Chapter 18
Prognostic Biomarkers in Lung Cancer

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ALK

The prognostic significance of *ALK* rearrangement in lung adenocarcinoma is controversial. The European Thoracic Oncology Platform Lungscape project has demonstrated better overall survival (OS) in patients with surgically resected lung adenocarcinoma whose tumors were considered ALK positive either by ALK immunohistochemistry or *ALK* FISH [1]. In contrast, study in Asian patients, never smokers, with *ALK*-positive surgically resected lung adenocarcinoma showed worse disease-free survival (DFS) [2]. This sharp difference could be related to the different ethnicity of study population. The prognostic role of *ALK* was also reported in patients with advanced NSCLC who were not candidate for surgical treatment. Patients with *ALK*-positive NSCLC showed improved survival after radiotherapy for brain metastases compared with *EGFR*, *KRAS*, or wild-type tumors. The median OS for *ALK*-positive patients was 26.3 months, while patients with *EGFR*, *KRAS*, or wild-type tumors showed 13.6, 5.7, and 5.5 months of OS, respectively [3]. Subsequent treatment with targeted therapy resulted in further improvement in OS.

BRAF

In contrast to other tumors, non-V600E *BRAF* mutations represent almost 50% of all *BRAF* mutations in lung cancer. The prognostic significance of *BRAF* mutations in lung cancer is still uncertain, because of the limited data. *BRAF* mutations may coexist with other mutations such as mutations in *EGFR, KRAS*, and *PIK3CA* genes.

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It has been shown that patients with these coexistent mutations have shorter OS than patients with *BRAF* mutations only [4]. Most of the published studies failed to show any prognostic significance of *BRAF* in NSCLC [5–8].

EGFR

To date, the prognostic value of *EGFR* mutations in NSCLC is controversial. Several studies have shown longer survival in surgically treated patients with *EGFR*-mutated lung carcinomas when compared to *EGFR* wild type, regardless of subsequent treatments [9–12]. Other studies and meta-analysis showed no prognostic value of *EGFR* status in surgically treated lung carcinomas [13–16].

Recently published updates on LUX-Lung3 and LUX-Lung6 trials showed that patients with exon 19 deletion treated with afatinib have a better OS when compared to platinum-chemotherapy subgroup [17]. It has been known from prior retrospective studies and a meta-analysis that all of the EGFR-TKIs are more active in patients with exon 19 deletions than in L858R mutations, but the LUX-Lung studies were the only ones that prospectively showed an OS benefit [18, 19].

The T790M mutations most frequently occur in patients who initially responded to EGFR-TKI treatment but may also occur in EGFR-TKI-naïve patients. The prognostic significance seems to be different depending on the EGFR-TKI treatment status. It has been suggested that patients with pretreatment T790M have shorter PFS when treated with EGFR-TKIs [20–22]. However, other studies showed potential positive prognostic value in post-TKI setting [23, 24].

KRAS

Many retrospective studies reported correlation between *KRAS* mutations and a poor overall survival in patients with resected NSCLC [25]. A meta-analysis of more than 53 retrospective studies identified *KRAS* mutations as a negative prognostic factor [26, 27]. However, a recent pooled analysis including four trials comparing platinum-based adjuvant chemotherapy to observation in early-stage resected NSCLC has shown that *KRAS* mutation status is not significantly prognostic [28].

ROS1

Retrospective studies have shown that ROS1 status has no prognostic impact in Western patients with NSCLC, while study in Asian population suggested a potential negative prognostic value of *ROS1* rearrangement [2, 29].

MET

A high *MET* gene copy number or protein expression has been associated with poor prognosis in patients with surgically resected NSCLC [30, 31].

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