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Targeting oncogenic drivers in lung cancer: Recent progress, current challenges and future opportunities

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ABSTRACT

Targeted therapies have changed the landscape of treatments for non-small cell lung cancer (NSCLC). Specific targeted therapies have been approved for NSCLC patients harboring genetic alterations in four oncogenes, and agents targeting additional oncogenic drivers are under investigation. Standard first-line chemotherapy has been supplanted by these targeted therapies due to superior efficacy and lower toxicity. Despite excellent response rates and durable responses in some cases, most patients experience relapse within a few years due to the development of acquired drug resistance. Next generation targeted therapies are being developed to overcome drug resistance and extend the duration of therapy. In this review, we summarize the current treatment strategies for the major targetable oncogenic mutations/alterations in NSCLC and discuss the mechanisms leading to acquired drug resistance.

Contents

Abbreviations: ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene serine/threonine kinase; CNS, central nervous system; EGFR, Epidermal growth factor receptor; FDA, Food and Drug Administration; KRAS, KRAS proto-oncogene GTPase; L858R, L858R substitution; MET, MET proto-oncogene receptor tyrosine kinase; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD-1, programmed cell death 1 protein; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; RET, Ret proto-oncogene; ROS1, ROS proto-oncogene 1 receptor tyrosine kinase; TKI, tyrosine kinase inhibitor; TRK, tropomyosin-related kinase; 19 Del, deletion in exon 19.

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1. Introduction

Since the groundbreaking work in the early 2000's that linked specific mutations in the tyrosine kinase domain of the epidermal growth factor receptor (*EGFR*) gene to exceptional responses to EGFR tyrosine kinase inhibitors, personalized therapeutic approaches have dramatically changed the management of advanced non-small cell lung cancer (NSCLC). This initial discovery inspired subsequent efforts to identify other actionable subsets ultimately leading to FDA approval of drugs targeting four unique molecular drivers –EGFR, anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 receptor tyrosine kinase (ROS1), and proto-oncogene B-Raf (BRAF)—and development of investigational drugs with promising anti-tumor activity against other oncogenes (Table 1). For several of these targets (e.g., EGFR and ALK), large phase 3 studies have shown that upfront treatment with targeted therapy induces more profound responses and improves survival relative to chemotherapy. Although similar studies have not been conducted for rarer molecular subsets, phase 2 studies have reported equally durable responses suggesting that targeted therapies should be prioritized when available. The remarkable success of personalized treatments in NSCLC is also attributable to the molecular advances that enabled identification of sensitizing alterations and the robust translational studies that have uncovered the molecular mechanisms that drive resistance to treatment. Indeed, the simultaneous study of sensitivity and resistance has propelled rapid development of potent and highly-effective next-generation inhibitors. With sequential use of increasingly potent targeted therapies, patients with NSCLC now live up to 3-4 years compared to 1 year for those without targetable mutations. However, despite these remarkable gains, targeted therapies rarely produce cures and nearly all patients with NSCLC will eventually succumb to their disease.

The effectiveness of targeted therapies is rooted in the biological phenomenon of "oncogene addiction" (Weinstein, 2002). Despite multiple genetic and epigenetic alterations within cancer cells, these cancers harbor one dominant oncogenic driver that is critical for tumor initiation and maintenance of the malignant phenotype. This notion has been supported by functional studies using transgenic mouse models with single driver oncogenes (Li et al., 2007; Politi et al., 2006; Soda et al., 2008) and by more recent genomic studies demonstrating early clonal emergence of these driver mutations (e.g. EGFR, MET, BRAF) in lung cancer evolution in the clinic (Jamal-Hanjani et al., 2017). There are three main types of genomic alterations that lead to activation of driver oncogenes; activating mutations (e.g. EGFR, BRAF), gene amplifications (e.g. MET, HER2) and gene fusions (e.g. ALK, ROS1). These result in constitutive activation of downstream growth and survival signaling pathways (e.g. MAPK, PI3K) that are normally tightly controlled in normal cells (Fig. 1). Cancers become "addicted" to these hyperactivated signaling pathways, thus inhibition of the single driver is sufficient to suppress tumor growth and induce apoptosis, the latter being a critical feature of effective targeted therapies (Faber et al., 2011). Indeed, the clinical success of targeted therapies has been the ultimate confirmation of this concept (Weinstein & Joe, 2008).

The past decade of experience with targeted therapies has also been a humbling reminder of the ability of NSCLC to adapt under therapeutic selective pressure. The insights gained have inspired a new wave of therapeutic approaches that seek to extinguish resistance in its infancy through early introduction of the most potent therapies and investigation of combinatorial strategies. In this review, we summarize the current treatment strategies for targetable drivers in NSCLC, discuss the mechanisms that mediate acquired resistance to these drugs, and preview emerging data that is driving a paradigm shift of how targeted therapies are being deployed in the clinic.

Table 1
Targetable mutations and FDA-approved drugs in NSCLC.

Targetable oncogene	Incidence	FDA-approved drugs
EGFR	15%	Erlotinib, gefitinib, afatinib, osimertinib
EGFR/HER2 exon 20 insertion	1%	
ALK	5%	Crizotininb, ceritinib, alectinib, brigatinib
ROS1	1–2%	Crizotinib
BRAF V600E	1%	Dabrafenib and trametinib combination
RET	1–2%	
TRK	<1%	
MET exon 14 skipping	2%	
KRAS	15-20%	

2. EGFR

Although EGFR tyrosine kinase inhibitors (TKIs) are now exclusively used for patients with NSCLCs that harbor sensitizing *EGFR* mutations, these drugs were initially developed for an unselected patient population based on the observation that a significant proportion of NSCLCs expressed EGFR (Fukuoka et al., 2003; Herbst et al., 2002). In early studies that explored EGFR TKIs unselected NSCLC patients, the overall activity of these drugs was largely disappointing (Gatzemeier et al., 2007; Giaccone et al., 2004; Herbst et al., 2004; Herbst et al., 2005; Kim et al., 2008; Maruyama et al., 2008; Shepherd, et al., 2005; Thatcher et al., 2005). However, erlotinib was initially approved in the United States for use in unselected patients after failure on chemotherapy based on a phase 3 trial (BR.21) demonstrating a small but significant improvement in survival compared with placebo (Shepherd, et al., 2005). Of note, based on subsequent data showing no benefit in patients with wild-type *EGFR*, this indication was subsequently limited in 2016 to only patients harboring *EGFR* mutations (Cicenas et al., 2016; Kawaguchi et al., 2014). Despite the overall failure of these early studies, it was noted that there was a small subgroup of patients–typically young, East Asian women with little or no smoking history–who experienced dramatic responses (Fujiwara et al., 2003). Analysis of tumor specimens from responders led to the discovery of an association between the presence of activating *EGFR* kinase domain mutations and response to EGFR TKIs (Lynch et al., 2004; Paez et al., 2004). Subsequent studies have shown that *EGFR* mutations occur in approximately 15% of NSCLCs in Western populations (Kris et al., 2014; Sholl et al., 2015) and most commonly involve an in-frame deletion in exon 19 (19 Del) or an L858R substitution in exon 21 (L858R). In phase 2 studies that exclusively enrolled patients with NSCLC harboring these mutations, treatment with EGFR TKIs resulted in an objective response rate (ORR) of 65%-78% and progression-free survival (PFS) of 8.9–9.7 months (Asahina et al., 2006; Inoue et al., 2006; Morita et al., 2009; Sequist et al., 2008; Sutani et al., 2006). These dramatic and durable responses were reproduced in phase 3 studies that also demonstrated that first-line treatment with gefitinib or erlotinib was superior to chemotherapy (62-83% vs. 18-47% as ORR and 9.2-13.1 months vs. 4.6-6.3 months as PFS) (Maemondo, et al., 2010; Mitsudomi et al., 2010; Mok et al., 2009; Rosell, et al., 2012; Zhou et al., 2011). Importantly, the IPASS trial demonstrated the importance of molecular genotyping to determine *EGFR* mutation status in order to select therapy, showing that EGFR inhibitors were inferior to chemotherapy in patients with similar clinical and demographic characteristics but who lacked activating *EGFR* mutations (Mok et al., 2009). These studies led to the approvals of erlotinib in 2013 and gefitinib in 2014 for first-line treatment of metastatic NSCLC patients whose tumors were positive for *EGFR* 19 Del or L858R mutations.

Despite dramatic and sometimes durable responses to these first-generation EGFR TKIs, patients invariably develop acquired resistance. The most common mechanism of resistance is a secondary single base substitution in *EGFR* exon 20, resulting in a T790M mutation (Kobayashi et al., 2005; Pao et al., 2005). T790M is seen in almost half of biopsies from tumors with resistance to first-generation EGFR TKIs

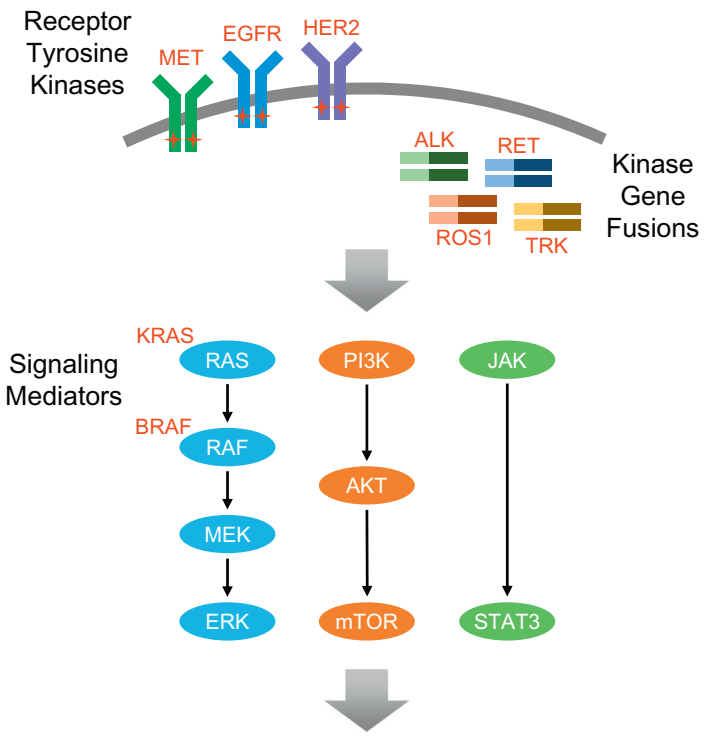

Fig. 1. Major oncogenic drivers in NSCLC. Activating genetic alterations in driver oncogenes (shown in red) lead to constitutive activation of downstream growth and survival signaling pathways.

(Sequist et al., 2011; Yu et al., 2013). This gatekeeper mutation decreases drug potency by increasing the ATP affinity of the mutated EGFR and hindering drug binding (Yun et al., 2008). To overcome resistance caused by T790M mutations, a class of irreversible inhibitors that covalently bind to C797 in EGFR was developed (Zhou et al., 2009). Afatinib, an irreversible second-generation EGFR inhibitor that is potent against the L858R/T790M and 19 Del/T790M compound mutations in preclinical models (Li et al., 2008), demonstrated only a 7% response rate in patients relapsing on gefitinib or erlotinib in a phase 2/3 study (LUX Lung 1); moreover, the drug was not well tolerated (Miller et al., 2012). The limited efficacy of afatinib against T790M and poor tolerability of the drug have been attributed to a narrow therapeutic window resulting from the fact that the concentration of afatinib required to inhibit T790M in patients exceeds the concentration at which the drug inhibits wild-type EGFR (Hirano et al., 2015). Due to increased selectivity of afatinib for EGFR 19 Del or L858R relative to wild-type EGFR, it is better tolerated as a first-line treatment where lower doses can be used. In phase 3 studies, first-line treatment with afatinib had superior ORR (56% vs. 23%) and PFS (11.1 months vs. 6.9 months) compared to chemotherapy (Sequist et al., 2013), leading to its approval for first-line treatment of metastatic NSCLC harboring *EGFR* 19 Del or L858R mutations in 2013. Another second-generation EGFR inhibitor, dacomitinib, has also shown promising clinical activity in a phase 3 trial (ARCHER 1050), with a superior PFS (14.7 months vs. 9.2 months) and a superior overall survival (34.1 months vs. 26.8 months) relative to gefitinib in the first-line setting (Mok et al., 2018; Wu et al., 2017).

Due to the limitations in inhibiting T790M posed by the narrow therapeutic window of second generation inhibitors, third-generation EGFR inhibitors were developed that potently and irreversibly inhibit EGFR 19 Del/T790M and L858R/T790M, yet exhibit low affinity for wild-type EGFR (Cross et al., 2014). The initial phase 1 study of osimertinib (AURA) demonstrated an impressive ORR of 61% and PFS of 9.6 months in patients with EGFR T790M-positive NSCLC after progression on first-line EGFR inhibitor therapy (Janne et al., 2015), In addition, osimertinib demonstrated a favorable toxicity profile compared with first and second-generation EGFR TKIs, with less skin rash and diarrhea that result from inhibition of wild-type EGFR. Subsequent phase 2 (AURA extension, AURA 2) confirmed response rates of 60-70% in T790M-positive patients (Goss et al., 2016; Yang et al., 2017) and led to the accelerated approval of osimertinib for these patients in 2015. Osimertinib received full approval for treatment of T790M-positive patients after progression on first-line EGFR inhibitor therapy in 2017 based on a phase 3 trial (AURA 3) demonstrating superiority over chemotherapy (71% vs. 31% as ORR and 10.1 months vs. 4.4 months as PFS) (Mok et al., 2017). Moreover, osimertinib was shown to have excellent central nervous system (CNS) penetration leading to CNS ORR and disease control rate of 54% and 92%, respectively (Goss et al., 2018).

Although osimertinib was largely developed to inhibit EGFR L858R/T790M and 19 Del/T790M compound mutations, it is also a highly potent inhibitor of EGFR 19 Del and L858R in the absence of T790M (Cross et al., 2014).This property, coupled with its ability to spare wild-type EGFR and penetrate the CNS, suggested that osimertinib might be an optimal drug for first-line treatment as well. Indeed, a phase 3 clinical trial (FLAURA) comparing osimertinib to first-line EGFR TKIs (gefitinib or erlotinib) reported a significant improvement in PFS with osimertinib (18.9 months. vs. 10.2 months) (Soria et al., 2018). These findings established osimertinib as the new standard of care and prompted the approval of osimertinib for the first-line treatment of metastatic EGFR-mutant NSCLC in 2018.

As mentioned above, *EGFR* T790M is not detected in approximately one-half of patients progressing on first-generation EGFR TKIs. In contrast to the established role of third-generation inhibitors like osimertinib for addressing T790M-mediated resistance, strategies to overcome other resistance mechanisms are still being developed. Activation of bypass signaling pathways through copy number gain or activating mutations is a common off-target resistance mechanism. *MET* amplification, the first bypass signal reported in TKI-resistant EGFR-mutant NSCLC, has been observed in approximately 5% of cases progressing

on gefitinib or erlotinib (Engelman et al., 2007; Yu et al., 2013). Similarly, *HER2* amplification has been detected in approximately 10% of cases (Takezawa et al., 2012). In addition to these amplification events, activating mutations in *BRAF* or *PIK3CA* have been detected in up to 1-2% of tumors (Ohashi et al., 2012; Sequist et al., 2011). Drug combination approaches that target bypass signaling pathways, such as combination EGFR and MET inhibitors, are currently being investigated in clinical trials. In a subset of cases lacking T790M mutations and activation of bypass signaling, phenotypic transformation has been observed (Yu et al., 2013). For example, small-cell transformation and epithelial-to-mesenchymal transition are observed in an estimated 10% and 1-2% biopsies from patients progressing on treatment with first-generation EGFR TKIs, respectively (D. R. Camidge, Pao, & Sequist, 2014; Sequist et al., 2011; Suda et al., 2011; Yu et al., 2013). EGFR-mutant NSCLC that undergo small cell transformation share key molecular features with classic small cell lung cancers and, thus, may respond to similar chemotherapy regimens (Niederst et al., 2015).

Widespread use of osimertinib as first-line treatment may change the spectrum of resistance mechanisms. Specifically, T790M is not expected to emerge at resistance since the drug effectively targets this mutation. Preclinical studies and analysis of clinical specimens from patients who have progressed after sequential treatment with first- and third-generation EGFR TKIs demonstrated that acquisition of a tertiary C797S mutation (i.e., L858R/T790M/C797S or 19 Del/T790M/C797S) confers resistance to third-generation EGFR TKIs like osimertinib in some patients (Niederst et al., 2015; Thress et al., 2015), and C797S mutations have also been observed in patients progressing on first-line osimertinib (Ramalingam et al., 2018). In other patients treated with third-generation EGFR inhibitors after the development of T790M, resistant T790 wild-type clones emerged, supporting the notion that both off-target and on-target resistance mechanisms can co-exist, with therapeutic exposures influencing which clonal populations will prevail (Piotrowska et al., 2015; Thress et al., 2015).

3. EGFR/HER2 exon 20 insertion

EGFR exon 20 insertion mutations are the third most common type of *EGFR* mutation encountered in NSCLC. These mutations are present in 4-9% of EGFR-mutant NSCLCs and confer intrinsic resistance to gefitinib and erlotinib (Yasuda et al., 2013; Yasuda, Kobayashi, & Costa, 2012). Osimertinib's activity against exon 20 insertions is being explored in ongoing clinical trials. Interestingly, poziotinib, a drug that was initially being developed for the more common *EGFR* mutations and is capable of fitting into the smaller binding pocket that results from the exon 20 insertion alteration, has demonstrated impressive efficacy in patients with *EGFR* exon 20 insertions. In a preliminary analysis of a phase 2 study which included 11 patients with *EGFR* exon 20 insertions, 64% of patients experienced objective response (Robichaux et al., 2018). Notably, analogous exon 20 insertions involving the *HER2* gene are present in 1-2% of NSCLCs (Arcila et al., 2012; Kris et al., 2014; Mazieres et al., 2013). Studies suggest that NSCLCs with *HER2* exon 20 insertions may respond to therapies originally developed for the treatment of *HER2*-amplified breast cancer (Mazieres et al., 2016). Poziotinib was also effective against the *HER2* exon 20 insertion in preclinical models and a patient treated in the phase 2 study (Robichaux et al., 2018).

4. ALK

Anaplastic lymphoma kinase (ALK) rearrangements are seen in approximately 5% of NSCLCs (Kris et al., 2014; Sholl et al., 2015). In 95% of ALK-rearranged NSCLCs, ALK is fused to EML4 through a translocation involving chromosome 2 (Lin, Zhu, et al., 2018). The promoter and oligomerization domain of EML4 mediate aberrant expression and ligand-independent activation of ALK (Soda et al., 2007). In 2011, the FDA approved the first-generation ALK TKI, crizotinib for treatment of chemotherapy-resistant ALK-rearranged NSCLC based on an ORR of 50-61% in phase 1 and 2 studies (PROFILE 1001 and 1005) (Camidge et al., 2012; Kwak et al., 2010). Subsequent phase 3 studies demonstrated that crizotinib was superior to chemotherapy in TKI-naïve patients across all lines of therapy (Shaw et al., 2013; Solomon et al., 2014). In the front-line setting, crizotinib improved PFS from 7.0 to 10.9 months and ORR from 45% to 74% compared to chemotherapy. These studies established crizotinib as the preferred first-line treatment for ALK-rearranged NSCLC.

Despite durable responses, a majority of patients relapse within a year of initiating crizotinib. In the largest series to date evaluating molecular mediators of crizotinib resistance, acquired mutations in the *ALK* tyrosine kinase domain were detected in 20% of crizotinib-resistant clinical specimens and *ALK* amplification was identified in 8% of resistant tumors (Gainor et al., 2016). In addition to these on-target mechanisms, off-target mechanisms (e.g., activation of EGFR and other bypass signaling pathways, epithelial-to-mesenchymal transformation, small cell lung cancer transformation) have been described (Cha, Cho, Kim, Lee, & Shim, 2016; Katayama et al., 2012; Kim et al., 2013). The pharmacological screen using patient-derived resistant cell lines identified EGFR and Src as canonical bypass signaling pathways in ALK-rearranged NSCLCs (Crystal et al., 2014). Similarly, IGF1R or other members of HER family were found as bypass signaling pathways and the combination therapies which target ALK and bypass signaling pathways were proposed to overcome off-target resistance mechanisms by using the preclinical models (Lovly et al., 2014; Miyawaki et al., 2017; Tanizaki et al., 2012).

More potent and selective second-generation ALK TKIs (ceritinib, alectinib, and brigatinib) have been subsequently developed and approved for treatment of crizotinib-refractory ALK-rearranged NSCLC (Kim et al., 2017; Shaw, Gandhi, et al., 2016; Shaw et al., 2014). Second-generation ALK TKIs induce responses in approximately 50% of patients who have progressed on crizotinib and result in disease stabilization for the majority of remaining patients confirming that ALK-rearranged NSCLCs that relapse on crizotinib remain addicted to ALK signaling. Interestingly, the structural differences of the second-generation ALK TKIs lead to distinct resistance profiles (Gainor, Dardaei, et al., 2016). As a result, approximately 50% of tumors progressing on a second-generation ALK TKI will harbor an *ALK* resistance mutation, but the spectrum of resistance mutations differs for each TKI; the most common mutation encountered, *ALK* G1202R, is highly-refractory and confers resistance to multiple second-generation TKIs (Gainor, Dardaei, et al., 2016). The increased contribution of *ALK* mutations to resistance to second-generation ALK TKIs relative to crizotinib supports the notion that more potent TKIs exert greater selective pressure.

The efficacy of second-generation ALK TKIs in the post-crizotinib setting generated significant interest in testing these drugs in the first-line setting. In the ASCEND-4 study, median PFS with first-line ceritinib was 16.6 months compared to 8.1 months with chemotherapy. Although these impressive findings led to expansion of ceritinib's label to include upfront treatment, the use of chemotherapy as a control is outdated and frequent side effects—including gastrointestinal side effects in more than two-thirds of patients—have limited uptake of ceritinib for first-line treatment (Soria et al., 2017). A recent phase 3 trial comparing alectinib to crizotinib in the first-line setting demonstrated a markedly superior PFS with alectinib (34.8 months vs. 10.9 months) (Camidge et al., 2018; Peters et al., 2017), leading to an approval of alectinib as first-line treatment.

The highly potent and selective third-generation ALK TKI lorlatinib, a drug designed to overcome the *ALK* mutations implicated in first- and second-generation TKI resistance (Johnson et al., 2014), is now in clinical trials. Lorlatinib can overcome all clinically-observed single *ALK* resistance mutations including the G1202R mutation (Zou et al., 2015). In a phase 1 trial of lorlatinib, 46% of patients who had received two or

more TKIs responded to lorlatinib (Shaw et al., 2017). Whereas no single *ALK* mutation has been shown to cause resistance to lorlatinib, early studies of lorlatinib-resistant cases have implicated compound mutations (i.e. two or more *ALK* mutations) in lorlatinib resistance (Shaw et al., 2016; Yoda et al., 2018). Preclinical models suggest that these compound mutations arise through selective pressure after sequential treatment with first-, second-, and third-generation ALK TKIs. This raises the question of whether a future strategy of first-line lorlatinib, which is currently being tested in clinical trials, might prevent resistance mutations from developing (see 12. Up-front treatment with next-generation drugs).

In current clinical practice, alectinib is the most commonly used TKI for first-line treatment for ALK-rearranged lung cancers. However, since alectinib has only recently been established as a first-line treatment option, there are no clinical data to guide second-line treatment in patients who have progressed on first-line alectinib. In an analysis of cases resistant to both alectinib and crizotinib, 29% harbored a solvent front G1202R mutation and another 12% harbored an I1171T/N/S mutation (Gainor, Dardaei, et al., 2016). These mutations are also expected to emerge with first-line treatment. Recent studies have demonstrated efficacy of other ALK TKIs against mutations that cause resistance to alectinib. For instance, lorlatinib is active against G1202R (Shaw et al., 2017), and ceritinib, brigatinib, or lorlatinib are options for I1171T/N/S (Gainor, Dardaei, et al., 2016; Ou et al., 2015). In cases relapsing on alectinib without *ALK* mutations, subsequent treatment with other ALK inhibitors may not be beneficial due to dependence on off-target mechanisms (i.e. ALK-independent resistance) (Shaw et al., 2017), and chemotherapy or investigational combination therapies may be considered. One promising future strategy may be the combination of an ALK TKI and a SHP2 inhibitor, given that the SHP2 phosphatase appears to be a common targetable node in ALK-rearranged NSCLC cell lines which harbor different bypass signaling resistance mechanisms (Dardaei et al., 2018). Significantly, this therapeutic strategy may represent an effective clinical approach that does not require determination of the specific bypass signaling pathways in each patient. ALK-rearranged NSCLCs exposed to multiple ALK TKIs—and in particular those treated with lorlatinib after progression on other ALK TKIs—are at risk for developing compound *ALK* mutations. Although the majority of compound mutations described to date are not predicted to respond to any of the commercially available ALK TKIs, the subset of compound mutations that include the L1198F mutation may respond to crizotinib (Shaw, Friboulet, et al., 2016). In cases that lack *ALK* mutations after progression on one or more next-generation ALK TKIs, treatment with additional ALK TKIs is unlikely to be effective (Fig. 2).

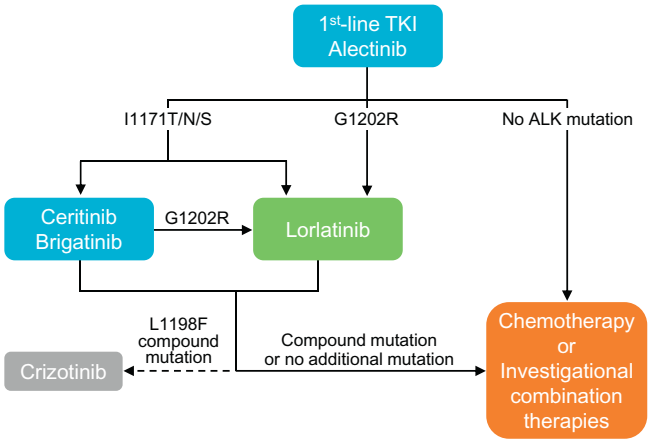

Fig. 2. Schema for the current clinical approach to ALK-rearranged NSCLC. A rational approach to sequencing treatment for patients with NSCLC harboring ALK rearrangement beginning with alectinib as a first-line treatment. Second-line and subsequent lines of therapy can be tailored to the acquired mechanism of resistance.

5. ROS1

ROS1 rearrangements are identified in 1% to 2% of NSCLC patients (Bergethon et al., 2012; Rikova et al., 2007). The most frequent fusion partner is CD74 (40-45%), but a larger number of fusion partners have been identified in ROS1-rearranged NSCLC than ALK-rearranged NSCLC (Lin & Shaw, 2017). Crizotinib, a multitargeted TKI that potently targets ROS1, is the only FDA-approved therapy for treatment of ROS1-rearranged NSCLC. Approval was based on an expansion cohort of the PROFILE 1001 phase 1 study where crizotinib induced an ORR of 72% with a PFS of 19.2 months (Shaw et al., 2014). Subsequent larger studies have confirmed that crizotinib treatment results in very durable responses (Wu et al., 2018).

Despite impressive responses, most patients will relapse within 2 years. In the largest cohort of crizotinib-resistant ROS1-rearranged NSCLC cases, 53% of the tumors harbored *ROS1* mutations (i.e., on-target resistance) (Gainor et al., 2017). The most frequently observed resistance mutation was the solvent front G2032R, which is analogous to *ALK* G1202R. The multitargeted TKI cabozantinib has preclinical activity against the solvent front mutations that have been identified at crizotinib resistance, including G2032R and D2033N (Katayama et al., 2015). Of note, cabozantinib salvaged treatment response in a patient who acquired a *ROS1* D2033N resistance mutation after treatment with crizotinib (Drilon et al., 2016). However, cabozantinib can be difficult drug to tolerate, which has limited its clinical use (Drilon et al., 2016). Lorlatinib is also a potent inhibitor of ROS1. Of the 12 patients with ROS1-rearranged NSCLC in a phase 1 study of lorlatinib, six achieved a confirmed partial response; two of these responders had previously received crizotinib (Shaw et al., 2017). The activity of lorlatinib against the most common resistance mutation, G2032R, is still under investigation. In preclinical studies, the concentration of lorlatinib required to inhibit G2032R is more than 100-fold higher than what is necessary to inhibit non-mutant ROS1 (Chong et al., 2017; Zou et al., 2015). TPX-0005 is an investigational ALK/ROS1/TRK inhibitor designed to overcome ROS1 G2032R (Cui et al., 2017), and is currently being investigated in clinical trials.

6. BRAF

BRAF alterations are present in approximately 2-4% of NSCLCs, with one-half being the classic V600E mutation and the other half being non-V600E mutations (Kris et al., 2014; Paik et al., 2011; Sholl et al., 2015). Experience with BRAF-mutant melanoma has heavily influenced management of BRAF-mutant NSCLC. Approximately 40 to 60% of melanomas harbor BRAF mutations, and 90% of these mutations are V600E (Davies et al., 2002; Hauschild et al., 2012). Dabrafenib was developed to selectively target BRAF monomers, a signaling mechanism unique to V600E-mutated BRAF, and succeeded in melanoma clinical trials (Hauschild et al., 2012). Further studies demonstrating that combination therapies increased efficacy and improved tolerability established the combination of BRAF inhibitors and MEK inhibitors as standard of care treatment for metastatic melanoma (Larkin et al., 2014; Robert et al., 2015). In chemotherapy-pretreated patients with NSCLCs harboring *BRAF* V600E, the combination of dabrafenib plus trametinib (MEK inhibitor) had an ORR of 64% (Planchard et al., 2017), whereas dabrafenib monotherapy had an ORR of 33% (Planchard et al., 2016). Median PFS was 9.7 months with the doublet vs. 5.5 months with dabrafenib monotherapy. Based on this, the combination of dabrafenib and trametinib was approved for treatment of patients with metastatic NSCLC whose tumors have *BRAF* V600E mutations. The efficacy of dabrafenib/trametinib in treatment-naïve patients is similar to that of chemotherapy-pretreated patients (median PFS 10.9 months and ORR 64%). Although molecular mechanisms underlying resistance to combination therapy are still being investigated, a recent case report identified an *NRAS* Q61K mutation in a patient progressing on dabrafenib/trametinib

suggesting that like melanoma and colorectal cancer, acquired MAPK pathway alterations may be key mediators of resistance (Abravanel, Nishino, Sholl, Ambrogio, & Awad, 2018).

7. RET

RET-rearrangements are seen in 1% to 2% of NSCLCs (Kohno et al., 2012; Lipson et al., 2012). The most frequent fusion partner is KIF5B (72%) (Gautschi et al., 2017). At this time, no drugs have been approved for RET-rearranged NSLCLs. However, several multi-targeted RET inhibitors (cabozantinib, lenvatinib, and vandetanib) have been approved for medullary thyroid cancer, which commonly harbors activating *RET* point mutations (Mulligan, 2014). In phase 2 clinical studies, cabozatinib and vandetanib elicited ORRs of 28% and 18%-47%, respectively, in NSCLC patients (Drilon, Rekhtman, et al., 2016; Lee et al., 2017; Yoh et al., 2017). As these multi-kinase inhibitors were originally developed to target other kinases and repurposed to treat RET-rearranged NSCLCs, they are associated with significant toxicity and lower ORR than the personalized therapies used for other molecular subsets (e.g. ALK, ROS1, EGFR). The combination of vandetanib and everolimus has been explored as a strategy to overcome resistance to monotherapy with multikinase inhibitors. In a phase 1 study of the combination, responses were observed in five patients with RET-rearranged NSCLC (Cascone et al., 2016). As many of the side effects of the multikinase inhibitors are related to concurrent inhibition of VEGFR, there have been efforts to develop RET TKIs that spare VEGFR. RXDX-105 is an investigational, VEGFR-sparing multikinase inhibitor with potent activity against RET in preclinical models that demonstrated durable extracranial and intracranial activity in a patient with RET-rearranged NSCLC (Li et al., 2017).

Recently, multiple selective RET inhibitors have entered clinical trials. The selectivity for RET combined with the sparing of VEGFR is expected to significantly improve efficacy and tolerability over the prior multi-targeted kinase inhibitors. BLU-667 is a RET-selective inhibitor developed to target *RET* mutations—including gatekeeper mutations—as well as the most common *RET* fusions. BLU-667 has increased potency against *RET* alterations in preclinical models compared to multikinase inhibitors (Subbiah et al., 2018). In a preliminary analysis of an ongoing phase 1 study which included 19 patients with NSCLC with *RET* fusions, an ORR of 50% was observed among 14 evaluable NSCLC patients, including heavily pretreated patients who had received prior RET-targeting agents (Subbiah et al., 2018 AACR annual meeting). Similarly, another potent and selective RET inhibitor, LOXO-292, has demonstrated impressive activity and tolerability in a phase I study, with an ORR of 65% in RET-rearranged NSCLC, as well as CNS responses in several patients (Drilon et al., 2018).

8. TRK

The tropomyosin-related kinase (TRK) proteins TrkA, TrkB and TrkC are receptor tyrosine kinases encoded by *NTRK1*, *NTRK2* and *NTRK3*. Oncogenic TRK fusions occur in a variety of tumor types—including virtually all mammary secretory analogue salivary gland carcinomas—but are quite rare in lung cancer (Vaishnavi, Le, & Doebele, 2015). Indeed, one study which screened 1378 NSCLCs only identified *NTRK* rearrangements in 0.1% of cases (Farago et al., 2015). To date, two studies have reported results from early phase studies investigating the efficacy of novel drugs designed to inhibit TRK in addition to ALK and ROS1. These studies have predominantly included patients with other tumor types but results for the handful of lung cancer patients included have been encouraging. For example, treatment with entrectinib led to complete intracranial response and durable extracranial response lasting longer than 15 months in a patient with NSCLC harboring SQSTM1-NTRK1 fusion (Farago et al., 2015). An ORR of 75% was observed among 55 patients with a variety of tumor types treated with larotrectinib in a phase 1 study, which included 4 patients with NSCLC (Drilon et al., 2018). In addition to establishing the remarkable efficacy of larotrectinib, this study provided insight into the mechanisms that drive resistance to therapy. Specifically, the analysis demonstrated that kinase domain mutations involving the *NTRK* gene are a major contributor to resistance.

9. MET exon 14 skipping

Somatic mutations in splice sites of exon 14 promote RNA-splicing-based skipping of *MET* exon 14, which increases MET stability by allowing the protein to escape from ubiquitin-mediated degradation. Genetic alterations leading to *MET* exon 14 skipping occur in approximately 2-3% of NSCLC and are particularly enriched in tumors with adenosquamous or sarcomatoid histology (Schrock et al., 2016). *MET* skipping alterations predict for sensitivity to MET-directed drugs. For example, ten (66%) of the first 15 patients treated with crizotinib in an expansion cohort of the PROFILE 1001 study achieved a response to therapy (Drilon et al., 2016). Case reports also demonstrate that cabozantinib and the investigational MET TKIs glesatinib and capamatinib are effective therapies for NSCLCs harboring this alteration (Engstrom et al., 2017; Paik et al., 2015). As observed with other molecular drivers, preclinical studies and case reports suggest that acquired tyrosine kinase domain mutations are critical mediators of resistance to MET inhibition (Engstrom et al., 2017; Heist et al., 2016; Schrock, Lai, Ali, Miller, & Raez, 2017). These mutations most often arise at the D1228 and Y1230 residues. Although these mutations confer resistance to type I MET inhibitors (e.g. crizotinib and capmatinib), they are still sensitive to inhibition with type II inhibitors like glesatinib and cabozantinib (Bahcall et al., 2016; Engstrom et al., 2017).

10. KRAS

Even though *KRAS* activating mutations were initially described in lung cancer cell lines 35 years ago (Shimizu et al., 1983) and 25-30% of NSCLC harbor *KRAS* mutations, KRAS remains an elusive target. In most of NSCLC cases, mutations occurred in exon 2; G12C (39%), G12D (17%), or G12V (21%) (Yu et al., 2015). Given that KRAS is farnesylated to translocate to the cell membrane and become active, farnesyl transferase inhibitors have been investigated for treatment of this disease. Although effective in mouse models (Gunning et al., 2003), farnesyl transferase inhibitors lacked activity in clinical trials (Riely et al., 2011). Attempts to target effectors downstream of KRAS including BRAF, MEK-ERK or PI3K-AKT have also been underwhelming (Papadimitrakopoulou et al., 2016), and combination therapies have been limited by toxicity. Direct inhibition of KRAS was thought to be impossible due to the lack of clear druggable pockets. However, a discovery of an allosteric pocket of KRAS led to development of an allosteric G12C-mutant-specific inhibitor, which stabilizes KRAS in an inactive form (Lito, Solomon, Li, Hansen, & Rosen, 2016; Ostrem, Peters, Sos, Wells, & Shokat, 2013). These drugs have shown promising results in the preclinical models and are expected to enter clinical trials soon (Janes et al., 2018). Preclinical studies have suggested that a significant proportion of KRAS-mutant cancers may be not be dependent on KRAS signaling (Singh et al., 2009), however the clinical significance of these findings remains to be determined.

11. Immunotherapy and targeted therapies

The development of immunotherapies targeting the programmed cell death 1 protein (PD-1) and the programmed cell death ligand 1 (PD-L1) has a major impact on the treatment of NSCLC. Phase 3 trials comparing single-agent immunotherapies with docetaxel initially established two anti-PD-1 antibodies (nivolumab and pembrolizumab) and an anti-PD-L1 antibody (atezolizumab) as second-line therapy of advanced NSCLC (Borghaei et al., 2015; Herbst et al., 2016; Rittmeyer, et al., 2017). Both tumor cell PD-L1 expression level and tumor mutation

burden have been associated with improved objective response, durable clinical benefit, and progression-free survival to PD-1 blockade (Borghaei et al., 2015; Fehrenbacher, et al., 2016; Garon et al., 2015; Herbst et al., 2016; Rizvi et al., 2015). More recently, first-line pembrolizumab has demonstrated improved survival in NSCLC patients (excluding those with *EGFR* mutations or *ALK* translocations), either as monotherapy for patients with PD-L1 expression greater than 50% (KEYNOTE-024) or in combination with chemotherapy irrespective of PD-L1 expression level (KEYNOTE-189, KEYNOTE-407) (Gandhi et al., 2018; Paz-Ares et al., 2018; Reck et al., 2016) (Brahmer et al., 2017 IASLC 18th WCLC).

One major caveat to the success of anti-PD-1/PD-L1 immunotherapies is that most of the major recent trials have excluded patients with sensitizing *EGFR* mutations or *ALK* translocations. Because these patients are typically light or never-smokers, tumor mutation burden and immune infiltration in these tumors is typically low, and consistent with this, responses to PD-1/PD-L1 inhibitor monotherapy are infrequent (Borghaei et al., 2015; Gainor et al., 2016). A recent meta-analysis of second-line PD-1/PD-L1 inhibitors showed no benefit compared to docetaxel in EGFR-mutant patients (Lee et al., 2018), and a recent phase II study of first-line pembrolizumab in EGFR-mutant patients was closed early due to a response rate of zero in the first ten patients, despite high PD-L1 expression (Lisberg et al., 2018). Other genomic alterations may define other subsets of NSCLC patients with poor responses to immunotherapies, such as loss of the STK11/LKB1 tumor suppressor which is observed in approximately 30% of patients with activating KRAS mutations (Skoulidis et al., 2018). To improve the efficacy of immunotherapies in these patients, strategies combining EGFR and ALK targeted therapies and anti-PD-1/PD-L1 antibodies are being tested. While it is not yet clear whether the addition of immunotherapies improves responses beyond that of targeted therapies alone, early experience has suggested that a cautious approach is warranted because unexpected severe toxicities can occur. For instance, in the recent JAVELIN Lung 101 trial, the combination of crizotinib and avelumab (anti-PD-L1 antibody) led to dose-limiting toxicities including severe hepatotoxicity in over 40% of ALK-positive patients (Alice Tsang Shaw et al., 2018). Importantly, the combination of lorlatinib and avelumab in this study did not cause any dose-limiting toxicities, suggesting an idiosyncratic crizotinib-specific rather than ALK-specific toxicity. In addition, there is concern that immunotherapies may potentiate known toxicities of targeted therapies, such as pneumonitis that can occur in patients treated with EGFR inhibitors (Ahn et al., 2016 European Lung Cancer Conference). Despite these challenges, the recently reported IMpower150 trial, which showed improved survival with the addition of atezolizumab to bevacizumab plus chemotherapy in patients with *EGFR* mutations and *ALK* translocations, suggesting that some of these patients may benefit from certain PD-1/PD-L1 combination therapies (Socinski, et al., 2018).

12. Up-front treatment with next-generation drugs

As discussed above, the third-generation EGFR inhibitor osimertinib, which was initially developed for T790M-mediated resistance, has now been approved for up-front use for EGFR-mutant NSCLCs. The longer PFS compared to first-generation EGFR inhibitors is likely the result of several factors including suppression of potential resistance by T790M

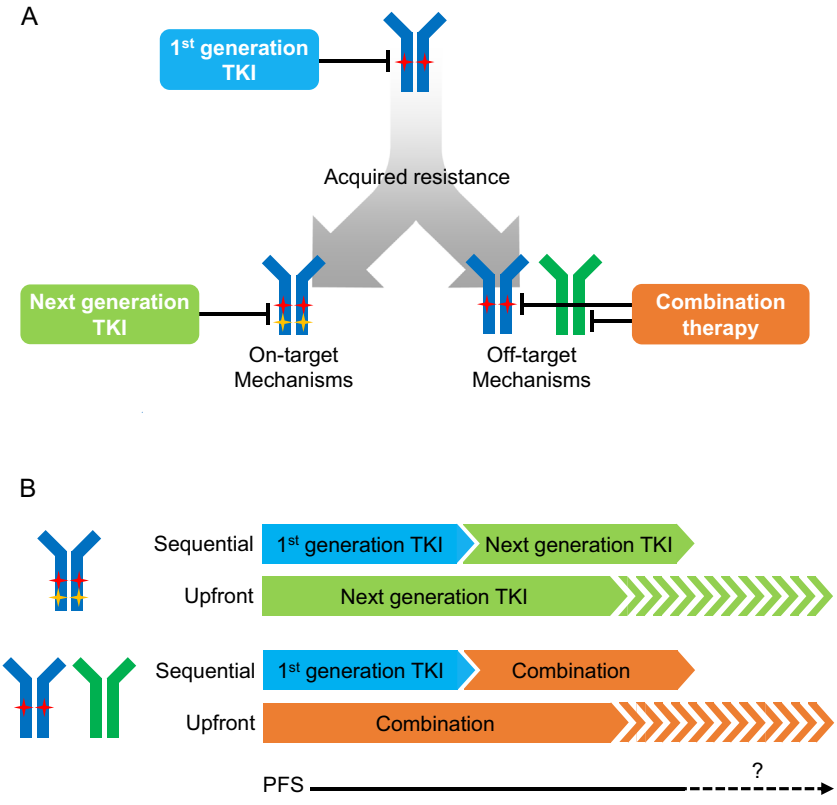

Fig. 3. Strategies for overcoming mechanisms of acquired resistance. A. Mechanisms of acquired resistance to TKIs can be classified into "on-target" (e.g. mutations, gene amplifcations) or "off-target" (e.g. activation of bypass signaling, lineage changes) mechanisms. These can be overcome by next-generation TKIs or drug combinations (Crystal et al., 2014), respectively. B. While next-generation therapies were originally designed to be used against resistant cancers, up-front use is expected to prevent specific mechanisms of resistance from developing and extend duration of response compared to first-generation therapies. However, an important consideration is whether up-front use of next-generation drugs results in longer overall duration of treatment compared to sequential treatment with first-generation followed by next-generation agents. Similarly, while combination therapies are currently being investigated in the second-line setting to overcome resistance mediated by off-target bypass signaling mechanisms, these are likely be brought into the first-line setting with the goal of prolonging treatment duration.

mutant clones, increased CNS penetration, and increased selectivity for the activating mutant over wild-type EGFR allowing improved drug dosing while minimizing toxicity. A similar paradigm has arisen for ALK-rearranged NSCLCs. Alectinib has now supplanted the first-generation ALK inhibitor crizotinib as first-line treatment. Alectinib more potently suppresses ALK kinase activity and can overcome most of crizotinib-resistant mutations. While the question of whether up-front use of more potent and selective next generation drugs results in overall longer treatment duration compared to sequential treatment with first-generation followed by next-generation TKIs remains (Fig. 3), this is unlikely to be directly tested in clinical trials. However, a recent retrospective analysis of a cohort of patients that received sequential treatment of crizotinib followed by alectinib reported a time to second progression of 22.6 months (Lin, Yeap, et al., 2018), which is considerably shorter than the PFS of 34.8 months of first-line alectinib in the ALEX study (Camidge et al., 2018). Even though such a historical comparison may include bias, this large difference supports the up-front use of alectinib. Current efforts are actively focused on strategies to pre-empt the emergence of known resistance mechanisms. For instance, preclinical modeling using Ba/F3 models has suggested that up-front lorlatinib may prevent the emergence of single and subsequently compound *ALK* mutations (Yoda et al., 2018). This hypothesis will be tested in an ongoing randomized phase III trial comparing lorlatinib with crizotinib as first-line therapy in advanced ALK-positive lung cancer (NCT03052608). A similar idea in EGFR-mutant NSCLC has motived several first-line clinical trials combining first-generation and third-generation EGFR inhibitors (NCT03122717, NCT03292133), which should prevent the emergence of C797S and T790M mutant clones, respectively (Niederst, Hu, et al., 2015).

13. Conclusion and perspectives

In this review, we have discussed the current landscape of targetable mutations in NSCLC with a focus on currently approved therapies. While the spectrum of clinically targetable mutations has expanded with the development of new inhibitors, there are no effective targeted therapies for more than a half of NSCLCs including those with KRAS mutations. In addition, even for those with effective therapies, acquired resistance remains a formidable problem. Next-generation inhibitors have been successful in overcoming on-target resistance mutations, especially for EGFR or ALK NSCLCs, however, this may lead to increased selection of off-target resistance mechanisms. To further improve clinical outcomes, novel combination or adaptive treatment strategies are needed that can maximize both anti-tumor efficacy and tolerability.

Conflict of interest statement

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