Example Clinical Lab System
123 Sample Avenue
City, Postal Code
Tel: +44 (123) 123-1234



| | | | |
|---|---|---|---|
| **Date of Birth:** | 01 Aug 1965 | **Primary Tumor Site:** | Lung |
| **Sex:** | Female | **Sample Type:** | FFPE |
| **Smoking Status:** | active smoker | **Sample ID:** | 435678-FFPE-321 |
| **Case Number:** | 9876543-1 | **Sample Collected:** | 09 May 2022 |

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

## Relevant Non-Small Cell Lung Cancer Findings

| Gene | Finding | Gene | Finding |
|---|---|---|---|
| ALK | None detected | NTRK1 | None detected |
| BRAF | None detected | NTRK2 | None detected |
| EGFR | None detected | NTRK3 | None detected |
| ERBB2 | None detected | RET | ***KIF5B-RET fusion*** |
| 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 |
|---|---|---|---|---|
| **I-A** | *KIF5B-RET fusion* | **pralsetinib** [1, 2]<br>**selpercatinib** [1, 2]<br>cabozantinib | **pralsetinib** [2]<br>**selpercatinib** [1, 2] | 10 |

**Public data sources included in relevant therapies: EMA**[1], ESMO, **FDA**[2], NCCN
**Tier Reference:** Mateo J, Chakravarty D, Dienstmann R et al. *A framework to rank genomic alterations as targets for cancer precision medicine: The ESMO Scale for Clinical Actionability of molecular Targets (ESCAT).* Annals of Oncology 2018; https://doi.org/10.1093/annonc/mdy263

Electronically Signed By J.C. Courtney, Ph.D. on 11 May 2022 06:27:44 PM

# Variant Details

## Gene Fusions (RNA)

| Genes | Variant ID | Locus |
|---|---|---|
| KIF5B-RET | KIF5B-RET.K15R12.COSF1232.1 | chr10:32317356 - chr10:43612032 |

# Biomarker Descriptions

**RET (ret proto-oncogene)**

Background: The RET gene encodes the RET receptor tyrosine kinase which is activated by a ligand family of glial cell line-derived neurotrophic factors (GDNF)[1]. RET is the target of recurrent chromosomal rearrangements that generate fusion proteins containing the intact RET tyrosine kinase domain combined with several fusion partner genes. RET fusion kinases are constitutively activated and drive oncogenic transformation which can lead to activation of PI3K/AKT, RAS/RAF/MEK/ERK, and PLCγ/PKC pathways resulting in cell survival and proliferation[2].

Alterations and prevalence: RET fusions occur in approximately 55% of papillary thyroid carcinomas (PTC) with even higher frequencies observed in PTC patients with radiation exposure[3,4,5]. RET rearrangement is also present in 1-2% of non-small cell lung cancer (NSCLC)[6]. Point mutations in RET are relatively common in sporadic medullary thyroid cancer (MTC), with 6% of patients found to contain germline mutations[7]. Somatic mutations (specifically at codon 918), which leads to increased kinase activity, have been observed in at least 25% of MTC cases[7].

Potential relevance: Selpercatinib[8] is approved (2020) for RET fusion-positive NSCLC and thyroid cancer. Selpercatinib[8] is also approved for RET-mutation positive medullary thyroid cancer (MTC). Additionally, the RET inhibitor, pralsetinib[9], was approved (2020) for RET fusion-positive NSCLC and thyroid cancer as well as RET mutation-positive MTC. The FDA approved small-molecule tyrosine kinase inhibitors, vandetanib (2011), and cabozantinib (2012), are recommended for the treatment of NSCLC patients with RET rearrangements[10]. Cabozantinib has also demonstrated clinical benefit in RET mutated medullary thyroid cancer patients[11]. Point mutations involving codons 804 and 806 have been shown to confer resistance to selective kinase inhibitors including vandetanib[12,13]. RET mutations at codon 918 are associated with high risk and adverse prognosis in patients diagnosed with MTC[14].

# Genes Assayed

## Genes Assayed for the Detection of DNA Sequence Variants

AKT1, AKT2, AKT3, ALK, AR, ARAF, BRAF, CDK4, CDKN2A, CHEK2, CTNNB1, EGFR, ERBB2, ERBB3, ERBB4, ESR1, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, GNA11, GNAQ, GNAS, HRAS, IDH1, IDH2, KIT, KRAS, MAP2K1, MAP2K2, MET, MTOR, NRAS, NTRK1, NTRK2, NTRK3, PDGFRA, PIK3CA, PTEN, RAF1, RET, ROS1, SMO, TP53

## Genes Assayed for the Detection of Copy Number Variations

ALK, AR, CD274, CDKN2A, EGFR, ERBB2, ERBB3, FGFR1, FGFR2, FGFR3, KRAS, MET, PIK3CA, PTEN

## Genes Assayed for the Detection of Fusions

ALK, AR, BRAF, EGFR, ESR1, FGFR1, FGFR2, FGFR3, MET, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, RET, ROS1, RSPO2, RSPO3

## Clinical Trials Summary

### KIF5B-RET fusion

| NCT ID | Title | Phase |
|---|---|---|
| NCT04222972 | A Phase III Study of BLU-667 as First-line Treatment in RET- Altered Advanced Non Small Cell Lung Cancer. | III |
| NCT04819100 | LIBRETTO-432: A Placebo-controlled Double-Blinded Randomized Phase III Study of Adjuvant Selpercatinib Following Definitive Locoregional Treatment in Participants With Stage IB-IIIA RET Fusion-Positive NSCLC | III |
| NCT04194944 | LIBRETTO-431: A Multicenter, Randomized, Open-Label, Phase III Trial Comparing Selpercatinib to Platinum-Based and Pemetrexed Therapy With or Without Pembrolizumab as Initial Treatment of Advanced or Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer | III |
| NCT02314481 | Deciphering Antitumour Response and Resistance With INtratumour Heterogeneity - DARWINII | II |
| NCT04131543 | "Phase II Study to Evaluate the Activity and Safety of Cabozantinib in Pretreated, Advanced RET-rearranged Non-small Cell Lung Cancer Patients: CRETA Trial" | II |
| NCT03157128 | A Study of Oral LOXO-292 in Patients With Advanced Solid Tumors, Including RET Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors With RET Activation (LIBRETTO-001) | I/II |
| NCT04591431 | The Rome Trial From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy | II |
| NCT04551521 | Continuous ReAssessment With Flexible ExTension in Rare Malignancies - CRAFT: The NCT-PMO-1602 Phase II Trial | II |
| NCT04589845 | Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial | II |
| NCT03899792 | A Phase I/II Study of the Oral RET Inhibitor LOXO 292 in Pediatric Patients With Advanced RET-Altered Solid or Primary Central Nervous System Tumors | I/II |

## Report Signed By

| Name | Role | Date |
|---|---|---|
| J.C. Courtney, Ph.D. | Laboratory Director | 11 May 2022 06:27:44 PM |

## References


1. Knowles et al. Structure and chemical inhibition of the RET tyrosine kinase domain. J. Biol. Chem. 2006 Nov 3;281(44):33577-87. PMID: 16928683
2. Ibáñez. Structure and physiology of the RET receptor tyrosine kinase. Cold Spring Harb Perspect Biol. 2013 Feb 1;5(2). PMID: 23378586
3. Santoro et al. Central role of RET in thyroid cancer. Cold Spring Harb Perspect Biol. 2013 Dec 1;5(12):a009233. PMID: 24296167
4. Elisei et al. RET/PTC rearrangements in thyroid nodules: studies in irradiated and not irradiated, malignant and benign thyroid lesions in children and adults. J. Clin. Endocrinol. Metab. 2001 Jul;86(7):3211-6. PMID: 11443191
5. Ciampi et al. RET/PTC rearrangements and BRAF mutations in thyroid tumorigenesis. Endocrinology. 2007 Mar;148(3):936-41. PMID: 16946010
6. Kohno et al. KIF5B-RET fusions in lung adenocarcinoma. Nat. Med. 2012 Feb 12;18(3):375-7. PMID: 22327624
7. Wohllk et al. Relevance of RET proto-oncogene mutations in sporadic medullary thyroid carcinoma. J. Clin. Endocrinol. Metab. 1996 Oct;81(10):3740-5. PMID: 8855832
8. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213246s002lbl.pdf
9. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214701s000lbl.pdf
10. NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 1.2022]
11. Sherman et al. Correlative analyses of RET and RAS mutations in a phase 3 trial of cabozantinib in patients with progressive, metastatic medullary thyroid cancer. Cancer. 2016 Dec 15;122(24):3856-3864. PMID: 27525386
12. Carlomagno et al. Disease associated mutations at valine 804 in the RET receptor tyrosine kinase confer resistance to selective kinase inhibitors. Oncogene. 2004 Aug 12;23(36):6056-63. PMID: 15184865
13. Carlomagno et al. Identification of tyrosine 806 as a molecular determinant of RET kinase sensitivity to ZD6474. Endocr Relat Cancer. 2009 Mar;16(1):233-41. doi: 10.1677/ERC-08-0213. Epub 2008 Nov 24. PMID: 19029224
14. NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2021]