**­Location Number:** DNA044601

**Histological Typing:** Consistent with carcinoma

The original diagnosis HAS NOT been reassessed. The sample sent was reviewed and was considered to contain 50**%** tumour cells within the area selected for analysis. No formal pathology review was conducted and this test result is based solely on an H&E prepared from the tissue provided and not from the original diagnostic slides. This pathology assessment is not a confirmation of malignancy, but verifies the presence of atypical cells consistent with tumour as diagnosed by the reporting pathologist. The PMCC pathologist did not have access to the original H&E, special stains, other ancillary and clinical information.

**LUNG PANEL MUTATION ANALYSIS REPORT**

|  |  |
| --- | --- |
| **Test Principle:**  Targeted next generation sequencing analysis of *EGFR* (exons 18, 19, 20 & 21), *KRAS* (exons 2, 3 & 4), *BRAF* (exons 11 & 15) and *MET* (exon 14) genes. | **RESULT SUMMARY:** |
| **KRAS EXON 2 and MET EXON 14 VARIANTS DETECTED**  **Unknown sensitivity to MET inhibitors** |

**Test Result:**

|  |  |  |  |
| --- | --- | --- | --- |
| **Gene** | **EXON** | **NUCLEOTIDE VARIANT** | **PROTEIN VARIANT** |
| ***EGFR*** |  | No variant detected |  |
| ***KRAS*** | ex2/6 | c.34G>T | NP\_203524.1:p.(Gly12Cys) |
| ***BRAF*** |  | No variant detected |  |
| ***MET*** | ex14/21 | c.2947C>T | NP\_000236.2:p.(Leu983Phe) |

**Clinical Interpretation:**

\*\*\*\*LUNG\* The KRAS c.34G>T p.(Gly12Cys) variant, also known as G12C results in constitutive activation of the MAPK signalling [1]. KRAS variants are typically mutually exclusive with EGFR mutations, as well as ALK and ROS1 genomic alterations [2].

Please Note: The Peter MacCallum Cancer Centre Clinical Trial Unit is currently recruiting to a Phase 1 study entitled Evaluating the Safety, Tolerability, PK, and Efficacy of AMG 510 in Subjects With Solid Tumors With a Specific KRAS Mutation. (KRAS G12C) (ClinicalTrials.gov Identifier: NCT03600883). Please contact PI: Jayesh Desai: jayesh.desai@petermac.org to discuss eligibility.\*\*\*

\*\*\*\*LUNG\*\*\*DRAFT combined comments with KRAS G12C\*\*\* The MET c.2947C>T p.(Leu983Phe) missense variant occurs within exon 14 of MET. There is currently no evidence supporting this variant being oncogenic. The effect of this variant, either alone or with a co-existing KRAS activating variant, on tumour response to Crizotinib in non-small cell lung carcinoma (NSCLC) is currently unknown. However, inferior clinical response to Crizotinib therapy has been described in KRAS-mutated NSCLC [3, 4]. \*\*\*

**General Comments:**

Mutations in exon 19 and 21 of EGFR are strong predictors of response to EGFR tyrosine kinase inhibitor (TKI) therapy and occur in up to 30% of metastatic NSCLC. Conversely most exon 20 insertions and T790M are associated with acquired resistance to first and second generation TKI therapies, however, T790M confers sensitivity to third generation TKIs. KRAS and BRAF mutations may also predict emergence of TKI resistance. NSCLC with MET exon 14 skipping mutations have increased sensitivity to MET inhibitors.

**Test Methodology:**

Amplicon-based NGS is performed on DNA extracted from macro-dissected FFPE tumour tissue followed by targeted sequencing on an Illumina MiSeq, 2x150bp. Aligned reads and called variants are analysed in PathOS. Variants are described according to HGVS nomenclature version 15.11 (<http://varnomen.hgvs.org/>) against RefSeq transcripts for EGFR NM\_005228.3 (NP\_005219.2), KRAS NM\_033360.2 (NP\_203524.1), BRAF NM\_004333.4 (NP\_004324.2) and MET NM\_000245.3 (NP\_000236.2), with minor differences in accordance with Molecular Pathology policy. The policy as it pertains to this report is available by contacting the laboratory on the number below. Synonymous changes and intronic variants outside of splice-sites are not reported. Analysis of low quality samples may be supplemented with additional techniques including Sanger sequencing, high resolution melt (HRM) analysis, real-time PCR, and Cobas® (Roche Molecular Diagnostics) mutation test assays. On samples meeting QC specifications, the assay has 99.9% sensitivity for SNPs and indels in the targeted genes. The assay does not detect copy number changes or structural rearrangements.

Please contact the laboratory on 03 8559 5405 if you wish to discuss this report further.

[1] Hunter JC et al. (2015). Biochemical and Structural Analysis of Common Cancer-Associated KRAS Mutations. Mol. Cancer Res. 13 (9), pp. 1325-35.

[2] Cancer Genome Atlas Research Network (2014). Comprehensive molecular profiling of lung adenocarcinoma. Nature 511 (7511), pp. 543-50.

[3] Suzawa K et al. (2019). Activation of KRAS Mediates Resistance to Targeted Therapy in MET Exon 14-mutant Non-small Cell Lung Cancer. Clin. Cancer Res. 25 (4), pp. 1248-1260.

[4] Liu SY et al. (2016). The Unique Characteristics of MET Exon 14 Mutation in Chinese Patients with NSCLC. J Thorac Oncol 11 (9), pp. 1503-10.

**Reported by: Gareth Lamb 24-Apr-2019 1:24 PM**

**«secondReviewer»«secondReviewedDate»**

**Authorised by: Timmy Chan 26-Apr-2019 4:07 PM**