

Targeting driver mutations in non-small cell lung cancer

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Lung cancer is one of the most common cancers worldwide, and the leading cancer killer in men and women¹. Approximately 80% of all lung cancers are non-small-cell lung cancers (NSCLC), among which adenocarcinomas and squamous-cell carcinomas account for the vast majority of cases. Investigation of the molecular and cellular biology of NSCLC has gradually unveiled a diverse roster of genomic alterations that have been linked with disease progression and have been classified as disease driver oncogenes².

Until recently, chemotherapy was the mainstay against metastatic NSCLC, irrespective of oncogene status. Although chemotherapeutic agents improved over the years, limited benefit was seen by patients, presenting with a median overall survival of 8-12 months and experiencing deteriorating quality of life and significant toxicities from therapy³. In recent years, the ability to molecularly profile NSCLC tumors gave researchers and clinicians the opportunity to design more effective and personalized treatment regimens aimed at targeting specific mutant oncogenes or even oncogene-activated signaling pathways in each individual patient. Several targeted agents are constantly being developed and clinical trials are yielding encouraging results, showing improved progression-free survival of selected NSCLC patients bearing specific mutations with targeted therapies⁴.

The epidermal growth factor receptor (EGFR) pathway is one of the most frequently dysregulated pathways in NSCLC. The EGFR family of receptors consists of transmembrane tyrosine kinase (TK) receptors and includes EGFR (or ERBB1 or HER1), HER2 (or ERBB2 or HER2), HER3 (or ERBB3 or HER3), and HER4 (or ERBB4 or HER4). The best-studied TK receptor in NSCLC is EGFR and its activating mutations are the prototype molecular targets against the disease. *EGFR* mutations and/or amplification occur more frequently in patients with adenocarcinoma, never smoking history, female sex, and/or East Asian ethnicity. For these patients with NSCLC, specific EGFR TK inhibitors (TKI), such as gefitinib and erlotinib, have yielded high response rates with significantly improved progression-free survival in clinical trials^{4,5}. In addition to EGFR status, the sensitivity to EGFR TKI therapy is also influenced by other family members such as HER2. HER2 is overexpressed in about 20% of NSCLC and this overexpression is linked with poor prognosis in early-stage lung adenocarcinoma⁶. However, *HER2* amplification rarely presents a clinical problem, since it is usually associated with EGFR gain-of-function and good response to EGFR TKI treatment. On the contrary, a

serious limitation of the TKI approach against NSCLC is the acquired resistance that develops during or after therapy. To this end, acquisition of the *EGFR*T790M point mutation is a well-described mechanism of secondary resistance in up to 68% of patients with tumors previously sensitive to EGFR-targeted therapy. In some cases, the amplification of *HER2* is responsible for acquired resistance to EGFR TKIs in treated patients harboring *EGFR* mutations⁷. The above observations dictate the necessity to repeatedly assess *HER2* and *EGFR* mutation status in patients with *EGFR*-mutant tumors that present acquired resistance to EGFR TKIs.

The phosphoinositide 3-kinase (PI3K) signaling pathway is also frequently abnormally activated in NSCLC through mutations in *PIK3CA*, *AKT1* or *PTEN* genes. It is noteworthy that *PIK3CA* is more frequently amplified in squamous-cell carcinomas than in adenocarcinomas, whereas loss-of-function mutations of the tumor suppressor *PTEN*, that negatively regulates *PIK3CA*, have been reported in about 10% of squamous-cell carcinomas^{8,9}. These genes are potential targets against squamous NSCLC and early preclinical studies have shown promising antitumor activity of inhibitors of this pathway.

Except from point mutations, amplifications, and deletions, gene translocations also exist in NSCLC. Soda et al. described a chromosomal translocation of the anaplastic lymphoma kinase (*ALK*) gene and its aberrant fusion with upstream 5'-partner echinoderm microtubule-associated protein-like 4 (*EML4*) gene leading to a cytoplasmic chimeric protein with constitutive kinase activity. The *ELM4/ALK* gene was shown to be a driver of lung tumorigenesis and patients harboring these fused proteins in their tumor specimens exhibit a good responsiveness to the ALK inhibitor crizotinib, rendering *ELM4/ALK* an important molecular target for the management of NSCLC¹⁰. Notably, ALK translocations occur only in *EGFR* wild-type lung adenocarcinomas of patients who have never smoked and are not influenced by ethnic differences, in contrast to EGFR mutations.

As most of the patients who harbor mutations in the *EGFR* or *ELM4/ALK* genes are never-smokers, the above cannot help the large proportion of patients with NSCLC who are active or former smokers. To this end, findings from older and recent genomic studies of NSCLC have solidified the cardinal molecular targets that drive lung cancer growth in smokers: *KRAS* mutations are the most common mutations in lung adenocarcinomas from smokers and their presence is associated with poor survival.

EGFR and *KRAS* mutations are mutually exclusive and aberrantly activated *KRAS* pathway is associated with primary resistance to EGFR TKIs¹¹. *KRAS* mutations result in the constitutive activation of the RAF–MEK–ERK pathway, and agents that target different components of this pathway have been developed and are under clinical investigation¹². In addition to *KRAS*, the tumor suppressor gene *TP53* (encoding the cell cycle safeguard P53 protein) is inactivated by mutation or single- or dual-allelic loss in smoking-associated NSCLC. Restoration of P53 function in patients with NSCLC by gene replacement therapy, using adenoviral or retroviral *TP53* expression vectors, showed some antitumor activity but further trials are awaited to determine the overall benefit of these therapies¹³.

In conclusion, molecular targeted therapies hold promise against NSCLC as agents superior to standard chemotherapy. Personalized treatment has already become a reality for a minority of NSCLC patients with *EGFR* and *ALK* alterations and is associated with better response rates, longer progression-free survival, lower toxicity, and improved quality of life. However, tumor heterogeneity, acquired resistance to existing targeted therapies, and missing targeted therapies for patients with *KRAS* and *TP53* mutations (among others) are serious limitations of current treatment options. While new molecular targets are continually emerging, therapeutic targeting of single oncogenic drivers seems to be insufficient for a disease with approximately thousand mutations per cancer genome¹⁴. New regimens and combined treatment strategies are obviously required to improve outcomes in patients with NSCLC. A new emerging and promising treatment option is immune-oncology that is designed to potentiate the patients' immune response to tumor cells¹⁵. It is anticipated that future research will help determine how and when immune-oncology agents can be used synergistically with molecularly targeted agents, in order to design individual precision therapeutic regimens for patients with NSCLC.

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