Targeted Therapy and Immunotherapy in the Treatment of Non–Small Cell Lung Cancer

Girish S. Shroff, MD[a], Patricia M. de Groot, MD[a], Vassiliki A. Papadimitrakopoulou, MD[b], Mylene T. Truong, MD[a], Brett W. Carter, MD[a,*]

KEYWORDS

• Lung cancer • Immunotherapy • Targeted therapy

KEY POINTS

- Targeted therapies for non–small cell lung cancer are directed at the product of specific mutations, such as epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (ALK).
- Specific oncogenic driver mutations in non–small cell lung cancer tend to result in different patterns of disease on computed tomography (CT) and fludeoxyglucose PET/CT.
- Immunotherapy facilitates the recognition of cancer as foreign by the host immune system, stimulates the immune system, and alleviates the inhibition that allows growth and spread of disease.
- Immune-related adverse effects, such as pneumonitis and colitis, may be encountered on imaging studies performed to evaluate patients treated with immunotherapy; radiologists should understand the appearance of these complications.

INTRODUCTION

The treatment strategy in advanced non–small cell lung cancer (NSCLC) has evolved from the use of empirical chemotherapy to a more personalized approach based on histology and molecular markers.[1] Gene mutations in receptors or protein kinases that result in the uncontrolled growth, proliferation, and survival of tumors (known as oncogenic driver mutations) are found in up to 60% of lung adenocarcinomas and up to 50% to 80% of lung squamous cell carcinomas.[2–4] Targeted therapies are directed at the products of these mutations and come in the form of receptor monoclonal antibodies (mAbs) or tyrosine kinase inhibitors (TKIs). Common targets include mutations of epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*). Targeted therapies have been shown to have significant clinical benefit in patients with advanced lung cancer.[5] Immunotherapy facilitates the recognition of cancer as foreign by the host immune system, stimulates the immune system, and relieves the inhibition that allows growth and spread of disease. In 2015, two immunomodulatory mAbs, nivolumab and pembrolizumab, were the first immunotherapeutic agents approved by the US Food and Drug Administration (FDA) for the treatment of advanced NSCLC.[5,6] Immunotherapy can result in a wide variety of immune-related adverse events, including colitis, hepatitis, and pneumonitis. In this article, the authors describe

[a] Department of Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA; [b] Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA
* Corresponding author. Department of Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1478, Houston, TX 77030.
E-mail address: bcarter2@mdanderson.org

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the role of targeted therapy and immunotherapy in the treatment of NSCLC.

TARGETED THERAPY

Receptor Tyrosine Kinases

Receptor tyrosine kinases (RTKs) are membrane-spanning glycoproteins that, once activated by binding of a ligand, activate numerous intracellular pathways and have an important role in normal processes, such as cell proliferation and differentiation. RTKs also have a critical role in the development and progression of many cancers. Examples of RTKs include receptors for *ALK*, epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF).

Epidermal Growth Factor Receptor–Mutant (Epidermal Growth Factor Receptor–Positive) Non–Small Cell Lung Cancer

Activation of *EGFR* by EGF leads to cellular growth, proliferation, and decreased apoptosis.[7] *EGFR* mutations are more common in lung adenocarcinomas, Asians, females, and never smokers.[4] Patients with *EGFR* mutations, the most common of which are a deletion in exon 19 and a point mutation in exon 21, are usually treated with *EGFR* TKIs, such as erlotinib or gefitinib; these agents enhance apoptosis and inhibit cell growth, angiogenesis, invasion, and metastasis.[7] Several studies have demonstrated the efficacy of *EGFR* TKIs in advanced *EGFR*-mutant lung cancer. The *I*ressa *P*an-*AS*ia *S*tudy (IPASS) showed that gefitinib was superior to carboplatin-paclitaxel chemotherapy in nonsmokers or former light smokers in East Asia with untreated advanced (stage IIIB or IV) lung adenocarcinoma.[4,8] In *EGFR*-positive patients, progression-free survival (PFS) was significantly longer with gefitinib than with chemotherapy; in *EGFR*-negative patients, PFS was significantly longer in the chemotherapy group.[8]

Despite the initial response to *EGFR* TKIs, drug resistance invariably develops,[2] most frequently through a secondary acquired *EGFR* mutation called *T790M*. In *T790M*, methionine replaces threonine at position 790 in the tyrosine kinase domain of *EGFR* and decreases the effectiveness of first- (erlotinib, gefitinib) and second-generation (afatinib) *EGFR* TKIs.[2,9–11] Osimertinib is a third-generation *EGFR* TKI that has proven to be effective in *T790M*+ advanced NSCLC (**Fig. 1**).[11]

Anaplastic Lymphoma Kinase Fusion Oncogene Positive Non–Small Cell Lung Cancer

ALK is another gene that encodes for a receptor tyrosine kinase. In 3% to 7% of patients with NSCLC, the *ALK* gene is fused to the echinoderm microtubule-associated proteinlike 4 (*EML4*) gene yielding the *EML4-ALK* fusion oncogene.[2,12] The *EML4-ALK* fusion oncogene (also referred to as ALK rearrangement) promotes cell growth and proliferation.[13] *ALK* rearrangement (*ALK* positivity) is more likely to be seen in younger patients with adenocarcinoma who are light or never-smokers.[2,4] The *ALK* TKI crizotinib is the treatment of choice for *ALK*-positive NSCLC. Newer-generation *ALK* inhibitors (eg, ceritinib, alectinib, brigatinib) are available for patients who develop resistance to or cannot tolerate crizotinib.

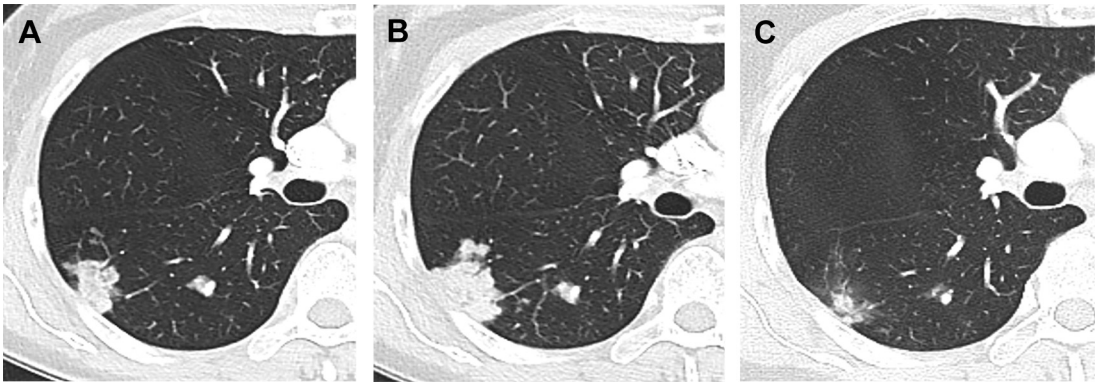

Fig. 1. *T790M* mutation. (*A*) Contrast-enhanced axial computed tomography (CT) shows right lower lobe *EGFR*+ adenocarcinoma and a separate tumor nodule in the same lobe. The patient was being treated with erlotinib. (*B*) Contrast-enhanced axial CT performed 9 months later shows increase in size of the dominant tumor. Biopsy (performed for molecular profiling) revealed *T790M* mutation. Osimertinib therapy was initiated. (*C*) Contrast-enhanced axial CT 3 months later shows response to osimertinib with decrease in size of the primary neoplasm and adjacent tumor nodule.