Focusing on the *ROS1* oncogene

A molecular biomarker

A member of the insulin receptor family, the *ROS1* oncogene encodes a receptor tyrosine kinase that is structurally related to ALK.[7,8] Although the ROS1 protein is absent in normal lung tissue, *ROS1* is highly expressed in a variety of tumour cell lines, including NSCLC.[8,10]

ROS1 is activated through genetic rearrangement with other genes called fusion partners.[7] This translocation, involving wildtype *ROS1*, results in the formation of a hybrid fusion gene.[8]

From oncogene to fusion protein

The fusion protein retains the ROS1 kinase domain, which is constitutively activated, driving downstream signal transduction pathways (MAPK, PI3K, and JAK-STAT) and promoting:[7]

Cell survival

Cell proliferation

Metastasis

A variety of techniques can be used to detect *ROS1* translocations, such as:[1]

- IHC
- FISH
- NGS
- PCR

Clinically, in patients with advanced-stage adenocarcinoma, the presence of *ROS1*-genetic rearrangements can be detected with **IHC**, providing they are **confirmed by a molecular or cytogenic method such as FISH**.[9]

ALK, anaplastic lymphoma kinase; FISH, fluorescence *in situ* hybridization; IHC, immunohistochemistry; JAK-STAT, Janus kinase-signal transducer and activator of transcription; MAPK, mitogen-activated protein kinase; NGS, next generation sequencing; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *ROS1*, c-ros oncogene 1.

ROS1 biomarker testing in NSCLC

Considerations for your next patient

ROS1 gene encodes for a receptor tyrosine kinase that is structurally related to ALK.[7,8] *ROS1* rearrangements activate downstream signaling pathways, driving **tumour cell survival, proliferation, and metastasis**.[7]

ROS1 rearrangements have been identified in **1–2% of patients with NSCLC**.[1]

ROS1 testing should be performed when diagnosing patients with advanced or metastatic NSCLC, along with *EGFR*, *ALK*, *BRAF*, and *PD-L1* testing.[1]

Patients with lung adenocarcinoma should be subjected to *ROS1* testing, **regardless of their clinical characteristics**.[9]

ALK, anaplastic lymphoma kinase; *BRAF*, B-rapidly accelerated fibrosarcoma; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; *PD-L1*, programmed death receptor ligand 1; *ROS1*, c-ros oncogene 1.

References:
1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Non-small cell lung cancer. 2020. **2.** Canadian Cancer Society Statistics Advisory Committee. Toronto, ON: Canadian Cancer Society; 2018. **3.** Zhang W, et al. *Proteomics.* 2014;14(6):795-803. **4.** Filosso PL, et al. *Lung Cancer.* 2011;74(1):25-29. **5.** Borczuk AC, et al. *Am J Pathol.* 2003;163(5):1949-1960. **6.** Lococo F, et al. *Ann Thorac Surg.* 2017;103(4):1142-1150. **7.** Melosky B, et al. *Curr Oncol.* 2018;25(1):73-82. **8.** Rossi G, et al. *Lung Cancer (Auckl).* 2017;8:45-55. **9.** Lindeman NI, et al. *Arch Pathol Lab Med.* 2018;142(3):321-346. **10.** National Center for Biotechnology Information. ROS1: ROS proto-oncogene 1, receptor tyrosine kinase [Homo sapiens (human)]. 2019.

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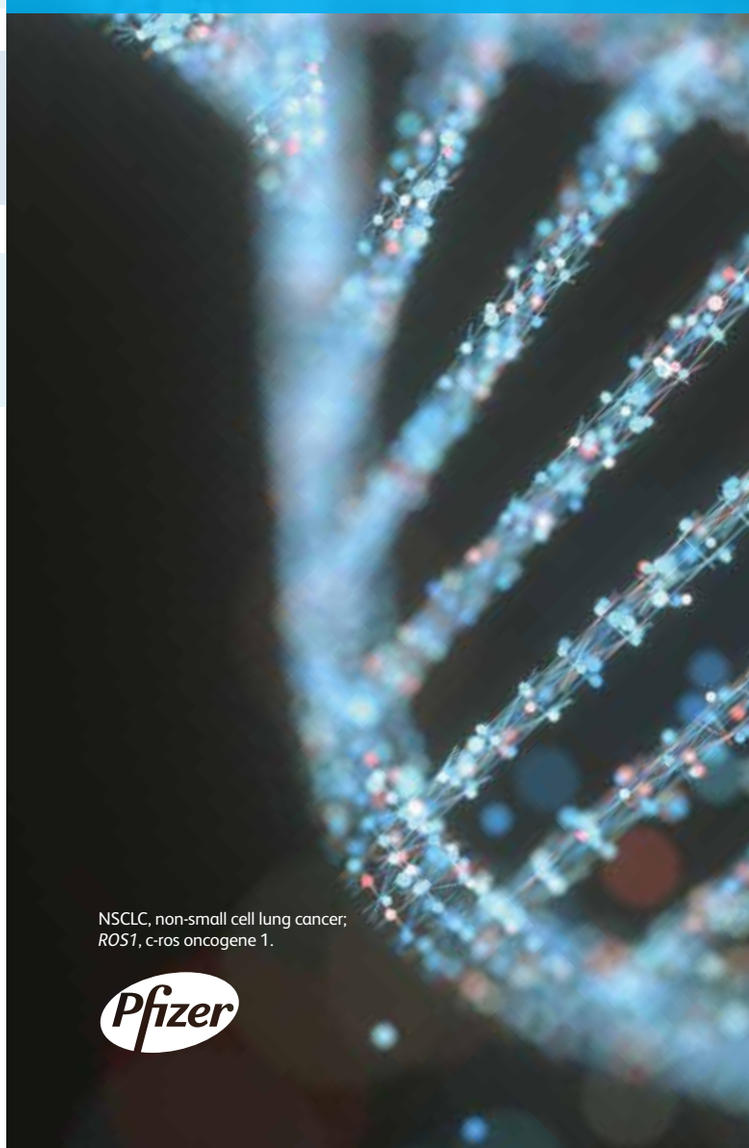
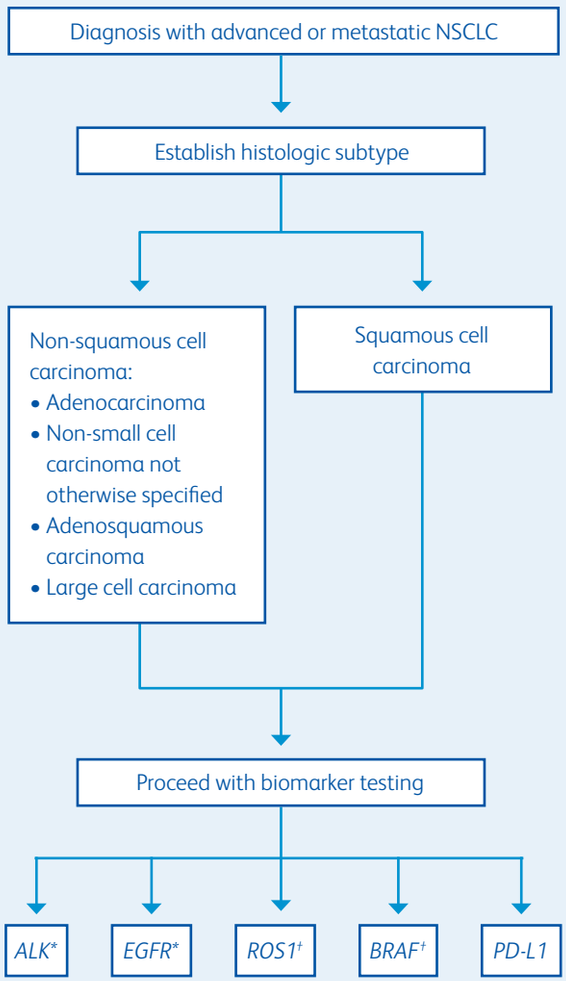
ROS1—AN IMPORTANT BIOMARKER TO TEST IN YOUR PATIENTS WITH METASTATIC OR ADVANCED NSCLC



NSCLC, non-small cell lung cancer; *ROS1*, c-ros oncogene 1.

Navigating your patients' diagnoses—from histopathologies to molecular biomarkers



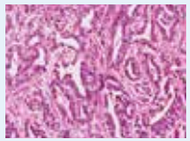
Adapted from NCCN Guidelines—Non-small cell lung cancer, 2020.[1]
* Squamous cell carcinoma: based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. To be considered in never smokers, small biopsy specimens, or mixed histology.
† Based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. For squamous cases, consider in small biopsy specimens or mixed histology.
ALK, anaplastic lymphoma kinase; *BRAF*, B-rapidly accelerated fibrosarcoma; *EGFR*, epidermal growth factor receptor; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; *PD-L1*, programmed death receptor ligand 1; *ROS1*, c-ros oncogene 1.

Your patients diagnosed with NSCLC—taking the next step to classify histologic subtypes

In Canada,[2]
- **More than 80%** of all lung cancer cases are **NSCLC**
- **47.1%** of NSCLC cases were diagnosed at **stage IV**

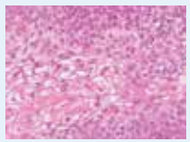
Classifying NSCLC according to histologic subtype

NSCLC can present as the following histologic classes:[1]



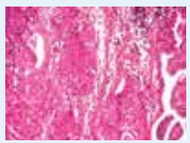
Adenocarcinoma (ADC)

HE stain of NSCLC primary tumour-derived xenograph[3]



Squamous cell carcinoma (SCC)

HE stain of NSCLC primary tumour-derived xenograph[3]

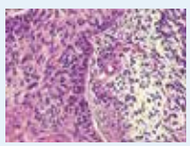


Adenosquamous carcinoma (AQSC)

Histological lung adenosquamous carcinoma specimen[4]

Large cell carcinoma (LCC)

Immunohistochemical stain of a tissue microarray block from a patient with NSCLC[5]



Sarcomatoid carcinoma

HE stain of NSCLC pleomorphic carcinoma[6]

During pathologic evaluation, small biopsies or cytology specimens that are intended for initial diagnosis are used:[1]
- To make an accurate diagnosis using the "2015 WHO Classification of Lung Tumors"
- To perform molecular testing on the preserved tissue, especially if the patient has advanced-stage disease

HE, hematoxylin and eosin; NSCLC, non-small cell lung cancer; WHO, World Health Organization.

Evaluating your patients for molecular biomarkers

Current recommendations

Lung cancers, such as NSCLC, have a high rate of genetic alterations compared to other tumours.[7] According to current NCCN Clinical Practice Guidelines in Oncology, molecular testing for the following biomarkers should be performed when diagnosing patients with advanced or metastatic NSCLC:[1]

Non-squamous histology	Squamous histology
• ***ROS1***	• ***ROS1****
• *ALK*	• *PD-L1*
• *EGFR*	• *BRAF**
• *BRAF*	• *ALK*†
• *PD-L1*	• *EGFR*†

ROS1 rearrangements occur in **1–2%** of patients with NSCLC.[1]

In a study of 727 stage IV lung adenocarcinoma patients, the following clinical characteristics were independently associated with *ROS1*-positive NSCLC:[8]

Female sex

Younger age at diagnosis

Absence of smoking history

When considering *ROS1* biomarker testing, **clinical characteristics should not contribute to patient selection.**[9]

Reflex testing algorithms—an institutional decision[9]

Reflex testing is molecular testing that is initiated **immediately after a positive lung cancer diagnosis** is obtained. It is initiated **regardless of the stage of the cancer** and includes early stage disease.[7] In institutions with established reflex testing programs, this method of testing represents a reasonable avenue for pathologists.[9]

* To be considered in small biopsy specimens or mixed histology.
† To be considered in never smokers, small biopsy specimens, or mixed histology.
ALK, anaplastic lymphoma kinase; *BRAF*, B-rapidly accelerated fibrosarcoma; *EGFR*, epidermal growth factor receptor; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; *PD-L1*, programmed death receptor ligand 1; *ROS1*, c-ros oncogene 1.