TABLE 56-2 MOLECULAR-GENOMIC SUBTYPES OF NSCLC

ONCOGENE	CLASS OF MOLECULAR-GENOMIC ALTERATIONS	CHARACTERISTICS
EGFR-mutant	Somatic missense mutations (most common with L858R in exon 21) and exon 19 deletions	More frequent in Asians, females, never-smokers or light smokers; most frequently adenocarcinoma subtype Sensitizing to EGFR inhibitors erlotinib, gefitinib, and afatinib T790M mutation in EGFR is resistant to the inhibitors.
EML4-ALK	ALK 2p23 chromosomal translocation	3-7% of NSCLCs More common in light smokers (<10 pack-years) or never-smokers Sensitizing to ALK inhibitor crizotinib
KRAS-mutant	Somatic mutations	Found in 15-25% lung adenocarcinomas Less common but can be present in squamous cell carcinomas More commonly seen in former or current cigarette smokers No effective targeted treatment at present
PIK3CA-mutant	Somatic mutations	The *PIK3CA* gene encodes the p110α, one of the catalytic subunits, of PI3K, which belongs to a family of lipid kinases involved in many cellular processes, including cell growth, proliferation, survival and motility. Mutated in 1-3% of all NSCLCs More common in squamous cell carcinoma *PIK3CA* shows significant potential as a candidate for targeted therapy
BRAF-mutant	Somatic mutations	Belong to a family of serine-threonine protein kinases Identified in 1-3% of cases Sensitizing to a mutated *BRAF*–specific inhibitor, vemurafenib, which has been approved by the FDA for treatment in V600E-*BRAF*–mediated cutaneous melanoma
HER2	Amplification, mutations, small insertions	*HER2* alterations were identified in ~2% to 4% of NSCLCs In the selected population of *EGFR/KRAS/ALK*-mutation–negative patients, *HER2* mutations can reach up to 6% Predominantly found in females, nonsmokers; predominantly adenocarcinoma subtype May be associated with sensitivity to HER2-targeting drugs (trastuzumab, lapatinib, pertuzumab, and T-DM1) used in breast cancer
LKB1	Inactivating mutations, deletion	A tumor suppressor gene also known as *STK11* Mutational frequency about 17-35% of NSCLCs in Caucasians but only 3-7% in the Asian population
RET-fusion	Chromosomal translocations	Recently found in some lung adenocarcinomas (1-2%)
ROS1-fusion	Chromosomal translocations	*ROS1* is a receptor tyrosine kinase of the insulin receptor family *ROS1*-fusions were identified in ~2% of NSCLCs More commonly found in younger people, more likely in never-smokers, and Asian patients are overrepresented *ROS1*-positive status may be associated with response to the kinase inhibitor crizotinib (ALK/MET inhibitor)
FGFR1	Amplification and mutations	Gene belongs to the family of FGFR TK members that includes FGFR types 1, 2, 3 and 4. Genomic alterations of FGFR1 have been identified predominantly in the squamous subtypes of lung cancer, raising the possibility of targeted therapy in this unique cancer subtype
MET	Alternative spliced variant, mutations, amplification, receptor overexpression	The *MET* proto-oncogene is a key invasive signaling axis. *MET* gene amplification can be found in 2-4% of NSCLCs, whereas overexpression of its receptor protein is much more common MET overexpression has been correlated with poor prognosis. A number of MET-targeting therapeutic agents have entered clinical trial studies. MET high expression may be a predictive biomarker of treatment response.
BCL2	Amplification, receptor overexpression	BCL2 overexpression is more common in SCLC than in NSCLC. Various BH3 mimetics have been developed to target the mitochondrial antiapoptotic marker BCL2 in human cancers (e.g. SCLC, CLL).

CLL, Chronic lymphocytic leukemia; EGFR, epithelial growth factor receptor; FDA, U.S. Food and Drug Administration; FGFR, fibroblast growth factor receptor; NSCLC, non–small cell lung cancer; PI3K, phosphatidyl 3-kinase; SCLC, small cell lung cancer; TK, tyrosine kinase.

most cases, *EML4-ALK* fusions do not overlap with other oncogenic mutations of *EGFR* or *KRAS*.

Mutant *KRAS*

KRAS gene mutations are uncommon in squamous cell carcinomas but are present in 15% to 25% of lung adenocarcinomas. *KRAS* mutations are more commonly seen in former or current cigarette smokers than in never-smokers or light smokers. There is currently no effective targeted treatment for mutated *KRAS*.

The Lung Cancer Genome

In the last decade, the TCGA project in comprehensive genomic analysis of human cancers has brought forth a renewed understanding of lung cancer at the genomic level.

The TCGA analysis mapped the hallmarks of lung adenocarcinoma and identified a relatively high exonic somatic mutation rate (mean, 12.0 events per megabase), similar to the rate found in squamous cell lung carcinoma. These lung cancer types also have similar copy number profiles. Three distinct expression subtypes of lung adenocarcinoma were identified from RNA-sequencing data: bronchioid, magnoid, and squamoid. In addition, multiple gene fusions were found to be expressed in lung adenocarcinomas, and multiple mechanisms for *CDKN2A* inactivation were uncovered.

For squamous cell NSCLCs, a most unexpected finding in the TCGA study was the identification of loss-of-function mutations in the *HLA-A* gene, which encodes a major histocompatibility complex that plays an important immune regulatory role on the