

Treatment for oncogene-driven lung cancers, other than epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK)

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Epidermal growth factor receptor (EGFR) inhibitors and anaplastic lymphoma kinase (ALK) inhibitors are the standard therapy in lung adenocarcinoma with *EGFR* activating mutations and *ALK* rearrangements, respectively. There are other driver genetic alterations (e.g., *ROS1* fusion, *NTRK1* fusion, *RET* fusion, *MET* mutation, *HER2* mutation, *KRAS* mutation, *BRAF* mutation) which could be targeted.

Chromosomal rearrangements involving *ROS1* have been identified in approximately 1-2% of lung adenocarcinomas. Among a phase I dose-expansion cohort of 50 patients with *ROS1*-rearranged advanced-stage NSCLC, crizotinib yielded responses in 72% of patients and a median progression-free survival of 19.2 months. With next-generation sequencing and FISH probes, Vaishnavi and colleagues reported an oncogenic fusion including the tyrosine receptor kinase *NTRK1* in 3 of 91 samples from patients with lung adenocarcinoma without known oncogenic alterations. Chromosomal rearrangements involving the *RET* proto-oncogene and mediating ligand-independent dimerization / activation of *RET* have been identified in 1-2% of lung adenocarcinomas. Responses with vandetanib and cabozantinib in *RET* fusion-positive tumors have been reported.

MET activation through exon 14 skipping (analysis of both DNA and RNA sequencing data suggested that exon 14 was not expressed in these samples) has been reported in lung adenocarcinomas. Exon 14 skipping results in the loss of a negative regulatory site, and is often the result of splice-site mutations. Responses to capmatinib in *MET*-mutant NSCLC have been reported in a small study. *HER2* exon 20 mutations were noted in 5% of lung adenocarcinoma. Responses to trastuzumab and afatinib have been reported. *KRAS* mutations are observed in 5-30% of lung adenocarcinoma. *KRAS* mutations are frequently seen in smokers and are associated with codons 12 (the most frequent, resulting in G12V), 13, or 61. These missense mutations

maintain *KRAS* in a constitutively active state. *BRAF* mutations are also reported in lung adenocarcinomas with the most frequently encountered *BRAF* mutations being V600E mutations. Although V600E mutations are generally more prevalent in women and associated with worse outcomes, non-V600E mutations are prevalent in smokers and are not associated with prognosis. In a phase II trial, dabrafenib showed promising activity in patients with lung adenocarcinoma harboring *BRAF* V600E mutations.