Targeted Therapies in Non-Small Cell Lung Cancer: Emerging Oncogene Targets Following the Success of Epidermal Growth Factor Receptor

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The diagnostic testing, treatment and prognosis of non-small cell lung cancer (NSCLC) has undergone a paradigm shift since the discovery of sensitizing mutations in the epidermal growth factor receptor (*EGFR*) gene in a subset of NSCLC patients. Several additional oncogenic mutations, including gene fusions and amplifications, have since been discovered, with a number of drugs that target each specific oncogene. This review focuses on oncogenes in NSCLC other than *EGFR* and their companion "targeted therapies." Particular emphasis is placed on the role of *ALK*, *ROS1*, *RET*, *MET*, *BRAF*, and *HER2* in NSCLC.
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Advanced and metastatic non-small cell lung cancer (NSCLC) carries a generally poor prognosis, with an estimated median overall survival of 10–12 months within the US population, and is responsible for the most cancer-related deaths worldwide.[1–4] Over the past 15 years, differential responses in therapy have produced improved efficacy and safety results in select adenocarcinoma populations,[5,6] improving upon clinical outcomes obtained with earlier clinical trials of platinum doublet therapy with an objective response rate (ORR) in the first-line setting from 19% to 30%, progression-free survival (PFS) of 3.4–4.5 months, and a median overall survival (OS) of 7.9–12.6 months in large randomized trials.[7,8] During this interval, preclinical and clinical investigators identified and characterized several key "oncogenic mutations"—where "mutations" is inclusive of genetic alterations resulting in amino acid substitutions, in-frame insertions or deletions, gene fusions resulting from chromosomal rearrangements, or gene amplification. These oncogenic mutations result in activation of key intracellular signal transduction pathways that allow unregulated tumor growth.[9] In some cases, targeting of these oncogenes with specific drugs led to dramatic clinical benefit and ushered in an era of "targeted therapy."[10,11] Characteristic mutations had been well described in different NSCLC subtypes, such as Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutations in adenocarcinoma. However, these have been used as prognostic markers and have not influenced treatment decisions.[12] Initial success with targeted therapy in NSCLC occurred with discovery of a subset of lung adenocarcinomas harboring epidermal growth factor receptor (*EGFR*) gene mutations and correlation to response to the EGFR tyrosine kinase inhibitor (TKI) gefitinib.[13,14] Since the discovery of *EGFR*-mutant NSCLC and their response to EGFR specific TKI's, additional molecular specific cohorts of NSCLC have been discovered, with rapid and often parallel development of targeted drugs specific to each respective abnormality. Specifically, data collected from patients with adenocarcinoma by the Lung Cancer Mutation Consortium and next-generation sequencing efforts have identified a number of patients harboring distinct oncogenic drivers and have established the incidence of these aberrations within the lung adenocarcinoma population as a whole.[15–17] Similar efforts are underway for squamous cell carcinoma with identifications of several potentially targetable molecular drivers[18–20] (Fig 1). Furthermore, the preclinical characterization of novel oncogenes has coincided with increased access to molecular testing of clinical specimens in a reasonable turnaround time, which allows molecular testing to impact real-time clinical

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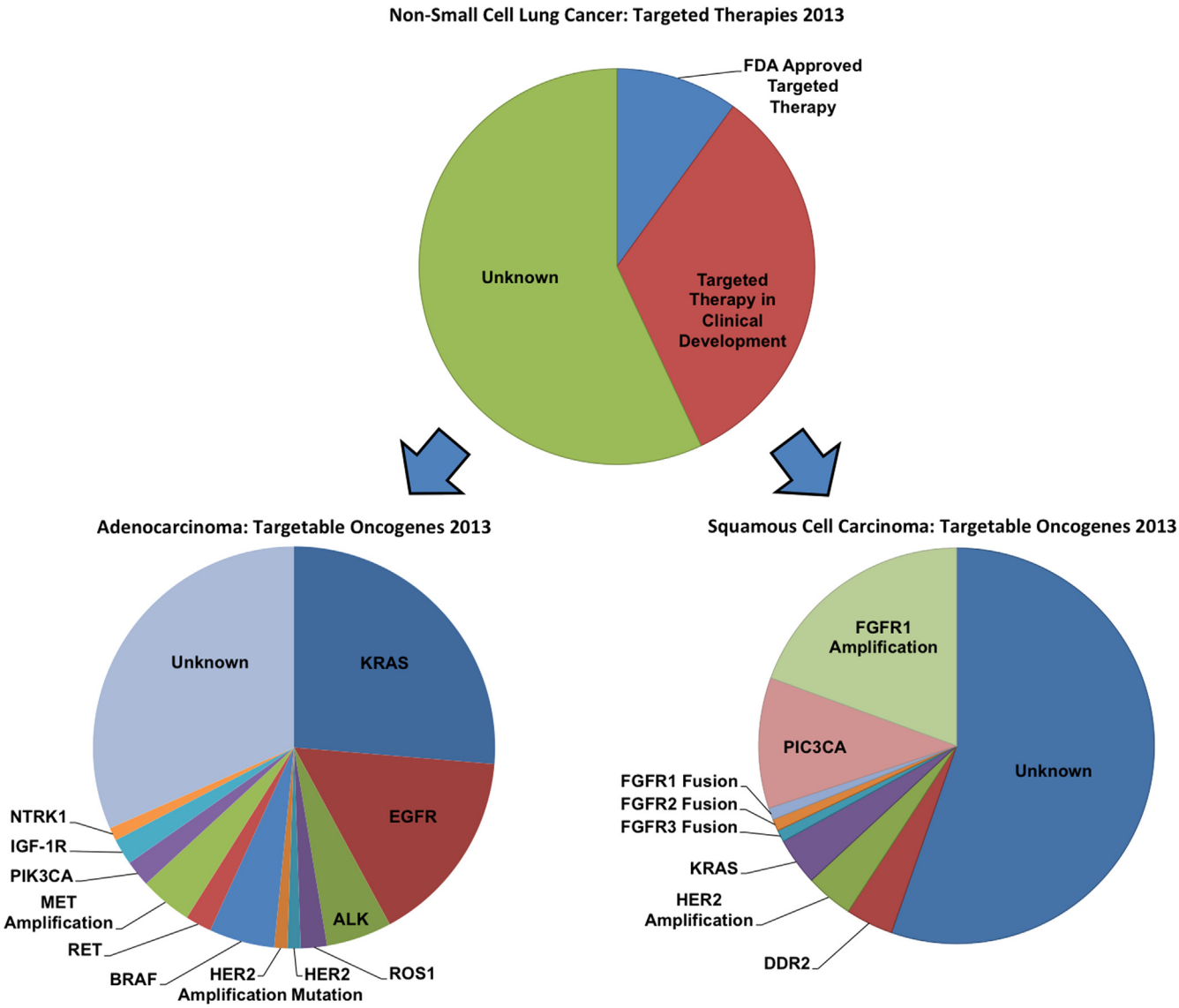

Figure 1. Graphic representations of targeted therapy in non-small cell lung cancer (NSCLC). Approximate representation of US Food and Drug Administration (FDA)-approved targeted therapies and therapies in development in NSCLC with approximate percentages of targetable oncogenes in adenocarcinoma and squamous cell carcinoma of the lung.

decisions.[21] This review will focus on the rapid progress in this field of NSCLC since the discovery of *EGFR* mutations, the growing body of literature supporting each oncogene, and how they can serve as predictive biomarkers for therapy. The safety and efficacy of specific targeted therapies will be discussed in detail where available.

ALK

Since the first description of an anaplastic lymphoma kinase (*ALK*) gene fusion from a Japanese patient with advanced lung adenocarcinoma, the field of *ALK* gene fusion positive (ALK+) NSCLC has garnered significant attention and intense study, progressing from initial discovery to US Food and Drug Administration (FDA) approval of the ALK TKI crizotinib in less than 5 years.[22,23] The predominant role of native ALK signaling occurs in prenatal neurogenesis and neuronal migration, and expression appears to be limited to the central nervous system in adults.[24] While *ALK* functions as an oncogene via gene amplification or kinase domain mutations in other tumor types, the transforming event in NSCLC is a translocation involving the short arm of chromosome 2 fusing the 3′ exons that encode the ALK kinase domain with a promoter and coding region for the N-terminus of another gene. The resultant fusion protein ("chimeric protein") is constitutively activated, leading to downstream activation of the canonical phosphatidylinositol 3-kinase (PI3K)/AKT, mitogen-activated protein kinase (MAPK)/extracellular-related kinase (ERK1/2), and signal transducer and activator of transcription