Example Clinical Lab System
123 Sample Avenue
City, Postal Code
+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-3
Case Number:	987654	**Sample Collected:**	02 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] **selpercatinib** [1, 2] cabozantinib	**pralsetinib** [2] **selpercatinib** [1, 2]	10

Public data sources included in relevant therapies: EMA[1], ESMO, **FDA**[2], NCCN
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.

Electronically Signed by Jane Doe, MD on 04 May 2022 01:24:27 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, CHEK2, CTNNB1, EGFR, ERBB2, ERBB3, ERBB4, ESR1, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, GNAS, HRAS, IDH1, IDH2, KIT, KRAS, MAP2K1, MAP2K2, MET, NRAS, NTRK1, NTRK2, NTRK3, PDGFRA, PIK3CA, PTEN, RAF1, RET, ROS1, TP53, KEAP1, STK11

Genes Assayed for the Detection of Copy Number Variations

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

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
Jane Doe, MD	Laboratory Director	04 May 2022 01:24:27 PM

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