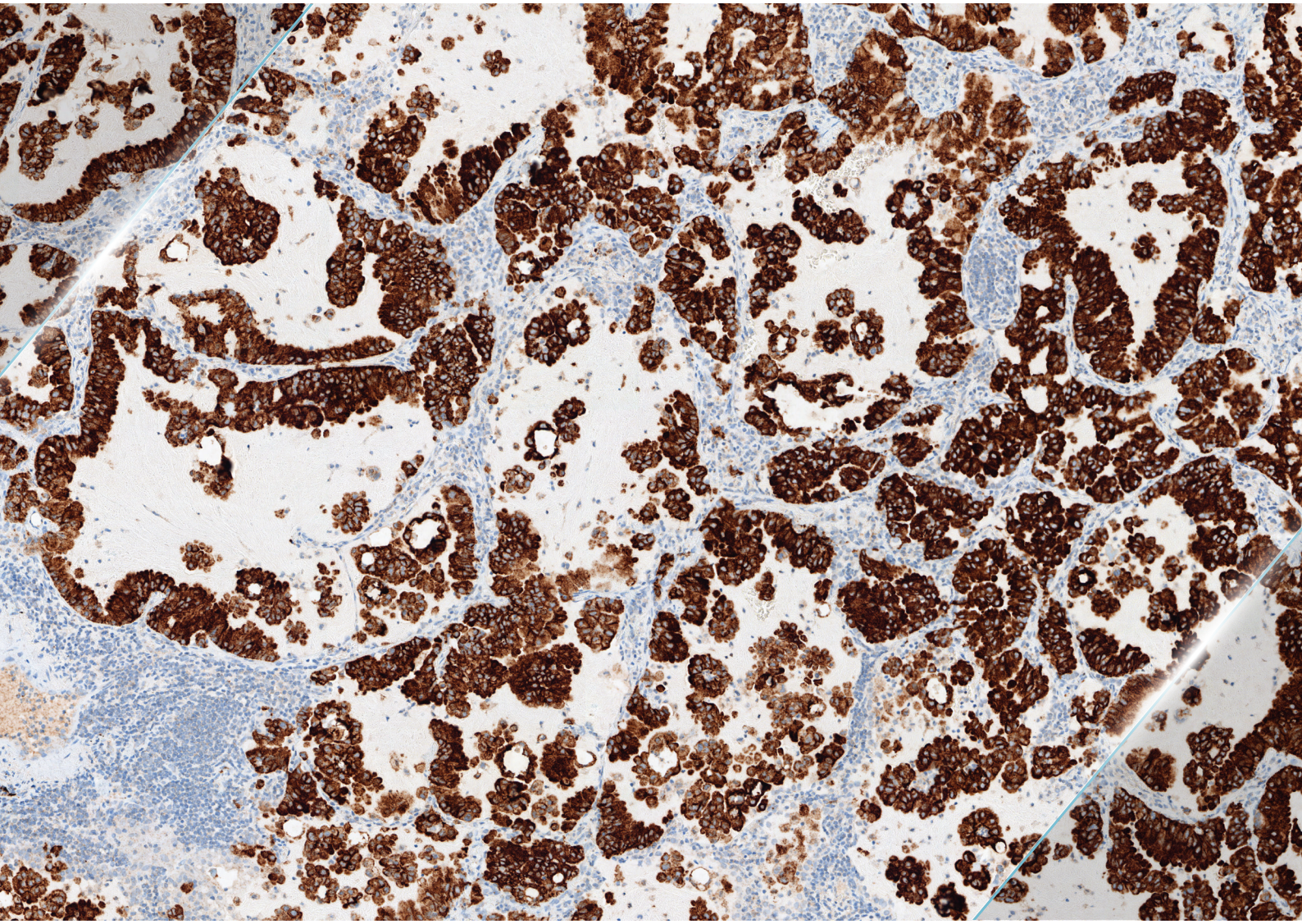
VENTANA ALK (D5F3) CDx Assay

Multiple targeted therapy options for ALK+ NSCLC patients



US FDA Approved

Predictive

VENTANA ALK (D5F3) CDx ASSAY

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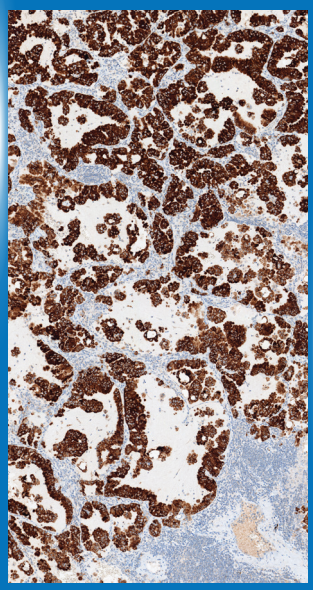

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VENTANA ALK (D5F3) CDx Assay* is intended for laboratory use in the detection of the anaplastic lymphoma kinase (ALK) protein in formalin-fixed, paraffin-embedded non-small cell lung carcinoma (NSCLC) tissue stained with the BenchMark series instruments.

*NSCLC tissue samples stained with the VENTANA ALK (D5F3) Assay and OptiView DAB Detection and Amp

Identify ALK+ NSCLC patients eligible for treatment with XALKORI,® ZYKADIA,® ALECENSA® or LORBRENA®

VENTANA ALK (D5F3) Assay stained with OptiView DAB IHC Detection and Amplification kits detects the ALK protein that is the target of therapy

Intended use

It is indicated as an aid in identifying patients eligible for treatment with XALKORI® (crizotinib), ZYKADIA® (ceritinib) or ALECENSA® (alectinib) or LORBRENA® (lorlatinib).

This product should be interpreted by a qualified pathologist in conjunction with histological examination, relevant clinical information and proper controls.

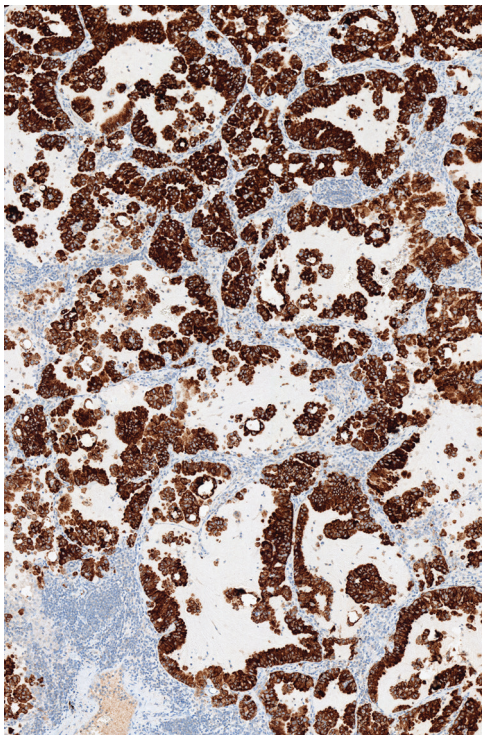
This antibody is intended for in vitro diagnostic (IVD) use.

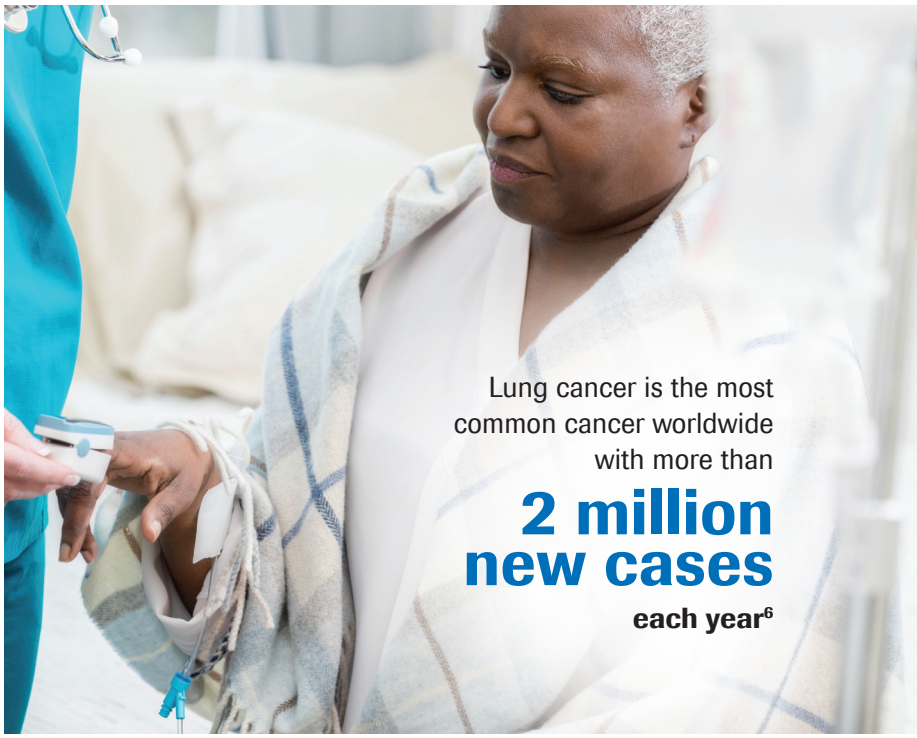
*Abbreviated to VENTANA ALK (D5F3) Assay

ALK IHC value points

- Clinical guidelines recommend rapid turnaround for earlier targeted therapies[1]
- According to the NCCN guidelines: FDA-approved IHC (ALK {D5F3} CDx Assay) can be utilized as a stand alone test, not requiring confirmation from FISH.[33]
- More immediate treatment decisions can be made for advanced NSCLC patients by using the VENTANA ALK (D5F3) Assay
- VENTANA ALK (D5F3) Assay has comparable sensitivity and specificity relative to FISH[3]
- XALKORI (crizotinib), ZYKADIA (ceritinib) and ALECENSA (alectinib) and LORBRENA® (lorlatinib) are clinically effective and recommended for the treatment of ALK-positive patients[2, 3, 4, 5]

About non-small lung cancer





Over the past three decades, lung cancer has shown the least improvement in survival rates when compared with other cancers.[7]

Lung cancer has been the most common cancer in the world for several decades and remains the leading cause of cancer deaths worldwide.[10] It is estimated to account for 12.9% of all new cancer cases and is responsible for nearly 1.59 million deaths annually worldwide, or approximately one in five cancer-related deaths.[8] Although improvements have been made in diagnosis and therapy options, prognosis remains poor with low long-term survival rates for all stages.

Non-small cell lung cancer (NSCLC), one of the two major types of lung cancer, accounts for approximately 85% of all lung cancer cases.[6] In more than half of patients newly diagnosed with NSCLC, the disease has already metastasized, greatly decreasing the likelihood of survival. The five-year relative survival rate for NSCLC diagnosed as distant disease is 4.7%.[17] The majority of patients with NSCLC present with inoperable, locally advanced disease (Stage IIIB) or metastatic disease (Stage IV), neither of which currently has any curative treatment options. On average, these patients die within a year of diagnosis. Improvement in the clinical outcome of lung cancer is likely to be achieved through better understanding of the molecular events that underlie its pathogenesis, identifying new biomarker targets and developing new treatment options.

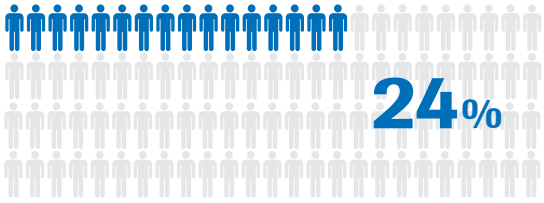
Lung cancer is the leading cause of cancer death for men and women globally with more than

4,000 people dying every day[10]

ALK is considered one of the key oncogenic drivers in NSCLC

Lung cancer is the most prevalent form of cancer in the world. Each year, more than 2 million new cases are diagnosed. Lung cancer also has the highest mortality rate. Five-year survival rates are as low as 24%. Adenocarcinoma, a subset of NSCLC, is the most common, comprising approximately 40% of all lung disease.[16, 17]

Five-year survival rate of patients after diagnosis with NSCLC is



ALK mutation in lung cancer

Genetic mutations are known to play critical roles in the progression to metastatic lung disease. The majority of these mutations are found in adenocarcinoma of young non-smokers. ALK is considered one of the key oncogenic drivers in NSCLC. The ALK gene codes for a transmembrane glycoprotein with tyrosine kinase activity. In-frame rearrangements with the known fusion partners place the ALK kinase domain under the control of a different gene promoter. This fusion results in a chimeric protein (like EML4-ALK) with constitutive tyrosine kinase activity that has been demonstrated to play a key role in controlling cell proliferation. This unique protein is also a potential target for ALK-specific tyrosine kinase inhibitor (TKI) therapy.[18, 8, 19]

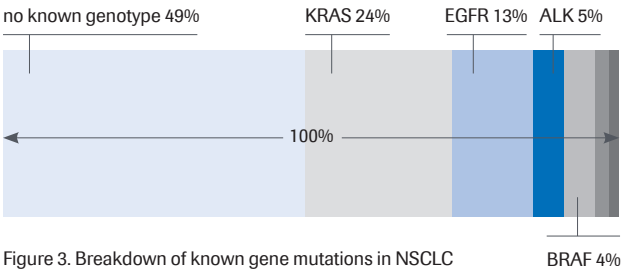


Figure 3. Breakdown of known gene mutations in NSCLC

Testing for lung cancer

Main types of lung cancer[11]

Poor 5-year survival rate
when compared to other cancers (U.S. only)[12]

Worldwide data varies from developed v middle income v low income countries. where early detection, adequate diagnosis and treatment greatly varies (Coleman et al., 2008)

With the introduction of targeted therapies that can result in dramatically different outcomes based on subtype, the importance of accurate classification has been amplified.[32]

Up to 30% of lung biopsies require adjunct IHC testing after morphologic evaluation.[14] IHC and more specifically, key panels of IHC antibodies, provides the necessary complement in the routine diagnosis and subtyping of lung cancer.[32]

Clinical guidelines recommend routine testing for genetic mutations in all adenocarcinomas including ALK EML[4] gene rearrangement. Testing is recommended immediately after establishing histology and is required prior to initiating targeted therapy for a patient. The current clinical practice and guidelines for ALK testing includes IHC and FISH.[7]

IHC is key in stratifying lung cancer

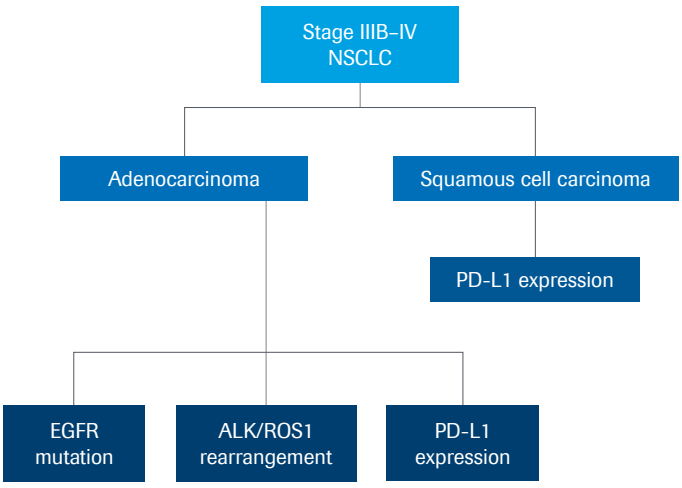
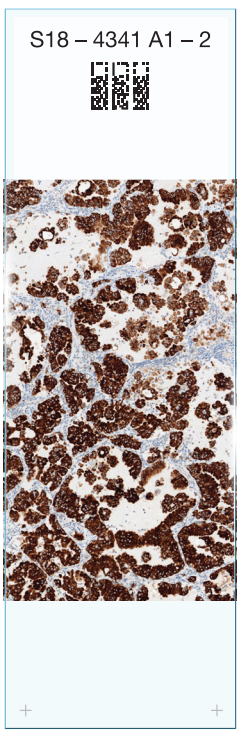


Figure 1. Common testing algorithm to determine indications for appropriate treatment in lung cancer

Treatment options for non-small cell lung cancer



XALKORI, ZYKADIA, ALECENSA and LORBRENA are indicated for the treatment of patients with metastatic NSCLC whose tumors are ALK-positive as detected by an approved testing method for ALK.[2, 3, 4, 5]

XALKORI (crizotinib) is indicated for the treatment of patients with ALK positive metastatic NSCLC and other kinases.[3]

ZYKADIA (ceritinib) is indicated for the treatment of patients with ALK-positive metastatic NSCLC who have had no previous treatment, or who have progressed on, or who are intolerant to, crizotinib.[4]

ALECENSA (alectinib) is indicated for the treatment of patients with ALK-positive metastatic NSCLC who have had no previous treatment, or who have progressed on, or who are intolerant to, crizotinib.[5]

LORBRENA (lorlatinib) is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on crizotinib and at least one other ALK inhibitor for metastatic disease; or alectinib as the first ALK inhibitor therapy for metastatic disease; or ceritinib as the first ALK inhibitor therapy for metastatic disease.[2]

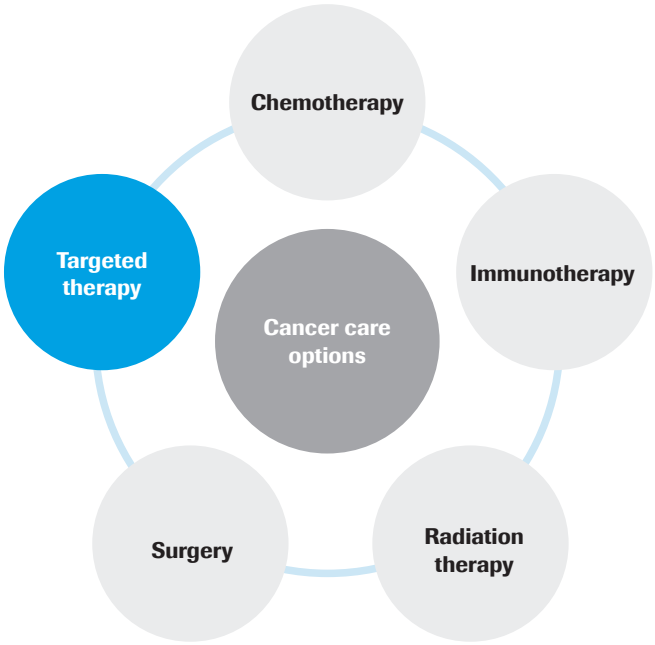
	PROFILE 1014 trial		ASCEND-4 trial		ALEX trial		CROWN trial	
Progression-Free Survival	**XALKORI (n=172)**	**Chemotherapy (n=171)**	**ZYKADIA (n=189)**	**Chemotherapy (n=187)**	**ALECENSA (n=152)**	**XALKORI (n=151)**	**LORBRENA (n=149)**	**XALKORI (n=147)**
Median, months (95% CI) [a]	10.9 (8.3, 13.9)	7.0 (6.8, 8.2)	16.6 (12.6, 27.2)	8.1 (5.8, 11.1)	34.8 (17.7-NR)	11.1 (9.1, 13.1)	NR	9.3
HR (95% CI) [b]	0.45 (0.35, 0.60)		0.55 (0.42, 0.73)		0.47 (0.34, 0.65)		0.28 (0.19, 0.41)	
p-valued [c]	<0.001		<0.0001		<0.0001		<0.001	

Figure 4. Clinical benefit of XALKORI, ZYKADIA and ALECENSA (progression free survival)
HR=hazard ratio; CI=confidence interval; BIRC=Blinded Independent Review Committee; NR=not reached; NE=not estimable
[a] Estimated using the Kaplan-Meier method. [b] A Cox regression model stratified by randomization stratification factors (WHO performance status: 0 vs. 1-2; presence or absence of BM, presence or absence of previous neo-/adjuvant chemotherapy) was used to estimate the hazard ratio of PFS, along with 95% CI based on the Wald test. [c] Based on the stratified log-rank test (same stratification as [b]).

Standardization of ALK IHC testing: Specimen type and controls

Patients with late stage lung cancer need a fast, reliable and standardized way to assess treatment options. Roche developed the VENTANA ALK (D5F3) Assay to be used with OptiView DAB IHC Detection and Amp to identify those patients who are eligible for ALK targeted therapy. A full range of human NSCLC tissue specimen types can be tested including resections, needle biopsies, bronchial biopsies and formalin-fixed, paraffin-embedded cell blocks.

A matched negative reagent control slide must be run for every specimen to aid in the interpretation of results. System-level controls must be run with patient samples. They can be either human appendix or known ALK-positive/negative NSCLC tissue samples.



Best in quality

The VENTANA ALK (D5F3) Assay stained with OptiView DAB Detection and Amp scored high in External Quality Assurance testing vs. all other ready-to-use antibodies for demonstration of ALK rearrangement.[20]

Easy to score

The sensitivity of the approved VENTANA ALK (D5F3) Assay stained with OptiView DAB Detection and Amp enables a reproducible, binary scoring system for evaluating staining results without the need for quantification of cells or staining.[21]

Fast turnaround time

The approved VENTANA ALK (D5F3) Assay stained with OptiView DAB Detection and Amp is a 4 1/2-hour, fully automated test to be stained with all other routine IHC testing for same-day results and to meet current CAP/IASLC/AMP guidelines for testing patients with lung cancer.[28]

Workflow efficiency

The VENTANA ALK (D5F3) Assay is fully optimized for use on BenchMark IHC/ISH automated staining instruments.

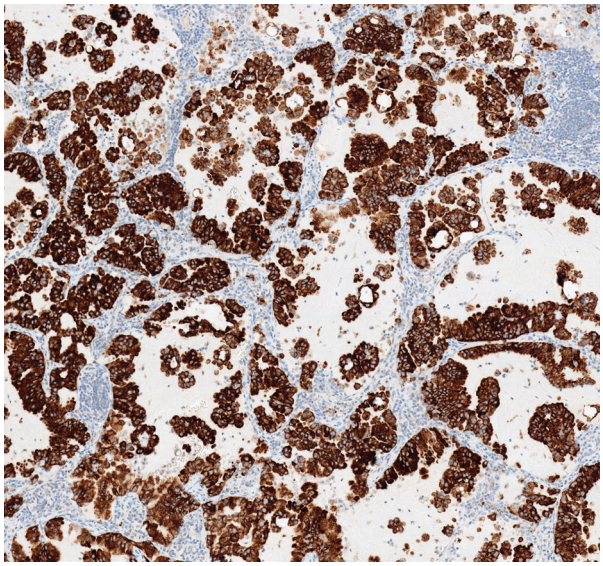
VENTANA ALK (D5F3) Assay vs. FISH

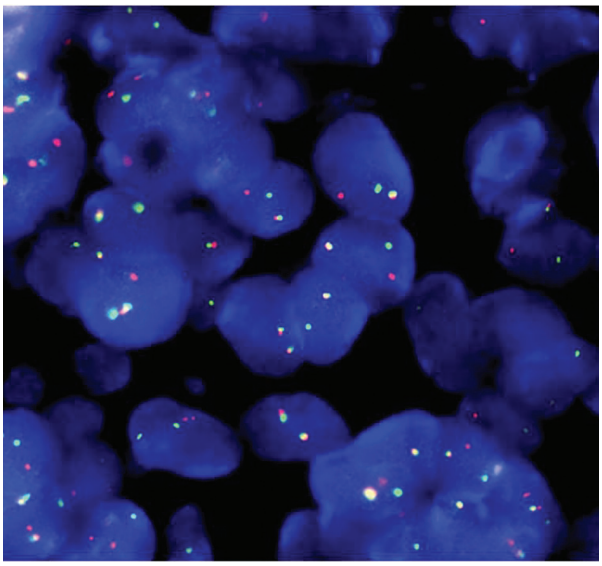
Technical benefits of IHC testing

ALK FISH can present technical challenges in evaluating patient results and offers the potential for false negatives. Recent studies indicate that the VENTANA ALK (D5F3) Assay stained with OptiView DAB Detection and Amp is sensitive and specific for determination of ALK status, and a better alternative to ALK FISH. There are reports of ALK IHC-positive, FISH-negative patients benefiting from treatment with XALKORI.[22, 23, 24, 25, 26]

One study, found that "Dichotomous ALK-IHC is superior to ALK-FISH on small biopsies and FNA to predict tumor response and survival to crizotinib for advanced NSCLC patients."[27]

Figure 5. Comparison of VENTANA ALK (D5F3) Assay stained with OptiView DAB Detection and Amp vs. FISH testing for determining ALK status

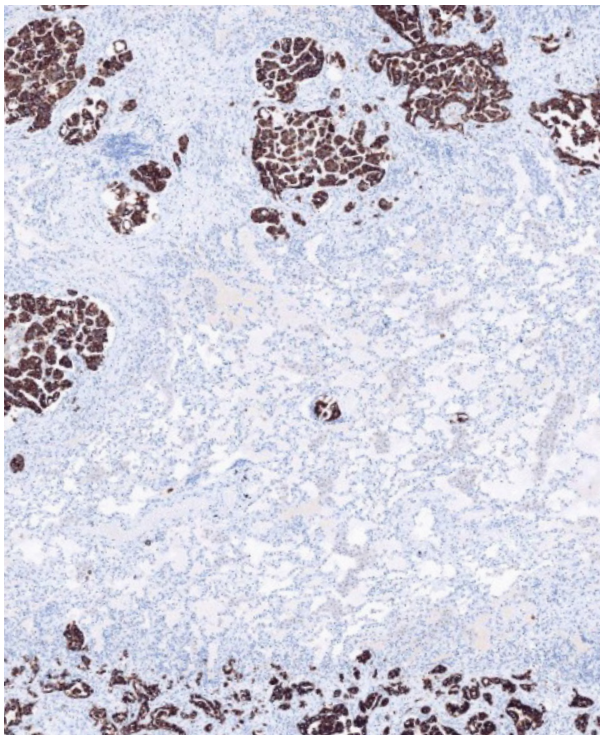




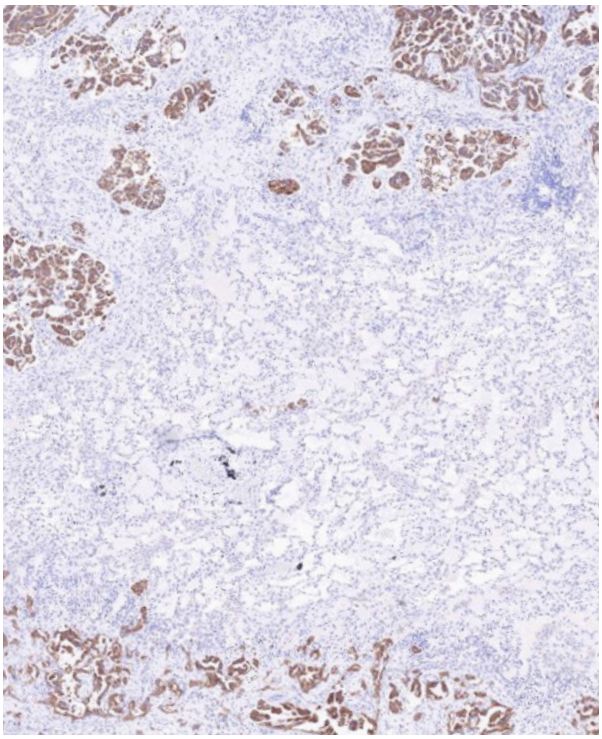
VENTANA ALK (D5F3) Assay with OptiView DAB Detection and Amp	ALK FISH
Scoring process ▪ Binary (+/-) scoring ▪ Presence of strong granular cytoplasmic staining in tumor cells (any percentage of positive tumor cells)	**Scoring process** ▪ Requires a dual color scoring algorithm ▪ Requires 50 enumerable cells and specific cutoff ratios to be calculated
Turnaround times ▪ 41/2 hours, fully automated ▪ Routine IHC testing	**Turnaround times** ▪ 12+ hours, semi-automated ▪ Typically batch or send-out testing
Brightfield vs. fluorescent staining ▪ Standard brightfield microscope ▪ Fully archivable results ▪ Full visibility of tumor morphology	**Brightfield vs. fluorescent staining** ▪ Requires a fluorescent microscope ▪ Staining and signal fade over time ▪ Loss of tissue morphology

VENTANA ALK (D5F3) Assay vs. other ALK IHC

Figure 6. NSCLC tissue samples stained with different ALK IHC antibodies clones



VENTANA ALK (D5F3) Assay with OptiView DAB Detection and Amp



ALK antibody, clone 5A4 with Polymer Detection

ALK antibody clones

The VENTANA ALK (D5F3) Assay stained with OptiView DAB Detection and Amp is the only assay approved as an aid to identify patients eligible for treatment with XALKORI, ZYKADIA, ALECENSA or LORBRENA.[21]

It consistently scores high performance for proficiency and technical External Quality Assessment schemes (CAP, ESP, NordiQC).[28, 29, 30]

Molecular testing

Current molecular testing does not identify all known ALK genetic variants and is not recommended as an alternative testing method to select patients for ALK inhibitor therapy.[7]

Over ten genetic variants of EML4-ALK mutations have been identified. VENTANA ALK (D5F3) Assay stained with OptiView DAB Detection and Amp identifies a conserved protein sequence common to known variants of the ALK mutation.

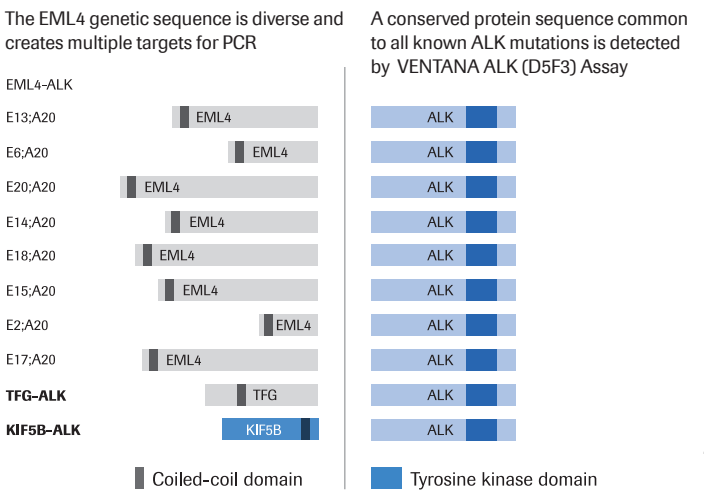
- There are multiple genetic variants of the ALK mutation that lead to NSCLC
- Molecular testing does not identify all ALK gene variants and can miss positive cases
- D5F3 clone is specific to the common kinase domain of all ALK mutations and should identify all genetic variants

Molecular testing techniques rely upon good sample integrity and require sophisticated computational analysis to interpret results. Formalin-fixed, paraffin-embedded tissues provide a significant challenge as genetic material is known to degrade in sample preparation. Even when properly performed, interpreting the results of these techniques is not standardized.[7]

ALK testing with VENTANA ALK (D5F3) Assay with OptiView DAB Detection and Amp offers many benefits:

- A fully automated test to select patients for treatment with XALKORI, ZYKADIA, ALECENSA or LORBRENA
- Fastest turnaround time to meet the current CAP/IASLC/AMP guidelines for testing lung patients
- Can be integrated into a routine IHC panel of antibodies to stratify NSCLC patients

Figure 7. Different variants of EML4-ALK and non-EML4 fusion partners[8]



Visit ALKihc.com and contact your local Roche representative to learn more.

Ordering information

Product name	Catalog number	Ordering code	Quantity
VENTANA-ALK (D5F3) CDx Assay	790-4796	06687199001	50 tests
Rabbit Monoclonal Negative Control Ig	790-4795	06683380001	250 tests
OptiView DAB IHC Detection Kit	760-700	06396500001	250 tests
OptiView Amplification Kit	760-099	06396518001	50 tests

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