



A Broader Recognition of Oncogene ALK-1 by Zeta-Antibody ZR305

A ZETA Corporation White Paper Authors: Dr. rer. nat. Andreas Herrmann and Peiguo Chu M.D. March, 2024

SUMMARY:

The receptor tyrosine kinase ALK has been identified eliciting oncogenic activity by a variety of MOAs including (i) protein overexpression due to gene amplification and (ii) gain-of-function mutation resulting in constitutively active kinase activity, and/or (iii) genetic aberration encoding ALK fusion oncoproteins. The Zeta-Antibody ALK-1 ZR305 offers a broad range recognition of ALK antigen and its variations in a variety of hematologic indications as well as solid tumors owed to the conservation of the ALK intracellular domain (ICD) throughout ALK proteins.

The Anaplastic Lymphoma Kinase ALK-1 (CD246) resides on the outer cell membrane. Human ALK was initially identified in 1994 as a moiety of the nucleophosmin (NPM)-ALK fusion in anaplastic large cell lymphomas while EML4-ALK was identified in lung adenocarcinoma (4%) and in inflammatory myofibroblastic tumors (50%)¹ (Figs. 1, 2).

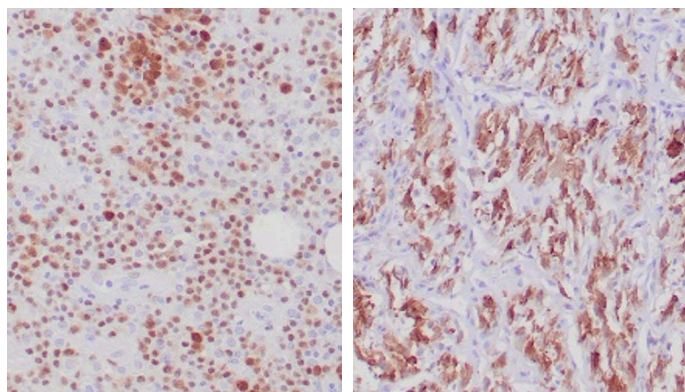


Figure 1: Zeta-Antibody ZR305 against ALK. IHC staining of ALK in human anaplastic lymphoma (left) and myofibroblastic tumor (right). Images property of Zeta Corporation.

Furthermore, ALK expression was observed in rhabdomyosarcoma, glioblastoma, melanoma, and retinoblastoma.¹

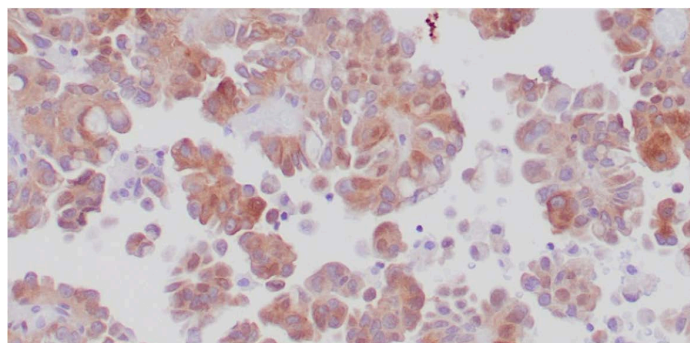


Figure 2: Zeta-Antibody ALK ZR305 in lung cancer. IHC staining of ALK in human lung adenocarcinoma. Image property of Zeta Corporation.

Additionally, genetic translocation and/or mutation of ALK has been reported for neuroblastoma, diffuse large B cell lymphomas, breast carcinoma, renal cell carcinomas, non-small cell lung cancer, and lung adenocarcinoma (Fig. 2).

The Zeta-Antibody ALK-1 ZR305 maps to the intracellular domain ICD of the receptor tyrosine kinase ALK-1 as well as to its ICD conserved in multiple ALK-fusion proteins (Fig. 3).^{2,3}

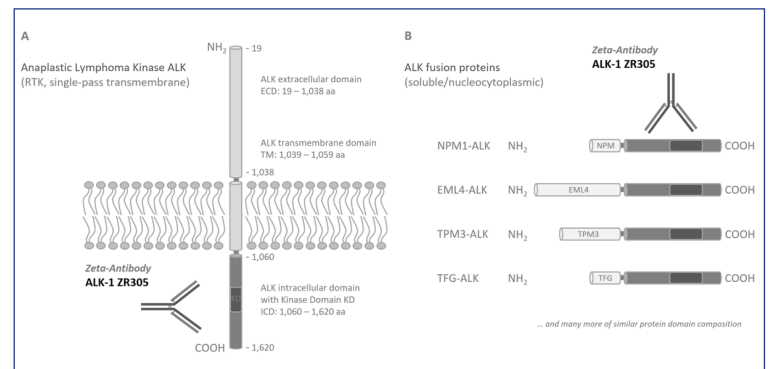


Figure 3: Zeta-Antibody ALK-1 ZR305 epitope mapping to the preserved intracellular domain. (A) Parental transmembrane protein ALK shown with its three protein domains. Domain borders indicated by aa numbering. (B) ALK fusion proteins illustrating ICD conservation allowing recognition ZR305.³

In striking contrast to other ALK-1 antibodies, the Zeta-Antibody ALK-1 ZR305 readily detects ALK fusion proteins in NPM-ALK+ anaplastic large cell lymphomas and EML4-ALK+ lung adenocarcinoma. Since the oncogenic potential of ALK is encoded by its ICD, the Zeta-Antibody ALK-1 ZR305 represents a unique molecular detection opportunity of disease driving ALK proteins.

References:

1. Aubry, A. *et al.* Targeting ALK in Cancer: Therapeutic Potential of Proapoptotic Peptides. *Cancers (Basel)* **11**:275 (2019).
2. Kourentzi, K. *et al.* Recombinant expression, characterization, and quantification in human cancer cell lines of the Anaplastic Large-Cell Lymphoma-characteristic NPM-ALK fusion protein. *Sci Rep* **10**:5078 (2020).
3. <https://www.uniprot.org/uniprotkb/Q9UM73/entry#structure>