | 1353 |
| MYC | p.(G123R) | c.367G>A | . | chr8:128750830 | 4.95% | NM_002467.4 | missense | 2000 |
| RET | p.(=) | c.2307G>T | . | chr10:43613843 | 99.75% | NM_020975.4 | synonymous | 1997 |
| MAP2K1 | p.(Y134F) | c.401A>T | . | chr15:66729193 | 5.71% | NM_002755.3 | missense | 1998 |

### Copy Number Variations

| Gene | Locus | Copy Number |
|---|---|---|
| CDK4 | chr12:58142052 | 5.62 |

## Biomarker Descriptions

**CDK4 (cyclin dependent kinase 4)**

Background: The CDK4 gene encodes the cyclin-dependent kinase-4 protein, a homologue of CDK6. Both proteins are serine/threonine protein kinases that are involved in the regulation of the G1/S phase transition of the mitotic cell cycle[1,2]. CDK4 kinase is activated by complex formation with D-type cyclins (e.g., CCND1, CCND2, or CCND3), which leads to the phosphorylation of retinoblastoma protein (RB), followed by E2F activation, DNA replication, and cell-cycle progression[3]. Germline mutations in CDK4 are associated with familial melanoma[4,5,6].

Alterations and prevalence: Recurrent somatic mutations of CDK4 codon K22 and R24 are observed in melanoma (1-2%) and lung cancer (approximately 0.1%). Codons K22 and R24 are necessary for binding and inhibition by p16/CDKN2A[7,8,9]. CDK4 is recurrently amplified in several cancer types, most notably in sarcomas (15-20%), glioma (10-15%), adrenocortical carcinoma (5%), lung adenocarcinoma (5%), and melanoma (3%)[10,11,12,13].

Potential clinical relevance: Currently, no therapies are approved for CDK4 aberrations. Small molecule inhibitors targeting CDK4/6--including palbociclib (2015), abemaciclib (2017), and ribociclib (2017)-- are FDA approved in combination with an aromatase inhibitor or fulvestrant for the treatment of hormone receptor-positive, HER2-negative advanced or metastatic breast cancer.

**CTNNB1 (catenin beta 1)**

Background: The CTNNB1 gene encodes catenin beta-1 (β-catenin), an integral component of cadherin-based adherens junctions involved in maintaining adhesion and regulating the growth of epithelial cell layers[14]. CTNNB1 binds to the APC protein in the cytoplasm and also interacts with TCF and LEF transcription factors in the nucleus to regulate WNT signaling[15]. Steady state levels of CTNNB1 are regulated by ubiquitin-dependent proteolysis[16,17,18].

Alterations and prevalence: Recurrent somatic mutations leading to CTNNB1 activation are common in cancer. The most prevalent alterations include missense mutations in exon 3 at codons S33, S37, T41, and S45 that block phosphorylation by GSK-β and inhibit CTNNB1 degradation[19,20,21,22]. These activating mutations are observed in diverse solid tumors and have a prevalence of 20-30% in hepatocellular carcinoma, 20% of uterine carcinoma, and 15% of adrenocortical carcinoma[10,11,23,24,25,26,27].

Potential clinical relevance: Currently, no therapies have been approved for CTNNB1 aberrations. CTNNB1 alterations in EGFR positive lung cancer have been proposed to promote cancer progression and limit the response to EGFR tyrosine kinase inhibitors[28].

## 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

### CDK4 amplification

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| abemaciclib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| palbociclib | ✖ | ✖ | ✖ | ✖ | ● (II) |

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

## Signatures

**Testing Personnel:** Zih-Yu Liu 2020.04.09 17:43:37 +08'00'

**Laboratory Supervisor:** 2020.04.09 17:43:57 +08'00'

**Pathologist:** 2020.04.09 17:44:15 +08'00'

## References

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