Current Oncology Reports (2019) 21: 21
https://doi.org/10.1007/s11912-019-0770-x

LUNG CANCER (H BORGHAEI, SECTION EDITOR)

Emerging Targeted Therapies for the Treatment of Non-small Cell Lung Cancer

Patrick R. Halliday[1,2] · Collin M. Blakely[1,2] · Trever G. Bivona[1,2]

Published online: 26 February 2019

Abstract

Purpose of Review Lung cancer remains the leading cause of cancer-related mortality worldwide. Genetic and molecular profiling of non-small cell lung cancer (NSCLC) has led to the discovery of actionable oncogenic driver alterations, which has revolutionized treatment for this disease. This review will move beyond traditional mutational drivers such as EGFR and ALK and will instead focus on emerging targets and the efficacy of new precision therapies.

Recent Findings Here, we discuss both established and emerging targeted therapy approaches, as well as ongoing challenges for the treatment of NSCLC patients harboring oncogenic alterations of the following types—gene fusions (ROS1, RET, NTRK), receptor tyrosine kinases (MET amplification and exon 14 mutations and EGFR/HER2 exon 20 insertion mutations), and MAPK signaling (SHP2 and altered BRAF and NF1).

Summary The treatment of lung cancer is increasingly biomarker-driven, as patients are selected for targeted agents based on the identification of genetic alterations amenable to inhibition. Our ability to further improve patient outcomes with this precision medicine approach will require continued efforts to identify, characterize, and target lesions driving lung cancer tumorigenesis and progression.

Keywords Lung cancer · Kinase · Targeted therapy · Therapeutic target · Precision medicine

Introduction

The discovery of molecular alterations that drive tumor initiation and progression in NSCLC has revolutionized clinical management of the disease. Treatment decisions for this disease are primarily based upon the presence or absence of molecular targets. This precision medicine approach has led to meaningful improvements in patient outcomes and quality of life when compared to traditional chemotherapy.

This article is part of the Topical Collection on *Lung Cancer*

Patrick R. Halliday is a Howard Hughes Medical Institute Medical Research Fellow.

✉ Trever G. Bivona
trever.bivona@ucsf.edu

[1] Department of Medicine, Division of Hematology and Oncology, University of California, San Francisco, San Francisco, CA, USA

[2] Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, 600 16th Street, N212D, San Francisco, CA 94158, USA

Perhaps the best example of how biomarker-driven targeted therapy has shifted the paradigm of lung cancer treatment is the management of *EGFR*-mutant NSCLC. Activating mutations of *EGFR* are the most prevalent targetable mutations in lung adenocarcinoma, for which there are currently four FDA-approved tyrosine kinase inhibitors (TKIs) in use. Watershed trials testing gefitinib (first generation), erlotinib (first generation), afatinib (second generation), and osimertinib (third generation) demonstrated superior progression-free survival (PFS), objective response rate (ORR), and quality of life compared to standard chemotherapy in patients whose tumors harbored canonical activating EGFR mutations [1–5]. Most recently, osimertinib was approved as first-line therapy for *EGFR*-mutant NSCLC, reducing the risk of progression or death by 54% compared to earlier-generation TKIs (erlotinib, gefitinib) [6••]. These data cemented the use of EGFR TKIs as standard therapy for patients with *EGFR*-mutant NSCLC, and provide a paradigm for the development of novel targeted therapy approaches in NSCLC.

The *EML4-ALK* gene rearrangement in lung adenocarcinoma is another prime example of how discovery of a targetable tumor genetic alteration can lead to improved NSCLC treatment [7]. The first-generation multikinase inhibitor crizotinib

was adopted as standard therapy shortly after demonstrating superiority over chemotherapy in the front-line setting [8]. Compared with crizotinib, the second-generation inhibitors, ceritinib, alectinib, and brigatinib, and the third-generation ALK inhibitor lorlatinib, exhibit enhanced activity against central nervous system (CNS) lesions and resistance-conferring secondary mutations in ALK that arise during crizotinib treatment [9–11, 12•, 13]. Alectinib is now the standard first-line therapy in *ALK*-positive NSCLC given its superiority over crizotinib in the ALEX trial, both in terms of PFS and control of CNS disease [14••]. With the successes and limitations of EGFR and ALK inhibitors already well characterized in the literature, this review will instead focus on actionable genetic alterations less commonly discussed in the lung cancer literature, as well as emerging therapies to target these lesions.

Oncogenic Gene Fusions

ROS1

ROS1 gene rearrangements are present in 1–2% of advanced-stage NSCLC patients [15]. The gene belongs to a family of insulin receptor tyrosine kinases and becomes constitutively activated by chromosomal rearrangement, leading to downstream activation of canonical PI3K-AKT, RAS-MAPK, and STAT3 signaling. These oncogenic fusions join the *ROS1* kinase domain with several known fusion partners, which forces aberrant ROS1 localization to different subcellular compartments leading to downstream signaling [16]. Patients with *ROS1*-rearranged lung cancer are similar demographically to those with *ALK* gene fusions, in that they tend to be younger (median age 49.8 years), female, non-smokers, and with lung adenocarcinoma [15].

ROS1 and ALK ATP-binding sites share 77% amino acid homology [17]. Given this structural similarity, traditional *ALK* inhibitors such as ceritinib and crizotinib have demonstrated efficacy in treating *ROS1*-mutant NSCLC. Crizotinib was tested in a trial of 50 *ROS1* fusion-positive NSCLC patients. The ORR was 72%, and the median PFS was 19.2 months, with a safety profile similar to that observed in *ALK*-rearranged NSCLC patients [18]. The success of this trial led the FDA to approve the use of crizotinib as front-line therapy for *ROS1*-rearranged NSCLC in 2016. However, as is the case with many TKIs, both innate and acquired resistance limits the efficacy of crizotinib. The most common mechanism of resistance in *ROS1*-positive NSCLC is the G2032R solvent-front mutation, which is structurally analogous to the G1202R solvent-front mutation that arises in *ALK*-rearranged NSCLC [19]. Solvent-front substitutions are on-target mutations of the solvent-exposed region of the kinase domain that sterically hinder drug binding, thereby conferring resistance to therapy.

Other *ALK* inhibitors have been investigated in *ROS1*-rearranged NSCLC. The second-generation *ALK* inhibitor ceritinib was studied in a phase II trial of 32 patients and demonstrated a similar efficacy to crizotinib among TKI-naïve individuals, with an ORR of 62% and PFS of 19.3 months, but with greater GI toxicities [20]. However, there has yet to be a trial examining the use of crizotinib and ceritinib head to head. Additionally, there are no data to support that crizotinib resistance can be overcome by the use of ceritinib. Lorlatinib, a third-generation ALK/ROS1 inhibitor, is being studied in an ongoing phase I/II study of *ROS1*-rearranged advanced-stage NSCLC. Among 13 TKI-naïve patients, the ORR was 76.9%, whereas crizotinib pre-exposed patients showed an ORR of 29.4% [21]. Entrectinib is a small molecule TKI that inhibits *NTRK*, *ROS1*, and *ALK* fusions. A recent integrated efficacy analysis of phase I/II studies of entrectinib in 53 treatment-naïve *ROS1*-rearranged patients yielded an impressive ORR of 77.4%, PFS of 19.0 months, and intracranial ORR of 55% in those individuals with baseline CNS disease [22]. With the exception of lorlatinib, none of the drugs previously mentioned have demonstrated significant efficacy in the crizotinib-resistant setting. Alternatively, cabozantinib, a multikinase inhibitor, has demonstrated activity against *ROS1* solvent-front resistance mutations, including G2032R, and could be a potential option for crizotinib-resistant patients, in particular those harboring a G2032R mutation [23]. A phase II trial of cabozantinib in NSCLC patients with *RET/ROS/NTRK* fusion or increased *MET/AXL* activity is ongoing (NCT01639508) and may shed light on the efficacy of this drug among *ROS1*-rearranged NSCLC patients (Table 1).

RET

The *RET* gene encodes a receptor tyrosine kinase that signals through the RAS/MAPK, PI3K/AKT, and JAK/STAT signaling pathways upon binding of native ligands [39]. Oncogenic *RET* gene rearrangements were first discovered in papillary thyroid cancer, primarily among patients exposed to ionizing radiation treatment or environmental radiation [40]. The first *RET* gene fusion to be detected in lung cancer involved the 3′ end of *RET* and the 5′ end of the kinesin family member 5B gene (KIF5B) [41]. *KIF5B-RET* and its variants are the best characterized *RET* fusions in NSCLC, but at least 12 other fusion partners have been identified to date [42]. Similar to *ROS1* fusions, the prevalence of *RET* rearrangements in NSCLC is approximately 1%, and *RET* rearrangement–positive patients tend to be young and never smokers [43].

While no *RET*-selective inhibitors are currently FDA approved, numerous multikinase inhibitors have been studied in patients with *RET*-rearranged lung cancer (Table 2). The GLORY study was a worldwide retrospective analysis that included 165 patients with *RET*+ NSCLC, of which 72%

Table 1 Clinical trials for the treatment of lung cancers with select targetable oncogenic drivers

Target	Agent	Trial identifier	Phase	Patient population	Results
BRAF V600E	Dabrafenib	NCT01336634	II	Treated and untreated BRAFV600E+ advanced NSCLC	ORR 33%, median PFS 5.5 months (previously treated) [24]
	Dabrafenib + trametinib	NCT01336634	II	Untreated BRAFV600E+ advanced NSCLC	ORR 64%, median PFS 10.9 months, median OS 24.6 months [25••]
EGFR exon 20 insertion	Poziotinib	NCT03066206	II	Treated and untreated metastatic EGFR exon20ins + NSCLC	ORR 58%, median PFS 5.6 months (abstract) [26]
	Osimertinib	NCT03191149	II	Stage IIIb–IV or recurrent EGFR exon20ins + NSCLC	Ongoing
	Afatinib + cetuximab	NCT03727724	II	Advanced EGFR exon20ins + NSCLC	Ongoing
HER2 alterations	Trastuzumab emtansine	NCT02289833*	II	HER2-overexpressing metastatic NSCLC previous tx w/ platinum-based chemo	ORR 20%, median PFS 2.7 months (high HER2 expression only) [27]
	Gemcitabine and cisplatin ± trastuzumab	NCT00016367*	II	Untreated advanced HER2-positive NSCLC	No clinical benefit [28]
	Neratinib ± temsirolimus	NCT01827267*	II	Stage IIIB/IV *HER2*-mutant NSCLC	ORR 19%, median PFS 4.1 months, median OS 15.8 months (neratinb + temsirolimus only) [29]
	Trastuzumab deruxtecan (DS-8201a)	NCT03505710	II	HER2-overexpressing or mutated, unresectable, and/or metastatic NSCLC	Ongoing
	Afatinib	NCT01542437	II	Advanced HER2-positive NSCLC progressive on chemotherapy	Ongoing
	Poziotinib	NCT03066206	II	Treated and untreated metastatic HER2 exon20ins + NSCLC	ORR 50%, DCR 83% (abstract) [26]
MET alterations	Crizotinib	NCT00585195	I	MET-amplified advanced NSCLC	ORR 40%, median PFS 6.7 months (high MET amp only) [30]
	Crizotinib	NCT00585195	I	MET exon 14-positive NSCLC	ORR 32%, median PFS 7.3 months (abstract) [31]
	Tepotinib	NCT02864992	II	Advanced NSCLC w/ MET exon 14 exon skipping mutation or MET amp	ORR 35%—independent review, ORR 57.5%—investigator assessment (abstract) [32]
	Capmatinib	NCT02414139	II	Advanced NSCLC w/ MET exon 14 exon skipping mutations	ORR 39.1%—pre-treated, ORR 72%—treatment-naïve (abstract) [33]
NF1	Trametinib	NCT03232892	II	Advanced NF1+ NSCLC, KRAS wildtype	Ongoing
NTRK fusions	Entrectinib	NCT02568267	II	Solid tumors that harbor an NTRK1/2/3, ROS1, or ALK gene fusion	Ongoing
	Larotrectinib (LOXO-101)	NCT02576431	II	Advanced solid tumors harboring a fusion of NTRK1, NTRK2, or NTRK3	Confirmed PR in three of four pre-treated NSCLC patients, no CNS progression (abstract) [34••]
	LOXO-195	NCT03215511	I/II	NTRK fusion cancers treated with a prior TRK inhibitor	Ongoing
RET fusions	Vandetanib	NCT01823068	II	Advanced NSCLC with RET rearrangement	ORR 18%, median PFS 4.5 months, median OS 11.6 months [35]
	Alectinib	NCT03131206	I/II	Advanced RET-rearranged NSCLC	Ongoing
	Ponatinib	NCT01813734*	II	Advanced RET-rearranged NSCLC	Not reported
	Lenvatinib	NCT01877083*	II	RET-rearranged NSCLC	ORR 16%, median PFS 7.3 months (abstract) [36]
	Sunitinib	NCT01829217*	II	RET-rearranged NSCLC, non-smokers, WT for EGFR, KRAS, ALK	Not reported
	Cabozantinib	NCT01639508	II	Advanced RET-rearranged NSCLC	ORR 28%, median PFS 5.5 months, median OS 9.9 months [37]
	LOXO-292	NCT03157128	I/II	RET-fusion solid tumors, medullary thyroid cancer, and other RET fusion tumors	ORR 74%—20/27 NSCLC patients (abstract) [38•]
ROS1 fusions	Crizotinib	NCT00585195	I	ROS1-fusion positive advanced NSCLC	ORR 72%, median PFS 19.2 months [18]

Table 1 (continued)

Target	Agent	Trial identifier	Phase	Patient population	Results
	Ceritinib	NCT01964157	II	ROS1-fusion positive advanced NSCLC	ORR 62%, median PFS 19.3 months [20]
	Lorlatinib	NCT01970865	I/II	ROS1-fusion positive advanced NSCLC	ORR 76.9% crizotinib naïve, ORR 29.4% crizotinib pre-exposed (abstract) [21]
	Entrectinib	NCT02568267	II	Solid tumors that harbor an NTRK1/2/3, ROS1, or ALK gene fusion	ORR 77.4%, PFS 26.3 months, intracranial ORR of 55% (abstract) [22]
	Cabozantinib	NCT01639508	II	Advanced ROS1-rearranged NSCLC	Ongoing
SHP2	RMC-4630	NCT03634982	I	Adult patients with relapsed/refractory solid tumors	Ongoing

*Completed trial

harbored the *KIF5B-RET* rearrangement. In that cohort, 53 patients received at least one multikinase inhibitor that demonstrated anti-*RET* activity in preclinical models or in vitro studies. Participants received carbozantinib (21 patients), vandetanib (11 patients), sunitinib (10 patients), sorafenib (2 patients), alectinib (2 patients), lenvatinib, (2 patients), nintedanib (2 patients), ponatinib (2 patients), and regorafenib (1 patient). Outcomes were modest when compared to the efficacy of TKIs targeting other NSCLC oncogenic drivers—median PFS was 2.3 months, and median OS was 6.8 months. Responding patients received cabozantinib (32% ORR), vandetanib (18% ORR), or sunitinib (22% ORR). No responses were reported with sorafenib, alectinib, ponatinib, or regorafenib [44]. There remains a pressing need to develop novel *RET*-targeted agents. LOXO-292 is a highly selective *RET* inhibitor that has shown preclinical activity against a variety of *RET* fusions, as well as the *RET* V804M gatekeeper resistance mutation [45]. The drug is currently being tested in a global phase I/II study of 82 *RET*-rearranged solid tumor patients, including 38 with NSCLC. Among the NSCLC patients, the ORR was 68%, with responses occurring irrespective of upstream fusion partner [38•].

NTRK

Neurotrophic receptor tyrosine kinase (NTRK) genes *NTRK1*, *NTRK2*, and *NTRK3* encode three tropomyosin receptor kinase (TRK) proteins, TrkA, TrkB, and TrkC, respectively. Trk proteins play a vital role in the growth, differentiation, and apoptosis of neurons in the peripheral and central nervous

Table 2 FDA-approved and investigational targeted therapies for the treatment of lung cancers with targetable oncogenic drivers

Target	% NSCLC patients	FDA-approved agents	FDA-approved agents (off-label use)	Investigational only
ALK fusions	3–7%	Crizotinib, ceritnib, brigatinib, alectinib, lorlatinib		Entrectinib, ensartinib
BRAF V600E	2–4%	dabrafenib/trametinib	Vemurafinib	
EGFR	10–20%	Afatinib, erlotinib, dacomitinib, gefitinib, osimertinib		Poziotinib, olmutinib, nazartinib
HER2 alterations	2–4%		Afatinib, ado-trastuzumab emtansine, neratinib, dacomitinib	Poziotinib, DS-8201a
KRAS	15–30%		Trametinib	Selumetinib
MET alterations	4–6%		Crizotinib, cabozantinib	Tepotinib, capmatinib
NF1	8–10%		Trametinib	
NTRK fusions	1–4%	Larotrectinib		Entrectinib, LOXO-195
RET fusions	1–2%		Cabozantinib, vandetanib, sunitinib	LOXO-292
ROS1 fusions	1–2%	Crizotinib	Ceritinib, lorlatinib, carbozantinib	Entrectinib
SHP2	Unknown			RMC-4630

systems [46]. Chromosomal rearrangements of *NTRK1* and *NTRK 2* are known drivers of oncogenesis in a diverse mix of over 20 pediatric and adult malignancies, including NSCLC, where the incidence is 3–4% [47, 48]. In NSCLC, *NTRK1* and *NTRK2* are known to form 5′ fusion partners with *CD74*, *MPRIP*, *SQSTM1*, and *TRIM24* [49].

Larotrectinib is a highly selective pan-TRK inhibitor that provided the first evidence of clinical benefit from TRK inhibition, in a patient with *TRK* fusion-positive metastatic soft tissue sarcoma [50]. Its efficacy was recently reported in a cohort of 55 adult and pediatric patients with a variety of *NTRK* fusion-positive cancers. The outcomes were promising with an ORR of 75% (median PFS had not yet been reached) [34••]. Four study participants are NSCLC patients, whose outcomes were reported separately at the 2018 World Conference on Lung Cancer. At the time of analysis, three of the four patients continued to have ongoing responses to the drug (ranging from 5.7 to 12 months), whereas one patient had stable disease that eventually progressed after 300 days of treatment [51]. These data highlight larotrectinib's potent antitumor activity in *NTRK* fusion-positive patients, regardless of age or tumor type. These findings led the FDA to grant accelerated approval of the drug for adult and pediatric patients with solid tumors harboring an *NTRK* fusion without a known resistance mutation, making this the first pan-cancer approval of a TKI [52]. The second-generation, TRK-selective inhibitor LOXO-195 has been used in two patients with *NTRK* fusion-positive cancer (colon and infantile fibrosarcoma) that developed resistance to larotrectinib. Both patients derived clear clinical benefit from the therapy [53]. A phase I study of LOXO-195 is now underway in patients with *NTRK* fusion-positive cancers who have progressed on a prior TRK inhibitor (NCT03215511).

Entrectinib is a first-generation pan-TRK inhibitor that also has activity against *ROS1* and *ALK* fusions. Preliminary safety and efficacy data from two phase I trials of entrectinib in *NTRK*-rearranged cancer (ALKA-372-001 and STARTRK-1) have been reported, which included one NSCLC patient with an *SQSTM1-NTRK* fusion, who experienced complete resolution of brain metastases and a durable partial response [54]. Recently, a pooled analysis of the ALKA-372-001, STARTRK-1, and STARTRK-2 trials reported on the efficacy of entrectinib in 54 patients with *NTRK* fusion-positive solid tumors, revealing an ORR of 57.4%, median PFS of 11.2 months, and median OS of 20.9 months [55].

Receptor Tyrosine Kinase Alterations

MET

The *MET* gene encodes hepatocyte growth factor receptor (HGFR), a receptor tyrosine kinase, which is activated by binding to the ligand HGF. The activated homodimer signals through downstream PI3K/AKT, Wnt/β-catenin, RAS/MAPK, and JAK/STAT signaling pathways [56]. Oncogenic *MET* activation in lung cancer occurs by either *MET* gene amplification or *MET* exon 14 skipping mutations. *MET* amplifications are known to occur in about 1 to 5% of NSCLC, whereas exon 14 skipping mutations are present in approximately 3% of cases [57, 58]. Patients with high-level *MET* amplification (defined by the ratio of *MET* gene copy number to the centromere of chromosome 7—*MET/CEP7*) can derive clinical benefit from crizotinib, whereas those with lower levels of *MET* amplification respond less favorably. A recent update from a phase I trial of crizotinib in *MET*-amplified NSCLC (NCT00585195) showed an ORR of 40% (8/20) in patients with high *MET* copy number (*MET/CEP7* ≥ 4) [30]. In addition to being an oncogenic driver, *MET* amplification is also an established cause of acquired resistance to EGFR-targeted therapies in lung cancer [59, 60].

MET exon 14 skipping mutations result in a MET protein lacking the E3 ubiquitin protein-ligase binding site. This mutated form of MET shows impaired ubiquitination-mediated degradation, contributing to sustained MET activation and tumorigenesis [61]. Multikinase inhibitors such as crizotinib and cabozantinib have demonstrated efficacy in advanced-stage NSCLC patients with *MET* exon 14 skipping mutations [62]. Most recently, an ongoing study (PROFILE 1001) of crizotinib in patients with *MET* exon 14-altered NSCLC reported an ORR of 32% in a cohort of 65 patients [31]. However, emerging mechanisms of resistance, such as the *MET* D1228 and Y1230 mutations, may limit the response to crizotinib in this population [63–65]. Furthermore, crizotinib has poor CNS penetration and is relatively ineffective at treating or preventing brain metastases in these patients. There is a case report of a patient with a *MET* exon 14 skipping mutation who experienced a rapid intracranial response to cabozantinib after developing resistance to crizotinib [66]. An ongoing phase II study of tepotinib (*MET*-selective oral inhibitor) in a similar patient population of 41 patients revealed an ORR of 35% [32]. A separate study is evaluating another *MET*-selective agent, capmatinib, in patients with *MET* exon 14 mutant or *MET* amplified advanced-stage NSCLC (NCT02414139). Results from 94 patients demonstrated ORRs of 39.1% and 72% among pretreated and treatment-naïve patients, respectively, highlighting that TKIs are frequently more effective when used in the first-line treatment setting. The drug also showed preliminary intracranial activity in patients with brain metastases [33].

HER2 Alterations

Mutations of *ERBB2* (*HER2*) occur in NSCLC and have been studied as potential drivers of oncogenesis. Approximately 2–4% of lung adenocarcinoma patients harbor *HER2* mutations [67, 68]. Nearly all of these mutations are small, kinase-

activating insertions in exon 20 and are typically present as the exclusive oncogenic driver in patient tumors [69, 70]. The treatment of *HER2*-altered NSCLC has been largely unsuccessful, and there is currently no approved targeted therapy for these patients. A retrospective study of 101 patients with *HER2* exon 20 insertions revealed an ORR of 50.9% for those who received trastuzumab or trastuzumab emtansine; ORR of 7.4% for those who received neratinib, lapatinib, or afatinib; and ORR of 43.5% in those treated with conventional chemotherapy [71]. A trial of 51 patients comparing treatment with trastuzumab and chemotherapy to chemotherapy alone did not show any clinical benefit, except in a small subgroup of 3+/FISH-positive patients [28]. Afatinib has previously shown some activity in treating a small number of patients and was more recently examined in a larger cohort of heavily pretreated patients [72, 73]. Among those with exon 20 insertions, the ORR was 33% and the DCR was 100% [74]. More recently, poziotinib, a small molecule inhibitor of *HER2* and *EGFR* exon 20 insertions, demonstrated promising preclinical and early clinical activity in one patient [75•]. A phase II study of poziotinib is ongoing in both *HER2* and *EGFR* exon 20-mutant NSCLC (NCT03066206). Among 12 evaluable patients harboring *HER2* exon 20 insertions, initial responses were observed in 6 (50%), with a median PFS of 5.1 months [26]. DS-8201a is another novel *HER2*-targeted agent consisting of a *HER2* antibody conjugated to a topoisomerase I inhibitor. Preliminary results from an ongoing phase I study show an ORR of 72.7% (8/11) [76]. A phase II study of this agent recently began accrual (NCT03505710). Lastly, a recent phase II basket trial of ado-trastuzumab emtansine (T-DM1) in 18 *HER2*-mutant NSCLC patients demonstrated a partial response rate of 44% and a median PFS of 5 months, and observed responses in patients with exon 20 insertions [77].

EGFR Exon 20 Insertions

The majority of patients with traditional *EGFR*-activating mutations (e.g., exon 19 deletions and L858R) experience dramatic clinical responses to *EGFR* TKIs such as erlotinib, gefitinib, and osimertinib [2, 6, 78]. However, a recent analysis of 14,483 NSCLC cases found 263 to have *EGFR* exon 20 insertions, representing 12% of all *EGFR*-mutant cases and 1.8% of all NSCLC [79]. Unfortunately, these patients typically have remarkably poor responses to current EGFR TKIs. In a compilation of clinical outcome data, the ORR with first-generation TKIs was 17%, while the ORR with second-generation TKIs was only 10% [80]. Even the third-generation EGFR TKI osimertinib seems to have limited activity in these patients. A retrospective study of osimertinib treatment in 17 patients with exon 20 insertions demonstrated an ORR of 6% and median PFS of 3.7 months [81]. However, osimertinib has shown some in vitro efficacy against a rare *EGFR* exon 20ins variant, D770_N771insNPG [82]. Additionally, a recent case report described an 80-year-old never-smoking patient who experienced a rapid partial response to osimertinib that was ongoing 5 months after starting therapy [83]. Osimertinib also demonstrated efficacy in exon20ins xenograft tumors in mice and in a single patient who was treated at a dose of 160 mg daily [84]. Thus, there may be a role for osimertinib in the treatment of *EGFR* exon 20ins NSCLC—however, additional study is needed to identify the subset(s) of patients that are likely to benefit from therapy. An ongoing phase II trial is examining the efficacy of high-dose osimertinib (160 mg daily) in patients with this mutation (NCT03191149). Interestingly, dual blockade with afatinib and cetuximab was effective in a small group of patients with *EGFR* exon 20 insertion advanced-stage NSCLC. Three of four patients experienced a partial response to therapy, with a median PFS of 5.4 months [85]. A clinical trial will soon be underway investigating this combination therapy in *EGFR* exon 20ins NSCLC (NCT03727724). Tarloxitinib is a prodrug that releases a HER2/EGFR TKI under hypoxic conditions. A previous trial of this agent (NCT02454842) in EGFR-mutant NSCLC was terminated due to lack of efficacy—however, the drug has shown promise in EGFR exon 20ins patient-derived tumor xenografts in mice and is set to be studied in a phase II trial [86, 87].

Structurally, *EGFR* exon 20 insertions restrict the drug-binding pocket, making it difficult for inhibitors to reach their target. Osimertinib possesses a large, rigid terminal group that likely limits its efficacy given the steric hindrance of exon 20 insertions. Conversely, the small molecule inhibitor, poziotinib, was found to be a potent and effective inhibitor of both *EGFR* and *HER2* exon 20 insertions given its small size and structural flexibility [75•]. A phase II trial of poziotinib in *EGFR* and *HER2* exon 20 insertions recently completed accrual of 50 *EGFR* exon 20ins patients (NCT03066206). Forty-four were evaluated for treatment response, which yielded an ORR of 55% and median PFS of 5.5 months. Responses were even observed in 8/13 (62%) of TKI-refractory patients; however, skin and GI toxicity associated with this drug are of potential concern [26].

MAPK Pathway Alterations

BRAF

Somatic mutations of *BRAF* occur in approximately 2–4% of NSCLC and promote RAF/MAPK pathway signaling [88, 89]. The most common *BRAF* mutation in lung cancer is the *BRAF* V600E mutation, accounting for 1–2% of lung adenocarcinomas and roughly 50% of *BRAF*-mutant NSCLC [90]. Unlike NSCLC patients with other molecular drivers such as *EGFR* and *ALK*, which are often associated with little to no smoking history, *BRAF*-mutant patients are more commonly

current or former smokers, particularly those with non-V600E mutations [91].

Treatment of *BRAF*-mutant NSCLC has closely mirrored that of malignant melanoma harboring *BRAF* V600 mutations. Two large phase II studies of dabrafenib/trametinib and vemurafenib/cobimetinib among patients with untreated *BRAF*-mutant melanoma achieved ORRs of 69% and 70% and OS of 25.1 months and 22.3 months, respectively [92, 93]. The successes of these trials led to FDA approval, and the adoption of combination Raf/MEK inhibition as the standard of care for these patients. Similarly, while monotherapy with Raf inhibitors such as vermurafenib and dabrafenib show efficacy in *BRAF*-mutant NSCLC, the addition of a MEK inhibitor potentiates therapeutic response, diminishes certain toxicities such as secondary hyperproliferative skin lesions, and improves clinical outcomes [24, 94, 95]. The combination of dabrafenib and trametinib was examined in a phase II study of previously untreated metastatic *BRAF* V600E-mutant NSCLC. The ORR of this cohort was 64%, and the median OS was 24.6 months [25••]. These results led to the 2017 FDA approval of the combination of dabrafenib and trametinib for advanced NSCLC harboring the *BRAF* V600E mutation, irrespective of prior therapy [96]. Unlike in melanoma, the combination of vemurafenib and cobimetinib has not been investigated in NSCLC.

Nearly half of all *BRAF*-mutant lung cancers harbor non-V600E mutations. Unlike the *BRAF*-V600E mutation, which confers constitutive BRAF activation as a monomer, most non-V600E mutations signal as dimers (similar to wild-type BRAF). While current Raf inhibitors potently inhibit mutant monomers, their binding at one site on a mutant dimer decreases binding affinity at the second, rendering therapy ineffective [97]. Thus, there is a pressing need to develop better therapeutic approaches for these patients. There are currently three approaches that are being pursued to meet this need. The first is to block downstream MEK signaling, for which trametinib has demonstrated in vitro efficacy in non-V600E NSCLC cell lines, as well as in melanoma patients with non-V600E mutations [98–100]. A second approach is to develop Raf inhibitors capable of targeting the oncogenic dimers of non-V600E mutants. There are several next-generation Raf inhibitors in development that may succeed in this purpose [101–103]. The third is to block RAS-mediated BRAF dimerization by inhibiting SHP2 signaling, which was recently shown to be an effective strategy for BRAF class III mutations (e.g., BRAF D594) that depend on RAS nucleotide cycling for growth [104].

NF1

NF1 is a tumor suppressor gene that encodes the protein neurofibromin and is a negative regulator of Ras activation and downstream signaling [105, 106]. Somatic loss-of-function (LOF) mutations of *NF1* occur in approximately 10% of NSCLC patients, and *NF1* mutations in this population of patients are highly heterogeneous, and the majority (75%) exist independently of other known oncogenic mutations [107]. The consequences and role of LOF mutations of *NF1* as a possible driver of oncogenesis has yet to be fully defined in NSCLC. The *NF1* gene has been well characterized in the setting of neurofibromatosis type 1, an autosomal dominant genetic disease that is characterized, in part, by the growth of tumors along nerves and elsewhere in the body [108, 109]. Interestingly, there is increasing evidence supporting the use of MEK inhibitors in patients with neurofibromatosis type 1. A phase I trial of the MEK1/2 inhibitor, selumetinib, was conducted in 24 children with neurofibromatosis type 1, resulting in confirmed partial responses in 71% (17/24) [110••]. More recently, the phase II study of selumetinib in this population of patients (NCT01362803) reported a similar response rate of 72% (36/50), with most responses sustained for beyond 6 months [111]. Given these findings, the FDA recently granted orphan drug status to selumetinib for the treatment of *NF1*. However, it remains to be determined whether MEK inhibition is effective in treating *NF1*-mutant NSCLC. An ongoing phase II trial examining the use of the MEK inhibitor trametinib in patients with metastatic or locally advanced NSCLC harboring *NF1* mutations aims to answer this question (NCT03232892). Intriguingly, a recent study described a novel subclass of NSCLC defined by concurrent *RASA1* (a Ras-GTPase-activating protein) and *NF1* loss. Cell lines harboring these two mutations were exquisitely sensitive to MEK inhibitors, providing rationale for clinical investigation of MEK inhibitors in this patient subset [112]. Recently, NSCLC cell lines and xenografts with *NF1* LOF mutations were shown to be sensitive to SHP2 inhibition, making this an attractive target for NSCLC patients whose tumors harbor these mutations [104].

SHP2

SHP2 (encoded by *PTPN11*) is a non-receptor protein tyrosine phosphatase that facilitates GTP loading and activation of RAS and downstream signaling [113, 114]. SHP2 is thought to play an oncogenic role in several malignancies, perhaps due to its putative function as a common signaling node, and parallel survival input for a diverse set of upstream driver mutations [115, 116]. Recently, preclinical studies have begun to shed light on the role SHP2 may play in lung adenocarcinoma. Among KRAS-mutant NSCLC cell lines, inhibition or silencing of SHP2 delayed tumor progression, whereas dual inhibition of SHP2 and MEK had a synergistic anti-tumor effect [117]. A separate study identified SHP2 signaling as a common mechanism of resistance in cell lines derived from patients whose tumors had grown resistant to ALK inhibition. This work demonstrated that co-treatment with SHP009, a

recently discovered small molecule SHP2 inhibitor, and the ALK TKI ceritinib restores sensitivity to ALK inhibition, suggesting that SHP2 might play a functional role in the development of TKI resistance in these patients [118•, 119]. The activity of the SHP2 inhibitor, RMC-4550, was studied in cancer models that are dependent on RAS nucleotide cycling for growth—such as those with NF1 LOF, class 3 mutants of BRAF, and KRAS G12C mutations. In these models, inhibition of SHP2 limits GTP loading of RAS, thereby suppressing RAS/MAPK signaling and halting tumor cell proliferation and tumor growth [104]. A phase I study of the clinical SHP2 inhibitor, RMC-4630, is underway in patients with relapsed or refractory solid tumors dependent on RAS/MAPK signaling (NCT0364982). It remains to be seen whether SHP2 inhibition will have efficacy in NSCLC patients. The preclinical data provide a rationale for future clinical investigation in these patient subsets, which currently lack an effective targeted therapy.

Conclusion

In 2004, erlotinib became the first FDA-approved molecular targeted therapy for the treatment of advanced-stage NSCLC in patients whose cancer had progressed on prior chemotherapy [120]. Notably, this approval was based on a 2-month PFS advantage compared to placebo, and no specific biomarker was required for its use. In the last 15 years, we have come to recognize the necessity of understanding the disease at a molecular level in order to identify specific molecular targets for which drugs can be identified or engineered to inhibit. This approach has proven to be remarkably successful, as there are now five molecular targets in advanced-stage NSCLC and over a dozen FDA-approved drugs for treatment with ORRs ranging from approximately 60 to 80%. In spite of this success, major challenges remain. Paramount among these include (1) targeting the "undruggable" oncogenic drivers such as mutant KRAS, (2) moving beyond RTK targets to modulate epigenetic alterations and transcriptional programs that drive cancer progression and resistance to therapy, and (3) understanding why responses to molecular targeted therapies in NSCLC are almost always incomplete and transient. With continued research, there is great promise for continued advances in the biomarker-driven treatment of patients with NSCLC.

Compliance with Ethical Standards

Conflict of Interest Patrick R. Halliday declares that he has no conflict of interest.

Collin M. Blakely has received research funding from AstraZeneca, Novartis, Roche, Spectrum Pharmaceuticals, Mirati Therapeutics, and MedImmune and has received compensation from Revolution Medicines and Jazz Pharmaceuticals for service as a consultant.

Trever G. Bivona has received research funding from Revolution Medicines and Novartis and has served as a consultant for Array BioPharma, and his spouse is an employee of Plexxikon, Inc., which develops cancer drugs.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung Cancer with mutated EGFR. N Engl J Med. 2010;362:2380–8.
2. Mok TS, Wu Y-L, Thongprasert S, Yang C-H, Chu D-T, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361:947–57.
3. Zhou C, Wu Y-L, Chen G, Feng J, Liu X-Q, Wang C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2011;12:735–42.
4. Wu Y-L, Zhou C, Hu C-P, Feng J, Lu S, Huang Y, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-lung 6): an open-label, randomised phase 3 trial. Lancet Oncol. 2014;15:213–22.
5. Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med. 2017;376:629–40.
6. •• Soria J-C, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med. 2018;378:113–25 **This trial established Osimertinib as first-line therapy for patients with EGFR-mutant NSCLC.**
7. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, et al. Identification of the transforming *EML4-ALK* fusion gene in non-small-cell lung cancer. Nature. 2007;448:561–6.
8. Solomon BJ, Mok T, Kim D-W, Wu Y-L, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in *ALK*-positive lung cancer. N Engl J Med. 2014;371:2167–77.
9. Friboulet L, Li N, Katayama R, Lee CC, Gainor JF, Crystal AS, et al. The ALK inhibitor ceritinib overcomes crizotinib resistance in non-small cell lung cancer. Cancer Discov. 2014;4:662–73.
10. Gadgeel SM, Gandhi L, Riely GJ, Chiappori AA, West HL, Azada MC, et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. Lancet Oncol. 2014;15:1119–28.
11. Kim D-W, Tiseo M, Ahn M-J, Reckamp KL, Hansen KH, Kim S-W, et al. Brigatinib in patients with crizotinib-refractory anaplastic

lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. J Clin Oncol. 2017;35:2490–8.

12.• Camidge DR, Kim HR, Ahn M-J, Yang JC-H, Han J-Y, Lee J-S, et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. N Engl J Med. 2018;379:2027–39 **This trial demonstrated superior PFS for ALK-rearranged NSCLC patients who received brigatinib compared to crizotinib.**

13. Shaw AT, Felip E, Bauer TM, Besse B, Navarro A, Postel-Vinay S, et al. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. Lancet Oncol. 2017;18:1590–9.

14.•• Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim D-W, et al. Alectinib versus crizotinib in untreated *ALK*-positive non-small-cell lung cancer. N Engl J Med. 2017;377:829–38 **This trial established alectinib as first-line therapy for ALK-positive NSCLC.**

15. Bergethon K, Shaw AT, Ignatius Ou S-H, Katayama R, Lovly CM, McDonald NT, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol. 2012;30:863–70.

16. Neel DS, Allegakoen DV, Olivas V, Mayekar MK, Hemmati G, Chatterjee N, et al. Differential subcellular localization regulates oncogenic signaling by ROS1 kinase fusion proteins. Cancer Res. 2018; canres.1492.2018. https://doi.org/10.1158/0008-5472.CAN-18-1492

17. Park S, Ahn B-C, Lim SW, Sun J-M, Kim HR, Hong MH, et al. Characteristics and outcome of ROS1-positive non-small cell lung cancer patients in routine clinical practice. J Thorac Oncol. 2018;13:1373–82.

18. Shaw AT, Ou S-HI, Bang Y-J, Camidge DR, Solomon BJ, Salgia R, et al. Crizotinib in *ROS1*-rearranged non-small-cell lung cancer. N Engl J Med. 2014;371:1963–71.

19. Gainor JF, Tseng D, Yoda S, Dagogo-Jack I, Friboulet L, Lin JJ, et al. Patterns of metastatic spread and mechanisms of resistance to crizotinib in ROS1-positive non-small-cell lung cancer. JCO Precision Oncol. 2017;1:1–13.

20. Lim SM, Kim HR, Lee J-S, Lee KH, Lee Y-G, Min YJ, et al. Open-label, multicenter, phase II study of ceritinib in patients with non-small-cell lung cancer harboring ROS1 rearrangement. JCO. 2017;35:2613–8.

21. Solomon BJ, Martini J-F, Ou S-HI, Chiari R, Soo RA, Bearz A, et al. 1380PD Efficacy of lorlatinib in patients (pts) with ROS1-positive advanced non-small cell lung cancer (NSCLC) and ROS1 kinase domain mutations. Ann Oncol. 2018;29:mdy292.003.

22. Doebele R, Ahn M, Siena S, Drilon A, Krebs M, Lin C, et al. OA02.01 Efficacy and safety of entrectinib in locally advanced or metastatic ROS1 fusion-positive non-small cell lung cancer (NSCLC). J Thorac Oncol. 2018;13:S321–2.

23. Lin JJ, Shaw AT. Recent advances in targeting ROS1 in lung cancer. J Thorac Oncol. 2017;12:1611–25.

24. Planchard D, Kim TM, Mazieres J, Quoix E, Riely G, Barlesi F, et al. Dabrafenib in patients with BRAFV600E-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial. Lancet Oncol. 2016;17:642–50.

25.•• Planchard D, Smit EF, Groen HJM, Mazieres J, Besse B, Helland Å, et al. Dabrafenib plus trametinib in patients with previously untreated BRAFV600E-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Lancet Oncol. 2017;18:1307–16 **This trial led to the approval of combination dabrafenib and trametinib for metastatic BRAF V600E NSCLC.**

26. Heymach J, Negrao M, Robichaux J, Carter B, Patel A, Altan M, et al. OA02.06 a phase II trial of poziotinib in EGFR and HER2 exon 20 mutant non-small cell lung cancer (NSCLC). J Thorac Oncol. 2018;13:S323–4.

27. Stinchcombe T, Stahel RA, Bubendorf L, Bonomi P, Villegas AE, Kowalski D, et al. Efficacy, safety, and biomarker results of trastuzumab emtansine (T-DM1) in patients (pts) with previously treated HER2-overexpressing locally advanced or metastatic non-small cell lung cancer (mNSCLC). JCO. 2017;35:8509.

28. Gatzemeier U, Groth G, Butts C, Van Zandwijk N, Shepherd F, Ardizzoni A, et al. Randomized phase II trial of gemcitabine-cisplatin with or without trastuzumab in HER2-positive non-small-cell lung cancer. Ann Oncol. 2004;15:19–27.

29. Gandhi L, Besse B, Mazieres J, Waqar S, Cortot A, Barlesi F, et al. MA04.02 Neratinib ± temsirolimus in her2-mutant lung cancers: an international, randomized phase ii study. J Thorac Oncol. 2017;12:S358–9.

30. Camidge DR, Otterson GA, Clark JW, Ou S-HI, Weiss J, Ades S, et al. Crizotinib in patients (pts) with MET-amplified non-small cell lung cancer (NSCLC): updated safety and efficacy findings from a phase 1 trial. JCO. 2018;36:9062.

31. Drilon A, Clark J, Weiss J, Ou S, Camidge DR, Solomon B, et al. OA12.02 Updated antitumor activity of crizotinib in patients with MET exon 14-altered advanced non-small cell lung cancer. J Thorac Oncol. 2018;13:S348.

32. Felip E, Sakai H, Patel J, Horn L, Veillon R, Griesinger F, et al. OA12.01 Phase II data for the MET inhibitor tepotinib in patients with advanced NSCLC and MET exon 14-skipping mutations. J Thorac Oncol. 2018;13:S347.

33. Wolf J, Seto T, Han J-Y, Reguart N, Garon EB, Groen HJM, et al. LBA52 Results of the GEOMETRY mono-1 phase II study for evaluation of the MET inhibitor capmatinib (INC280) in patients (pts) with METΔex14 mutated advanced non-small cell lung cancer (NSCLC). Ann Oncol. 2018;29:mdy424.090.

34.•• Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, et al. Efficacy of larotrectinib in *TRK* fusion-positive cancers in adults and children. N Engl J Med. 2018;378:731–9 **The success of this trial led to FDA approval for adult and pediatric patients with solid tumors harboring NTRK gene fusions. This is the first pan-cancer approval of a TKI.**

35. Lee S-H, Lee J-K, Ahn M-J, Kim D-W, Sun J-M, Keam B, et al. Vandetanib in pretreated patients with advanced non-small cell lung cancer-harboring RET rearrangement: a phase II clinical trial. Ann Oncol. 2017;28:292–7.

36. Velcheti V, Hida T, Reckamp KL, Yang JC, Nokihara H, Sachdev P, et al. Phase 2 study of lenvatinib (LN) in patients (Pts) with RET fusion-positive adenocarcinoma of the lung. Ann Oncol. 2016;27:1204PD.

37. Drilon A, Rekhtman N, Arcila M, Wang L, Ni A, Albano M, et al. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. Lancet Oncol. 2016;17:1653–60.

38.• Oxnard G, Subbiah V, Park K, Bauer T, Wirth L, Velcheti V, et al. OA12.07 Clinical activity of LOXO-292, a highly selective RET inhibitor, in patients with RET fusion+ non-small cell lung cancer. J Thorac Oncol. 2018;13:S349–50 **LOXO-292 is a promising targeted agent for RET-rearranged NSCLC patients, for whom there are no RET-selective inhibitors currently FDA approved.**

39. Wang R, Hu H, Pan Y, Li Y, Ye T, Li C, et al. *RET* fusions define a unique molecular and clinicopathologic subtype of non-small-cell lung cancer. J Clin Oncol. 2012;30:4352–9.

40. Nikiforov YE, Nikiforova MN. Molecular genetics and diagnosis of thyroid cancer. Nat Rev Endocrinol. 2011;7:569–80.

41. Ju YS, Lee W-C, Shin J-Y, Lee S, Bleazard T, Won J-K, et al. A transforming KIF5B and RET gene fusion in lung adenocarcinoma revealed from whole-genome and transcriptome sequencing. Genome Res. 2012;22:436–45.

42. Ferrara R, Auger N, Auclin E, Besse B. Clinical and translational implications of RET rearrangements in non-small cell lung cancer. J Thorac Oncol. 2018;13:27–45.

43. Takeuchi K, Soda M, Togashi Y, Suzuki R, Sakata S, Hatano S, et al. RET, ROS1 and ALK fusions in lung cancer. Nat Med. 2012;18:378–81.
44. Gautschi O, Milia J, Filleron T, Wolf J, Carbone DP, Owen D, et al. Targeting RET in patients with RET-rearranged lung cancers: results from the global, Multicenter RET Registry. J Clin Oncol. 2017;35:1403–10.
45. Subbiah V, Velcheti V, Tuch BB, Ebata K, Busaidy NL, Cabanillas ME, et al. Selective RET kinase inhibition for patients with RET-altered cancers. Ann Oncol. 2018;29:1869–76.
46. Nakagawara A. Trk receptor tyrosine kinases: a bridge between cancer and neural development. Cancer Lett. 2001;169:107–14.
47. Vaishnavi A, Capelletti M, Le AT, Kako S, Butaney M, Ercan D, et al. Oncogenic and drug sensitive NTRK1 rearrangements in lung cancer. Nat Med. 2013;19:1469–72.
48. Wang W, Xu C, Zhu Y, Liu Y, Chen Y, Zhang Q, et al. P2.03-09 the real world of NTRK fusion data in the Chinese lung cancer populations: a multicenter study. J Thorac Oncol. 2018;13:S719.
49. Kheder ES, Hong DS. Emerging targeted therapy for tumors with NTRK fusion proteins. Clin Cancer Res. 2018;24:5807–14.
50. Doebele RC, Davis LE, Vaishnavi A, Le AT, Estrada-Bernal A, Keysar S, et al. An oncogenic NTRK fusion in a patient with soft-tissue sarcoma with response to the tropomyosin-related kinase inhibitor LOXO-101. Cancer Discov. 2015;5:1049–57.
51. Farago A, Kummar S, Ibabekci S, Corsi-Travali S, Cruickshank S, Cox M, et al. P1.13-40 rapid, robust and durable responses to Larotrectinib in patients with TRK fusion non-small cell lung Cancer. J Thorac Oncol. 2018;13:S597–8.
52. Research C for DE and. Approved Drugs - FDA approves larotrectinib for solid tumors with NTRK gene fusions [Internet]. [cited 2018 Dec 1]. Available from: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm626720.htm
53. Drilon A, Nagasubramanian R, Blake JF, Ku N, Tuch BB, Ebata K, et al. A next-generation TRK kinase inhibitor overcomes acquired resistance to prior TRK kinase inhibition in patients with TRK fusion-positive solid tumors. Cancer Discov. 2017;7:963–72.
54. Drilon A, Siena S, Ou S-HI, Patel M, Ahn MJ, Lee J, et al. Safety and antitumor activity of the multitargeted Pan-TRK, ROS1, and ALK inhibitor entrectinib: combined results from two phase I trials (ALKA-372-001 and STARTRK-1). Cancer Discov. 2017;7:400–9.
55. Demetri GD, Paz-Ares L, Farago AF, Liu SV, Chawla SP, Tosi D, et al. LBA17 Efficacy and safety of entrectinib in patients with NTRK fusion-positive (NTRK-fp) tumors: pooled analysis of STARTRK-2, STARTRK-1 and ALKA-372-001. Ann Oncol. 2018;29:mdy424.017.
56. Organ SL, Tsao M-S. An overview of the c-MET signaling pathway. Ther Adv Med Oncol. 2011;3:S7–19.
57. Awad MM, Oxnard GR, Jackman DM, Savukoski DO, Hall D, Shivdasani P, et al. *MET* exon 14 mutations in non-small-cell lung cancer are associated with advanced age and stage-dependent *MET* genomic amplification and c-met overexpression. J Clin Oncol. 2016;34:721–30.
58. Drilon A, Cappuzzo F, Ou S-HI, Camidge DR. Targeting MET in lung cancer: will expectations finally be MET? J Thorac Oncol. 2017;12:15–26.
59. Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park JO, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science. 2007;316:1039–43.
60. Bean J, Brennan C, Shih J-Y, Riely G, Viale A, Wang L, et al. MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. PNAS. 2007;104:20932–7.
61. Kong-Beltran M, Seshagiri S, Zha J, Zhu W, Bhawe K, Mendoza N, et al. Somatic mutations Lead to an oncogenic deletion of met in lung Cancer. Cancer Res. 2006;66:283–9.
62. Paik PK, Drilon A, Fan P-D, Yu H, Rekhtman N, Ginsberg MS, et al. Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping. Cancer Discov. 2015;5:842–9.
63. Dong H-J, Li P, Wu C-L, Zhou X-Y, Lu H-J, Zhou T. Response and acquired resistance to crizotinib in Chinese patients with lung adenocarcinomas harboring MET exon 14 splicing alternations. Lung Cancer. 2016;102:118–21.
64. Heist RS, Sequist LV, Borger D, Gainor JF, Arellano RS, Le LP, et al. Acquired resistance to crizotinib in NSCLC with MET exon 14 skipping. J Thorac Oncol. 2016;11:1242–5.
65. Schrock AB, Lai A, Ali SM, Miller VA, Raez LE. Mutation of MET Y1230 as an acquired mechanism of crizotinib resistance in NSCLC with MET exon 14 skipping. J Thorac Oncol. 2017;12:e89–90.
66. Klempner SJ, Borghei A, Hakimian B, Ali SM, Ou S-HI. Intracranial activity of cabozantinib in MET exon 14-positive NSCLC with brain metastases. J Thorac Oncol. 2017;12:152–6.
67. Pillai RN, Behera M, Berry LD, Rossi MR, Kris MG, Johnson BE, et al. HER2 mutations in lung adenocarcinomas: a report from the lung cancer mutation consortium. Cancer. 2017;123:4099–105.
68. Song Z, Yu X, Shi Z, Zhao J, Zhang Y. HER2 mutations in Chinese patients with non-small cell lung cancer. Oncotarget. 2016;7:78152–8.
69. Arcila ME, Chaft JE, Nafa K, Roy-Chowdhuri S, Lau C, Zaidinski M, et al. Prevalence, clinicopathologic associations, and molecular spectrum of ERBB2 (HER2) tyrosine kinase mutations in lung adenocarcinomas. Clin Cancer Res. 2012;18:4910–8.
70. Mazières J, Peters S, Lepage B, Cortot AB, Barlesi F, Beau-Faller M, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. JCO. 2013;31:1997–2003.
71. Mazières J, Barlesi F, Filleron T, Besse B, Monnet I, Beau-Faller M, et al. Lung cancer patients with HER2 mutations treated with chemotherapy and HER2-targeted drugs: results from the European EUHER2 cohort. Ann Oncol. 2016;27:281–6.
72. De Grève J, Teugels E, Geers C, Decoster L, Galdermans D, De Mey J, et al. Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu. Lung Cancer. 2012;76:123–7.
73. Chuang JC, Stehr H, Liang Y, Das M, Huang J, Diehn M, et al. ERBB2-mutated metastatic non-small cell lung cancer: response and resistance to targeted therapies. J Thorac Oncol. 2017;12:833–42.
74. Peters S, Curioni-Fontecedro A, Nechushtan H, Shih J-Y, Liao W-Y, Gautschi O, et al. Activity of Afatinib in heavily pretreated patients with ERBB2 mutation-positive advanced NSCLC: findings from a global named patient use program. J Thorac Oncol. 2018;13:1897–905.
75.• Robichaux JP, Elamin YY, Tan Z, Carter BW, Zhang S, Liu S, et al. Mechanisms and clinical activity of an EGFR and HER2 exon 20-selective kinase inhibitor in non-small cell lung cancer. Nat Med. 2018;24:638–46 **Promising HER2/EGFR exon20ins-selective agent, however skin and GI toxicities are concerning.**
76. Tsurutani J, Park H, Doi T, Modi S, Takahashi S, Nakagawa K, et al. OA02.07 Updated results of phase 1 study of DS-8201a in HER2-expressing or -mutated advanced non-small-cell lung cancer. J Thorac Oncol. 2018;13:S324.
77. Li BT, Shen R, Buonocore D, Olah ZT, Ni A, Ginsberg MS, et al. Ado-trastuzumab emtansine for patients with HER2-mutant lung cancers: results from a phase II basket trial. JCO. 2018;36:2532–7.

78. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13:239–46.
79. Riess JW, Gandara DR, Frampton GM, Madison R, Peled N, Bufill JA, et al. Diverse EGFR exon 20 insertions and co-occurring molecular alterations identified by comprehensive genomic profiling of NSCLC. J Thorac Oncol. 2018;13:1560–8.
80. Kobayashi Y, Mitsudomi T. Not all epidermal growth factor receptor mutations in lung cancer are created equal: perspectives for individualized treatment strategy. Cancer Sci. 2016;107:1179–86.
81. Van Veggel B, Van Der Wekken A, Hashemi S, Cornelissen R, Monkhorst K, Heideman D, et al. P2.13-42 Osimertinib treatment for patients with EGFR exon 20 insertion positive non-small-cell lung cancer. J Thorac Oncol. 2018;13:S815.
82. Hirano T, Yasuda H, Tani T, Hamamoto J, Oashi A, Ishioka K, et al. In vitro modeling to determine mutation specificity of EGFR tyrosine kinase inhibitors against clinically relevant EGFR mutants in non-small-cell lung cancer. Oncotarget. 2015;6:38789–803.
83. Piotrowska Z, Fintelmann FJ, Sequist LV, Jahagirdar B. Response to osimertinib in an EGFR exon 20 insertion-positive lung adenocarcinoma. J Thorac Oncol. 2018;13:e204–6.
84. Riess J, Floch N, Martin M, Orme J, Staniszewska A, Menard L, et al. Antitumor activity of osimertinib in NSCLC harboring EGFR exon 20 insertions. JCO. 2017;35:9030.
85. van Veggel B, de Langen AJ, Hashemi SMS, Monkhorst K, Heideman DAM, Thunnissen E, et al. Afatinib and cetuximab in four patients with EGFR exon 20 insertion-positive advanced NSCLC. J Thorac Oncol. 2018;13:1222–6.
86. Estrada-Bernal A, Doak AE, Le AT, Zhu H, Chen N, Silva S, et al. Abstract A157: antitumor activity of tarloxotinib, a hypoxia-activated EGFR TKI, in patient-derived lung cancer cell lines harboring EGFR exon 20 insertions. Mol Cancer Ther. 2018;17:A157.
87. Rain Therapeutics Closes $18 Million Series A Financing — Rain Therapeutics [Internet]. Rain Thera. [cited 2018 Dec 2]. Available from: https://www.rainthera.com/rain-therapeutics-closes-18-million-series-a-financing/
88. Paik PK, Arcila ME, Fara M, Sima CS, Miller VA, Kris MG, et al. Clinical characteristics of patients with lung adenocarcinomas harboring *BRAF* mutations. J Clin Oncol. 2011;29:2046–51.
89. Villaruz LC, Socinski MA, Abberbock S, Berry LD, Johnson BE, Kwiatkowski DJ, et al. Clinicopathologic features and outcomes of patients with lung adenocarcinomas harboring BRAF mutations in the lung cancer mutation consortium. Cancer. 2015;121:448–56.
90. Tissot C, Couraud S, Tanguy R, Bringuier P-P, Girard N, Souquet P-J. Clinical characteristics and outcome of patients with lung cancer harboring BRAF mutations. Lung Cancer. 2016;91:23–8.
91. Cardarella S, Ogino A, Nishino M, Butaney M, Shen J, Lydon C, et al. Clinical, pathologic, and biologic features associated with BRAF mutations in non-small cell lung cancer. Clin Cancer Res. 2013;19:4532–40.
92. Ascierto PA, McArthur GA, Dréno B, Atkinson V, Liszkay G, Di Giacomo AM, et al. Cobimetinib combined with vemurafenib in advanced BRAFV600-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol. 2016;17:1248–60.
93. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet. 2015;386:444–51.
94. Gautschi O, Milia J, Cabarrou B, Bluthgen M-V, Besse B, Smit EF, et al. Targeted therapy for patients with BRAF-mutant lung cancer results from the European EURAF cohort. J Thorac Oncol. 2015;10:1451–7.
95. Long GV, Stroyakovsky DL, Gogas H, Levchenko E, de Braud F, Larkin JMG, et al. COMBI-d: a randomized, double-blinded, phase III study comparing the combination of dabrafenib and trametinib to dabrafenib and trametinib placebo as first-line therapy in patients (pts) with unresectable or metastatic BRAFV600E/K mutation-positive cutaneous melanoma. JCO. 2014;32:9011.
96. Research C for DE and. Approved Drugs - FDA grants regular approval to dabrafenib and trametinib combination for metastatic NSCLC with BRAF V600E mutation [Internet]. [cited 2018 Nov 7]. Available from: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm564331.htm
97. Yao Z, Torres NM, Tao A, Gao Y, Luo L, Li Q, et al. BRAF mutants evade ERK-dependent feedback by different mechanisms that determine their sensitivity to pharmacologic inhibition. Cancer Cell. 2015;28:370–83.
98. Joshi M, Rice SJ, Liu X, Miller B, Belani CP. Trametinib with or without vemurafenib in BRAF mutated non-small cell lung cancer. PLoS One. 2015;10:e0118210.
99. Dahlman KB, Xia J, Hutchinson K, Ng C, Hucks D, Jia P, et al. BRAF(L597) mutations in melanoma are associated with sensitivity to MEK inhibitors. Cancer Discov. 2012;2:791–7.
100. Kim KB, Kefford R, Pavlick AC, Infante JR, Ribas A, Sosman JA, et al. Phase II study of the MEK1/MEK2 inhibitor trametinib in patients with metastatic *BRAF*-mutant cutaneous melanoma previously treated with or without a BRAF inhibitor. J Clin Oncol. 2013;31:482–9.
101. Zhang C, Spevak W, Zhang Y, Burton EA, Ma Y, Habets G, et al. RAF inhibitors that evade paradoxical MAPK pathway activation. Nature. 2015;526:583–6.
102. Okimoto RA, Lin L, Olivas V, Chan E, Markegard E, Rymar A, et al. Preclinical efficacy of a RAF inhibitor that evades paradoxical MAPK pathway activation in protein kinase BRAF-mutant lung cancer. PNAS. 2016;113:13456–61.
103. Yao Z, Gao Y, Su W, Yaeger R, Tao J, Na N, et al. RAF inhibitor PLX8394 selectively disrupts BRAF dimers and RAS-independent BRAF-mutant-driven signaling. Nat Med. 2018;1 (accepted).
104. Nichols RJ, Haderk F, Stahlhut C, Schulze CJ, Hemmati G, Wildes D, et al. RAS nucleotide cycling underlies the SHP2 phosphatase dependence of mutant BRAF-, NF1- and RAS-driven cancers. Nat Cell Biol. 2018;20:1064–73.
105. Xu G, O'Connell P, Viskochil D, Cawthon R, Robertson M, Culver M, et al. The neurofibromatosis type 1 gene encodes a protein related to GAP. Cell. 1990;62:599–608.
106. Martin GA, Viskoohil D, Bollag G, McCabe PC, Crosier WJ, Haubruck H, et al. The GAP-related domain of the neurofibromatosis type 1 gene product interacts with ras p21. Cell. 1990;63:843–9.
107. Redig AJ, Capelletti M, Dahlberg SE, Sholl LM, Mach S, Fontes C, et al. Clinical and molecular characteristics of NF1-mutant lung cancer. Clin Cancer Res. 2016;22:3148–56.
108. Rasmussen SA, Friedman JM. NF1 gene and neurofibromatosis 1. Am J Epidemiol. 2000;151:33–40.
109. Søsrensen SA, Mulvihill JJ, Nielsen A. On the natural history of von Recklinghausen neurofibromatosis. Ann N Y Acad Sci. 1986;486:30–7.
110.•• Dombi E, Baldwin A, Marcus LJ, Fisher MJ, Weiss B, Kim A, et al. Activity of selumetinib in neurofibromatosis type 1-related plexiform neurofibromas. N Engl J Med. 2016;375:2550–60 **Important trial highlighting the effectiveness of MEK inhibition in NF1, and provided rationale that this approach could be adopted in *NF1*-positive NSCLC.**

111. Gross AM, Wolters P, Baldwin A, Dombi E, Fisher MJ, Weiss BD, et al. SPRINT: phase II study of the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886) in children with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN). JCO. 2018;36:10503.
112. Hayashi T, Desmeules P, Smith RS, Drilon A, Somwar R, Ladanyi M. RASA1 and NF1 are preferentially co-mutated and define a distinct genetic subset of smoking-associated non-small cell lung carcinomas sensitive to MEK inhibition. Clin Cancer Res. 2018;24:1436–47.
113. Neel BG, Gu H, Pao L. The 'Shping news': SH2 domain-containing tyrosine phosphatases in cell signaling. Trends Biochem Sci. 2003;28:284–93.
114. Feng GS, Hui CC, Pawson T. SH2-containing phosphotyrosine phosphatase as a target of protein-tyrosine kinases. Science. 1993;259:1607–11.
115. Bentires-Alj M, Paez JG, David FS, Keilhack H, Halmos B, Naoki K, et al. Activating mutations of the Noonan syndrome-associated SHP2/PTPN11 gene in human solid tumors and adult acute myelogenous leukemia. Cancer Res. 2004;64:8816–20.
116. Matozaki T, Murata Y, Saito Y, Okazawa H, Ohnishi H. Protein tyrosine phosphatase SHP-2: a proto-oncogene product that promotes Ras activation. Cancer Sci. 2009;100:1786–93.
117. Ruess DA, Heynen GJ, Ciecielski KJ, Ai J, Berninger A, Kabacaoglu D, et al. Mutant KRAS-driven cancers depend on PTPN11/SHP2 phosphatase. Nat Med. 2018;24:954–60.
118.• Chen Y-NP, LaMarche MJ, Chan HM, Fekkes P, Garcia-Fortanet J, Acker MG, et al. Allosteric inhibition of SHP2 phosphatase inhibits cancers driven by receptor tyrosine kinases. Nature. 2016;535:148–52 **Demonstrated that SHP2 inhibition is a valid treatment approach for cancers.**
119. Dardaei L, Wang HQ, Singh M, Fordjour P, Shaw KX, Yoda S, et al. SHP2 inhibition restores sensitivity in *ALK*-rearranged non-small-cell lung cancer resistant to ALK inhibitors. Nat Med. 2018;24:512–7.
120. Genentech: Press Releases | Thursday, Nov 18, 2004 [Internet]. [cited 2018 Dec 20]. Available from: https://www.gene.com/media/press-releases/7947/2004-11-18/fda-approves-tarceva-for-patients-with-a