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Personalizing Therapy in Advanced Non–Small Cell Lung Cancer

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Abstract

The recognition that non–small cell lung cancer (NSCLC) is not a single disease entity, but rather a collection of distinct molecularly driven neoplasms, has permanently shifted the therapeutic landscape of NSCLC to a personalized approach. This personalization of NSCLC therapy is typified by the dramatic response rates seen in *EGFR* mutant NSCLC when treated with targeted tyrosine kinase inhibitor therapy and in *ALK* translocation–driven NSCLC when treated with *ALK* inhibitors. Targeted therapeutic approaches in NSCLC necessitate consideration of more invasive biopsy techniques aimed at providing sufficient tissue for both histological determination and molecular profiling in all patients with stage IV disease both at the time of diagnosis and at the time of disease progression. Comprehensive genotyping efforts have identified oncogenic drivers in 62% lung adenocarcinomas and an increasing proportion of squamous cell carcinomas of the lung. The identification of these oncogenic drivers and the triage of patients to clinical trials evaluating novel targeted therapeutic approaches will increasingly mold a landscape of personalized lung cancer therapy where each genotype has an associated targeted therapy. This review outlines the state of personalized lung cancer therapy as it pertains to individual NSCLC genotypes.

Keywords

non–small cell lung cancer; personalized therapy; oncogenic driver mutations

Lung cancer is the leading cause of cancer mortality in the United States and worldwide.¹ An estimated 228,190 new cases of lung cancer will be diagnosed in 2013 in the United States alone, and 159,480 lung cancer deaths are estimated to occur. The 5-year survival for all lung cancer patients is a dismal 15%. Historically, non–small cell lung cancer (NSCLC) was treated as a single disease entity, and palliative chemotherapy in the metastatic setting resulted in modest survival prolongation and preservation of quality of life.^{2–6} A series of large randomized controlled phase 3 clinical trials established platinum-based doublets as the standard of care in the treatment of metastatic NSCLC with response rates of 20 to 30% and a median survival of 8 to 11 months.^{7–11}

Recent advances in the treatment of metastatic NSCLC have come from recognition that NSCLC is not a single disease entity, but rather a collection of distinct molecularly driven neoplasms. Lynch et al and Paez et al first described a subset of patients with NSCLC harboring activating mutations in the *EGFR* gene who responded to treatment with EGFR tyrosine kinase inhibitors (TKIs).^{12,13} This discovery permanently shifted the landscape of NSCLC therapy to a personalized approach based on the molecular alterations of a patient's tumor; a paradigm typified not only by targeted therapies in *EGFR* mutant lung adenocarcinomas but also in *ALK* translocation driven adenocarcinomas of the lung, and more recently, the therapeutic advances in lung adenocarcinomas harboring *ROS1* gene rearrangements and *BRAF* mutations.^{14–16} This review highlights these and other molecular subsets of NSCLC in which targeted therapies have been shown to be or are potentially more effective than conventional chemotherapy.

Practical Considerations in Molecular Testing

The historical approach to the diagnosis of lung cancer placed emphasis on noninvasive techniques, often fine needle aspiration (FNA), with the goal of distinguishing histology: small cell lung cancer (SCLC) from NSCLC. Personalized lung cancer therapy has necessitated a shift toward more invasive techniques with an emphasis on core biopsies to ensure adequate tissue to both distinguish histology (not just SCLC from NSCLC, but also nonsquamous from squamous cell carcinoma) and to complete the molecular profiling needed to guide treatment decisions. Protein expression as identified by immunohistochemistry (IHC) is no longer sufficient; patient tumors should undergo molecular testing using direct sequencing techniques and fluorescent in situ hybridization (FISH) for the identification of oncogenic drivers that have or may have important therapeutic implications. Although tumor heterogeneity is an issue, from a pragmatic standpoint, only one site of metastatic disease is typically biopsied; the utility of biopsying multiple sites of metastatic disease is an unresolved question and not routinely done outside of a clinical trial setting. Bone lesions, while often the most accessible site of disease, are no longer acceptable because the decalcification process precludes interrogation of the DNA. The issue of tissue acquisition invariably requires a close collaborative effort between medical oncologists, pulmonologists, thoracic surgeons, and interventional radiologists.

Molecular testing should be performed in all patients with metastatic adenocarcinoma of the lung. Although our knowledge of the oncogenic drivers in squamous cell carcinoma of the lung is increasing, there is limited evidence to guide targeted therapies outside of the clinical trial setting. In the adjuvant setting, there are limited data with regard to the use of targeted agents, and molecular testing is not routinely recommended. The caveat is that, in patients with locally advanced disease with mediastinal lymph node involvement, it is worthwhile at least to consider molecular testing due to a high risk of metastatic disease recurrence. Historically associated with the nonsmoking phenotype, comprehensive profiling of lung adenocarcinomas for *EGFR* mutations in a North American population reveals a prevalence of 43% in never-smokers and 11% in smokers; that is, 1 in 10 smoking patients with lung adenocarcinoma will harbor an *EGFR* mutation that has important therapeutic implications.¹⁷ Whereas 85 to 90% of newly diagnosed lung cancers occur in patients who are smokers, 10 to 15% of cases occur in never-smokers, making lung cancer in never-

smokers one of the leading causes of cancer-related mortality.^{18–20} It is therefore important to consider molecular testing for all patients with newly diagnosed metastatic NSCLC of adenocarcinoma histology regardless of smoking history, because of the therapeutic implications of finding an actionable oncogenic driver.

Molecular testing should be performed at the time of diagnosis. A common thread among the oncogenic drivers is the eventual development of resistance to targeted therapies. As such, it is important to consider rebiopsy of patients at the time of progression on a targeted therapy to understand the mechanisms of resistance and possible ways to overcome this resistance. Data from the Lung Cancer Mutation Consortium (LCMC) identified an oncogenic driver in 62% of lung adenocarcinomas that undergo molecular profiling for 10 of the most common oncogenic drivers and that these oncogenic drivers are 97% mutually exclusive.²¹ When tissue availability is an issue, it is reasonable to do molecular testing concurrently for the currently actionable genotypes (*EGFR* and *ALK*), then proceed to more extensive profiling if these initial tests are negative, to triage a patient to a clinical trial for a potentially actionable mutation.²¹ If tissue and resources allow, one can also consider testing more broadly as part of the initial oncogenic screen, and consider utilizing a next-generation sequencing (NGS) platform, which includes both the actionable and the putative oncogenic drivers, as well as genotypic abnormalities for which the functional or therapeutic significance is as yet unknown. Using these techniques, the proportion of actionable oncogenic drivers will only increase over time. Principally, the development of targeted therapeutic approaches in novel molecular subsets of NSCLC is predicated on the adequacy of the biopsy specimen and, of equal importance, the availability and usage of more extensive testing.

Actionable Oncogenic Drivers in NSCLC

EGFR

EGFR is a member of the ErbB (or HER) receptor tyrosine kinase family that is a crucial component of the activation of cell signaling pathways, which include the RAS-RAF-MEK pathway and the phosphoinositide 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) pathway (Fig. 1).²² These pathways can in turn be modulated by other receptor tyrosine kinases, such as the insulin-like growth factor-1 receptor (IGF1-R) and mesenchymal epithelial transition factor (MET) and, in concert, effect cell proliferation, local invasion, metastasis, resistance to apoptosis, and angiogenesis.²² Sensitizing *EGFR* mutations most commonly occur as in-frame deletions of exon 19 (45%) and the *L858R* substitution in exon 21 (40–45%), whereas nucleotide substitutions in exon 18 and in-frame insertions of exon 20 account for another 5%.²³ *EGFR* gene mutations are present in up to 15% of Caucasians, 30 to 50% of East Asians, and more than 50% of Asian never-smokers with adenocarcinoma histology (Fig. 1).^{21,23}

The recognition of the central role of targeted therapy in *EGFR*-mutant lung adenocarcinoma is rooted in the landmark Iressa Pan-Asia Study (IPASS), a randomized phase 3 clinical trial that evaluated the efficacy of gefitinib versus carboplatin/paclitaxel as first-line therapy in patients clinically selected on the basis of adenocarcinoma histology, Asian ethnicity, and never- or light-smoking status.²⁴ The IPASS clinical trial illustrates first

and foremost that targeted therapy with the EGFR TKI gefitinib is superior to conventional chemotherapy in the *EGFR* mutant population and is associated with a 71.2% response rate (RR) and a 52% relative risk reduction for progression-free survival (PFS) compared with chemotherapy ($p < 0.001$; Table 1). The converse is that first-line gefitinib is associated with inferior RRs (1.1% vs and 23.5%, respectively; Table 1) and worse PFS compared with conventional chemotherapy in the *EGFR* wild-type population (HR 2.85, $p < 0.001$; Table 1). Although targeted therapy is highly effective in the *EGFR* mutant population, there is potential harm associated with first-line targeted therapy in *EGFR* wild-type patients; it is therefore insufficient to treat patients with EGFR TKI therapy based on clinical selection criteria alone. It is important whenever possible to test all patients for *EGFR* activating mutations prior to determining the best first-line therapy. The corollary is that in patients in whom the *EGFR* mutational status is unable to be determined in a timely manner, as in patients who present in extremis due to large tumor burdens, platinum-based chemotherapy is favored because chemotherapy performs better in *EGFR* mutant patients compared with *EGFR* wild-type patients (Table 1).

The benefit of EGFR TKI therapy in the *EGFR* mutant population has been confirmed in a series of six randomized controlled phase 3 clinical trials evaluating the role of gefitinib, erlotinib, and afatinib in molecularly selected patients with activating *EGFR* mutations. In this series of trials, EGFR TKIs were consistently associated with RRs of 55 to 86%, doubling the RRs associated with conventional chemotherapy, and were associated with remarkable prolongation in PFS (Table 1).^{25–30} Of note, there was no significant difference in overall survival (OS) in the IPASS clinical trial between gefitinib and chemotherapy in the *EGFR* mutant population (HR 1.00, $p < 0.990$; Table 1); 64.3% of *EGFR* mutation positive patients treated with first-line carboplatin/paclitaxel went on to receive second-line EGFR TKI therapy.³¹ Similarly, the phase 3 clinical trials conducted by Rosell et al (EURTAC), Maemondo et al, and Mitsudomi et al (WJTOG 3405) in molecularly selected populations failed to demonstrate a statistically significant OS advantage with targeted therapy.^{25,27,28} These trials had similar rates of crossover from conventional chemotherapy to EGFR TKI therapy at the time of progression: a 76% crossover rate in Rosell et al, 95% crossover rate in Maemondo et al, and 91% crossover rate in Mitsudomi et al.^{25,27,28}

The corollary to this is whether the sequencing of EGFR TKI therapy with conventional chemotherapy in patients with *EGFR* mutant lung adenocarcinoma ultimately impacts patient outcomes. As is illustrated in these clinical trials, it is unlikely that first- versus second-line EGFR TKI therapy significantly impacts OS; however, it is important to note that, although the majority of patients with *EGFR* mutant lung adenocarcinoma cross over to targeted therapy at the time of disease progression, there remain a small proportion of patients with *EGFR* mutant lung adenocarcinoma who might experience rapid progression of their disease on first-line conventional chemotherapy and who might miss the opportunity for exposure to second-line EGFR TKI therapy.³² First-line EGFR TKI therapy therefore optimizes the chance a patient with an activating *EGFR* mutation will be exposed to the targeted therapy.

Perhaps the most critical issue in the targeted therapy of *EGFR* mutant lung adenocarcinoma is the emergence of resistance. Sixty-three to 68% of patients with acquired resistance to

EGFR TKIs develop a secondary mutation in exon 20 that results in the *T790M* substitution altering the affinity of the EGFR adenosine triphosphate (ATP)-(ATPbinding pocket).^{33,34} In the LUX-Lung 1 clinical trial, the novel irreversible TKI of EGFR and HER2, afatinib, was evaluated in patients who had progression of their disease on erlotinib or gefitinib.³⁵ Although this study failed to demonstrate an OS advantage with afatinib compared with best supportive care (HR 1.08, $p = 0.74$), there was a significant increase in PFS with afatinib (HR 0.38, $p < 0.0001$; Table 1). Preclinical mouse models suggest that the combination of afatinib and the monoclonal antibody to EGFR, cetuximab, is highly effective in tumors harboring the *T790M* mutation.³⁶ An early-phase clinical trial is currently ongoing to assess the safety and efficacy of this combination in humans (NCT 0109001). Repeat biopsies of patients with *EGFR* mutant lung adenocarcinomas with acquired resistance to EGFR TKI therapy have also demonstrated amplification of *MET* in 5 to 20% of patients, *HER2* amplification in ~ 12% of patients, *BRAF* mutations in 1% of patients, and transformation to small cell lung cancer (SCLC) in 3 to 14% of patients.^{33,34,37–41} The repeat biopsy at the time of progression is critical to the development of highly effective therapies in patients with acquired resistance to EGFR TKIs.

ALK

ALK is a receptor tyrosine kinase that is believed to play a role in the development of the brain and exerts its effects on specific neurons in the nervous system.⁴² It modulates several signaling pathways such as the PI3K–AKT, MAPK, and JAK-STAT pathways in synergy with other receptor tyrosine kinases (Fig. 1). The interest in *ALK* soared in 2007 when the fusion of *ALK* with the *EML4* gene was identified in a group of NSCLC patients.⁴³ Multiple *EML4-ALK* variants, the predominant *ALK* fusion in NSCLC, have been identified, as well as other fusion products, including *KIF5B-ALK*, *TFG-ALK*, and *KLC1-ALK*.⁴⁴ The fusion of *EML4-ALK* results from a small inversion within chromosome 2p leading to the fusion of *EML4* to the intracellular kinase domain of *ALK*. Several studies have revealed the transforming and oncogenic activity of *EML4-ALK* in vivo and in vitro.^{45–47} In unselected NSCLC patients, the frequency of *ALK* rearrangements is ~ 5%, but clinicopathological features demonstrate that patients with adenocarcinoma histology, males, with a light- or never-smoking history and no other oncogenic drivers are more likely to harbor *ALK* rearrangements.^{48,49} Data from the LCMC indicate a frequency of 8% in lung adenocarcinomas (Fig. 1).²¹

Crizotinib, a multitargeted small molecule TKI that inhibits not only ALK but MET and ROS 1 as well, was approved by the U.S. Food and Drug Administration (FDA) in 2011 based on phase 1 and 2 clinical trial data. The first results of the phase 1 trial were presented by Kwak et al, in which 82 *ALK* positive NSCLC patients received crizotinib with an RR of 57%.¹⁴ The updated analysis of this trial presented results on 149 *ALK*-positive NSCLC patients in whom crizotinib was associated with an RR of 60.8%, including three patients with complete responses, and a PFS of 9.7 months (Table 1).⁵⁰ A single-arm phase 2 clinical trial evaluating the efficacy of crizotinib in previously treated *ALK*-positive patients (PROFILE 1005) echoed these results; in 255 patients evaluable for response, crizotinib was associated with an RR of 53% and a PFS of 8.5 months (Table 1).⁵¹ Furthermore, *ALK*-positive patients who receive crizotinib have improved survival compared with *ALK*-

positive patients who are crizotinib-naïve as demonstrated in a retrospective analysis by Shaw et al.⁵² More specifically, patients who received crizotinib compared with those who did not had a 1-year OS of 70% versus 44% and a 2-year OS of 55% versus 12%, respectively.

In the first-line setting, the ongoing PROFILE 1014 phase 3 randomized clinical trial is evaluating the efficacy of crizotinib versus platinum/pemetrexed in *ALK*-positive NSCLC patients with the primary end point of PFS (NCT01154140). In the second-line setting, the phase 3 randomized clinical trial, PROFILE 1007, compared crizotinib with standard chemotherapy (pemetrexed or docetaxel) in *ALK*-rearranged NSCLC.⁵³ This study accrued a total of 347 patients and demonstrated a PFS of 7.7 months with crizotinib versus 3 months for chemotherapy (HR 0.49, $p < 0.001$; Table 1) and an RR of 65% with crizotinib versus 20% with chemotherapy ($p < 0.001$; Table 1). The immature OS results showed no difference between the two arms of the trial, but crossover among patients in the chemotherapy group should be taken into account in evaluating the final survival analysis.

Despite the impressive response rates of crizotinib in *ALK*-positive NSCLC patients, the time-limited efficacy of the drug reveals the need of exploring the mechanisms of resistance and developing second-generation *ALK* inhibitors. Several mechanisms of resistance have been described, the most common of which is a secondary resistance mutation located in the *ALK* tyrosine kinase domain, the L1196M mutation, which acts as a gatekeeper mutation analogous to the T790M mutation in *EGFR* mutant NSCLC.^{54–56} Additional resistance mutations that have been described are the *G1269A* substitution in the ATP binding pocket and the *G1202R* and *G1206Y* mutations in the solvent-exposed region of the kinase domain.^{57,58} In a series of 11 *ALK*-positive patients with acquired resistance to crizotinib, 2 patients, one with a resistance mutation, exhibited amplification of *ALK*.⁵⁷ Indeed, *EML4-ALK* gene amplification was associated with the emergence of resistance in *EML4-ALK* NSCLC cell lines treated with increasing doses of crizotinib.⁵⁵ In addition to secondary *ALK* mutations and *ALK* gene amplification, activation of other kinases, including increased autophosphorylation of *EGFR* and amplification of *KIT*, could contribute to maintenance of downstream signaling and diminish the efficacy of crizotinib.^{58,59} Finally, *KRAS* mutations were identified in 2 out of 14 patients with acquired resistance to crizotinib in a study by Doebele et al, implicating *KRAS* mutations as a possible resistance mechanism.⁵⁷

LDK378 is a potent and selective second-generation *ALK* inhibitor, which was evaluated in a phase 1 clinical trial of 88 evaluable patients with *ALK*-positive NSCLC and was associated with an RR of 70%.⁶⁰ In the subset of 64 patients with crizotinib-resistant disease, LDK378 was associated with a remarkable RR of 73% (Table 1). CH5424802 is another second-generation *ALK* inhibitor, which was evaluated in a phase 1/2 clinical trial in crizotinib-naïve *ALK*-positive NSCLC patients and was associated with an impressive 93.5% RR in 46 evaluable patients.⁶¹ Ganetespib, a potent inhibitor of heat shock protein 90 (HSP 90), was evaluated as monotherapy in a phase 2 clinical trial of genotypically defined NSCLC patients, in which four patients experienced partial responses, all of whom harbored an *ALK* gene rearrangement retrospectively detected by FISH.⁶² This appears to be an HSP 90-dependent effect because other HSP 90 inhibitors, AUY922 and IPI-504, have also been

associated with responses in *ALK*-positive NSCLC patients.^{63,64} Ganetespib induces the degradation of the EML4-*ALK* protein by targeting the chaperone dependency of *ALK*, rather than the kinase directly. The known and unknown mechanisms of resistance remain to be further elucidated to develop more effective therapeutic strategies.

ROS1

ROS1 is a receptor tyrosine kinase of the insulin receptor family with 49% homology with *ALK* within the tyrosine kinase domain and 77% identity with *ALK* in the ATP-binding site.^{65,66} *ROS1* gene rearrangements were originally described in glioblastoma multiforme, resulting from fusion with the *FIG* gene, and have been shown to be transforming in transgenic mice.^{67–70} To date, seven distinct *ROS1* gene fusions have been described in solid tumors leading to aberrant kinase activity and activation of the PI3K–AKT–mTOR pathway, the RAS–RAF–MEK pathway, in addition to the Src-homology 2 domain-containing phosphatase (SHP)-1 and -2 pathways and the vav 3 guanine nucleotide exchange factor 1 (VAV3) pathway, with subsequent aberrant cell proliferation, survival, metastases, and migration (Fig. 1).⁷¹ Using FISH, this oncogenic driver was identified in 1.7% (18/1,073) patients with NSCLC; it occurred in a mutually exclusive fashion with *ALK* translocations and was more likely to be present in patients who were younger, never-smokers with adenocarcinoma histology, with a predilection for Asian ethnicity.¹⁵ A Japanese series identified *ROS1* fusions in 0.9% NSCLC patients (13/1,476) and 1.2% patients with adenocarcinoma histology (13/1,116).⁷² Using IHC and confirming with FISH or reverse transcriptase polymerase chain reaction, Rimkunas et al reported *ROS1* rearrangements in 1.6% NSCLC (9/556) and 3.3% (8/246) lung adenocarcinomas from Chinese patients.⁷³ Taken together, *ROS1* gene rearrangements occur at a frequency of ~ 1 to 3% (Fig. 1). Crizotinib has been shown to inhibit *ROS1* phosphorylation in the *ROS1*-rearranged NSCLC cell line HCC78 and in HEK 293 cells transfected with a *CD74-ROS1* fusion gene expression construct.¹⁵ To test if crizotinib has activity in *ROS1*-rearranged NSCLC, a 31-year-old never-smoking patient with *ROS1*-positive bronchoalveolar carcinoma was enrolled on the expansion cohort of the original phase 1 clinical trial of crizotinib. Having presented with hypoxia, this patient had complete resolution of his respiratory insufficiency after 2 weeks of therapy, with near complete response in his multifocal tumor on restaging scans at 8 weeks, suggesting exquisite sensitivity of *ROS1*-positive NSCLC to inhibition with crizotinib.¹⁵ In a subsequent series of 25 patients with *ROS1*-positive NSCLC, crizotinib was associated with a 56% response rate.¹⁶ The *ROS1*-rearranged NSCLC expansion cohort of the original crizotinib phase 1 clinical trial is currently accruing to further assess the efficacy of this targeted therapy (NCT 00585195).

BRAF

BRAF is a member of the RAF kinase family of serine/threonine protein kinases, which have diverse roles in mediating proliferation and survival. Upon activation by RAS, *BRAF* phosphorylates MEK leading to activation of ERK and the ERK signaling pathway (Fig. 1). Several *BRAF* mutations have been described in cancers, most prominently in melanoma (60%), colorectal (8–15%), and lung (2%) cancers (Fig. 1).^{74–77} The most commonly observed mutation in *BRAF* is a valine (V) to glutamic acid (E) substitution at residue 600 (*BRAF* V600E). This substitution results in mutant *BRAF* protein, which no longer requires

dimerization for its activity. Therefore the BRAF V600E protein is constitutively active and is transforming in vitro.⁷⁸ Although the *BRAF*^{V600E} mutation accounts for almost 80 to 90% of all *BRAF* mutations in metastatic melanoma, only 50% of *BRAF* mutations are *BRAF*^{V600E} in metastatic NSCLC, and additional mutations, which have transforming ability in vitro, have been identified including *BRAF*^{G469A} (39%) and *BRAF*^{D593G} (11%).⁷⁷ Lung cancer patients with *BRAF* mutations are more likely to be Caucasian and current or former smokers.

Two selective BRAF inhibitors, vemurafenib and dabrafenib, have shown significant clinical activity in *BRAF*^{V600E} mutant NSCLC in the metastatic setting.^{79–81} Recently, interim results of a phase 2 study with the BRAF-specific inhibitor dabrafenib in *BRAF*^{V600E} mutation–positive NSCLC patients was presented at the 2013 American Society of Clinical Oncology Annual Meeting.⁸¹ This trial enrolled patients with stage IV *BRAF*^{V600E} mutant disease who had progressed after at least one line of prior chemotherapy. At the time of analysis, efficacy data were available on the first 20 patients and safety data on the first 25 patients. Remarkably, the study was positive for its primary end point of investigator-assessed overall RR. The investigators observed a 54% overall RR with durable responses as long as 49 weeks. The overall disease control rate was 60%, including a partial responses rate of 40% and stable disease rate of 20%. PFS and OS data were not mature enough at the time of presentation.⁸¹ Regardless, the observed ORR and overall disease control rates compare favorably with what has previously been seen in metastatic melanoma where the BRAF inhibitor, vemurafenib, is FDA approved in the first-line setting.⁷⁸ Currently, there is tremendous enthusiasm that dabrafenib may be effective therapy for *BRAF*^{V600E} mutant NSCLC. Unfortunately, similar to melanoma, acquired resistance to BRAF inhibitors in NSCLC has already been observed.⁸² A study is already under way examining the use of MEK inhibitors in *BRAF*^{V600E} mutant NSCLC, and this may be one strategy for overcoming acquired resistance (NCT00888134). Finally, although 50% of *BRAF* mutations in lung cancer are non- *V600E* mutations, little is known about the potential response to either BRAF-specific inhibitors or downstream inhibition through MEK1 inhibitors.

Putative Oncogenic Drivers

In addition to the oncogene drivers already discussed and the mutant *KRAS* yet to be discussed, there are a series of putative oncogene drivers (*MET*, *KIF5B–RET*, *HER2*, *PIK3CA*, *AKT1*, *MAPK2K1*)⁸³ for which mutational testing is being performed at many institutions or through the LCMC. In addition, we are continuing to find new translocations that may be targetable (*NTRK1* gene fusions). For many of these targets, the therapeutic significance of these alterations has not been determined, but inhibitors of these pathways may have a role in a small subset of patients.

MET

The MET protein is a receptor tyrosine kinase, which, upon binding its only known physiological ligand, hepatocyte growth factor/scatter factor (HGF/SF) activates a series of downstream processes that are critical for oncogenesis, including cell proliferation, survival, invasion/migration, and metastasis.⁸⁴ Upon binding of HGF to the Sema domain of MET,

dimerization and subsequent autophosphorylation occur, leading to the activation of the MET receptor and downstream signaling through the RAS-ERK, PI3K-AKT-mTOR, and STAT pathways (Fig. 1).⁸⁴ In addition, activated MET has been demonstrated to have significant crosstalk with the EGFR pathway.⁸⁴ Aberrant signaling through the MET pathway has been observed in several tumor types and can occur through mutation, amplification or overexpression of the *MET*, or overexpression of *HGF*.⁸⁵ Although mutations in the *MET* gene are rare in NSCLC,⁸⁶ the *MET* gene is amplified in adenocarcinoma of the lung in 2 to 20% of cases examined.^{87–89} Recently, a large study by the LCMC suggested the *MET* gene is only amplified in ~ 1% of adenocarcinomas of the lung (Fig. 1).²¹ Interestingly, *MET* amplification is a common mechanism of acquired resistance to EGFR TKIs and is found in up to 20% of patients who have acquired resistance to EGFR TKIs.^{40,41} In addition to mutations or amplification of *MET*, the MET protein is overexpressed in a significant number of cases of advanced NSCLC. In fact, a recent phase 2 study (yet to be discussed) has suggested that MET may be overexpressed in 54% of advanced NSCLC.⁹⁰

Given the critical role of the MET pathway in tumorigenesis, metastasis, and acquired resistance to targeted therapy, there are more than a dozen MET-targeted therapies in clinical trials that target its ligand HGF (rilotumumab, ficlatuzumab), the extracellular portion of the MET receptor (onartuzumab—METMab), or the intracellular kinase activity of the MET receptor (tivantinib, crizotinib, cabozantinib).⁸⁵ Although anti-MET therapy as monotherapy or in combination in unselected patient populations has been disappointing to date, a recent phase 2 trial comparing onartuzumab (MetMab) and erlotinib versus erlotinib alone in the second-and third-line setting for metastatic NSCLC found a significant advantage in PFS and OS for the combination in the “MET high” population.⁹⁰ Furthermore, 54% of patient samples were defined as MET high (50% or greater cells on the diagnostic slide with a staining intensity of 2 or 3), which suggests that a significant fraction of patients with metastatic lung cancer may be at least partially MET dependent. This concept is now being tested in global phase 3 randomized, multicenter, double-blind, placebo-controlled study testing this combination versus erlotinib only in the MET high population (NCT01456325). In addition to monoclonal antibodies targeting MET, there are several MET tyrosine kinase inhibitors in development and/or FDA-approved agents (crizotinib), and these agents are being used to target the MET pathway in mutationally defined subsets such as *KRAS* mutant NSCLC (discussed in the *KRAS* section) and in the acquired resistance to EGFR TKI therapy setting.⁹¹ Interestingly, several case reports have suggested that patient tumors with *MET* amplification may be MET “addicted,” and dramatic responses have been seen with MET TKI monotherapy.^{92,93} These observations have led to the development of a *MET*-amplified-only cohort on a current phase 1 study looking at crizotinib in advanced NSCLC as well as other solid tumor types (NCT00585195).

KIF5B-RET

The *KIF5B-RET* fusion oncogene involves the RET receptor tyrosine kinase, which is involved in cell proliferation, neuronal navigation, cell migration, and differentiation.⁹⁴ Although germline and somatic mutations in *RET* cause the multiple endocrine neoplasia type 2 syndrome and medullary thyroid carcinoma, somatic *RET* fusion products, such as

CCDC6-RET and *NCOA4-RET* are associated with the sporadic and radiation-induced forms of papillary thyroid carcinoma.^{95–99} The *KIF5B-RET* fusion protein retains the full RET kinase domain and the *KIF5B* coiled-coil domain, which likely participates in homodimerization leading to aberrant activation of the kinase function of RET.^{100–102} Indeed, *KIF5B-RET* expression in H1299 human lung cancer cells leads to phosphorylation of the activation loop of the RET kinase site in the absence of serum activation, indicative of aberrant RET kinase activity.¹⁰³ Expression of exogenous *KIF5B-RET* results in morphological transformation and anchorage-independent growth of NIH3T3 fibroblasts, which is suppressed by treatment with the multi-tyrosine kinase inhibitor, vandetanib.¹⁰³

The *KIF5B-RET* fusion transcript has been demonstrated in 1.9% (6/319) of Japanese lung adenocarcinomas, 1.3% (1/80) of U.S. lung adenocarcinomas, and 0% (0/34) of Norwegian lung adenocarcinomas.¹⁰³ In another Japanese series, *RET* fusions were demonstrated in 0.9% (13/1,482) of NSCLC patients and 1.2% (13/1,119) of lung adenocarcinoma patients.⁷² A surgical series concurred; *RET* fusions occurred in 1.4% (13/936) of NSCLCs and 1.7% (11/633) of lung adenocarcinomas and were more likely associated with a poorly differentiated histology, a never-smoking status, and a younger age.¹⁰⁴ In a former light smoker with lung adenocarcinoma, a *KIF5B-RET* translocation was demonstrated after molecular profiling was unrevealing for other oncogenic drivers (mutations in *EGFR*, *KRAS*, *BRAF*, *HER2*, *MET* amplification and rearrangements of *ROS1* and *ALK*).¹⁰⁵ The patient, who was refractory to first-line platinum-based chemotherapy, was treated with vandetanib with a complete response after 4 weeks of treatment. Vandetanib (NCT 01823068) and the other *RET* tyrosine kinase inhibitors, cabozantinib (NCT 01639508) and ponatinib (NCT 01813734), are the subjects of ongoing phase 2 clinical trials assessing their efficacy in patients with *RET*-driven NSCLC.

HER2

The human epidermal growth factor 2 (HER2, Neu, ErbB-2) protein, which is encoded by the *ERBB2* gene, is a member of the erbB1 family of receptor tyrosine kinases, which include EGFR (HER1), HER3, and HER4. There are no known ligands for HER2, rather HER2 is activated by homo- or heterodimerization with other HER family members.¹⁰⁶ Activation drives proliferation and survival through its downstream PI3K–AKT and MEK–ERK pathways (Fig. 1). *HER2* when overexpressed or amplified is an oncogenic driver in metastatic breast cancer; however, the role of the HER2 pathway in lung cancer is less well characterized. Previous studies have demonstrated that the *ERBB2* gene is amplified in 10 to 20% of lung cancer tumors,¹⁰⁷ and the HER2 protein is overexpressed in ~ 20% of NSCLC; however, this does not appear to predict response to HER2-targeted therapy.¹⁰⁸ *HER2* mutations are seen in ~ 2 to 4% of NSCLC and are more common in females, nonsmokers, and adenocarcinoma histologies (Fig. 1).^{109–12} Furthermore, these mutations appear to be mutually exclusive with other known driver mutations (*EGRF*, *ALK*, *KRAS*).¹¹² A recent retrospective analysis identified *HER2* mutations in 65 (1.7%) out of 3,800 patients tested and analyzed the outcome of the 22 *HER2* mutant patients that received HER2-directed therapy (trastuzumab, afatinib). Remarkably, an overall response rate and disease control rate of 50% and 82%, respectively, were observed, suggesting that HER2-directed therapy may be beneficial in *HER2* mutant NSCLC.¹¹² There are several studies that are now testing

this prospectively with HER-targeted TKIs (NCT01827267) or trastuzumab (NCT00004883 and NCT00758134).

Other Putative Targets

Alterations in the majority of receptor tyrosine kinases described earlier and KRAS lead to activation of the PI3K–AKT and MAPK pathways (Fig. 1). There has thus been a great interest in targeting these pathways in adenocarcinoma of the lung. PI3K is a member of the lipid kinase family and plays an important role in cell growth proliferation and survival. Mutations in the PI3K family of lipid kinases are found in the catalytic subunit of PI3K, in the p110 α , which is encoded by the *PIK3CA* gene. Mutations are found in ~ 1% of adenocarcinomas and do not appear to be mutually exclusive with other known oncogene drivers (*EGFR*, *KRAS*, *ALK*; Fig. 1).^{21,113} In adenocarcinoma of the lung in possible contrast to squamous cell carcinoma of the lung, it is not clear whether *PIK3CA* mutations represent a true driver oncogene, and single-agent activity has been disappointing to date.^{114,115} Signaling through the PI3K pathway leads to activation of the AKT1/protein kinase B, which is a Ser-Thr kinase that phosphorylates several downstream substrates, leading to diverse effects on cellular metabolism, survival, and proliferation (Fig. 1). Mutations in the *AKT1* gene have been observed in ~ 1% of NSCLC and appear to be limited to squamous cell carcinoma of the lung (Fig. 1).^{21,116,117} The AKT1 inhibitor MK2206 is currently being tested as a single agent and in combination with other pathways inhibitors or cytotoxic agents, and efficacy results are still pending (NCT00848718 and NCT01294306).¹¹⁸

Mitogen-activated protein kinase 1 (MAPKK1) or MEK1 is a Ser-Thr kinase that activates MAPK (ERK1), leading to cellular proliferation (Fig. 1). MAPKK1 is a direct downstream target of BRAF, and mutations have been found in ~ 1% of NSCLC (Fig. 1).¹¹⁹ Although these mutations are mutually exclusive of *EGFR*, *KRAS*, *HER2*, and *BRAF* mutations, it is not known whether this represents a true driver oncogene. Several MEK1 inhibitors are currently being tested in selected (*KRAS* mutant)^{120–122} and unselected populations (NCT01809210) and appear to show activity in combination with chemotherapy, at least in the *KRAS* mutant cohort (yet to be described).

In addition to the pathways already described, novel potential driver oncogenes are still being identified in meta-static adenocarcinoma of the lung. Recently, two novel *NTRK1* gene fusions (*MPRIP-NTRK1* and *CD74-NTRK100*) were identified that result in a constitutively active TrkA kinase and ability to transform cells in vitro. Interestingly, several panTrk inhibitors as well as crizotinib have activity against these translocations in vitro.¹²³ Because NTRK1 alterations may be present in as many as 3% of pan negative (*EGFR*, *KRAS*, *ALK*, *ROS1* wild-type) patients, *NTRK1* fusions may be a promising target in a small subset of patients. Interestingly, a recent report has described that the commonly observed translocation in acute lymphoblastic leukemia, *E2A-PBX1*, is also present in 12.5% of NSCLC cases, although it does not appear to be mutually exclusive with other known driver mutations.¹²⁴ Interestingly, leukemias expressing this translocation appear to be sensitive to dasatinib¹²⁵ and as such, *E2A-PBX1* translocations may represent a novel therapeutic target for lung cancer.

Unmet Needs

KRAS

The KRAS protein or V-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue is a member of the RAS family of guanosine triphosphatases. When bound to guanosine-5'-triphosphate and recruited to the plasma membrane, KRAS is activated and signals through multiple growth regulatory cascades including the RAF/MEK/ERK, PI3K/AKT/mTOR and RAL pathways (Fig. 1). KRAS activity is normally tightly regulated by a series of GTPase-activating proteins (GAPs) and guanine-nucleotide exchange factors (GEFs) as well as upstream activation and recruitment to the plasma membrane. In a variety of solid tumors, *KRAS* is mutated at codon position 12,13, or 61, leading to a loss of intrinsic GTPase activity, and conversely becomes constitutively active, leading to cellular transformation.¹²⁶ The first mutations in the *KRAS* oncogene in NSCLC were discovered almost 3 decades ago^{127,128}; however, there are no current therapies targeting this critical oncogene.¹²⁹ *KRAS* is mutated in one third of all malignancies and ~ 25% of all NSCLC (Fig. 1).^{21,129} As such, mutant *KRAS* is the most frequently observed driver mutation in metastatic adenocarcinoma of the lung. Furthermore, NSCLC patients with a *KRAS* mutation have an increased risk of recurrence in early-stage disease and have a worse prognosis with metastatic disease.^{129,130} Although *KRAS* mutations are found in both never-smokers and smokers, never-smokers are more likely to have transition mutations versus transversion mutations compared with current or former smokers.¹³¹ In an analysis of the *KRAS* amino acid substitutions in NSCLC patients treated on the Biomarker-integrated Approach of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial, the presence of GLY→YS or GLY→VAL substitutions was associated with worse outcomes.¹³² Although other studies were not suggestive of prognostic differences in the spectrum of *KRAS* amino acid substitutions, one series has suggested a worse prognosis with *KRAS* codon 13 mutations versus codon 12 mutations.^{133,134}

Given its importance in NSCLC, multiple strategies have been proposed to target the KRAS pathway, including direct inhibition of the KRAS protein, use of antisense strategies, inhibition of its localization to the plasma membrane, and inhibition of its downstream effectors. To date none of these strategies have been successful.¹²⁶ However, several novel therapeutics are currently in early-phase clinical trials for mutant *KRAS* and have demonstrated some promise. A recent phase 2 double-blind, randomized study of the MEK1/MEK2 inhibitor selumetinib plus docetaxel versus docetaxel plus placebo as second-line treatment for advanced *KRAS* mutant NSCLC demonstrated efficacy. Median PFS was 5.3 months in the selumetinib group and 2.1 months in the placebo group (HR 0.58; $p=0.014$). Remarkably 16 (37%) patients in the selumetinib group versus zero patients in the placebo group had an objective response ($p<0.0001$). Although the primary end point of OS was not met, there was a strong trend toward an improvement in median OS: 9.4 months in the selumetinib group compared with 5.2 months in the placebo group (HR 0.80; $p=21$). Unfortunately, this combination was accompanied by significant neutropenia, and further investigation of this combination in *KRAS* mutant NSCLC will be dependent on the development of revised dosing schedules of the combination.¹³⁵ However, a second MEK1/MEK2 inhibitor in combination with docetaxel in a phase 1/1b trial in second-line treatment

for advanced *KRAS* mutant NSCLC has demonstrated efficacy and appears to have an improved side-effect profile.¹²¹

In addition to inhibiting MEK1 in *KRAS* mutant NSCLC, there has been an effort to inhibit parallel pathways (EGFR and MET) in *KRAS* mutant NSCLC. A recent phase 2 trial examined the combination of a putative MET inhibitor (ARQ-197/tivantinib) and the EGFR inhibitor (erlotinib) versus erlotinib alone in second-line treatment of NSCLC.¹³⁶ Although the study did not meet its prespecified primary end point (PFS), a preplanned exploratory survival analysis revealed a trend toward benefit in nonsquamous and *EGFR* wild-type populations. Remarkably, in the 16 *KRAS* mutant patients in the study, a significant benefit in PFS was seen (HR 0.18; $p < 0.01$; interaction $p = 0.006$) and a trend for OS (HR 0.43; $p = 0.17$). These findings led to an LCMC phase 2 trial of the combination of tivantinib and erlotinib versus standard chemotherapy in the second-line treatment for advanced *KRAS* NSCLC (NCT01395758). This trial is currently nearing its accrual, and we are awaiting the results of this study.

In addition to these current efforts, the role of HSP 90 inhibitors such as ganetespib and IPI-504 are being tested based on interesting preclinical efficacy in *KRAS* mutant cell lines and mouse models.^{137,138} Interestingly, early-phase trials with ganetespib either as monotherapy⁶² or in combination with chemotherapy¹³⁹ or other targeted therapies have suggested that *KRAS* mutant tumors may benefit from HSP 90 inhibitor therapy. This hypothesis is currently being tested in several ongoing clinical trials with ganetespib (Galaxy 2 trial)¹⁴⁰ and other HSP 90 inhibitors such as IPI-504 (NCT01348126, NCT01798485, NCT01427946). Finally, inhibition of the mTOR pathway may benefit patients with *KRAS* mutant NSCLC. A recent study examined the activity of the mTOR inhibitor ridaforolimus in *KRAS* mutant advanced NSCLC in the second- and third-line setting.¹⁴¹ This phase 2 study used a randomized discontinuation design and found that patients with stable disease at 8 weeks who were randomized to continue therapy had a significantly improved PFS; 4 months versus 2 months for the placebo. In addition, there was a trend toward improved median OS from randomization (18 months vs 5 months, HR 0.46, $p = 0.09$). Because the response rate (partial responses: 1/79 patients) was extremely low with ridaforolimus it is likely that future studies with mTOR inhibition will require the mTOR inhibitor to be combined with a second agent.

NSCLC of Squamous Cell Histology

An issue of critical importance is the elucidation and development of targeted therapeutic approaches in the second most common type of lung cancer, squamous cell carcinoma (SQCC) of the lung. Although *EGFR* and *KRAS* mutations occur quite commonly in adenocarcinoma of the lung, they are rarely associated with SQCC; indeed, in a series of 95 SQCC, verified by IHC as p63 positive and TTF-1 negative, there were no *EGFR* or *KRAS* mutations identified.¹⁴² While initial genotyping identified 16 *EGFR/KRAS* mutant “SQCCs,” detailed morphological and IHC reevaluation led to the reclassification of these tumors as either adenosquamous carcinoma or poorly differentiated adenocarcinoma with squamoid morphology, suggesting that the occurrence of these oncogenic drivers in SQCC are a consequence of incomplete sampling or morphological overlap.¹⁴²

Comprehensive genotyping of SQCC was performed as part of The Cancer Genome Atlas (TCGA) project with the goal of identifying potential opportunities for therapy. The most significantly mutated genes were *TP53* (81% SQCC samples), *MLL2* (20%), *PIK3CA* (16%), and *CDKN2A* (15%). Occurring less frequently were mutations in *KEAP1*, *NFE2L2*, *PTEN*, *HLA-A*, *NOTCH1*, and *RBI*.¹⁴³ Mutation and copy number alterations of *NFE2L2* and *KEAP1* and/or deletions of *CUL3* (genes involved in the oxidative stress response) were present in 34% of cases.

Overexpression/amplification of *SOX2* and *TP53*, loss-of-function mutations in *NOTCH1* and *NOTCH2* and *ASCL4*, and focal deletions in *FOXP1* (all genes with known roles in squamous cell differentiation) were found in 44% of samples.¹⁴³ Only one sample harbored a *KRAS* codon 61 mutation, and although no *EGFR* exon 19 deletion or *L858R* substitutions were identified, *EGFR* amplifications were demonstrated in 7% cases and two *EGFR L861Q* substitutions were identified (a sensitizing mutation to erlotinib and gefitinib).¹⁴³ Ninety-six percent of SQCCs harbored one or more mutations in tyrosine kinases, serine/threonine kinases, PI3K catalytic and regulatory subunits, nuclear hormone receptors, G-protein-coupled-receptors, proteases, and tyrosine phosphatases; 50 to 77% of the mutations were predicted to have medium or high functional effects, suggesting the presence of new potential therapeutic targets.¹⁴³

Fibroblast growth factor receptor 1 (*FGFR1*) is a receptor tyrosine kinase that regulates cell proliferation by the MAPK and PI3K pathways. In an analysis of 155 SQCCs using a single nucleotide polymorphism array, frequent and focal amplification was identified on 8p12, which includes *FGFR1*.¹⁴⁴ This region was amplified at high amplitude (four or more copies) in 9.7% (15/155) cases, 11 of whom were smokers and none were never-smokers, and no *FGFR1* amplification was identified in a cohort of lung adenocarcinoma patients.¹⁴⁴ Patients with SQCC and very high *FGFR1* amplification (copy number > 9 by FISH) had a nonsignificant trend toward inferior survival compared with patients without *FGFR1* amplification.¹⁴⁴ The prevalence was verified in independent cohorts of SQCC patients in whom *FGFR1* amplification was identified in 21 % of patients (12/57) and 22% (34/153) of patients; in the latter series, 27 were current smokers and none were never-smokers.¹⁴⁵ Treatment with the non-isoform-specific FGFR inhibitor PD173074 induces apoptosis in *FGFR1*-amplified cells and tumor shrinkage in mice engrafted with *FGFR1*-amplified cells.¹⁴⁴ The dual FGFR/vascular endothelial growth factor receptor (VEGFR) inhibitor brivanib (BMS-582664) was evaluated in a randomized discontinuation study of unselected patients with advanced solid tumors and was associated with no responses¹⁴⁶; there are, however, ongoing phase 2 clinical trials evaluating novel FGFR inhibitors in the targeted *FGFR1* amplified SQCC population (NCT 01861197; NCT 01795768).

DDR2 is a receptor tyrosine kinase that binds collagen as its endogenous ligand and promotes cell migration, proliferation, and survival. Sequencing of *DDR2* in a series of 290 primary SQCCs demonstrated a frequency of 3.2% (9/277) and identified mutations both in the kinase domain and in other regions of the protein sequence; no copy number alterations were identified.¹⁴⁷ Of the limited clinical information available in this case series, there was no association between *DDR2* mutations and age, sex, or smoking history.¹⁴⁷ The tyrosine kinase inhibitor, dasatinib, was found to inhibit growth in SQCC cell lines harboring *DDR2*

mutations and in xenograft mouse models engrafted with *DDR2* mutant cell lines.¹⁴⁷ In an early-phase clinical trial evaluating the role of dasatinib versus the combination of erlotinib and dasatinib in patients with advanced-stage lung cancer, one of the seven subjects with SQCC exhibited tumor shrinkage while undergoing therapy with erlotinib and dasatinib—a 59-year-old woman with a former smoking history of 11 pack-years.¹⁴⁷ A subsequent molecular analysis of her pretreatment specimen demonstrated an S768R *DDR2* kinase domain mutation, suggestive of a potentially targetable oncogenic driver; there is currently an ongoing phase 2 clinical trial evaluating the role of dasatinib in *DDR2* mutant SQCC (NCT 01514864).

PI3K is a member of the lipid kinases and plays an important role in cell growth proliferation and survival. Aberrant activation of the PI3K pathway is associated with amplification or gain-of-function mutations of the *PIK3CA* gene, which encodes the catalytic subunit of class I PI3K α , or loss of function of the *PTEN* tumor suppressor gene, a negative regulator of the PI3K pathway.^{148–150} Screening for *PIK3CA* mutations in several types of human cancer reveals an incidence of ~ 1.5% in NSCLC.^{151,152} In a series of 92 NSCLC tissues, *PIK3CA* amplification was found in 11 tissues (12%), 2 of which also harbored *PIK3CA* mutations.¹⁵³ *PIK3CA* copy number gains were more likely to occur in male smokers with squamous cell histology, and a *PIK3CA* copy number ≥ 3 was associated with an inferior overall survival compared with a copy number < 3 .¹⁵³ The presence of *PIK3CA* mutations has been associated with inferior survival in SQCC of the lung and a predilection for brain metastases.¹⁵⁴ In a series of 41 lung adenocarcinomas and 43 SQCC samples, *PIK3CA* amplification is found in 37% SQCC and only 5% of lung adenocarcinomas, mutations in 9% of SQCCs and 0% of adenocarcinomas, and loss of PTEN immunostaining in 21% SQCCs and 4% of adenocarcinomas.¹⁵⁵ Although 70% (16/23) of patients with *PIK3CA* mutant lung adenocarcinoma have coexisting oncogenic drivers (including *KRAS*, *MEK*, *BRAF*, *ALK* rearrangements, and *EGFR*), *PIK3CA* mutations rarely occur with other oncogenic drivers in SQCC.^{113,142} Cell lines harboring pathway alterations are exquisitely sensitive to the PI3K inhibitor GDC-0941.¹⁵⁵ This compound and other PI3K inhibitors are currently being studied in NSCLC with pathway alterations in PI3K in the context of phase 1 and 2 clinical trials (NCT 01297491; NCT 00974584).

Conclusion

In conclusion, the elucidation of oncogenic drivers in NSCLC has permanently shifted the landscape of NSCLC therapy to a personalized approach. Personalized NSCLC therapy necessitates a multidisciplinary approach to the issue of tissue acquisition and consideration of more invasive biopsy techniques to ensure there is adequate tissue both to distinguish histology and to perform molecular profiling. Adequate tissue acquisition at the time of diagnosis of metastatic disease is critical to identifying molecular subsets of patients in whom targeted therapy may be more effective than conventional chemotherapy; a paradigm exemplified by targeted TKI therapy in the *EGFR* mutant and the *ALK* rearranged subsets of NSCLC. In addition, strong consideration should be given to a repeat biopsy at the time of progressive disease to better understand the mechanisms of resistance among these oncogenic drivers and to direct patients to clinical trials evaluating novel targeted therapies.

While the story of personalized lung cancer therapy is most mature in *EGFR* mutant and *ALK* rearranged NSCLC, there have been major advances in the last year in *ROS1* rearranged and *BRAF* mutant NSCLC. Comprehensive genotyping efforts have been successful in identifying an oncogenic driver in 62% of lung adenocarcinomas; the proportion of NSCLCs in which an oncogenic driver is identified will only increase with the incorporation of next generation sequencing into routine clinical practice. Although this is encouraging, it also highlights the ongoing need for the development of effective therapies for each of these NSCLC molecular subsets, the greatest priorities being the *KRAS* mutant lung adenocarcinoma subset and the molecular subsets of SQCC. Historically, NSCLC was treated as a single disease entity with limited response rates and guarded survival. Personalized NSCLC therapy has sculpted an evolving therapeutic landscape of highly effective therapies for molecular subsets of lung cancer.

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Fig. 1. Key signaling pathways in non-small cell lung cancer and the frequency of oncogenic driver mutations and gene rearrangements in adenocarcinoma of the lung.

Table 1

Selected clinical trials evaluating targeted therapies in NSCLC

Study	Setting	Study arms	No. patients	RR (%)	PFS (mo)	OS (mo)
<i>EGFR Clinically selected</i>						
IPASS ^{24,31}	First-line <i>EGFR mutant</i>	Gefitinib Carboplatin/paclitaxel	132 129	71.2 47.3	9.5 6.3	21.6 21.9
	<i>EGFR wild-type</i>	Gefitinib Carboplatin/paclitaxel	91 85	1.1 23.5	1.5 5.5	11.2 12.7
FIRST-SIGNAL ¹⁵⁶	First-line <i>EGFR mutant</i>	Gefitinib Cisplatin/gemcitabine	26 16	84.6 37.5	8.0 6.3	27.2 25.6
	<i>EGFR wild-type</i>	Gefitinib Cisplatin/gemcitabine	27 27	25.9 51.9	2.1 6.4	18.4 21.9
LUX-Lung1 ³⁵	Acquired TKI resistance	Afatinib Placebo	390 195	11 0.5	3.3 1.1	10.8 12.0
<i>Molecularly selected patients</i>						
EURTAC ²⁵	First-line	Erlotinib Chemotherapy	77 76	54.5 10.5	9.4 5.2	22.9 18.8
OPTIMAL ²⁶	First-line	Erlotinib Carboplatin/gemcitabine	82 72	86 36	13.1 4.6	NM
Maemondo et al ²⁷	First-line	Gefitinib Carboplatin/paclitaxel	115 115	73.7 30.7	10.8 5.4	30.5 23.6
WJTOG ²⁸ 3405	First-line	Gefitinib Cisplatin/docetaxel	86 86	62.1 32.2	9.2 6.3	35.5 38.8
LUX-Lung 3 ²⁹	First-line	Afatinib Cisplatin/pemetrexed	230 115	56 23	11.1 6.9	NM
LUX-Lung 6 ³⁰	First-line	Afatinib Cisplatin/gemcitabine	242 122	66.9 23.0	11.0 5.6	NM
<i>ALK</i>						
Camidge et al ⁵⁰	All lines	Crizotinib	143	60.8	9.7	NM
PROFILE 1005 ⁵¹	Second-line and beyond	Crizotinib	255	53	8.5	NM
PROFILE 1014	First-line	Crizotinib Cisplatin/pemetrexed	Ongoing			
PROFILE 1007 ⁵³	Second-line	Crizotinib Docetaxel or pemetrexed	173 174	65 20	7.7 3.0	NM

Study	Setting	Study arms	No. patients	RR (%)	PFS (mo)	OS (mo)
Shaw et al ⁶⁰	All lines Crizotinib resistant	LDK378	88	70	NM	NM
			64	73		
Nakagawa et al ⁶¹	Crizotinib naive	CH5424802	46	93.5	NM	NM
<i>ROS1</i>						
Ou et al ¹⁶	All lines	Crizotinib	25	56	NM	NM
<i>BRAF</i>						
Planchard et al ⁸¹	Second-line and beyond	Dabrafenib	13	54	NM	NM

mo, months; NM, not mature; OS, overall survival; PFS, progression-free survival; RR, response rate; TKI, tyrosine kinase inhibitor.