Published in final edited form as:

Semin Oncol. 2014 February ; 41(1): 110–125. doi:10.1053/j.seminoncol.2013.12.006.

Targeted Therapies in NSCLC: Emerging oncogene targets following the success of EGFR

Eamon M Berge, MD and Robert C Doebele, MD, PhD

Department of Medicine, Division of Medical Oncology, University of Colorado, Aurora, CO

Abstract

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.

INTRODUCTION

Advanced and metastatic non-small cell lung cancer (NSCLC) carries a generally poor prognosis, with an estimated median overall survival 10 to 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 to 4.5 months, and a median overall survival (OS) of 7.9 to 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

Corresponding Author: Eamon M. Berge, M.D. Department of Medicine, Division of Medical Oncology, University of Colorado, Aurora, CO, Campus Box 8117, 12801 E. 17th Avenue, MS 8117, Aurora, CO 80045 USA, Phone: 303-724-3872, Fax: 303-724-3889, eamon.berge@ucdenver.edu.

DISCLOSURES:

Eamon Berge: no financial conflicts of interest to disclose.

Robert C. Doebele: Advisory board for Pfizer and Boehringer Ingelheim, research grants from Pfizer, Eli Lilly and ImClone, patent filed with USPTO for NTRK1 as a predictive biomarker.

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 Furthermore, the preclinical characterization of novel oncogenes has coincided with increased access to molecular testing of clinical specimens in a reasonable turn-around-time, which allows molecular testing to impact real-time clinical 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 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 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 (STAT) pathways.^{22, 24, 25} The most commonly encountered gene fusion pairs *ALK* with the N' terminus of echinoderm microtubule protein-like 4 (*EML4*) via a paracentric inversion. Several other fusion *EML4-ALK* fusion variants and other fusion partners, most notably kinesin factor 5B (*KIF5B*), have been described.^{26, 27} Fluorescence *in situ* hybridization (FISH) remains the gold standard for clinical detection of *ALK* gene rearrangements and is the only commercially available *ALK* screening modality, although evaluation of immunohistochemistry (IHC) and reverse transcription polymerase chain reaction (RT-PCR) based platforms have yielded similar sensitivity (100% RT-PCR and IHC) and specificity (100% and 75%-87.5%, RT-PCR and IHC, respectively) when compared to FISH.²⁷⁻³⁰

ALK+ NSCLC occurs at a rate between 5-7% of lung adenocarcinoma, with enrichment in younger and never smoker cohorts.³¹ Different histological patterns such as signet-ring histology have been reported in association with *ALK* rearrangements, but these features are not exclusively associated with *ALK* positivity.³² While the majority of *ALK* gene rearrangements commonly occur independently of *KRAS* and *EGFR* driver mutations, these mutations are not mutually exclusive, as multiple cases of dual oncogenic mutations have been reported.³³

The first attempt at targeting ALK+ NSCLC was described by Kwak *et al* who published initial phase I data on the multikinase TKI crizotinib (formerly PF-02341066) within a pre-planned dose expansion cohort (250mg BID) consisting entirely of patients with ALK+ NSCLC.²³ Initial ORR in this heavily pretreated population (n=82) was 57%, with an additional 33% patients experiencing stable disease. Survival data, while still maturing, revealed a median PFS of 9.7 months and an estimated OS of 74.8% at 12 months).³⁴ Retrospective analysis on a cohort of ALK+ NSCLC patients revealed similar 2 year survival on crizotinib of 57% when compared to an *EGFR* mutation positive NSCLC cohort treated with the *EGFR* TKI erlotinib with 2 year OS of 52%.³⁵ Results from the single-arm open label phase II trial of crizotinib in 255 ALK+ NSCLC patients showed an ORR of 53% with a disease control rate of 85% at 12 weeks and PFS of 8.5 months.³⁶ In 2011, US FDA approved the use of crizotinib in patients in ALK+ NSCLC as confirmed by a companion diagnostic FISH assay based on the impressive results available on the phase I and II trials while phase III registration trials were enrolling. The phase III PROFILE 1007 randomized ALK+ NSCLC patients who progressed on first line platinum-containing therapy to either pemetrexed or docetaxel vs. crizotinib with a primary endpoint of PFS.³⁷ Median PFS was superior for the crizotinib group compared to chemotherapy (7.7 vs. 3.0 mos; HR 0.49; 95% CI 0.37-0.64; p<0.001) with a significant difference in ORR (65% vs. 20%; p<0.001) per independent radiologic review. While still maturing, OS data showed no statistically significant difference between crizotinib and chemotherapy (20.3 vs. 22.8 mos; HR 1.02; 95% CI 0.68-1.54; p= 0.54) with 62% of patients in the pemetrexed/docetaxel arm crossing over to crizotinib at progression.

Toxicity data demonstrate that crizotinib is well tolerated. The most frequent adverse events as reported in phase III trial were gastrointestinal (nausea, vomiting, constipation, and diarrhea), peripheral edema and visual disturbances.³⁷ Gastrointestinal events were predominately mild, with grade 1/2 diarrhea occurring in 60% of patients (0% grade 3/4) with grade 1/2 nausea and vomiting occurring at rates of 55% and 47% respectively with only 1% experiencing any grade 3/4 nausea or vomiting. Visual disturbances were described as light trails, flashes, or brief image persistence ('postflashbulb effect') that occurred predominantly at the edge of the visual field and were more striking on the transition from low to bright light conditions. These effects were transient and were not associated with any permanent visual field defect or abnormality on ophthalmologic examination. Flipped dark-light registration of high-contrast images, such as stripes, was also reported. Investigators reported that these visual effects usually occurred at the edges of the visual field and were most pronounced on changing from low to bright light conditions. Visual effects were all grade 1/2, with no patients needing dose interruption, dose reduction, or permanent

discontinuation of crizotinib. Other grade 3/4 adverse events were seen in 36 patients with the most common being neutropenia (13%), ALT/AST elevation (16%) and pneumonitis (n=3). In aggregate, the incidence of treatment related adverse events was similar in the crizotinib and chemotherapy arms (33% vs. 32%, respectively) with only 6% of patients discontinuing crizotinib due to treatment related toxicity compared to 10% of patients in the chemotherapy arm. As experience with crizotinib grows, the toxicity profile has become more refined. Recently, a retrospective analysis revealed rapid suppression of serum testosterone levels in men within 14-21 days from starting crizotinib.³⁸ Testosterone decrease to below normal reference limit was 84% in this 32 patient cohort, while it was present in only 32% of a similarly matched cohort of men with stage IV NSCLC who did not receive crizotinib. Discontinuation led to rapid recovery of pre-treatment testosterone levels and improvement in fatigue by patient assessment.

Despite impressive ORR and PFS data, ALK+ NSCLC patients inevitably develop resistance to crizotinib. Many patients develop resistance in an ALK-dependent manner, where signaling through the ALK pathway is maintained but the ALK fusion protein is no longer inhibited by crizotinib due to the presence of ALK kinase domain mutations. The most described mutation, L1196M occurs within the ATP binding site of the kinase, decreasing binding of crizotinib in the ATP domain and restoring downstream signal transduction despite the presence of crizotinib.^{39, 40} Numerous other kinase domain mutations that generate resistance have been described in patient samples.^{40, 41} Unlike the T790M mutation in EGFR+ NSCLC, there does not appear to be one dominant ALK-dependent mechanism of resistance, with *ALK* copy number gain and multiple point mutations - both within and outside of the ALK kinase domain - described in the literature.^{41, 42} ALK-independent mechanisms of resistance have also been described, with emergence of separate oncogenic drivers such as *KRAS* and *EGFR* occurring with both with persistence of the *ALK* gene rearrangement and loss of *ALK* fusion at rebiopsy.⁴¹ Bypass signaling via ligand-driven activation of EGFR and KIT have also been described in preclinical models and patient samples.^{40,43}

Several novel second generation ALK inhibitors are in various stages development (Table 1) for both ALK TKI naïve patients and patients with required resistance to crizotinib. Updated phase I results of the dual ALK/EGFR TKI AP26113 demonstrate a PR in 19/31 ALK+ patients with prior exposure to crizotinib.⁴⁴ Preliminary results were presented on another second generation ALK TKI LDK378 with an ORR of 56% within a subpopulation of 79 ALK+ NSCLC that had progressed on crizotinib with a median duration of response of 7.4 months.⁴⁵ A single arm phase II trial utilizing LDK378 that specifically enrolls crizotinib resistant ALK+ NSCLC is currently open (NCT01685060). Lastly, phase I/II results using the ALK specific TKI alectinib (formerly CH5424802/RO5424802) on 4 ALK+, crizotinib-naïve NSCLC patients in initial phase I/II studies revealed an ORR was 93.5% with median PFS data not yet mature. f note, treatment related visual disorders on this agent were rare, with an noted increase of serum creatinine in 17/58 (29%) of assessable patients.⁴⁶ A separate phase I trial of alectinib in ALK+, crizotinib-resistant NSCLC resulted in an ORR 54.5 (24/44 assessable patients), including CNS and leptomeningeal responses to therapy, with the median duration of treatment not yet reached.⁴⁷

ROS1

The c-ros oncogene 1, receptor tyrosine kinase (*ROS1*) gene encodes a receptor tyrosine kinase of the insulin receptor superfamily with significant homology to ALK.⁴⁸ *ROS1* gene fusions have been previously described in glioblastoma, and have demonstrated oncogenic transformation in nude mice.⁴⁹ Recently, Bergethon et al. identified *ROS1* gene fusion in a multi-institution cohort via FISH with an initial prevalence of 1.7%.⁵⁰ Additional cohorts have confirmed a prevalence of *ROS1* gene fusions between 1-2% in unscreened populations of NSCLC.⁵¹⁻⁵³ Many of the *ROS1*+ NSCLC patients share similar characteristics to patients with ALK+ NSCLC such as adenocarcinoma histology, young age at diagnosis, and higher prevalence in never smokers, although *ROS1* gene fusions have also been identified in patients squamous cell lung cancer.⁵² Several different gene fusion partners for *ROS1* have been described in NSCLC, including *CD74*, *SDC4*, and *SLC34A2* amongst others.^{48, 52, 53} Co-existent *EGFR* mutations with *ROS1* fusions have been observed.⁵⁴ Little is known about the signaling of native *ROS1*, as no ligand has been identified to date, and mice lacking native *ROS1* appear healthy outside of minor reproductive tract abnormalities.⁵⁵⁻⁵⁷

Crizotinib has significant activity against the *ROS1* kinase and inhibits growth of a *ROS1*+ NSCLC cell line.^{52, 58} Patients treated with the TKI crizotinib have demonstrated marked clinical response similar to those seen in ALK+ NSCLC.^{50, 52} Updated crizotinib phase I data (PROFILE 1001) in a *ROS1*+ NSCLC dose expansion cohort demonstrates an ORR of 56% in 25 response evaluable patients, with 16 week disease control rate (DCR) of 60% and 6 month PFS of 71%.⁵⁹ The toxicity profile of *ROS1*+ NSCLC patients in this trial mirrors that of crizotinib treated ALK+ NSCLC patients, and includes visual disturbances, diarrhea, and nausea. A kinase domain mutation, G2032R, which interferes with crizotinib inhibition of the *ROS1* kinase has been described in a *ROS1*+ NSCLC patient progressing on crizotinib.⁶⁰ Pre-clinical models of *ROS1*+ NSCLC cell lines show that *EGFR* signaling can also mediate resistance to crizotinib.⁶¹ The ALK/*ROS1* TKI AP26113 can inhibit the activity of *ROS1* fusion *in vitro* and a phase II trial of AP26113 plans enrollment of *ROS1*+ NSCLC patients (NCT01449461).⁶² Foretinib (GSK1363089/XL880) also has shown activity in preclinical studies of *ROS1*+ NSCLC and retains activity against the G2032R resistance mutation and is currently under study in NSCLC.⁶³ Lastly, a phase I/II trial utilizing a combination of crizotinib plus the heat shock protein (Hsp90) inhibitor AT13387 (NCT01712217) is enrolling ALK+ and *ROS1*+ NSCLC after progression on crizotinib (Table 1).

KRAS

The *KRAS* gene is one of the first described oncogenes, and has a prevalence of approximately 20-25% in lung adenocarcinoma and 4% in lung squamous cell carcinoma.^{64, 65} Unlike *ALK* gene fusions and *EGFR* mutations, *KRAS* mutations appear at a lower frequency in never smokers when compared to current/light smokers and are relatively rare in East Asian patient cohorts.^{66, 67} *KRAS* belongs to family of GTPase proteins that transduce growth signals from a wide variety of tyrosine kinase receptors, commonly to the RAF/MEK/ERK signal transduction cascade. Activating mutations in exon

12 and 13 of *KRAS* are most common, but can also occur in codon 61.⁶⁵ In a meta-analysis of NSCLC patients, those with an activating *KRAS* mutation had a worse overall prognosis when compared to wild type patients.⁶⁸ However, a recent large retrospective study found no difference in prognosis by *KRAS* exon 12 mutation in patients with early stage NSCLC, calling into question the role of *KRAS* mutations as prognostic biomarkers.⁶⁹

Unfortunately, multiple attempts at targeting *KRAS* have yet to lead to an US FDA approved targeted therapy, in spite of the high mutation prevalence and its long known status as an oncogenic driver. Trials that attempted to directly inhibit mutant *KRAS* via farnesyl transferase inhibition failed to meet primary efficacy endpoints.⁷⁰ Most attempts thereafter have focused on the downstream RAF/MEK/ERK signaling cascade. Sorafenib, a multi-kinase TKI with weak RAF inhibition, has been evaluated in refractory NSCLC with modest efficacy in multiple trials.^{71, 72} Promising phase II results have been reported for the MEK1/2 inhibitor selumetinib (formerly AZD6244), where 87 *KRAS*-mutant NSCLC that progressed on first line therapy were randomized to docetaxel plus selumetinib or placebo.⁷³ Overall survival was numerically higher but not statistically significant in the selumetinib group compared to placebo (9.4 vs. 5.2 months, HR 0.80; 80% CI 0.56-1.14; p=0.21). However, improvement in median PFS was statistically significant (5.3 vs. 2.1 mos; HR 0.58; 80% CI 0.42-0.79; p=0.014) with an ORR of 37% in selumetinib versus 0% in the placebo arm (p<0.0001). Toxicity of the docetaxel + selumetinib combination is a concern, as there was a greater frequency of grade 3/4 adverse events with selumetinib (45%) compared to placebo (4%), including febrile neutropenia (14% vs. 0%) and pneumonia (9% vs. 0%).

Other MEK inhibitors are also under investigation, with mixed results. For example, a recent phase II trial in where patients were randomized in a second line setting to the MEK1/2 TKI trametinib (MEK114653) or docetaxel failed to meet its primary endpoint of PFS (11.7 vs. 11.4 weeks; HR 1.14; p=0.5197).^{74, 75} There are currently many active trials with *KRAS* mutation specific cohorts including additional trial featuring the MEK TKI's selumetinib and trametinib with other salvage chemotherapy drugs (Table 1), generating optimism that the largest molecular cohort in NSCLC may soon have an approved targeted therapy.

HER2

Human epithelial receptor 2 (HER2, ErbB2) is transmembrane protein kinase within the ErbB family of receptor protein kinases that also includes EGFR. Upon undergoing homo- or hetero dimerization with another member of the ErbB family (ErbB 1-4) signal transduction proceeds via the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway.⁷⁶⁻⁷⁸ The predictive and prognostic factors of *HER2* amplification in breast and esophageal adenocarcinoma are well known, with established US FDA approved HER2 monoclonal antibodies directed against the extracellular domain (trastuzumab, ado-trastuzumab emtansine, pertuzumab) and a TKI that targets the intracellular ATP binding domain (lapatinib).^{10, 79, 80}

HER2 overexpression in NSCLC occurs in 13-20% of NSCLC when evaluated by IHC, although 3+ overexpression occurs in only 2-4%.⁸¹ Similarly, amplification by FISH occurs

in 2-4% and shows inconsistent correlation with high expression by IHC.^{81, 82} Overexpression by IHC or FISH is more prevalent within the adenocarcinoma subgroup.⁸¹ Furthermore, there is a subgroup of NSCLC patients that harbor an in-frame insertion of 3-12 base pairs in exon 20 of *HER2* that causes oncogenic transformation in preclinical models.⁸³ Two different NSCLC patient cohorts have been evaluated for *HER2* mutations with an approximate prevalence of 2-4% in adenocarcinoma and 1.2% in an overall NSCLC cohort, with mutations more prevalent within never-smokers.^{84, 85} *HER2* amplification was established as a poor prognostic factor in a recent meta-analysis, with HR for OS of 1.48 (95% CI 1.22-1.80) for NSCLC and a HR of 1.95 (95% CI 1.56-2.43) for lung adenocarcinoma specifically.⁸⁶ *HER2* amplification was not predictive within lung squamous histology cohort (HR 0.87; 95% CI 0.61-1.25) when evaluated by FISH. The prognostic value of *HER2* insertions in NSCLC is yet to be determined.

Response to *HER2* targeted therapy for *HER2* amplification, overexpression and exon 20 insertions have been evaluated in several preclinical models. Trastuzumab has demonstrated synergistic tumor activity when added to different cytotoxic therapies in *HER2* overexpressed NSCLC.⁸⁷ The EGFR/*HER2* TKI lapatinib has also shown efficacy in NSCLC cell lines with a known *HER2* exon 20 insertion.⁸⁷ The clinical benefit of *HER2* targeted therapies in *HER2* overexpressing or *HER2* mutant NSCLC remains under investigation. A phase II trial which randomized *HER2* overexpressed NSCLC by IHC or FISH to trastuzumab combined with gemcitabine and cisplatin or gemcitabine/cisplatin alone, failed to demonstrate clinical benefit.⁸⁸ Subgroup analysis revealed a significant improvement in 6 month PFS (80% vs. 64%) and ORR (83% vs. 41%) in patients with 3+ *HER2* expression or *HER2* FISH amplification compared to the trastuzumab-treated population as a whole.⁸⁸ Similarly structured trials utilizing lapatinib demonstrated no clinical benefit.⁸⁹ A recently published report of stage IV NSCLC patients with a *HER2*+ mutation demonstrated an ORR of 50% and disease control rate (DCR) of 83% with use of *HER2*+ targeted therapy as either first line or salvage therapy, including a DCR of 93% in patients receiving trastuzumab in combination with chemotherapy.⁹⁰ Currently, there are multiple trials investigating the utility of next-generation irreversible pan-*HER* or *HER2* TKI's, including dacomitinib, afatinib, and neratinib (Table 1). A randomized phase II trial is currently enrolling *HER2* mutation positive NSCLC patients to *HER2* TKI neratinib with or without mTOR inhibitor temsirolimus (NCT01827267, Table 1) with other TKI's being evaluated in an unselected NSCLC population (Table 2).

BRAF

BRAF is a member of the RAF kinase family that lies immediately downstream from the canonical MAPK pathway from the RAS kinases. *BRAF* mutations were initially described in malignant melanoma with subsequent reports in colorectal adenocarcinoma and papillary thyroid cancer, amongst others.⁹¹⁻⁹³ *BRAF* targeted therapies have gained recent notoriety in melanoma, as the *BRAF*-specific TKI vemurafenib gained FDA approval as the first targeted therapy for *BRAF* mutant metastatic melanoma.⁹⁴

BRAF mutations are found in approximately 1-5% of NSCLC, almost exclusively in adenocarcinomas.^{95, 96} *BRAF* V600E mutations that induce constitutive kinase activity

occur in NSCLC, but there also multiple ‘non-V600E’ mutations that in aggregate constitute nearly 50% of the known *BRAF* mutations in NSCLC and occur within exons 11 and 15.⁹⁶ When compared to the non-V600E population, V600E *BRAF* mutations occur predominantly in light/never smokers, are more common amongst women and are associated with micropapillary histology. In addition, a non-V600E *BRAF* mutant cohort was associated with lower overall survival when adjusted for age, gender, and smoking status (HR 2.18; $p=0.014$) when compared to a *BRAF* wild-type cohort.⁹⁶

Interim results from 17 *BRAF* V600E mutated NSCLC patients treated in a single arm open-label phase II trial utilizing the *BRAF* TKI dabrafenib demonstrate a durable partial response (29 to 49 weeks) in 7 of 13 evaluable patients (ORR 54%). Experience with vemurafenib in *BRAF*+ NSCLC is limited to case reports only, with a published report of PR without clinical benefit in a patient with poor performance status.⁹⁷ Preclinical data suggest a differential response to the *BRAF* TKI vemurafenib with respect to the type of *BRAF* mutation with sensitivity in V600E *BRAF* mutant cell lines and resistance in non-V600E *BRAF* mutant melanoma cell lines.⁹⁸ Additional preclinical data suggests that *BRAF* activating mutations may predict sensitivity to downstream MEK TKI's, which is supported by clinical benefit seen with MEK inhibition in *BRAF* mutated melanoma.^{99, 100} *BRAF*-specific trials in NSCLC are utilizing different *BRAF* molecular cohorts in their trial designs, including V600E-specific trials, as seen in the phase II trial utilizing *BRAF* inhibitor GSK2118436 (NCT01336634) and trials evaluating downstream MEK and AKT inhibition in *BRAF* mutant NSCLC regardless of the specific *BRAF* mutation (Table 1).

RET

Rearranged in transfection (RET) is a receptor tyrosine with known oncogenic properties in thyroid cancer.¹⁰¹ Activating amino acid substitutions encoded by germline mutations have been described in multiple endocrine neoplasia (MEN) 2A and 2B, sporadic missense mutations in non-MEN related medullary thyroid cancer, and gene fusions discovered in a subset of papillary thyroid cancers.^{101, 102} Oncogenic properties in NSCLC were discovered via transcriptome analysis of banked tumor samples and next generation sequencing, revealing oncogenic *KIF5B-RET* gene fusions that occur through a paracentric inversion on chromosome 10.^{53, 103, 104} These results have been replicated with FISH analysis, with overall incidence of approximately 1-2%, with enrichment strategies for lung adenocarcinoma patients negative for other known biomarkers (*ALK*, *EGFR*, *KRAS*, *ROS1*) yielding rates up to ~15%.¹⁰⁵ Additional gene fusion partners have been discovered, including *CCD6*, *NCOA4*, and *TRIM33*.^{106, 107} There is a higher prevalence of RET+ NSCLC amongst never/light smoker and younger cohorts. The majority of RET+ NSCLC occur in patients with adenocarcinoma and the mutation occurs more frequently in poorly differentiated tumors.¹⁰⁸

As with other molecular cohorts such as HER2 and *BRAF* mutated NSCLC, current clinical experience is somewhat limited to case reports with off-label utilization of clinically available multi-kinase TKI's with RET activity including vandetanib and sunitinib or a preliminary report from a phase II trial utilizing cabozantinib where 2 of 3 patients achieved a PR.^{105, 107} RET-specific trials are planned or are underway with a variety of different

multi-kinase TKI's with RET activity, including vandetanib, cabozantinib, and ponatinib (Table 1).

MET

The *MET* gene codes for the hepatocyte growth factor receptor (HGFR), a transmembrane receptor that, upon binding the HGF ligand, undergoes homodimerization, autophosphorylation, and initiates downstream signaling via the PI3K pathway.¹⁰⁹ *MET* gene amplification in NSCLC has been reported at variable rates ranging from 1.4% of a Japanese cohort to 21% of a European NSCLC population in both squamous and adenocarcinoma histologies.^{109, 110} In addition to being a primary oncogenic event, *MET* amplification acts as a mechanism of resistance to EGFR TKI's in EGFR+ NSCLC via 'oncogene switch' in approximately 5-20% of patients.¹¹¹ *MET* mutations occur at a lower frequency and are clustered around the sema and juxtamembrane domains of HGFR.¹¹² The oncogenic potential of these mutations in NSCLC are unknown.¹¹² Transcriptome sequencing also recently identified exon 14 deletions in *MET* from NSCLC tumor samples that have been previously demonstrated as oncogenic alterations in lung cancer^{113,114}.

While there is little mature data with *MET* targeted therapy for *MET*-specific cohorts, there have been several trials utilizing different approaches to inhibit *MET* in unselected NSCLC patients. Onartuzumab, a monovalent monoclonal antibody that targets the sema domain of HGFR, has been evaluated in a recent phase II trial that randomized NSCLC patients undergoing second or third line salvage therapy to erlotinib plus onartuzumab versus erlotinib plus placebo.¹¹⁵ Of the 137 randomly assigned patients, 52% (n=66) were *MET* positive by IHC (defined as 2+ or 3+). There was a statistically significant improvement in OS for the *MET*-positive subgroup receiving onartuzumab compared to placebo (12.6 mos. vs. 3.8 mos., HR 0.37; 95% CI 0.19-0.72p=0.002). Onartuzumab is currently being evaluated in several trials in NSCLC (Table1, Table 2) with different enrollment criteria regarding histology and *MET* biomarkers. Onartuzumab in combination with erlotinib is being evaluated in a phase III trial as salvage therapy for patients with *MET*+ NSCLC (NCT01456325). Two phase II first-line trials include a study of onartuzumab or placebo in combination with carboplatin/cisplatin and paclitaxel in untreated patients with squamous cell carcinoma (NCT01519804) and a study of onartuzumab or placebo plus bevacizumab/carboplatin/paclitaxel or cisplatin/pemetrexed in NSCLC patients (NCT01496742). Additional *MET* antibodies including ficlatuzumab (formerly AV-299, NCT01039948) and rilotumumab (formerly AMG 102, NCT01233687) have been well tolerated in phase I trials and are both currently being evaluated in NSCLC regardless of *MET* status (Table2).

Many multi-kinase TKI's possess *MET* activity, with two agents having limited clinical data available for review. The allosteric, reversible TKI tivantinib (formerly ARQ197) possess high affinity for the inactive kinase domain of *MET*. Due to rapid and extensive metabolism via CYP2C19, recommending dosing in phase II trials differ based upon early pharmacokinetic data from patient with different CYP2C19 genotypes. In a recent phase II trial, previously treated EGFR TKI naïve NSCLC patients were randomized to erlotinib plus tivantinib or placebo.¹¹⁶ The trial arms were balanced with regard to *MET* amplification as defined by ≥ 4 gene copy number/cell (26% per arm). While the TKI combination was well

tolerated, the erlotinib plus tivantinib arm failed to meet its primary endpoint, with numerically better PFS that was not statistically significant in the entire cohort (HR 0.81; 95% CI, 0.57-1.16; $p=0.24$) or within the MET-positive cohort (HR 0.71; 95% CI 0.33-1.54; $p=0.387$).

While FDA approved for its use in ALK + NSCLC, the TKI crizotinib initially demonstrated preclinical activity towards MET and was initially developed as a MET inhibitor.¹¹⁷ There have been case reports describing a prolonged PR in an ALKnegative, MET-amplified patient on crizotinib while a MET- specific dose expansion cohort continues to accrue patients.¹¹⁸ Other MET TKI's are in clinical development, including the multi-kinase inhibitor foretinib and the aforementioned multi-kinase TKI cabozantinib (Table 2).

Other Emerging Targets in NSCLC: PI3K, DDR2, IGF-1R, FGFR, NTRK1

With a variety of new genomic screening strategies such as next generation sequencing and whole transcriptome sequencing becoming less expensive and increasingly available, several additional molecular markers have been identified within NSCLC whose role in oncogenesis and susceptibility to targeted therapy have yet to be completely defined. While by no means complete, this group of potential driver mutations includes PIC3CA mutations, fibroblast growth factor receptor 1 (FGFR1), insulin-like growth factor receptor 1 (IGF1R), discoidin domain receptor 2 (DDR2) and neurotrophic tyrosine kinase, receptor, type 1 (*NTRK1*).

PIC3CA

As a signal mediator between several different transmembrane growth factor receptors and downstream pathways, *PIK3CA* deregulation in NSCLC occurs via kinase mutations or gene amplification. *PIK3CA* mutations occur at a rate of ~2% of NSCLC with suggestion of increased frequency (~11%) in a recently published squamous cell cohort.¹⁹ However, the role of *PIK3CA* mutations in oncogenesis is unclear, as mutations frequently occur in the presence of other known activating mutations such as *EGFR* and *KRAS*.¹¹⁹ The role of *PIK3CA* amplification in NSCLC is also not well established.¹²⁰ Oral *PIC3CA* inhibitors are in development, most notably buparlisib (formally BKM120) in NSCLC in *PIK3CA* abnormal cohorts (Table 2).

DDR2

In contrast to *ALK*, *EGFR*, *ROS1* and other aforementioned oncogenes, mutations in the *DDR2* gene occur more frequently in patients with squamous cell histology at a rate of ~4%.¹²¹ *DDR2* functions normally as a transmembrane protein that binds to collagen and facilitates cell proliferation and migration. *DDR2* kinase mutations are susceptible to preclinical and clinical inhibition with the ABL kinase family of drugs and most notably with dasatinib. However, kinase mutations in *DDR2* only represent ~50% of the total known mutations, and there does not appear to be a dominant set of point mutations within the exons that encode *DDR2* kinase domain.¹²¹ While *DDR2* mutation specific trials with dasatinib are ongoing, phase II results with dasatinib in unselected NSCLC cohorts are disappointing.¹²²

IGF1R

IGF1R is a transmembrane receptor that mediates cellular proliferation through RAS/RAF/MAPK pathways and PI3K/AKT pathways. Activation of IGF1R occurs via several different mechanisms, including overexpression of the receptor, increase in the circulating IGF-1R ligand insulin-like growth factor (IGF), and decreased expression of the inhibitory IGF binding protein.¹²³ The IGF1R pathway also serves as a mechanism of resistance in to EGFR TKI's in preclinical models.¹²⁴ While preclinical studies validate that IGF1R plays a role in NSCLC oncogenesis, the frequency of these IGF1R deregulations in NSCLC patient cohorts has not been fully defined. A randomized phase II trial with the IGF1R humanized monoclonal antibody figitumumab demonstrated clinical activity by ORR (54% figitumumab plus chemotherapy, 42% chemotherapy alone) but further clinical trials were abandoned due to excessive toxicity.¹²⁵ Currently, there are several clinical trials utilizing IGF1R inhibitors in unselected NSCLC patients, most notably with the dual IGF1R linsitinib (formerly OSI-906), which is being investigated as a single agent and in combination with erlotinib.

FGFR

Much like EGFR and IGF1R, FGFR is a transmembrane tyrosine kinase that induces signal cascades via the RAS/RAF/MAPK and PI3K/AKT pathways. *FGFR1* amplification occurs at a frequency to ~20% in squamous cell carcinoma.¹⁹ *FGFR1* amplification is a relatively rare occurrence in adenocarcinoma, occurring at a rate of ~1-3%.¹²⁶ There are several FGFR1 inhibitors in clinical development including the dual FGFR1/VEGFR TKI brivanib (formerly BMS-582664), the FGFR1 TKI AZD4547 (NCT01824901, Table 2), and a phase II trial utilizing the multi-kinase TKI dovitinib with enrollment restricted to an *FGFR*-amplified squamous cell cohort (Table 1, NCT018611970). Although no phase II FGFR1-specific trials are mature, brivanib has been evaluated in a randomized discontinuation trial that enrolled 396 patients with five different tumor types.¹²⁷ While SD was seen in 24 of the 42 NSCLC patients in the trial, none of the unselected NSCLC patients had a response of PR or better. Activating mutations in the *FGFR2/3* genes that are oncogenic and drug sensitive have recently been described in lung squamous cell cancers.¹²⁸ Oncogenic gene fusions involving the *FGFR1/2/3* genes have recently been discovered in tumor samples from lung squamous cell cancers and may provide an additional predictive biomarker for FGFR-directed therapy.^{129, 130}

NTRK1

The neurotrophic tyrosine kinase, receptor, type 1 (*NTRK1*) gene encodes the TRKA protein, which is a transmembrane kinase receptor that, upon nerve growth factor (NGF) binding, undergoes autophosphorylation and signal propagation via the RAS/RAF/MAPK pathway. Germline mutations in *NTRK1* have been noted in patients with congenital insensitivity to pain, and sporadic chimeric gene fusions have been observed in papillary thyroid cancer and colon cancer.¹³¹⁻¹³³ Recent reports describe novel gene fusions of *NTRK1* in 3/91 (3.3%) of NSCLC that were negative for other known oncogenic alterations via FISH and next generation sequencing.¹³⁴ These gene fusions (*MPRIP-NTRK1* and

CD74-NTRK1) transformed murine fibroblast (NIH3T3) and bone marrow (Ba/F3) cell lines. While there are no clinical trials for NTRK1 inhibitors currently, several preclinical compounds showed inhibition of the oncogenic TRKA fusions.¹³⁵

DISCUSSION

The concept of ‘personalized medicine’ and ‘targeted therapy’ continue to evolve since the discovery of *EGFR* driver mutations and utilization of EGFR-specific TKI’s in NSCLC. Molecular techniques such as multiplex PCR, FISH, and next generation sequencing have improved in quality and cost to where multiple platforms now exist to identify clinically significant driver mutations, gene amplifications, or chimeric fusions from tumor tissue at the time of diagnosis or progression. Clinical investigators are now able to use these tools in real time to guide patients toward driver specific therapies as either standard of care or via clinical trials. In situations where no driver is found, clinical and translational researchers are employing enrichment strategies on these ‘pan-negative’ populations to identify novel driver oncogenes that may exist at lower frequency.^{105, 134} Lastly, novel trial designs such as the Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial and the ‘master protocol’ for SCC (SWOG 1400) are stratifying patients by oncogene driver status in order to prospectively identify predictive and prognostic biomarkers for oncogene specific drugs.⁷²

Despite these encouraging advancements, the advent of targeted therapy in NSCLC has presented several distinct challenges. While the majority of patients experience an initial clinical benefit, crizotinib-treated ALK+ NSCLC and erlotinib/gefitinib-treated EGFR+ NSCLC patients eventually develop resistance, doing so by additional point mutations, gene amplifications, or by switching to different driver oncogenes entirely.^{41, 111} There are several ongoing trials utilizing repeat biopsy at the time of clinical resistance to route patients towards second generation inhibitors in ALK+ NSCLC once resistance occurs (Table 1). An additional approach has been to consider trials that utilize heat shock protein (HSP90) inhibitors, as many of these oncogenes are large multi-domain proteins which require chaperones for protein folding, in effect targeting multiple different oncogenic drivers.¹³⁶ In addition, despite improvements in computerized tomography and ultrasound guided biopsy for molecular testing, obtaining tumor for molecular diagnostics remains a rate limiting step that in many cases is not logistically possible. Techniques that allow for a ‘liquid biopsy’ and molecular diagnosis of *ALK* and *EGFR* mutations via circulating tumor cells are being evaluated with promising initial results, but await prospective validation before they replace current companion diagnostic tests.^{137, 138} Lastly, there is significant heterogeneity in mutation prevalence amongst different NSCLC histologies, and while progress has been made in defining molecular subtypes in squamous cell carcinoma, the molecular landscape for this and rarer NSCLC histologic subtypes is not well characterized.¹⁹

Regardless, the pace of discovery of molecular drivers and the development of corresponding targeted agents is accelerating, and the future of targeted therapies in NSCLC remains bright. New companion diagnostic tests, next generation sequencing tests and innovative approaches to the discovery and implementation of oncogene-specific therapies

have led to improved length and quality of life for many patients with advanced solid tumors, including NSCLC. As molecular medicine becomes increasingly nuanced, and as the number of oncogenes, targeted agents, and oncogenespecific mechanisms of resistance continues to grow, some have advocated for a paradigm shift away from an organ and histology specific classification and toward an oncogene-specific classification to better streamline drug development and translational research.¹³⁹ Significant hurdles remain, but the time may come when our approach changes from viewing NSCLC as an entity with many different molecular subtypes and instead categorize solid tumors regardless of histology and tissue of origin - by their distinct oncogenic drivers and a set of targeted agents.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin.* 2010; 60(5):277–300. [PubMed: 20610543]
2. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev.* 2010; 19(8):1893–907. [PubMed: 20647400]
3. Howlader, N.; Noone, A.; Krapcho, M., et al. SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations). Available from URL: http://seer.cancer.gov/csr/1975_2009_pops09/
4. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol.* 2007; 2(8):706–14. [PubMed: 17762336]
5. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med.* 2006; 355(24):2542–50. [PubMed: 17167137]
6. Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies. *Oncologist.* 2009; 14(3):253–63. [PubMed: 19221167]
7. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med.* 2002; 346(2):92–8. [PubMed: 11784875]
8. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol.* 2008; 26(21):3543–51. [PubMed: 18506025]
9. Weinstein IB. Cancer. Addiction to oncogenes--the Achilles heel of cancer. *Science.* 2002; 297(5578):63–4. [PubMed: 12098689]
10. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med.* 2001; 344(11):783–92. [PubMed: 11248153]
11. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med.* 2003; 348(11):994–1004. [PubMed: 12637609]
12. Slebos RJ, Kibbelaar RE, Dalesio O, et al. K-ras oncogene activation as a prognostic marker in adenocarcinoma of the lung. *N Engl J Med.* 1990; 323(9):561–5. [PubMed: 2199829]
13. Kosaka T, Yatabe Y, Endoh H, Kuwano H, Takahashi T, Mitsudomi T. Mutations of the epidermal growth factor receptor gene in lung cancer: biological and clinical implications. *Cancer Res.* 2004; 64(24):8919–23. [PubMed: 15604253]
14. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med.* 2009; 361(10):947–57. [PubMed: 19692680]
15. Govindan R, Ding L, Griffith M, et al. Genomic landscape of non-small cell lung cancer in smokers and never-smokers. *Cell.* 2012; 150(6):1121–34. [PubMed: 22980976]
16. Imielinski M, Berger AH, Hammerman PS, et al. Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing. *Cell.* 2012; 150(6):1107–20. [PubMed: 22980975]

17. Ding L, Getz G, Wheeler DA, et al. Somatic mutations affect key pathways in lung adenocarcinoma. *Nature*. 2008; 455(7216):1069–75. [PubMed: 18948947]
18. Govindan, R.; Hammerman, PS.; Hayes, DN., et al. Comprehensive genomic characterization of squamous cell carcinoma of the lung. *ASCO Meeting Abstracts*; 2012. p. 7006
19. Paik, PK.; Hasanovic, A.; Wang, L.; Rekhtman, N.; Ladanyi, M.; Kris, MG. Multiplex testing for driver mutations in squamous cell carcinomas of the lung. *ASCO Meeting Abstracts*; 2012. p. 7505
20. Comprehensive genomic characterization of squamous cell lung cancers. *Nature*. 2012; 489(7417): 519–25. [PubMed: 22960745]
21. Sequist LV, Heist RS, Shaw AT, et al. Implementing multiplexed genotyping of non-small-cell lung cancers into routine clinical practice. *Ann Oncol*. 2011; 22(12):2616–24. [PubMed: 22071650]
22. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature*. 2007; 448(7153):561–6. [PubMed: 17625570]
23. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med*. 2010; 363(18):1693–703. [PubMed: 20979469]
24. Pulford K, Lamant L, Espinos E, et al. The emerging normal and disease-related roles of anaplastic lymphoma kinase. *Cell Mol Life Sci*. 2004; 61(23):2939–53. [PubMed: 15583856]
25. Kutok JL, Aster JC. Molecular biology of anaplastic lymphoma kinase-positive anaplastic large-cell lymphoma. *J Clin Oncol*. 2002; 20(17):3691–702. [PubMed: 12202671]
26. Wang R, Pan Y, Li C, et al. The use of quantitative real-time reverse transcriptase PCR for 5' and 3' portions of ALK transcripts to detect ALK rearrangements in lung cancers. *Clin Cancer Res*. 2012; 18(17):4725–32. [PubMed: 22791881]
27. Sanders HR, Li HR, Bruey JM, et al. Exon scanning by reverse transcriptase-polymerase chain reaction for detection of known and novel EML4-ALK fusion variants in non-small cell lung cancer. *Cancer Genet*. 2011; 204(1):45–52. [PubMed: 21356191]
28. Conklin CM, Craddock KJ, Have C, Laskin J, Couture C, Ionescu DN. Immunohistochemistry is a reliable screening tool for identification of ALK rearrangement in non-small-cell lung carcinoma and is antibody dependent. *J Thorac Oncol*. 2013; 8(1):45–51. [PubMed: 23196275]
29. Tuononen K, Sarhadi VK, Wirtanen A, et al. Targeted resequencing reveals ALK fusions in non-small cell lung carcinomas detected by FISH, immunohistochemistry, and real-time RT-PCR: a comparison of four methods. *Biomed Res Int*. 2013; 2013:757490. [PubMed: 23484153]
30. Yi ES, Boland JM, Maleszewski JJ, et al. Correlation of IHC and FISH for ALK gene rearrangement in non-small cell lung carcinoma: IHC score algorithm for FISH. *J Thorac Oncol*. 2011; 6(3):459–65. [PubMed: 21278610]
31. Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol*. 2009; 27(26):4247–53. [PubMed: 19667264]
32. Rodig SJ, Mino-Kenudson M, Dacic S, et al. Unique clinicopathologic features characterize ALK-rearranged lung adenocarcinoma in the western population. *Clin Cancer Res*. 2009; 15(16):5216–23. [PubMed: 19671850]
33. Santelmo C, Ravaioli A, Barzotti E, et al. Coexistence of EGFR mutation and ALK translocation in NSCLC: literature review and case report of response to gefitinib. *Lung Cancer*. 2013; 81(2): 294–6. [PubMed: 23683537]
34. Camidge DR, Bang YJ, Kwak EL, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. *Lancet Oncol*. 2012; 13(10):1011–9. [PubMed: 22954507]
35. Shaw AT, Yeap BY, Solomon BJ, et al. Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis. *Lancet Oncol*. 2011; 12(11):1004–12. [PubMed: 21933749]
36. Kim, D-W.; Ahn, M-J.; Shi, Y., et al. Results of a global phase II study with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC). *ASCO Meeting Abstracts*; 2012. p. 7533
37. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013; 368(25):2385–94. [PubMed: 23724913]

38. Weickhardt AJ, Doebele RC, Purcell WT, et al. Symptomatic reduction in free testosterone levels secondary to crizotinib use in male cancer patients. *Cancer*. 2013; 119(13):2383–90. [PubMed: 23585220]
39. Choi YL, Soda M, Yamashita Y, et al. EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. *N Engl J Med*. 2010; 363(18):1734–9. [PubMed: 20979473]
40. Katayama R, Shaw AT, Khan TM, et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung Cancers. *Sci Transl Med*. 2012; 4(120):120ra17.
41. Doebele RC, Pilling AB, Aisner DL, et al. Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. *Clin Cancer Res*. 2012; 18(5):1472–82. [PubMed: 22235099]
42. Sasaki T, Koivunen J, Ogino A, et al. A novel ALK secondary mutation and EGFR signaling cause resistance to ALK kinase inhibitors. *Cancer Res*. 2011; 71(18):6051–60. [PubMed: 21791641]
43. Tanizaki J, Okamoto I, Okabe T, et al. Activation of HER family signaling as a mechanism of acquired resistance to ALK inhibitors in EML4-ALK-positive non-small cell lung cancer. *Clin Cancer Res*. 2012; 18(22):6219–26. [PubMed: 22843788]
44. Camidge, DR.; Bazhenova, L.; Salgia, R., et al. First-in-human dose-finding study of the ALK/EGFR inhibitor AP26113 in patients with advanced malignancies: Updated results. *ASCO Meeting Abstracts*; 2013. p. 8031
45. Shaw, AT.; Mehra, R.; Kim, D-W., et al. Clinical activity of the ALK inhibitor LDK378 in advanced, ALK-positive NSCLC. *ASCO Meeting Abstracts*; 2013. p. 8010
46. Seto T, Kiura K, Nishio M, et al. CH5424802 (RO5424802) for patients with ALK-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1-2 study. *Lancet Oncol*. 2013; 14(7):590–8. [PubMed: 23639470]
47. Ou, SH.; Gadgeel, SM.; Chiappori, A., et al. Safety and efficacy analysis of alectinib (CH424802/RO542802) in anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) patients who have failed crizotinib in a dose-finding phase I study. 2013 European Society of Medical Oncology Annual Meeting Abstracts; 2013. Abstract # 44 LBA
48. Davies KD, Doebele RC. Molecular Pathways: ROS1 Fusion Proteins in Cancer. *Clin Cancer Res*. 2013; 19(15):4040–5. [PubMed: 23719267]
49. Birchmeier C, Sharma S, Wigler M. Expression and rearrangement of the ROS1 gene in human glioblastoma cells. *Proc Natl Acad Sci U S A*. 1987; 84(24):9270–4. [PubMed: 2827175]
50. Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. *J Clin Oncol*. 2012; 30(8):863–70. [PubMed: 22215748]
51. Li C, Fang R, Sun Y, et al. Spectrum of oncogenic driver mutations in lung adenocarcinomas from East Asian never smokers. *PLoS One*. 2011; 6(11):e28204. [PubMed: 22140546]
52. Davies KD, Le AT, Theodoro MF, et al. Identifying and targeting ROS1 gene fusions in non-small cell lung cancer. *Clin Cancer Res*. 2012; 18(17):4570–9. [PubMed: 22919003]
53. Takeuchi K, Soda M, Togashi Y, et al. RET, ROS1 and ALK fusions in lung cancer. *Nat Med*. 2012; 18(3):378–81. [PubMed: 22327623]
54. Rimkunas VM, Crosby KE, Li D, et al. Analysis of receptor tyrosine kinase ROS1-positive tumors in non-small cell lung cancer: identification of a FIG-ROS1 fusion. *Clin Cancer Res*. 2012; 18(16):4449–57. [PubMed: 22661537]
55. Acquaviva J, Wong R, Charest A. The multifaceted roles of the receptor tyrosine kinase ROS in development and cancer. *Biochim Biophys Acta*. 2009; 1795(1):37–52. [PubMed: 18778756]
56. El-Deeb IM, Park BS, Jung SJ, et al. Design, synthesis, screening, and molecular modeling study of a new series of ROS1 receptor tyrosine kinase inhibitors. *Bioorg Med Chem Lett*. 2009; 19(19):5622–6. [PubMed: 19700314]
57. Sonnenberg-Riethmacher E, Walter B, Riethmacher D, Godecke S, Birchmeier C. The c-ros tyrosine kinase receptor controls regionalization and differentiation of epithelial cells in the epididymis. *Genes Dev*. 1996; 10(10):1184–93. [PubMed: 8675006]
58. McDermott U, Iafrate AJ, Gray NS, et al. Genomic alterations of anaplastic lymphoma kinase may sensitize tumors to anaplastic lymphoma kinase inhibitors. *Cancer Res*. 2008; 68(9):3389–95. [PubMed: 18451166]

59. Shaw, AT.; Camidge, DR.; Engelman, JA., et al. Clinical activity of crizotinib in advanced non-small cell lung cancer (NSCLC) harboring ROS1 gene rearrangement. ASCO Meeting Abstracts; 2012. p. 7508
60. Awad MM, Katayama R, McTigue M, et al. Acquired resistance to crizotinib from a mutation in CD74-ROS1. *N Engl J Med*. 2013; 368(25):2395–401. [PubMed: 23724914]
61. Davies KD, Mahale S, Astling DP, et al. Resistance to ROS1 Inhibition Mediated by EGFR Pathway Activation in Non-Small Cell Lung Cancer. *PLoS One*. 2013 in press.
62. Squillace RM, Anjum R, Miller D, et al. AP26113 possesses pan-inhibitory activity versus crizotinib-resistant ALK mutants and oncogenic ROS1 fusions. AACR Ann Meeting Abstracts. 2013
63. Davare MA, Saborowski A, Eide CA, et al. Foretinib is a potent inhibitor of oncogenic ROS1 fusion proteins. *Proc Natl Acad Sci U S A*. 2013
64. Santos E, Martin-Zanca D, Reddy EP, Pierotti MA, Della Porta G, Barbacid M. Malignant activation of a K-ras oncogene in lung carcinoma but not in normal tissue of the same patient. *Science*. 1984; 223(4637):661–4. [PubMed: 6695174]
65. Kris, MG.; Johnson, BE.; Kwiatkowski, DJ., et al. Identification of driver mutations in tumor specimens from 1,000 patients with lung adenocarcinoma: The NCI's Lung Cancer Mutation Consortium (LCMC). ASCO Meeting Abstracts; 2011. p. CRA7506
66. Riely GJ, Kris MG, Rosenbaum D, et al. Frequency and distinctive spectrum of KRAS mutations in never smokers with lung adenocarcinoma. *Clin Cancer Res*. 2008; 14(18):5731–4. [PubMed: 18794081]
67. Sun Y, Ren Y, Fang Z, et al. Lung adenocarcinoma from East Asian never-smokers is a disease largely defined by targetable oncogenic mutant kinases. *J Clin Oncol*. 2010; 28(30):4616–20. [PubMed: 20855837]
68. Masciaux C, Iannino N, Martin B, et al. The role of RAS oncogene in survival of patients with lung cancer: a systematic review of the literature with meta-analysis. *Br J Cancer*. 2005; 92(1):131–9. [PubMed: 15597105]
69. Shepherd FA, Domerg C, Hainaut P, et al. Pooled analysis of the prognostic and predictive effects of KRAS mutation status and KRAS mutation subtype in early-stage resected non-small-cell lung cancer in four trials of adjuvant chemotherapy. *J Clin Oncol*. 2013; 31(17):2173–81. [PubMed: 23630215]
70. Adjei AA, Mauer A, Bruzek L, et al. Phase II Study of the Farnesyl Transferase Inhibitor R115777 in Patients With Advanced Non-Small-Cell Lung Cancer. *Journal of Clinical Oncology*. 2003; 21(9):1760–66. [PubMed: 12721252]
71. Smit EF, Dingemans AM, Thunnissen FB, Hochstenbach MM, van Suylen RJ, Postmus PE. Sorafenib in patients with advanced non-small cell lung cancer that harbor K-ras mutations: a brief report. *J Thorac Oncol*. 2010; 5(5):719–20. [PubMed: 20421765]
72. Printz C. BATTLE to personalize lung cancer treatment. Novel clinical trial design and tissue gathering procedures drive biomarker discovery. *Cancer*. 2010; 116(14):3307–8. [PubMed: 20602437]
73. Janne PA, Shaw AT, Pereira JR, et al. Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study. *Lancet Oncol*. 2013; 14(1):38–47. [PubMed: 23200175]
74. Blumenschein, GR.; Smit, EF.; Planchard, D., et al. MEK114653: A randomized, multicenter, phase II study to assess efficacy and safety of trametinib (T) compared with docetaxel (D) in KRAS-mutant advanced non-small cell lung cancer (NSCLC). ASCO Meeting Abstracts; 2013. p. 8029
75. Gandara, DR.; Hiret, S.; Blumenschein, GR., et al. Oral MEK1/MEK2 inhibitor trametinib (GSK1120212) in combination with docetaxel in KRAS-mutant and wild-type (WT) advanced non-small cell lung cancer (NSCLC): A phase I/Ib trial. ASCO Meeting Abstracts; 2013. p. 8028
76. Klapper LN, Glathe S, Vaisman N, et al. The ErbB-2/HER2 oncoprotein of human carcinomas may function solely as a shared coreceptor for multiple stroma-derived growth factors. *Proc Natl Acad Sci U S A*. 1999; 96(9):4995–5000. [PubMed: 10220407]

77. Karunagaran D, Tzahar E, Beerli RR, et al. ErbB-2 is a common auxiliary subunit of NDF and EGF receptors: implications for breast cancer. *EMBO J*. 1996; 15(2):254–64. [PubMed: 8617201]
78. King CR, Kraus MH, Aaronson SA. Amplification of a novel v-erbB-related gene in a human mammary carcinoma. *Science*. 1985; 229(4717):974–6. [PubMed: 2992089]
79. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med*. 2006; 355(26):2733–43. [PubMed: 17192538]
80. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet*. 2010; 376(9742):687–97. [PubMed: 20728210]
81. Hirsch FR, Varella-Garcia M, Franklin WA, et al. Evaluation of HER-2/neu gene amplification and protein expression in non-small cell lung carcinomas. *Br J Cancer*. 2002; 86(9):1449–56. [PubMed: 11986780]
82. Heinmoller P, Gross C, Beyser K, et al. HER2 status in non-small cell lung cancer: results from patient screening for enrollment to a phase II study of herceptin. *Clin Cancer Res*. 2003; 9(14):5238–43. [PubMed: 14614004]
83. Shimamura T, Ji H, Minami Y, et al. Non-small-cell lung cancer and Ba/F3 transformed cells harboring the ERBB2 G776insV_G/C mutation are sensitive to the dual-specific epidermal growth factor receptor and ERBB2 inhibitor HKI-272. *Cancer Res*. 2006; 66(13):6487–91. [PubMed: 16818618]
84. Stephens P, Hunter C, Bignell G, et al. Lung cancer: intragenic ERBB2 kinase mutations in tumours. *Nature*. 2004; 431(7008):525–6. [PubMed: 15457249]
85. Shigematsu H, Takahashi T, Nomura M, et al. Somatic mutations of the HER2 kinase domain in lung adenocarcinomas. *Cancer Res*. 2005; 65(5):1642–6. [PubMed: 15753357]
86. Liu L, Shao X, Gao W, et al. The role of human epidermal growth factor receptor 2 as a prognostic factor in lung cancer: a meta-analysis of published data. *J Thorac Oncol*. 2010; 5(12):1922–32. [PubMed: 21155183]
87. Wang SE, Narasanna A, Perez-Torres M, et al. HER2 kinase domain mutation results in constitutive phosphorylation and activation of HER2 and EGFR and resistance to EGFR tyrosine kinase inhibitors. *Cancer Cell*. 2006; 10(1):25–38. [PubMed: 16843263]
88. Gatzemeier U, Groth G, Butts C, et al. Randomized phase II trial of gemcitabine-cisplatin with or without trastuzumab in HER2-positive non-small-cell lung cancer. *Ann Oncol*. 2004; 15(1):19–27. [PubMed: 14679114]
89. Ross HJ, Blumenschein GR Jr, Aisner J, et al. Randomized phase II multicenter trial of two schedules of lapatinib as first- or second-line monotherapy in patients with advanced or metastatic non-small cell lung cancer. *Clin Cancer Res*. 2010; 16(6):1938–49. [PubMed: 20215545]
90. Mazieres J, Peters S, Lepage B, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. *J Clin Oncol*. 2013; 31(16):1997–2003. [PubMed: 23610105]
91. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. *Nature*. 2002; 417(6892):949–54. [PubMed: 12068308]
92. Yuen ST, Davies H, Chan TL, et al. Similarity of the phenotypic patterns associated with BRAF and KRAS mutations in colorectal neoplasia. *Cancer Res*. 2002; 62(22):6451–5. [PubMed: 12438234]
93. Kimura ET, Nikiforova MN, Zhu Z, Knauf JA, Nikiforov YE, Fagin JA. High prevalence of BRAF mutations in thyroid cancer: genetic evidence for constitutive activation of the RET/PTC-RAS-BRAF signaling pathway in papillary thyroid carcinoma. *Cancer Res*. 2003; 63(7):1454–7. [PubMed: 12670889]
94. Flaherty KT, Puzanov I, Kim KB, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. *N Engl J Med*. 2010; 363(9):809–19. [PubMed: 20818844]
95. Naoki K, Chen TH, Richards WG, Sugarbaker DJ, Meyerson M. Missense mutations of the BRAF gene in human lung adenocarcinoma. *Cancer Res*. 2002; 62(23):7001–3. [PubMed: 12460919]

96. Marchetti A, Felicioni L, Malatesta S, et al. Clinical features and outcome of patients with non-small-cell lung cancer harboring BRAF mutations. *J Clin Oncol.* 2011; 29(26):3574–9. [PubMed: 21825258]
97. Gautschi O, Pauli C, Strobel K, et al. A patient with BRAF V600E lung adenocarcinoma responding to vemurafenib. *J Thorac Oncol.* 2012; 7(10):e23–4. [PubMed: 22743296]
98. Yang H, Higgins B, Kolinsky K, et al. RG7204 (PLX4032), a selective BRAFV600E inhibitor, displays potent antitumor activity in preclinical melanoma models. *Cancer Res.* 2010; 70(13):5518–27. [PubMed: 20551065]
99. Pratilas CA, Hanrahan AJ, Halilovic E, et al. Genetic predictors of MEK dependence in non-small cell lung cancer. *Cancer Res.* 2008; 68(22):9375–83. [PubMed: 19010912]
100. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med.* 2012; 367(2):107–14. [PubMed: 22663011]
101. Santoro M, Chiappetta G, Cerrato A, et al. Development of thyroid papillary carcinomas secondary to tissue-specific expression of the RET/PTC1 oncogene in transgenic mice. *Oncogene.* 1996; 12(8):1821–6. [PubMed: 8622903]
102. Santoro M, Carlomagno F, Romano A, et al. Activation of RET as a dominant transforming gene by germline mutations of MEN2A and MEN2B. *Science.* 1995; 267(5196):381–3. [PubMed: 7824936]
103. Kohno T, Ichikawa H, Totoki Y, et al. KIF5B-RET fusions in lung adenocarcinoma. *Nat Med.* 2012; 18(3):375–7. [PubMed: 22327624]
104. Lipson D, Capelletti M, Yelensky R, et al. Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. *Nat Med.* 2012; 18(3):382–4. [PubMed: 22327622]
105. Varella-Garcia, M.; Xu, LG.; Mahale, S., et al. RET rearrangements detected by FISH in “pan-negative” lung adenocarcinoma. *ASCO Meeting Abstracts*; 2013. p. 8024
106. Suzuki M, Makinoshima H, Matsumoto S, et al. Identification of a lung adenocarcinoma cell line with CCDC6-RET fusion gene and the effect of RET inhibitors in vitro and in vivo. *Cancer Sci.* 2013
107. Drilon A, Wang L, Hasanovic A, et al. Response to Cabozantinib in Patients with RET Fusion-Positive Lung Adenocarcinomas. *Cancer Discov.* 2013; 3(6):630–5. [PubMed: 23533264]
108. Wang R, Hu H, Pan Y, et al. RET fusions define a unique molecular and clinicopathologic subtype of non-small-cell lung cancer. *J Clin Oncol.* 2012; 30(35):4352–9. [PubMed: 23150706]
109. Onozato R, Kosaka T, Kuwano H, Sekido Y, Yatabe Y, Mitsudomi T. Activation of MET by gene amplification or by splice mutations deleting the juxtamembrane domain in primary resected lung cancers. *J Thorac Oncol.* 2009; 4(1):5–11. [PubMed: 19096300]
110. Beau-Faller M, Ruppert AM, Voegeli AC, et al. MET gene copy number in non-small cell lung cancer: molecular analysis in a targeted tyrosine kinase inhibitor naive cohort. *J Thorac Oncol.* 2008; 3(4):331–9. [PubMed: 18379349]
111. Bean J, Brennan C, Shih JY, et al. MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. *Proc Natl Acad Sci U S A.* 2007; 104(52):20932–7. [PubMed: 18093943]
112. Gherardi E, Birchmeier W, Birchmeier C, Vande Woude G. Targeting MET in cancer: rationale and progress. *Nat Rev Cancer.* 2012; 12(2):89–103. [PubMed: 22270953]
113. Kong-Beltran M, Seshagiri S, Zha J, et al. Somatic mutations lead to an oncogenic deletion of met in lung cancer. *Cancer Res.* 2006; 66(1):283–9. [PubMed: 16397241]
114. Seo JS, Ju YS, Lee WC, et al. The transcriptional landscape and mutational profile of lung adenocarcinoma. *Genome Res.* 2012; 22(11):2109–19. [PubMed: 22975805]
115. Spigel DR, Ervin TJ, Ramlau RA, et al. Randomized Phase II Trial of Onartuzumab in Combination With Erlotinib in Patients With Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol.* 2013; 31(32):4105–14. [PubMed: 24101053]
116. Sequist LV, von Pawel J, Garmey EG, et al. Randomized phase II study of erlotinib plus tivantinib versus erlotinib plus placebo in previously treated non-small-cell lung cancer. *J Clin Oncol.* 2011; 29(24):3307–15. [PubMed: 21768463]

117. Zou HY, Li Q, Lee JH, et al. An orally available small-molecule inhibitor of c-Met, PF-2341066, exhibits cyto-reductive antitumor efficacy through antiproliferative and antiangiogenic mechanisms. *Cancer Res.* 2007; 67(9):4408–17. [PubMed: 17483355]
118. Ou SH, Kwak EL, Siwak-Tapp C, et al. Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification. *J Thorac Oncol.* 2011; 6(5): 942–6. [PubMed: 21623265]
119. Chaffa JE, Arcila ME, Paik PK, et al. Coexistence of PIK3CA and other oncogene mutations in lung adenocarcinoma-rationale for comprehensive mutation profiling. *Mol Cancer Ther.* 2012; 11(2):485–91. [PubMed: 22135231]
120. Kawano O, Sasaki H, Okuda K, et al. PIK3CA gene amplification in Japanese non-small cell lung cancer. *Lung Cancer.* 2007; 58(1):159–60. [PubMed: 17681398]
121. Hammerman PS, Sos ML, Ramos AH, et al. Mutations in the DDR2 kinase gene identify a novel therapeutic target in squamous cell lung cancer. *Cancer Discov.* 2011; 1(1):78–89. [PubMed: 22328973]
122. Johnson FM, Bekele BN, Feng L, et al. Phase II study of dasatinib in patients with advanced non-small-cell lung cancer. *J Clin Oncol.* 2010; 28(30):4609–15. [PubMed: 20855820]
123. Scagliotti GV, Novello S. The role of the insulin-like growth factor signaling pathway in non-small cell lung cancer and other solid tumors. *Cancer Treat Rev.* 2012; 38(4):292–302. [PubMed: 21907495]
124. Casa AJ, Dearth RK, Litzenburger BC, Lee AV, Cui X. The type I insulin-like growth factor receptor pathway: a key player in cancer therapeutic resistance. *Front Biosci.* 2008; 13:3273–87. [PubMed: 18508432]
125. Karp DD, Paz-Ares LG, Novello S, et al. Phase II study of the anti-insulin-like growth factor type 1 receptor antibody CP-751,871 in combination with paclitaxel and carboplatin in previously untreated, locally advanced, or metastatic non-small-cell lung cancer. *J Clin Oncol.* 2009; 27(15): 2516–22. [PubMed: 19380445]
126. Dutt A, Ramos AH, Hammerman PS, et al. Inhibitor-sensitive FGFR1 amplification in human non-small cell lung cancer. *PLoS One.* 2011; 6(6):e20351. [PubMed: 21666749]
127. Ratain, MJ.; Schwartz, GK.; Oza, AM., et al. Brivanib (BMS-582664) in advanced solid tumors (AST): Results of a phase II randomized discontinuation trial (RDT). *ASCO Meeting Abstracts*; 2011. p. 3079
128. Liao RG, Jung J, Tchaicha J, et al. Inhibitor-Sensitive FGFR2 and FGFR3 Mutations in Lung Squamous Cell Carcinoma. *Cancer Res.* 2013; 73(16):5195–205. [PubMed: 23786770]
129. Wu YM, Su F, Kalyana-Sundaram S, et al. Identification of targetable FGFR gene fusions in diverse cancers. *Cancer Discov.* 2013; 3(6):636–47. [PubMed: 23558953]
130. Majewski IJ, Mittempergher L, Davidson NM, et al. Identification of recurrent FGFR3 fusion genes in lung cancer through kinome-centred RNA sequencing. *J Pathol.* 2013; 230(3):270–6. [PubMed: 23661334]
131. Greco A, Miranda C, Pagliardini S, Fusetti L, Bongarzone I, Pierotti MA. Chromosome 1 rearrangements involving the genes TPR and NTRK1 produce structurally different thyroid-specific TRK oncogenes. *Genes Chromosomes Cancer.* 1997; 19(2):112–23. [PubMed: 9172002]
132. Chao MV, Rajagopal R, Lee FS. Neurotrophin signalling in health and disease. *Clin Sci (Lond).* 2006; 110(2):167–73. [PubMed: 16411893]
133. Martin-Zanca D, Hughes SH, Barbacid M. A human oncogene formed by the fusion of truncated tropomyosin and protein tyrosine kinase sequences. *Nature.* 1986; 319(6056):743–8. [PubMed: 2869410]
134. Doebele, RC.; Vaishnavi, A.; Capelletti, M., et al. NTRK1 gene fusions as a novel oncogene target in lung cancer. *ASCO Meeting Abstracts*; 2013. p. 8023
135. Vaishnavi A, Capelletti M, Le AT, et al. Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer. *Nat Med.* 2013; 19(11):1469–72. [PubMed: 24162815]
136. Trepel J, Mollapour M, Giaccone G, Neckers L. Targeting the dynamic HSP90 complex in cancer. *Nat Rev Cancer.* 2010; 10(8):537–49. [PubMed: 20651736]

137. Mok, T.; Wu, YL.; Lee, JS., et al. Detection of EGFR-activating mutations from plasma DNA as a potent predictor of survival outcomes in FASTACT 2: A randomized phase III study on intercalated combination of erlotinib (E) and chemotherapy (C). ASCO Meeting Abstracts; 2013. p. 8021
138. Pailler E, Adam J, Barthelemy A, et al. Detection of Circulating Tumor Cells Harboring a Unique ALK Rearrangement in ALK-Positive Non-Small-Cell Lung Cancer. J Clin Oncol. 2013; 31(18): 2273–81. [PubMed: 23669222]
139. Mano H. ALKoma: a cancer subtype with a shared target. Cancer Discov. 2012; 2(6):495–502. [PubMed: 22614325]

Figure 1.

Graphic representations of targeted therapy in Non-small cell lung cancer (NSCLC). Approximate representation of 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.

TABLE I

Targeted Therapies in Oncogene Driver-Specific Cohorts*

TRIAL / NCT NUMBER	MOLECULAR COHORT	PHASE	THERAPY	PRIMARY OUTCOME	ESTIMATED COMPLETION DATE*
NCT01685138	ALK+ NSCLC; crizotinib naïve	II	LDK 378	OS	August 2014
NCT01685060	ALK+ NSCLC; crizotinib resistant	II	LDK 378	ORR	September 2015
NCT01828112	ALK+ NSCLC; crizotinib resistant	III	LDK378 vs. Pemetrexed (500mg/m ²) or docetaxel (75mg/m ²)	PFS	July 2017
NCT01871805	ALK+ NSCLC; crizotinib resistant	I/II	Alectinib (RO5424802/CH542802)	Safety/ORR	July 2015
NCT01449461	ALK+, EGFR+, or ROS1+ NSCLC, other ALK+ tumors	I/II	AP26113	RP2D/ORR	September 2015
NCT01712217	ALK+ or ROS1+ NSCLC, crizotinib resistant	I/II	AT13387 + crizotinib (phase I) AT13387 plus crizotinib vs. AT13387 (phase II)	MTD/ORR	November 2014
NCT01945021	ROS1+ NSCLC, East Asian ethnicity	II	Crizotinib	ORR	July 2016
NCT01859026	KRAS + NSCLC	I/IB	MEK162 + erlotinib	MTD	May 2016
NCT01229150	KRAS+ NSCLC	II	Selumetinib + erlotinib vs. selumetinib	PFS	September 2014
NCT01395758	KRAS+ NSCLC	II	Tivantinib (ARQ 197) + erlotinib vs. chemotherapy	PFS	December 2014
NCT01427946	KRAS+ NSCLC	Ib/II	Retaspimycin HCl (IPI-504) + everolimus	ORR	August 2015
NCT01750281	KRAS+ NSCLC	II	Selumetinib + docetaxel (75mg/m ²) vs. selumetinib + docetaxel (60mg/m ²) vs. placebo + docetaxel (75mg/m ²)	PFS	July 2014
NCT01933932	KRAS+ NSCLC	III	Selumetinib + docetaxel (75mg/m ²) vs. placebo + docetaxel (75mg/m ²)	PFS	July 2016
NCT01827267	HER2+ NSCLC	II	Neratinib vs. neratinib + temsirolimus	ORR	April 2016
NCT01336634	BRAF+ NSCLC (V600E only)	II	Dabrafenib (GSK2118436)	ORR	September 2019
NCT01514864	BRAF+ or DDR2 + NSCLC	II	Dasatinib	ORR	July 2017
NCT01306045	BRAF+, PI3K+, KRAS+, HER2+	II	Selumetinib (BRAF, KRAS), MK-2206 (PI3K), lapatinib (HER2)	ORR	January 2017
NCT01639508	RET+ NSCLC	II	Cabozantinib	ORR	July 2015
NCT01823068	RET+ NSCLC	II	Vandetanib	ORR	September 2016
NCT01813734	RET+ NSCLC	II	Ponatinib	ORR	June 2015
NCT01877083	RET+ NSCLC	II	Levatinib	ORR	November 2014
NCT01456325	MET+ NSCLC	III	Onartuzumab + erlotinib vs. erlotinib + placebo	OS	June 2015

TRIAL / NCT NUMBER	MOLECULAR COHORT	PHASE	THERAPY	PRIMARY OUTCOME	ESTIMATED COMPLETION DATE*
NCT01900652	MET+ NSCLC (previous EGFR therapy)	II	LY285358+ erlotinib vs. LY285358	ORR	November 2014
NCT01861197	FGFR1+ NSCLC	II	Divotinib	ORR	January 2015

* Trial status accessed November 13, 2013. (<http://www.clinicaltrials.gov>)

NSCLC: Non small cell lung cancer; OS: Overall survival; PFS: Progression free survival; ORR: Objective response rate; MTD: Maximum tolerated dose; RP2D: Recommended phase II dose
ALK: Anaplastic Lymphoma Kinase; KRAS: Kirsten ras oncogene homolog; HER2: Human epithelial receptor 2; RET: Rearranged in Transfection; PI3K: phosphatidylinositol 3-kinase; FGFR1: Fibroblast growth factor receptor 1

TABLE II

Targeted Therapies in Biomarker-Unselected NSCLC Cohorts*

TRIAL/NCT NUMBER	PHASE	TARGET	COHORT	THERAPY	PRIMARY OBJECTIVE	ESTIMATED COMPLETION DATE
NCT01542437	II	HER2	NSCLC	Afatimib (BIBW 2992)	ORR	December 2014
NCT01496742	II	MET	NSCLC	Onartuzumab/placebo + bevacizumab, platinum + paclitaxel; Onartuzumab/placebo + pemetrexed, platinum	PFS	December 2013
NCT01519804	II	MET	NSCLC (first line)	Onartuzumab + platinum, paclitaxel	PFS	June 2015
NCT01068587	I/II	MET	NSCLC	Foretinib (GSK1363089) + erlotinib vs. erlotinib	Safety/ORR	December 2013
NCT01866410	II	MET	NSCLC	Cabozatinib + erlotinib	ORR	January 2015
NCT01121575	I	MET	NSCLC	Grizotinib + daconitinib (PF-00299804)	Safety	December 2013
NCT01039948	IB/II	MET	NSCLC (Asian Ethnicity)	Ficlatuzumab (AV-299) + gefitinib	Safety /ORR	April 2013
NCT01233687	I/II	MET	NSCLC (prev. EGFR therapy)	Rilotumumab (AMG 102) + erlotinib	Safety/RP2D	December 2014
NCT00975767	I/II	MET	NSCLC	MGCD265 + erlotinib/MGCD265 + docetaxel	Safety/ORR	December 2013
NCT01570296	IB	PIK3CA	NSCLC (EGFR+) [†]	Buparlisib (BKM 120) + gefitinib	RP2D	December 2013
NCT01487265	I/II	PIK3CA	NSCLC (EGFR+) [†]	Buparlisib (BKM 120) + erlotinib	MTD/ 3 month PFS	May 2015
NCT01297491	II	PIK3CA	NSCLC	Buparlisib (BKM 120) + docetaxel (squamous); Buparlisib (BKM 120) + docetaxel/pemetrexed (nonsquamous)	PFS	February 2015
NCT01723800	I	PIK3CA	NSCLC (non-squamous)	Buparlisib (BKM 120) + carboplatin + pemetrexed	Safety	January 2017
NCT01820325	IB/II	PIK3CA	NSCLC (squamous)	Buparlisib (BKM 120)/placebo + carboplatin + paclitaxel	PFS	December 2016
NCT01493843	II	PIK3CA	NSCLC	GDC-0941/placebo + carboplatin + paclitaxel +/- bevacizumab	PFS	August 2015
NCT00955305	II	IGF-1R	NSCLC (squamous)	Cixutumab(IMC A-12) + carboplatin + paclitaxel+ bevacizumab	PFS	May 2015
NCT01561456	II	IGF-1R	NSCLC	AXL1717 vs. docetaxel	PFS	April 2013
NCT01676714	II	FGFR1	NSCLC	Divotinib	ORR	October 2016
NCT01824901	I/II	FGFR1	NSCLC	AZD 4547 + docetaxel	MTD/PFS	April 2016

* Trial status accessed July 7, 2013. (<http://www.clinicaltrials.gov>).

[†] Trial intended for secondary mutation in EGFR cohorts after EGFR tyrosine kinase inhibitors.

NSCLC: Non small cell lung cancer; PFS: Progression free survival; ORR: Objective response Rate; MTD: Maximum tolerated dose; RP2D: Recommended phase II dose
HER2: Human epithelial receptor 2; PIC3CA: phosphatidylinositol 3-kinase; IGF -1R: Insulin-like growth factor receptor 1; FGFR1: Fibroblast growth factor receptor 1