New Targets in Non–Small Cell Lung Cancer

Soo J. Park, MD, Soham More, Ayesha Murtuza, MD, Brian D. Woodward, Hatim Husain, MD*

KEYWORDS

• NSCLC • ROS1 • RET • NTRK • MET • BRAF • KRAS • Driver mutations

KEY POINTS

- With the implementation of genomic technologies into clinical practice, we have examples of the benefit of targeted therapy for oncogene-addicted cancer and identified unique molecular dependencies in non–small cell lung cancer.
- The clinical success of tyrosine kinase inhibitors against epidermal growth factor receptor and anaplastic lymphoma kinase activation has shifted treatment to emphasize the genomically defined subsets of lung cancer and genotype-directed therapy.
- Continued advances in our understanding of lung cancer biology have validated numerous oncogenic driver genes and have led to the rapid development of targeted agents.
- The current available data on ROS1, RET, NTRK, MET, BRAF, and KRAS aberrations in non–small cell lung cancer are presented.
- The current state of available trials in this space, mechanism of action of the oncogene, mechanisms of resistance to therapy are presented.

INTRODUCTION

Lung cancer remains the leading cause of cancer-related deaths worldwide.[1,2] Historically, the treatment of advanced epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) wild-type non–small cell lung cancer (NSCLC) has relied on platinum-based chemotherapy with a median overall survival (OS) of approximately 1 year.[2,3] Within the last several years, immune checkpoint inhibitors have demonstrated efficacy in both squamous and nonsquamous histologies and are now approved agents for second-line treatment, largely based on improved OS.[4,5]

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Division of Hematology and Oncology, Moores Cancer Center, University of California, San Diego, La Jolla, CA 92093, USA

* Corresponding author. Moores Cancer Center, University of California, San Diego, 3855 Health Sciences Drive, #0987, La Jolla, CA 92093.

E-mail address: hhusain@ucsd.edu

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The past decade has seen a paradigm shift in the treatment of NSCLC based on the implementation of broad-based genomics to identify driver mutations and drug development against these targets. Across genotypes, the use of targeted agents for the treatment of patients with EGFR and ALK-mutated NSCLC has improved response rates, time to disease progression, and OS when compared with conventional systemic therapy.[6,7] More than 60% of patients with lung adenocarcinoma have a presumably mutually exclusive oncogenic driver.[3] This article reviews driver mutations, including ROS1 fusions, RET fusions, NTRK1 fusions, c-MET amplification, exon 14 skipping mutations, BRAF mutations, and KRAS mutations, their downstream signaling (**Table 1**; **Fig. 1**), and the current clinical trials that are exploring compounds against these pathways.

Table 1
Genetic alterations and their frequency in lung adenocarcinoma

Target	Alteration	Frequency (%)
ROS1	ROS1 fusion	2
RET	RET fusion	1
NTRK1	NTRK1 fusion	3.3
c-MET	Amplification	2–4
	Exon 14 skipping mutation	3–4
BRAF	V600E mutation	1–4
KRAS	Mutations in codons 12, 13, and 61	15–25

THE ONCOGENIC ROS1 FUSION

ROS1 is a receptor tyrosine kinase (RTK) that belongs to the same insulin receptor superfamily as ALK. The function of ROS1 remains largely unknown, although some studies have suggested that this oncogene may play a role in epithelial cell differentiation.[8] Further progress in the characterization of ROS1 has been difficult owing to the absence of an identified ligand.[9] Expression of the ROS1 fusion protein results in constitutive kinase activity and activation of cellular pathways involved in cell growth and proliferation. Chromosomal rearrangements involving the *ROS1* gene were described originally in glioblastoma cell lines and have since been reported in cholangiocarcinoma and NSCLC.[10–12]

ROS1 gene fusions are found in approximately 2% of NSCLC and have been associated with a younger age of onset and a nonsmoking history, and seem to be mutually exclusive with other oncogenic driver genes.[13] Such demographic characteristics are similar to the clinical profile of patients with ALK-rearranged NSCLC and may be owing in part to the high level of homology between the kinase domains.[14,15] Crizotinib, a small molecule multikinase inhibitor originally developed as a MET kinase inhibitor and approved by the US Food and Drug Administration (FDA) for the treatment of ALK-rearranged NSCLC, was shown to have potent inhibitory activity against ROS1.[13] Results from the expansion cohort of the PROFILE 1001 (A Study Of Oral PF-02341066, A c-Met/Hepatocyte Growth Factor Tyrosine Kinase Inhibitor, In Patients With Advanced Cancer) trial showed that 72% of the participants experienced a complete or partial response in tumor burden, an effect that lead to a median duration of response of 17.6 months.[16] These findings led to recent FDA approval of crizotinib for patients with ROS1-rearranged NSCLC. Other trials with crizotinib are ongoing (**Table 2**). Ceritinib, ASP3026, and AP26113 exhibit activity against ROS1

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