Title: CURRENT LANDSCAPE OF TARGETED THERAPY IN LUNG CANCER

Authors: Manasi K. Mayekar[1,2,3] and Trever G. Bivona[1,2,3]

Affiliations: [1]Department of Medicine, [2]Department of Cellular and Molecular Pharmacology, [3]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco

Correspondence to: Trever G. Bivona MD PhD (trever.bivona@ucsf.edu)

ABSTRACT

Lung cancer is the leading cause of cancer mortality worldwide. Comprehensive genomic profiling of lung cancers revealed their genetic heterogeneity and complexity and identified numerous targetable oncogenic driver alterations. These molecular profiling efforts have made it possible to exploit the potential of molecularly-targeted therapies. Selection of patients for targeted therapies is becoming biomarker-driven, where the oncogenic drivers in patient tumors are first identified, and subsequently patients bearing drug-sensitizing genetic aberrations are matched to the appropriate targeted therapy. Success of this design of clinical trials and practice was first demonstrated in EGFR inhibitor trials in lung cancer and has since been incorporated into subsequent targeted therapy trials including ALK, ROS1, and BRAF V600E-targeted therapies. In this review, we discuss the current landscape of clinically approved and other promising molecularly-targeted approaches for treatment of lung cancers, the challenges with these approaches and the strategies that could be deployed to overcome these challenges.

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INTRODUCTION

Discovery of therapies targeting the specific oncogenic-driver proteins in cancers has revolutionized cancer therapy. Targeted therapies elicit remarkable responses in several molecularly defined cancer subtypes and improve patient outcomes. The success of the monoclonal antibody trastuzumab in the treatment of HER2-positive breast cancers and the small-molecule inhibitor imatinib in the inhibition of BCR-ABL fusion kinase in chronic myeloid leukemia demonstrated the potential of therapies directed against oncogenic tyrosine kinases that are critical for the survival and growth of these cancers.

Prior to advent of targeted therapy, systemic cytotoxic chemotherapy was used to treat all cancers. However, this one-size-fits-all approach has worked only on some cancers. Hence, the search for better approaches to treat many cancers continued to avoid the high toxicities caused by standard chemotherapy and elicit a durable response. While standard cytotoxic chemotherapy remains the current mode of treatment for small cell lung cancers, which represents about 15% of lung cancers, it has not been effective at treating non-small cell lung cancers (NSCLC) which constitute 85% of lung cancers. This observation stimulated efforts to devise treatments for lung cancer based on histological and molecular profiling.

The potential of targeted therapy in treating lung cancer was revealed after the observed efficacy of gefitinib therapy in lung cancer patients with EGFR inhibitor sensitizing mutations. The early clinical trials with EGFR inhibitors underscored the importance of identifying the oncogenic drivers. This design of clinical trials of testing the efficacy of targeted therapies in selected patient populations with inhibitor sensitizing genetic alterations was adopted in subsequent EGFR inhibitor trials. The success of this design prompted its incorporation into subsequent targeted therapy trials in lung cancer with other actionable oncogenic drivers.

Molecular profiling of lung cancers has also revealed the genetic heterogeneity in lung cancers, where certain subtypes are associated with profound mutational burden and other less so. Smoking, which is the major risk factor for lung cancer, has been implicated as the driver of genetic heterogeneity in this disease. However, certain lung cancer subtypes such as those with oncogenic EGFR and ALK and ROS1 gene rearrangements are thought to be less genetically complex due to the fact that these cancers often arise in individuals with less tobacco exposure. Concerted efforts to sequence the genomes of several hundred cancerous lung tumors have gradually led to the identification of predominant oncogenic drivers and rare oncogenic genetic lesions, while enabling the filtering of passenger mutations [1,2]. Table 1 lists the oncogenic drivers that have been successfully targeted with the indicated small molecule inhibitors to provide FDA-approved superior therapeutic interventions to standard chemotherapy or are currently under further investigation to be effectively targeted with monotherapy or combination therapy for treatment of lung cancers.

ACTIONABLE GENETIC ALTERATIONS

EGFR-activating genetic lesions

EGFR (epidermal growth factor receptor)/ERBB1/HER1 is a member of the EGFR family of receptor tyrosine kinases, which also includes three other closely related receptors: ERBB2/HER2, ERBB3/HER3 and ERBB4/HER4 [3]. Upon binding its ligands such as EGF, EGFR activates downstream effector pathways such as RAS-MAPK, PI3K-AKT and STAT signaling pathways. Interest in molecularly targeting EGFR was sparked after EGFR was found to be overexpressed in several lung cancers. However, clinical trials testing the small molecule EGFR inhibitor gefitinib demonstrated only modest success in unselected NSCLC patients who had progressed on standard chemotherapy. Nonetheless, it still prompted the accelerated FDA approval of gefitinib for patients with advanced stage NSCLC who had progressed on standard chemotherapy because at that time no other treatment options were available for NSCLC patients in the third-line setting [4]. The overall objective response (ORR) to gefitinib in this trial was 10.6% (15 out of 142 patients) and median duration of response was 7 months. Similar results in the BR.21 trial led to the FDA approval of the EGFR inhibitor erlotinib for treatment of advanced stage NSCLC patients who had failed on standard chemotherapy [5]. However, upon further analysis of such trials, it emerged that a subset of patients having genetic aberrations in the EGFR gene show a superior response to EGFR inhibitors [6]. This prompted the use of targeted approaches in lung cancer in a biomarker-driven manner. It also justified directing efforts towards the identification of the broader genomic landscape of lung cancers to uncover additional actionable targets in lung cancer.

EGFR exon 19 deletion and EGFR L858R mutations have been frequently observed as the drivers of oncogenic EGFR signaling in NSCLC. Mutations in EGFR gene are observed at a

frequency of 10-15% in lung adenocarcinoma patients mainly young, non-smokers [1]. Strong evidence for adopting gefitinib as a therapy for treating EGFR mutant lung adenocarcinomas in the first-line setting came from the revolutionary IPASS trial in East Asia (Iressa Pan-Asia Study) [7]. This study showed that treatment-naïve never- or light-smoking NSCLC patients with activating EGFR mutations (EGFR exon 19 deletion and EGFR L858R) had significantly longer progression-free survival (PFS) upon receiving gefitinib treatment instead of carboplatin/paclitaxel chemotherapy. Thus, the IPASS trial nominated EGFR mutational status as a predictive biomarker for response to EGFR inhibitors such as gefitinib.

The first-generation EGFR inhibitors, although more effective than standard cytotoxic chemotherapy, failed to elicit a durable response. In nearly 50% of relapsed patients, the EGFR gatekeeper mutation T790M was implicated as the cause of resistance to EGFR inhibitor therapy. To more effectively block signaling through EGFR, more potent second-generation irreversible EGFR inhibitors such as afatinib, were developed and tested. Afatinib is a pan-HER EGFR inhibitor. Efficacy of afatinib in treating untreated EGFR-mutation positive advanced stage lung adenocarcinoma patients compared to standard chemotherapy was tested in the LUX-Lung 3 (pemetrexed-cisplatin chemotherapy) and LUX- Lung 6 (gemcitabine-cisplatin chemotherapy) clinical trials. Afatinib treatment was found to improve the overall survival compared to chemotherapy in EGFR del19 positive patients but not in EGFR L858R positive patients in LUX-Lung 3 and LUX-Lung 6 trials. Thus, while both EGFR exon 19 deletion and EGFR L858R are EGFR activating mutations, differences in their ability to activate downstream signaling could result in variable response to targeted therapies as indicated in these and other studies [8]. The LUX-Lung7 trial showed no significant difference in the overall survival between afatinib and gefitinib when used for treating, advanced stage (IIIb/IV), EGFR-mutation positive

NSCLC patients [9]. However, the second-generation EGFR inhibitor dacomitinib has demonstrated better efficacy than gefitinib in terms of progression-free survival (14.7 vs 9.2) but not ORR (75% vs 72%) in treatment-naïve EGFR-activating mutation positive advanced NSCLC patients in the first-line setting in ARCHER 1050 trial (ASCO 2017; Abstract LBA9007).

Second generation EGFR inhibitors were mainly developed to overcome the EGFR T790M-mediated resistance and were shown to be active against T790M mutant protein in pre-clinical studies. However, the toxicity caused by irreversible inhibition of wild-type EGFR has been a limiting factor for the use of these inhibitors in clinic [10]. The wild-type sparing, irreversible, third-generation EGFR inhibitor, osimertinib was developed to tackle these problems. Osimertinib was granted accelerated FDA approval for treating EGFR T790M positive patients who had progressed on EGFR-TKI treatment after demonstrating impressive success in the phase I (ORR 61% and mPFS 9.6 months) and phase II (ORR 66% and mPFS 11 months) of the AURA trial in EGFR mutant NSCLC patients [11]. In the phase III of the AURA study osimertinib further demonstrated superior efficacy over platinum plus pemetrexed chemotherapy in T790M-positive advanced stage NSCLC patients who progressed on EGFR-TKI therapy with a longer PFS (10.1 vs 4.4 months) inducing response even in patients with brain metastases and better ORR (71% vs 31%) [12]. However, on-target resistance to osimertinib treatment has been observed due to the EGFR C797S mutation that disrupts the covalent bond formation of osimertinib with EGFR [13]. Many other third generation EGFR inhibitors, which are wild-type-sparing similar to osimertinib, are also being tested which include olmutinib (HM61713), ASP8273, nazartinib (EGF816), avitinib, PF-06747775 and HS-10296. Some of these irreversible third generation inhibitors are also refractory to EGFR C797S such as olmutinib and ASP8273 since they also rely on the EGFR C797 residue for irreversible binding [14].

EGFR-independent mechanisms of resistance to EGFR inhibitors include amplification of MET, AXL, HER2, NRAS or KRAS or BRAF V600E mutation or PIK3CA mutations [10,15]. Combination therapies can block the emergence of EGFR-independent resistance. A clinical trial is currently testing the efficacy of the combination of erlotinib with the AXL inhibitor BGB324 in advanced stage NSCLC patients (NCT02424617). Furthermore, clinical trials are also underway to determine if drugs such as MET inhibitor INC280 or MEK inhibitor selumetinib or the antibody against the immune checkpoint inhibitor PD-L1 can be combined with osimertinib to elicit a more durable response (NCT02143466). An ongoing clinical trial is also testing if the combination of osimertinib, with an antibody against EGFR, necitumumab, can overcome resistance to on-target mutations in advanced stage EGFR positive NSCLC patients who have relapsed on an EGFR inhibitor therapy (NCT02496663).

ALK rearrangements

ALK translocations encoding fusion proteins of ALK kinase domain with 5' partners such as EML4, NPM and TFG, which drive hyperactivation of ALK, were identified as oncogenic drivers in NSCLC in 2007 [16,17]. ALK fusions are expressed in about 3-7% of NSCLC patients, mostly young and non-smokers [18]. Soon after the discovery of the EML4-ALK fusions, crizotinib (PF-02341066), which was originally developed against c-MET but also found to target ALK, was repurposed and tested in clinical trials to treat ALK-positive NSCLC patients. After demonstrating promising success, with an ORR in 61% of the 149 heavily pretreated ALK-positive patients enrolled in the trial (NCT00585195) and median PFS of 10 months, crizotinib was rapidly granted FDA approval for treatment of ALK-positive locally advanced or metastatic NSCLC [19]. Subsequently, crizotinib was confirmed to be superior to standard chemotherapy in

the first-line setting as well with an ORR of 74% and median PFS of 10.9 months [20]. However, resistance to crizotinib therapy was observed due to on-target mechanisms such as the C1156Y substitution, solvent-exposed mutation G1202R, the gatekeeper mutation L1196M, and ALK copy number gain and brain metastasis was observed due to poor penetration of crizotinib across the blood-brain barrier [21]. Hence the search for better ALK inhibitors continued.

Second generation ALK inhibitors ceritinib and alectinib are more potent than crizotinib and can block some of the on-target mechanisms of resistance to crizotinib such as the gatekeeper mutation L1196M and copy number gain and have better ability to cross the blood-brain barrier. Ceritinib was granted accelerated FDA approval for patients with metastatic ALK-positive NSCLC who are intolerant to crizotinib or had progressed after treatment with crizotinib. This approval was prompted by the encouraging results from the ASCEND-1 trial which demonstrated an ORR of 72% (60 of 83) and a median PFS of 18.4 months in ALK-inhibitor-naïve patients treated with ceritinib and an ORR of 56% (92 of 163) and median PFS of 6.9 months in ALK-inhibitor-pretreated patients treated with ceritinib, [22]. The remarkable success of alectinib was one of the highlights of this year's ASCO meeting. The ALEX clinical trials comparing the efficacy of alectinib with crizotinib in advanced stage, crizotinib-naïve ALK-fusion positive patients, have demonstrated spectacular efficacy for alectinib over crizotinib with a prolongation of median PFS to 25.7 months (Abstract LBA9008). Brigatinib, another second-generation ALK inhibitor, was granted FDA approval after showing remarkable efficacy in crizotinib-resistant ALK-positive NSCLC patients [23]. The higher dose regimen of brigatinib demonstrated an ORR and median PFS of 54% and 12.9 months, respectively with acceptable toxicity levels. A substantial response was observed in patients with brain metastases as well with an ORR of 67%. Additional second generation ALK inhibitors which are being

tested include ensartinib and entrectinib. However, the second-generation ALK inhibitors are not effective against the ALK G1202R substitution. The third generation ALK inhibitor lorlatinib can not only target the ALK mutant G1202R but also block several other ALK mutations conferring resistance to other ALK inhibitors such as L1152R, C1156Y, L1196M, G1269A, F1174L and S1206Y [18]. Furthermore, it also has improved ability to penetrate the blood-brain barrier. However, the ALK substitution L1198F can confer resistance to lorlatinib but is sensitive to crizotinib and actually enhances the binding of crizotinib to ALK. The lack of overlap in the on-target mechanism of resistance between lorlatinib and crizotinib can be exploited to design effective sequential therapy. This was demonstrated in a patient enrolled in a clinical trial testing lorlatinib (NCT01970865) in patients pre-treated with other ALK inhibitors. Lorlatinib helped overcome acquired resistance to crizotinib and when the tumor acquired resistance to lorlatinib by gaining L1198F mutation, it was resensitized to crizotinib [24]. Early clinical trial results indicate a clinical benefit with lorlatinib in ALK-positive NSCLC patients pre-treated with one or more ALK inhibitors (ASCO 2017, Abstract 9006).

Activation of the bypass signaling pathway through mutations in EGFR, RAS, MEK1 or IGF1R or amplification in MET1 or c-KIT or transformation to small cell lung cancer are some of the mechanisms that can limit response to these targeted therapies [25]. Combination strategies with MEK inhibitor trametinib to overcome resistance and elicit a durable response are under development based on the findings from our group that oncogenic signaling by EML4-ALK driven adenocarcinomas is driven mainly through downstream RAS-MAPK pathway and hence amplification of RAS also confers resistance to ALK inhibitors (NCT03087448) [26].

ROS1 rearrangements

ROS1 belongs to the family of insulin receptor tyrosine kinases. Chromosomal rearrangements involving ROS1 fusions with SLC34A2 or CD74 were first found in 2007 in a NSCLC cell line, HCC78, and a patient tumor during a study assessing tyrosine kinase signaling in 41 NSCLC cell lines and over 150 NSCLC tumors [16]. Oncogenic activation of ROS1 leads to activation of STAT3, PI3K-AKT and RAS-MAPK pathways. ROS1 fusions are found in 1-2% of NSCLC patients, mostly young and non-smokers. CD74-ROS1 is the most prevalent ROS1 fusion. In addition to SLC34A2 and CD74, other 5' fusion partners of ROS1 observed in NSCLC include FIG, CDC4, EZR and CCDC6 [27]. ALK inhibitors such as crizotinib and ceritinib have also been shown to inhibit ROS1. Crizotinib demonstrated anti-tumor activity in a clinical trial assessing the effect of crizotinib treatment on ROS1 fusion positive NSCLC patients (50). The observed ORR was 72% and median PFS was 19.2 months [28]. This success prompted the FDA approval of crizotinib in 2016 for treatment of patients harboring ROS1 fusion positive advanced stage NSCLC tumors.

A substitution in the solvent front residue of CD74-ROS1 G2032R has been shown to confer resistance to crizotinib [29]. The ALK inhibitor, ceritinib, which has been shown to inhibit the crizotinib-resistant gatekeeper mutation L2026M, was also shown to confer clinical benefit in a CD74-ROS1 positive NSCLC patient who had relapsed 13 months after crizotinib treatment [30]. The drug cabozantinib, which is more selective for ROS1 than ALK and has also shown efficacy in inhibiting the clinically-reported crizotinib-resistant CD74-ROS1 G2032R protein and pre-clinically observed crizotinib-refractory ROS1 substitutions such as the solvent front L1951R substitution and the gatekeeper mutation L2026M, is also being tested on ROS1 fusion positive NSCLC patients in clinical trials (NCT01639508) [31,32]. Clinical trials are ongoing to test the

efficacy of the third generation ALK inhibitor lorlatinib (NCT0292734) in ROS1-fusion positive advanced NSCLC patients based on the marked efficacy of lorlatinib in pre-clinical studies against CD74-ROS1 mutations G2032R and L2026M, and FIG-ROS1 [33]. Furthermore, the ROS1, pan-Trk and ALK inhibitor entrectinib has also demonstrated anti-tumorigenic effects on ROS1 positive NSCLC patients [34].

RET rearrangements

Similar to ROS1 rearrangements, the prevalence of RET rearrangements in NSCLC patients is also 1-2% and are mainly observed in young never-smokers. The 5' fusion partners of RET identified in NSCLC include KIF5B, NCO4, EML4, CCDC6 and TRIM33 [35]. Clinical trials are underway to test the efficacy of cabozantinib in RET fusion positive NSCLC patients which along with ROS1 and RET, also inhibits VEGFR2 and c-MET. A global clinical trial tested multi-kinase FDA or EMA-approved inhibitors including drugs with RET-inhibitory activity in pre-clinical models or observed to have RET-inhibitory activity in *in vitro* studies such as cabozantinib (21 patients) and 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) on 165 RET-fusion positive advanced stage NSCLC patients of which 72% harbored the KIF5B-RET rearrangement [36]. This trial demonstrated modest efficacy compared to other targeted therapies in lung cancer with a median PFS of 2.3 months and a median overall survival of 6.8 months. The authors postulate that the lack of a robust response may be due to toxicities caused by off-target effects of these kinase inhibitors, resulting in suboptimal-dosing and hence incomplete RET inhibition or the effect of 5' fusion partners on the level of inhibition. The RET inhibitor RXDX-105 has demonstrated inhibitory effect against

RET in RET rearranged NSCLC cells *in vitro* and *in vivo* and induced significant tumor regression in an advanced stage NSCLC RET-fusion positive patient [37].

NTRK rearrangements

Chromosomal translocations in the neurotrophic tyrosine kinase (NTRK) genes have been identified in several solid cancers including lung cancers where their prevalence is about 2-3% [38]. NTRK1, 2 and 3 code for tropomyocin-related kinase proteins (Trk), TrkA, TrkB and TrkC, respectively [39]. NTRK1 and NTRK2 translocations with 5' fusion partners such as TRIM24, CD74 and SQSTM1 have been observed in lung cancer patients [40]. Entrectinib, a pan-Trk inhibitor, with inhibitory activity against ROS1 and ALK inhibitor as well, has shown significant antitumor effect in an NSCLC patient harboring SQSTM1-NTRK1 fusion [2,41]. The efficacy of the pan-TRK inhibitor larotrectinib (LOXO-101) on NTRK fusion in different cancers on both adult and pediatric patients is currently being tested in three clinical trials (NCT02122913, n=8 adults; NCT02637687, n=12 pediatric patients and NCT02576431, n=35 adult/adolescent patients). This trial includes five lung cancer patients. The results of the ongoing trial were presented at the ASCO meeting 2017. The results appear promising, with an ORR of 88% in the 46 patients evaluated. However, resistance caused due to solvent front mutations have blunted the response in four patients. However, a second-generation Trk inhibitor, LOXO-195 has shown early, albeit preliminary, clinical efficacy in such cases [42].

BRAF mutations

Mutations in BRAF are observed in 1-4% of NSCLC and 50-55 % of them encode the BRAF V600E mutant protein [43]. Most oncogenic BRAF mutations induce constitutive activation of BRAF and hence its downstream MAPK pathway [44]. BRAF mutations are often found in NSCLC patients who are former/current smokers. Approaches that are being deployed to treat BRAF-mutant melanoma are also being tested in BRAF-mutant NSCLC. BRAF inhibitors such as dabrafenib and vemurafenib as monotherapy have shown limited efficacy in BRAF V600E NSCLC patients with response rates of 33% and 42% and median PFS of 5.1 and 7.3 months, respectively [45,46].

However, dabrafenib plus trametinib combination therapy has shown marked efficacy in a recent clinical trial (NCT01336634) and hence, was recently approved for the treatment of BRAF V600E mutant metastatic NSCLC patients. An ORR of 63% and median duration of response of 12.6 months was observed in patients who had progressed after platinum-based chemotherapy (n=57) and in the treatment naive group of patients (n=36) the observed ORR was 61% and the responses lasted over 6 months in 59% of patients [47].

Current challenges in this molecular subtype of lung cancer include overcoming resistance to BRAF/MEK dual blockade and developing therapeutic agents that can inhibit non-V600 mutant forms of BRAF that occur in approximately half of all BRAF mutant NSCLCs. Current strategies include concurrent inhibition of EGFR with mutant BRAF and the use of next-generation BRAF inhibitors such as the paradox breaker drug PLX8394 to more selectively suppress downstream MEK-ERK signaling in both V600 and non-V600 BRAF mutations [48-50].

OTHER ONCOGENIC ALTERATIONS

HER2 mutations

1–2% of NSCLC patients, mostly non-smokers, harbor mutations in the HER2 gene, which mainly include in-frame insertions in exon 20 and HER2 amplification. However, HER2 amplifications have not always been observed to induce HER2 protein overexpression in NSCLC [51]. A clinical trial failed to show superiority of the HER2-targeting antibody trastuzumab, which has improved patient outcome in HER2-positive breast cancers, over standard chemotherapy (n=50) in advanced stage HER2-positive NSCLC patients (n = 51) [52]. However, this study found that six patients who were strongly positive for HER2 (HER2 3+ in IHC analysis) benefited from the combination of chemotherapy and trastuzumab compared to chemotherapy alone (Response rate 83% vs 41%). Few pre-clinical and clinical studies have observed anti-tumor activity of the pan-HER inhibitors, afatinib and dacomitinib, in HER2-mutant NSCLC patients [53,54]. There is an ongoing clinical trial to test the efficacy of afatinib in advanced stage NSCLC patients with HER2 mutations who have progressed on chemotherapy treatment (NCT02597946).

MET activating genetic lesions

MET encodes the hepatocyte growth factor receptor (HGFR), which is activated upon binding to its ligand, HGF. Oncogenic activation of MET signaling due to MET amplification or MET exon 14 skipping has been observed as an oncogenic driver in 4-5% of lung adenocarcinomas or (for MET amplification) a pathway conferring resistance to other TKI therapies such EGFR or ALK-inhibitor therapies [1]. Positive clinical responses to multikinase inhibitors that target MET such as crizotinib and cabozantinib have been observed in advanced stage NSCLC patients harboring

genetic alterations in MET exon 14 [55-57]. On-target substitution mutations such as MET D1228N and Y1230C have been identified as putative mechanisms of resistance to crizotinib in NSCLC patients harboring MET exon 14 skipping mutation [58,59]. Additionally, crizotinib has failed to prevent brain metastasis due to poor ability of crizotinib to permeate the blood-brain barrier. Cabozantinib has been shown to generate intracranial response in a MET exon 14 NSCLC patient who showed intracranial progression on crizotinib and also inhibit the crizotinib resistant mutation MET D1228V [60,61]. Clinical trials are also ongoing to test MET-specific inhibitors such as capmatinib in MET exon 14 positive NSCLC patients who have progressed on other MET-directed TKIs (NCT02750215). A clinical trial is also underway to test the efficacy of the MET and AXL inhibitor MGCD265 in advanced stage NSCLC patients with MET amplifications or other activating mutations in the MET gene such as exon-14 skipping mutants, who have progressed on chemotherapy (NCT02544633).

KRAS activating mutations

KRAS mutations are identified in approximately 30% of lung adenocarcinoma patients, mostly smokers [1]. Although KRAS mutant adenocarcinomas show hyperactivation of the RAS-MAPK pathway, inhibition of the downstream protein, MEK, with drugs such as trametinib and selumetinib, has been largely ineffective in these patients. Clinical trials comparing the efficacy of selumetinib or trametinib and docetaxel combination to docetaxel alone in previously-treated advanced stage KRAS-mutant NSCLC patients failed to show superiority of the combinations over docetaxel alone [62,63]. The drug ARS853, has demonstrated impressive activity against KRAS G12C in pre-clinical studies by trapping KRAS G12C in its GDP-bound inactive form [64]. Such direct KRAS targeted inhibitors warrant clinical investigation.

Furthermore, activation of the Hippo-YAP pathway has been shown in preclinical models and clinical samples to promote resistance to RAS-RAF-MEK-ERK blockade [65]. Thus, co-inhibition of YAP signaling is a promising approach to enhance response to such agents in KRAS-mutant patients.

DISCUSSION

Concerted efforts to identify actionable oncogenic driver mutations in lung cancer have revolutionized the care of lung cancer patients with tumors harboring such mutations. Targeted therapy is replacing conventional cytotoxic chemotherapy as standard treatment for patients with targetable oncogenic drivers, improving not only the overall survival of these patients but also reducing the side effects of the treatment (Table 1). Furthermore, it has greatly improved our understanding of biology of lung cancer, which is among the most genetically heterogeneous and hence genetically complex diseases.

Although the value of identifying genomic vulnerabilities of tumors has been successfully demonstrated in lung cancer, many challenges remain unresolved. Most of the drugs have been developed against the highly conserved, functionally important ATP-binding pocket of the oncogenic kinases. This approach affords the tumor cells lesser opportunity to evade the binding of the drug by acquiring a mutation because the accumulation of resistant mutations in the drug-binding site of the kinase could also functionally impair the kinases. However, this approach also makes it more difficult to design inhibitors that will specifically target just a single kinase since kinases show similarity in the functionally important ATP-binding pocket. Hence, most kinase inhibitors have multiple targets in addition to the one they are desired to have

inhibitory effect on, blockade of which leads to unwanted side effects and limits the doses at which the drugs can be administered. Suboptimal dosing results in incomplete inhibition of the oncogenic pathway. Tyrosine kinase inhibitors such as sorafenib and cabozantinib have an off-target inhibitory effect on VEGF signaling. Because VEGF signaling is important for cardiac function, cardiotoxicity is one of the observed side effect with these drugs [66]. Dose-limiting on-target toxicities may also result from the importance of the targeted kinase in normal cells such as skin cells or gastrointestinal cells. The on-target toxicities can be reduced by use of inhibitors that are selective towards the oncogenic forms of the protein. Osimertinib, which is a wild-type sparing EGFR inhibitor, was found to greatly reduce skin and gastrointestinal toxicities observed with previous EGFR inhibitors that inhibit both mutant and wild-type EGFR [67,68].

In some cases, the off-target effects have been beneficial by enabling the blockade of the bypass pathway and hence co-inhibiting the main oncogenic-driver pathway and the pathway that could mitigate the effects of inhibition of the oncogenic driver. This can overcome resistance and prolong the duration of response. This has been observed in an ALK-fusion positive patient who progressed on the second-generation ALK inhibitor alectinib and responded to crizotinib [69]. Inhibition of MET-signaling induced by MET amplification that prevented response to alectinib was implicated as the underlying mechanism for the effect of crizotinib, which inhibits both ALK and MET, in overcoming resistance to alectinib.

Furthermore, the genetic heterogeneity in tumors precludes a complete response in almost all patients. Hence, sequencing should be performed on biopsies obtained from more than one site within the same tumor and in multiple tumors from the same patient in the case of advanced lung cancer cases. This could facilitate the identification of truncal mutations which are present in a majority of the tumor cells. Targeting truncal mutations may eliminate the bulk of the tumor

cells in patients, although it is possible that subclonal diversification will blunt this response when the treatment is applied later during tumor evolution such as at the time of acquired resistance to the initial treatment.

The response to targeted therapies could also be blunted by the escape of few tumor cells, which could adapt and continue to evolve leading to the tumor-regrowth. Work from our group and others has identified a crucial role for adaptive stress response pathway, NF-κB in the survival of few tumors cells even in the presence of effective drugs targeting their genetic vulnerability. Hence, co-targeting the crucial pro-survival stress response pathway along with the primary oncogenic pathway could more effectively eliminate the residual tumor cells and hence generate a more durable response as demonstrated through pre-clinical studies by our group [70].

Drug repurposing, based on the multi-kinase effects of several kinase inhibitors also seems to be an attractive strategy especially for targeting the rare oncogenic drivers. This approach can greatly shorten the time from discovery of a novel actionable oncogenic driver in a patient to a clinical benefit.

Adoption of molecular profiling of tumors into standard of care practice for NSCLC is also essential. The importance of molecular profiling in NSCLC was suggested in a large scale clinical trial in France (NCT01700582) [71]. Molecular profiling was routinely performed in patients with advanced NSCLC to identify genetic aberrations in six commonly mutated genes- EGFR, ALK, KRAS, BRAF, PIK3CA, HER2. 50% of the patients had mutations in one of these genes. Subsequently, 51% of these patients received the relevant targeted therapy. The presence of genetic lesion significantly improved patient outcome with a PFS of 10 months and an overall survival of 16.5 months as compared to patients without an alteration in these six drivers (PFS- 7.1 months and OS-11.8 months) indicating a prognostic value and/or therapeutic advantage

gained by the presence of a targetable oncogenic driver. This study supports the notion that treating patients with therapies based on their genetic vulnerabilities may be clinically beneficial.

To fully unleash the potential of targeted therapies, combinatorial or sequential approaches with potent drugs will have to be deployed, but judiciously. Combinatorial therapies enhance the toxicities while sequential therapies may not always be effective because with increasing lines of treatment, the complexity of tumors increases, making the tumors less responsive to treatments than they would have been in the first-line setting. Overall, continued pursuit of the biological basis of tumor initiation, progression, and drug resistance will continue to improve treatment options for patients with NSCLC and hopefully lead to transformative leaps in clinical outcomes.

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Targeted oncogenic driver	FDA approved drugs	Drugs under study	% NSCLC patients
EGFR	Gefitinib, erlotinib, afatinib, osimertinib	Dacomitinib, olmutinib (HM61713), ASP8273, nazartinib (EGF816), avitinib, PF-06747775, HS-10296	10-15%
ALK	Crizotinib, ceritinib, alectinib, brigatinib	Ensartinib, entrectinib, lorlatinib	3-7%
ROS1	Crizotinib	Ceritinib, cabozantinib, entrectinib, lorlatinib	1-2%
RET		RXDX-105, cabozantinib, vandetanib, sunitinib, sorafenib, alectinib, lenvatinib, nintedanib, ponatinib, regorafenib	1-2%
NTRK		Entrectinib, larotrectinib (LOXO-101), LOXO-195	1-2%
BRAF	Dabrafenib and trametinib combination	Vemurafenib, PLX8394, selumetinib	1-4%
HER2		Afatinib, dacomitinib, trastuzumab	1-2%
MET		Crizotinib, cabozantinib, capmatinib, MGCD265	4-5%
KRAS		Selumetinib, trametinib, ARS853	15-30%

Table 1: FDA-approved and promising targeted therapies for treatment of lung cancers with targetable oncogenic drivers.