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Managing Resistance to EFGR- and ALK-Targeted Therapies

Christine M. Lovly, MD, PhD,

Puneeth Iyengar, MD, PhD,

Justin F. Gainor, MD

Division of Hematology and Oncology, Vanderbilt University School of Medicine, Nashville, TN; Department of Radiation Oncology, Thoracic Disease Oriented Team, Thoracic Radiation Oncology Program, Simmons Comprehensive Cancer Center, The University of Texas Southwestern Medical Center, Dallas, TX; Harvard Medical School, Massachusetts General Hospital, Boston, MA.

OVERVIEW

Targeted therapies have transformed the management of non–small cell lung cancer (NSCLC) and placed an increased emphasis on stratifying patients on the basis of genetic alterations in oncogenic drivers. To date, the best characterized molecular targets in NSCLC are the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK). Despite steady advances in targeted therapies within these molecular subsets, however, acquired resistance to therapy is near universal. Recent preclinical models and translational efforts have provided critical insights into the molecular mechanisms of resistance to EGFR and ALK inhibitors. In this review, we present a framework for understanding resistance to targeted therapies. We also provide overviews of the molecular mechanisms of resistance and strategies to overcome resistance among *EGFR*-mutant and *ALK*-rearranged lung cancers. To date, these strategies have centered on the development of novel next-generation inhibitors, rationale combinations, and use of local ablative therapies, such as radiotherapy.

Treatment strategies for advanced NSCLC have evolved in recent years because of an improved understanding of the genetic underpinnings of the disease. Indeed, the identification of genetic alterations in key oncogenic drivers (critical mediators of cancer initiation, growth, and maintenance) has informed the development of various small-molecule tyrosine kinase inhibitors (TKIs) aimed at disrupting dysregulated signaling networks in select patient populations. To date, the best characterized examples of this treatment paradigm are lung cancers that harbor genetic alterations in the *EGFR* and *ALK* genes. Each defines a distinct molecular subset of NSCLC, marked by exquisite sensitivity to treatment with genotype-specific TKIs.[1–3] In randomized phase III trials, EGFR and ALK TKIs have consistently demonstrated greater efficacy than cytotoxic chemotherapy,[4–7] which effectively established targeted therapy as the standard of care in each respective patient population.

Corresponding author: Justin F. Gainor, MD, Massachusetts General Hospital, 55 Fruit St., Boston, MA 02114; jgainor@partners.org.

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On the basis of the success of targeted therapies in patients with *EGFR*-mutant and *ALK*-positive disease, molecular profiling of lung cancers now is routine.[8,9] Furthermore, efforts to identify and therapeutically exploit additional molecular targets are ongoing. Despite the impact of targeted therapies in NSCLC, however, resistance is ubiquitous and represents a major clinical challenge.[10] This review, therefore, provides a clinical overview of resistance to targeted therapies in NSCLC and emphasizes therapeutic strategies aimed at overcoming resistance.

FRAMEWORK FOR EVALUATING RESISTANCE TO TARGETED THERAPIES

Intrinsic Versus Acquired Resistance

Resistance to targeted therapies can be classified as either intrinsic (i.e., primary) or acquired (i.e., secondary). Intrinsic resistance implies a de novo lack of response to a given therapy, whereas acquired resistance refers to disease progression after a period of initial clinical benefit.[11] In general, intrinsic resistance to targeted therapies among *EGFR*-mutant and *ALK*-positive NSCLCs is uncommon, and insights into the mechanisms underlying intrinsic resistance are limited.[12] Recent examples include the following: (1) differential TKI sensitivities among specific *EGFR* mutations (e.g., exon 20 insertions)[13] or *EML4-ALK* variants,[14,15] (2) the presence of pre-existing, drug-resistant subclones (e.g., de novo *EGFR* T790M; see EGFR TKI Resistance),[16,17] (3) defects in apoptotic machinery (e.g., Bcl2-like protein 11 [BIM]),[18,19] (4) phenotypic changes (e.g., epithelial-mesenchymal transition [EMT]),[20] and (5) false-positive genotyping, among others. Because of limited clinical data on intrinsic resistance, the remainder of this review will focus on acquired resistance to targeted therapies.

Overview of Molecular Mechanisms of Acquired Resistance

Molecular mechanisms of acquired resistance to targeted therapies can be characterized broadly as either on target or off target. The former refers to the development of additional genetic alterations in the primary oncogenic target (e.g., *EGFR*, *ALK*) that enable continued downstream signaling. Typically, this occurs via secondary point mutations and/or gene amplification of the target. Secondary point mutations generally confer resistance through steric interference or via conformational changes that alter drug binding, whereas target amplification likely mediates resistance by shifting the equilibrium back in favor of the kinase.

Beyond genetic alterations in the target, resistance also may be mediated by target-independent, or off-target, mechanisms. To date, the best described examples of off-target mechanisms of resistance involve the upregulation of bypass signaling pathways—commonly through activation of alternative receptor tyrosine kinases.[21] Ultimately, bypass tracts allow reactivation of downstream mediators of growth and survival despite continued target engagement. In addition to bypass tract activation, other off-target mechanisms of resistance include changes in tumor histology (i.e., lineage changes); increased growth factor production; and overexpression of drug efflux pumps.[11,22–24]

Oligoprogression Versus Multisite Progression

When resistance to targeted therapies in NSCLC is evaluated, other important considerations are the site and nature of progression. Patients frequently experience diffuse or multisite progression, which generally requires that clinicians consider a change in systemic therapies. However, resistance to targeted agents also may be heterogeneous,[25] which results in more limited sites of progression. For example, the term “oligoprogression” refers to isolated progression in one or two anatomic sites, with continued clinical response or stability elsewhere. Most notably, oligoprogression in the central nervous system (CNS) is a relatively frequent complication in *EGFR*-mutant and *ALK*-positive NSCLC—often because of limited penetration of TKIs beyond the blood-brain barrier.[26,27] Distinguishing oligoprogression from multisite progression may have important implications for the use of local ablative therapies, such as radiotherapy.

EGFR TKI RESISTANCE: MECHANISMS AND THERAPEUTIC APPROACHES

Therapeutic Targeting of EGFR Mutations in Lung Cancer

Recurrent activating mutations in the exons that encode the tyrosine kinase domain of *EGFR* are found in 10% to 15% of patients with NSCLC in the United States and in up to 30% of occurrences in Asian populations.[1,2,28] In the United States, approximately 20,000 patients die as a result of *EGFR*-mutant lung cancer each year. *EGFR* mutations, most commonly small in-frame deletions in exon 19 (exon 19 del), which eliminate an LREA motif in the protein, and a point mutation in exon 21, which leads to substitution of an arginine for a leucine at position 858 (L858R), are associated with sensitivity to EGFR TKIs. To date, three generations of EGFR TKIs have entered the clinic. First-generation TKIs are competitive inhibitors of EGFR, while second-generation TKIs irreversibly bind to EGFR and other erbB family members. Multiple phase III trials have shown that patients with *EGFR*-mutant tumors display greater than 70% objective response rates (ORRs) and a statistically significant improved progression-free survival (PFS) when treated with first-generation (erlotinib, gefitinib) or second-generation (afatinib) EGFR TKIs (Table 1) compared with standard platinum-based chemotherapy for NSCLC.[29–32] As a result of these studies, prospective tumor genotyping for *EGFR* mutations is now the standard of clinical care, and erlotinib, gefitinib, and afatinib are approved by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic *EGFR*-mutant NSCLC.

Acquired Resistance to Wild-Type EGFR TKIs: Erlotinib, Gefitinib, and Afatinib

Unfortunately, despite these markedly improved outcomes, patients whose tumors initially respond to erlotinib, gefitinib, and afatinib eventually display disease progression, typically within a year of starting treatment.[4,31,32] The most common mechanisms of acquired resistance—occurring in approximately 60% of tumors resistant to erlotinib/gefitinib/afatinib—is acquisition of the T790M second-site mutation in the *EGFR* kinase domain.[22,33–35] The T790M gatekeeper mutation confers drug resistance through steric hindrance, which interferes with drug binding and through alterations in the ATP affinity of the kinases.[36] Target-independent (i.e., independent of the driver kinase, *EGFR*) resistance mechanisms also have been described; these include *MET* amplification[35];

HER2 amplification[37]; *PIK3CA* mutations[22]; autocrine hepatocyte growth factor (HGF) production[17]; EMT[22,38,39]; and transformation to small cell lung cancer.[22,40]

Overcoming T790M-Mediated Resistance With Mutant-Selective EGFR TKIs

Recently, a new class of drugs that irreversibly inhibit mutant *EGFR* has been developed. These mutant-selective, or third-generation, EGFR TKIs were designed to overcome the effects of the T790M resistance mutation but relatively spare wild-type EGFR. These agents also are highly potent against the original *EGFR* activating mutations (del 19 and L858R). There are several such mutant-selective EGFR inhibitors (Table 1), including osimertinib (AZD9291),[41] rociletinib,[42] and nazartinib.[43] Preclinically, these drugs potently inhibit signaling pathways and cellular growth in *EGFR*-mutant cell lines, xenografts, and transgenic mouse models.

Clinically, mutant-selective EGFR TKIs induce high ORRs and, often, durable responses in patients with *EGFR*-mutant lung cancer. The most well-studied mutant-selective EGFR TKI to date is osimertinib. In the phase I trial of this agent, the ORR was 61% and the median PFS was 9.6 months in patients with *EGFR* T790M–positive disease[44] who had experienced progression during treatment with prior erlotinib, gefitinib, or afatinib. On the basis of these results, osimertinib was approved by the FDA in November 2015 for the treatment of patients with metastatic *EGFR* T790M mutation–positive NSCLC. Osimertinib also has proven more effective than platinum-based chemotherapy for second-line treatment. In an international phase III trial (AURA 3), 419 patients with T790M-positive advanced *EGFR*-mutant lung cancer who experienced disease progression after first-line EGFR TKI therapy were randomly assigned to receive osimertinib or cisplatin/carboplatin plus pemetrexed.[45] The median PFS was 10.1 months in the osimertinib group versus 4.4 months in the platinum/pemetrexed group. The ORR also favored osimertinib (71% for osimertinib vs. 31% for chemotherapy). Notably, osimertinib also has demonstrated efficacy against CNS metastases. In the AURA 3 study, among 144 patients with CNS metastases, the median PFS was 8.5 months for patients who received osimertinib compared with 4.2 months for patients who received platinum chemotherapy.

Notably, osimertinib has shown promising results when used as first-line therapy—that is, in patients who are EGFR TKI naive, before the acquisition of T790M. In the AURA trial (NCT01802632), the ORR was 77% and the median PFS was 19.3 months for osimertinib therapy in treatment-naive patients with *EGFR*-mutant lung cancer.[46] The ongoing, global, phase III FLAURA trial (NCT02296125) is directly comparing first-line osimertinib with typical firstline therapy of erlotinib/gefitinib. Results from this trial are eagerly awaited.

Several other *EGFR*-mutant specific TKIs are being evaluated in clinical trials (Table 1), including rociletinib (CO-1686), olmutinib (BI1482694/HM61713), nazartinib (EGF816), and ASP8273. Preliminary results with olmutinib were presented recently[47]; the ORR was 54% and the median duration of response was 8.3 months in patients with *EGFR* T790M–containing tumors after progression on first- or secondgeneration EGFR TKIs. In a phase II trial of rociletinib, the ORR in patients with T790M-positive disease was 59%,[48] but this agent is no longer being developed.

Acquired Resistance to Mutant-Selective EGFR TKIs

As with the first- and second-generation wild-type–specific EGFR TKIs, the magnitude and duration of response to osimertinib and other third-generation EGFR TKIs are variable, and resistance inevitably develops. Mechanisms of acquired resistance to mutant-selective EGFR TKIs are only beginning to be defined. Analogous to resistance to the wild-type EGFR TKIs, resistance to mutant-selective TKIs can be mediated through target-dependent and target-independent mechanisms (Table 2). For example, acquisition of a tertiary *EGFR* mutation, C797S, has been reported in patients with acquired resistance to osimertinib.[49,50] This cysteine residue is the site where the mutant specific inhibitors covalently bind to the EGFR ATP binding pocket. In addition, an additional tertiary mutation, *EGFR* L718Q, has been detected in a patient with osimertinib resistance.[51] To date, the frequency of these tertiary *EGFR* mutations (C797S and L718Q) has not been clearly defined. Other studies have reported loss of the *EGFR* T790M mutation or *EGFR* amplification at the time of resistance to the mutant-selective EGFR TKI rociletinib.[25] Target-independent resistance mechanisms have been described, including *HER2* or *MET* amplification and *KRAS* mutation, at the time of osimertinib resistance.[52,53] *KRAS* mutations have been identified in preclinical models of osimertinib resistance.[54] Finally, small cell transformation has been identified in patients with rociletinib resistance.[25] Overall, the data that have been reported to date for resistance to mutant-selective EGFR TKIs have come from case reports or small case series. Additional studies are needed to expand the knowledge about resistance to this novel class of EGFR TKIs.

Overcoming Acquired Resistance to MutantSelective EGFR TKIs

At present, there are no FDA-approved targeted therapies for patients who experience disease progression on a mutant-selective EGFR TKI, and the current standard of care is cytotoxic chemotherapy. However, several clinical trials currently are exploring novel therapeutic options for this cohort of patients. For example, preclinical evidence supports the idea of vertical EGFR and MAPK inhibition in *EGFR*-mutant lung cancer,[54,55] and the phase IB TATTON trial (NCT02143466) currently is investigating osimertinib plus the MEK inhibitor selumetinib in patients who have experienced progression during treatment with osimertinib monotherapy.[56] The TATTON trial also includes an arm to evaluate the combination of osimertinib plus the MET inhibitor savolitinib. Other studies are looking at the combination of osimertinib plus the EGFR monoclonal antibody necitumumab (NCT02496663, NCT02789345) to attempt to prolong the initial response to osimertinib monotherapy. In addition, the combination of osimertinib with a Bcl-2 (B-cell lymphoma 2) inhibitor, navitoclax, is being tested in a phase I clinical trial. This combination stems from preclinical work showing that the Bcl-2 inhibitor restored sensitivity to EGFR TKIs in vitro.[57] Finally, a fourth generation of mutantselective EGFR allosteric inhibitors, such as EAI045,[58] are being developed. EAI045 in combination with the EGFR monoclonal antibody cetuximab is effective in mouse models of lung cancer driven by *EGFR* (L858R/T790M) and by *EGFR* (L858R/T790M/C797S). Future studies are anticipated to bring EAI045 or similar EGFR allosteric inhibitors into the clinic, driving home the paradigm that patients can and will be treated with multiple lines of EGFR-directed therapies.

ALK TKI RESISTANCE: MECHANISMS AND THERAPEUTIC APPROACHES

Therapeutic Targeting of ALK Rearrangements in Lung Cancer

ALK rearrangements are present in 3% to 5% of patients with NSCLC and define an important molecular subgroup of the disease.[59] Shortly after the discovery of *ALK* rearrangements in NSCLC in 2007,[60] it was recognized that *ALK* rearrangements confer exquisite sensitivity to ALK inhibition.[3] Crizotinib is a first-in-class ALK/ROS1/MET inhibitor that was approved initially by the FDA in 2011 for the treatment of advanced, *ALK*-positive NSCLC. In two randomized phase III trials (PROFILE 1014 and 1007), crizotinib produced significant improvements in ORR, PFS, and quality of life compared with first- and second-line cytotoxic chemotherapy.[6,7] On the basis of these studies, crizotinib emerged as a standard first-line therapy for advanced ALK-positive NSCLC. Although crizotinib has transformed the management of *ALK*-positive NSCLC, patients ultimately still experience progression during therapy—commonly within 1 to 2 years.[6,7]

Acquired Resistance to Crizotinib

Efforts to identify molecular mechanisms of resistance to crizotinib initially focused upon on-target resistance mechanisms. In one early report, Katayama et al[61] identified secondary resistance mutations in the *ALK* kinase domain in four (22%) of 18 patients with *ALK*-positive disease who experienced progression during treatment with crizotinib. In addition, one (6.7%) of 15 patients in this series had high-level amplification of the *ALK* fusion gene without concurrent resistance mutations, which suggests that amplification alone was sufficient to confer resistance. In a separate report, Doebele and colleagues[62] found *ALK* resistance mutations and *ALK* copy number gains in four (36%) and two (18%) of 11 patients, respectively. Collectively, across all series, the most common crizotinib resistance mutations have been *ALK* G1269A and the gatekeeper mutation *ALK* L1196M, which is analogous to *EGFR* T790M.[61–63] However, in contrast to the experience with *EGFR*-mutant NSCLC, in which T790M is the lone dominant resistant mutation to first- and second-generation inhibitors, various different *ALK* resistance mutations have been described. Furthermore, these mutations are distributed throughout the kinase domain.[61–65]

Although secondary *ALK* mutations are well-established mediators of resistance to crizotinib, most patients lack these alterations. In such cases, bypass signaling pathways have been implicated frequently in resistance. To date, various bypass signaling pathways have been identified. One of the earliest examples was EGFR pathway activation via upregulation of EGFR ligands and/or the receptor itself—independent of *EGFR* mutations or genomic amplification.[61,65,66] More recently, Wilson and colleagues[67] identified ligand-mediated HER2/3 activation and protein kinase C activation (via P2Y receptors) as drivers of crizotinib resistance by using an open-reading frame library screen. In addition, *cKIT* amplification, insulin-like growth factor 1 receptor (IGF-1R) activation, and upregulation of SRC proto-oncogene, non-receptor tyrosine kinase (SRC) signaling all have been identified separately as mediators of crizotinib resistance in patient-derived specimens.[61,68,69] In addition, patients treated with crizotinib may progress in the CNS as a result of limited blood-brain barrier penetration (i.e., pharmacokinetic failure) rather than true biological resistance.

Overcoming Acquired Resistance to Crizotinib

To address the clinical challenge of crizotinib resistance, multiple second-generation ALK inhibitors have been developed (Table 3). These agents generally have greater selectivity, potency, and CNS penetration than crizotinib. Second-generation ALK inhibitors also are generally able to overcome common crizotinib-resistant *ALK* mutations (e.g., L1196M).[70] To date, two second-generation ALK inhibitors, ceritinib and alectinib, have received regulatory approval in the United States for the management of crizotinib-resistant or -intolerant, ALK-positive NSCLC. Ceritinib was approved on the basis of ASCEND-1, a single-arm, phase I study that demonstrated an ORR of 56% and a median PFS of 6.9 months among 163 patients pretreated with crizotinib.[71,72] The activity of alectinib in the crizotinib-resistant setting has been evaluated in two single-arm studies (NP28673 and NP28761), which demonstrated ORRs of 48% to 50% and median PFS times of 8.1 to 8.9 months.[73,74] In addition to ceritinib and alectinib, brigatinib, another second-generation ALK inhibitor, recently received breakthrough therapy designation by the FDA for the treatment of crizotinib-resistant or -intolerant, *ALK*-positive NSCLC. In a preliminary phase I/II study and randomized phase II trial (ALTA), brigatinib was highly active (ORRs, 45% to 62%; median PFS times, 8.8 to 15.6 months) in previously treated patients with *ALK*-positive disease.[75,76]

Given the activity and enhanced CNS penetration of second-generation ALK inhibitors, there has been a growing interest in moving these agents to the first-line setting. In one recent study (ASCEND-4), patients with *ALK*-positive disease who received first-line ceritinib experienced a prolonged median PFS of 16.6 months; however, the control arm in this study was platinum/pemetrexed rather than the current standard, crizotinib.[77] Several other randomized studies comparing second-generation ALK inhibitors with crizotinib in the treatment-naive setting are ongoing. For example, in a preliminary report from the phase III J-ALEX study, alectinib demonstrated impressive improvements in ORR and PFS compared with crizotinib among 207 ALK inhibitor–naive Japanese patients.[78] A parallel global study to evaluate alectinib versus crizotinib (ALEX; NCT02075840) is ongoing. A central question, however, is whether upfront use of more potent second-generation ALK inhibitors will translate into long-term survival benefits that surpass the combined benefit of use of crizotinib and second-generation ALK inhibitors sequentially.

Acquired Resistance to Second-Generation ALK Inhibitors: Ceritinib, Alectinib, and Brigatinib

Like the experience with crizotinib in *ALK*-positive NSCLC, resistance almost invariably develops after treatment with second-generation ALK inhibitors. Interestingly, the frequency of *ALK* resistance mutations in this setting is actually higher than after crizotinib, which likely reflects the greater potency of second-generation ALK inhibitors.[63,70] Indeed, in a recent analysis of 48 biopsies from patients with *ALK*-positive disease who experienced progression during treatment with second-generation ALK inhibitors (ceritinib, n = 24; alectinib, n = 17; brigatinib, n = 7), *ALK* resistance mutations were found in 56% of patients (ceritinib, 54%; alectinib, 53%; brigatinib, 71%),[63] and each ALK inhibitor had a distinct spectrum of *ALK* resistance mutations, which likely reflected structural differences between agents. Notably, the frequency of one particular resistance mutation, *ALK* G1202R,

increased significantly after treatment with all second-generation ALK inhibitors. Although *ALK* G1202R was found in only 2% of crizotinib-resistant specimens, it was detected in 21% to 43% of biopsies from patients who experienced progression during treatment with second-generation ALK inhibitors.[64] This alteration confers high-level resistance to available first- and second-generation ALK inhibitors via steric hindrance.[61,70,79]

In addition to *ALK* resistance mutations, target-independent mechanisms of resistance to second-generation ALK inhibitors have been described (Table 2). These include MAPK pathway reactivation,[69] SRC activation,[63,69] *PIK3CA* mutations,[63,69] and *MET* amplification.[80] Of note, *MET* amplification has not been reported in crizotinib-resistant specimens to date, likely because crizotinib inhibits both ALK and MET. By contrast, second-generation ALK inhibitors do not have anti-MET activity. In addition to bypass signaling pathways, several isolated cases of small cell transformation among patients with *ALK*-positive disease who experienced disease progression during treatment with crizotinib and alectinib also have been reported.[81–83] However, the frequency of this lineage change is less clear. In a large series of 103 repeat biopsies from patients with *ALK*-positive disease who experienced progression during treatment with first- and second-generation ALK inhibitors, no occurrences of SCLC were observed, which suggests that this is a rare event.[63] In this same series, however, five (42%) of 12 post-ceritinib biopsies showed phenotypic changes consistent with EMT, such as loss of E-cadherin staining and gain of vimentin expression. It should be noted, however, that three of five patients with EMT also had concomitant *ALK* resistance mutations; thus, the role of EMT in driving clinical resistance warrants additional investigation.

Overcoming Acquired Resistance to SecondGeneration ALK Inhibitors

On the basis of the success of second-generation ALK inhibitors in overcoming resistance to crizotinib, recent efforts have centered on developing additional novel ALK inhibitors (Table 3). For example, lorlatinib is a potent, third-generation ALK inhibitor that has demonstrated in vitro activity against all known *ALK* resistance mutations, including G1202R.[79] In preliminary results from an ongoing phase I/II study (NCT01970865), lorlatinib demonstrated significant activity; ORRs were 57% and 42% among patients with *ALK*-positive disease previously treated with one or with two or more ALK TKIs, respectively.[84] Furthermore, responses also were seen in patients with baseline CNS metastases (intracranial ORR, 39%) and patients with *ALK* G1202R. The phase II portion of this study is ongoing.

Because each ALK inhibitor is associated with a different spectrum of *ALK* resistance mutations,[63] another emerging strategy to combat resistance is to administer ALK inhibitors sequentially on the basis of resistance profiles. One proof-of-principle example of this approach involved the case of a patient with *ALK*-positive disease who had a dual *ALK* mutation (C1156Y and L1198F) after sequential treatment with crizotinib, ceritinib, and lorlatinib. Interestingly, this compound mutation paradoxically resensitized cells to crizotinib, which resulted in another clinical response to crizotinib.[85]

In addition to the discussed strategies, cytotoxic chemotherapy continues to play a role in the management of *ALK*-positive patients progressing on second-generation

inhibitors. Additionally, ALK inhibitor combinations also are being explored in an effort to overcome potential bypass signaling pathways. For example, Hrustanovic and colleagues[86] recently found that upfront polytherapy with ALK and MEK inhibitors improved responses and eliminated the emergence of resistance in preclinical models, forming the basis for clinical trials of similar combinations. Currently, clinical trials evaluating ALK inhibitors in combination with CDK4/6 inhibitors (NCT02292550), mTOR inhibitors (NCT02321501), and antiangiogenesis agents (NCT02521051) also are ongoing. In addition, given the broad success of immune checkpoint inhibitors in NSCLC, several trials combining ALK and PD-1/PD-L1 inhibitors have been launched (e.g., NCT01998126, NCT02511184, NCT02393625), though preclinical data to support such combinations are lacking.[87] Ultimately, additional insights into the molecular mechanisms of resistance to second-generation ALK inhibitors are needed, which may in turn inform more rationale combination approaches.

ROLE OF RADIATION IN METASTATIC NSCLC

Thus far, this review has focused on multisite progression and switching to other systemic agents at the time of disease progression. However, consideration also should be given to the use of local therapy, potentially in the form of stereotactic ablative radiotherapy (SABR), as a means of controlling disease that has progressed in salvage settings or to spur the immune system action on distant sites in an abscopal mechanism. Both of these efforts could permit patients to remain on systemic agents that appear to be working in a predominant number of disease sites, aided by the use of local therapy in the resistant areas of disease. SABR is a refined radiation treatment approach, also referred to as stereotactic body radiation therapy (SBRT), that is able to deliver ablative doses of radiation using a highly conformal approach with image guidance. SABR is delivered in five or fewer treatments, providing a short course regimen that is effective in controlling local disease, noninvasive, and safely able to reach disease in most anatomical locations.

Currently, the major arguments for aggressive local treatment of metastatic disease include a general lack of ability of systemic therapy to cure solid tumors, failures most often presenting in original sites of gross disease, heterogeneity in response to systemic therapy secondary to disease biology, and reduced effectiveness of subsequent lines of systemic agents. All of these points collectively support the notion that local therapy might enhance overall tumor control, because local therapies are more effective at reducing tumor bulk, are less likely to be rendered ineffective by multidrug resistance mutations, and may reduce additional metastases by successful gross tumor control.

Reports of long-term survival of patients after surgical resection of metastases began to surface as early as the 1930s in patients with limited metastases.[88,89] In general with respect to solid tumors and particularly lung cancer metastases, intracranial disease was one of the earliest sites in which SABR/SBRT based radiosurgery technologies was utilized with a local therapy approach. The state of limited metastatic disease without widespread progression, however, ultimately was termed oligometastasis in 1995.[90] Oligometastasis now is recognized as a unique clinical entity in which aggressive, ablative therapies can result in long-term cure, primarily identified in patients with sarcoma, with colorectal

cancer, and with limited brain metastases treated with surgery or radiation.[88,89] It is in this setting of oligometastases that one would expect salvage local therapy to have the potential to help systemic therapy the most with respect to PFS.

There are no prospective studies to compare surgical resection to radiation therapy for the salvage treatment of oligometastatic disease. Indeed, nonoperative approaches may be preferred for some patients with oligometastasis because of the risks of surgical morbidity and mortality as well as comorbid conditions common in patients with NSCLC, which may increase such surgical risks. Furthermore, patients with metastatic disease generally are treated with systemic therapy for long periods of time; therefore, any local therapy that prevents or delays patients from receiving subsequent systemic therapy would be detrimental. SABR adapts the techniques of stereotactic radiosurgery for intracranial disease to the delivery of highly conformal radiation to extracranial targets, which increasingly is used to treat oligometastasis.[91]

With the current knowledge, one can argue that there is really no role for the use of radiation in widely metastatic disease states of progression except for palliation. Radiation in oligoprogression is most likely to show some benefit, especially because first failures occur in sites of original gross disease. The concept of radiation eliciting an abscopal response in unirradiated disease is still in its infancy for NSCLC and, therefore, will elicit no additional discussion in this narrative. Should salvage be given in the form of SABR without systemic therapy afterward? Should we continue the targeted therapy that may have been working for microscopic disease or for a majority of original lesions? With new generations of targeted agents, should patients switch to the new generation before local therapy is considered? Evidence is provided for some rationalizations about treatment paradigms for targeted therapy–resistant NSCLC, with a focus on extra cranial progression that may benefit from radiation.

Oligoprogression

Radiation to treat oligoprogression in NSCLC treated with targeted therapies has come to the forefront only recently after the more widespread use of targeted therapies themselves. The University of Colorado Cancer Center has published its experience with local therapies combined with targeted agents in the management of *EGFR*- and *ALK*-positive NSCLC. In one retrospective evaluation, 65 patients with either *ALK*-positive or *EGFR*-mutated tumors were identified.[92] Of these patients who received the appropriate kinase inhibitors, 51 experienced progression. Twenty-five of these 51 patients received local therapy, primarily in the form of SABR. Thereafter, patients were maintained on their original targeted therapy. The median PFS was 6.2 months after local therapy. Nineteen of 25 patients experienced progression again and required a reconsideration of this treatment approach. The authors concluded that the local therapy, which added no notable toxicity, permitted continued benefit and use of predominantly effective systemic therapies. In a second study from this same group, 38 patients with *ALK*-positive NSCLC were treated with crizotinib.[93] Thirty-three experienced disease progression during crizotinib treatment; 14 of them had extracranial oligoprogressive disease treated with SABR. There was no notable toxicity associated with SABR. All patients treated with radiation continued to receive crizotinib.

Those patients who were eligible to receive SABR remained treated with crizotinib for a median of 28 months, compared with 10.1 months for those patients who did not fit the profile to receive SABR. When patients were treated with crizotinib for greater than 12 months, their 2-year overall survival was 72%; overall survival was 12% for those who were not. These data suggest a synergy between SABR and continuation of targeted therapy, though the findings could have been simply secondary to a difference in biology between patients with oligoprogressive versus widely progressive disease states.

In 2013, Yu and colleagues[94] from Memorial Sloan Kettering Cancer Center identified 18 patients with NSCLC who had been treated with extracranial local therapy in the form of surgery, SABR, or radiofrequency ablation for *EGFR*-mutant tumors that had developed resistance to EGFR TKIs. These patients had been identified from prospective tissue biopsy trials. There were no notable complications from local treatments, and 85% of patients restarted either erlotinib or gefitinib within 1 month of completion of local therapy. From completion of local therapy, the median PFS was 10 months, the time to change of systemic therapy was 22 months, and the median overall survival was 41 months. Ultimately, it appeared that the local therapy was well tolerated, allowed treatment to be maintained on targeted agents that were probably active against a majority of gross and microscopic disease, and helped these patients with respect to survival.

A single arm, prospective, phase II trial subsequently was conducted jointly at The University of Texas Southwestern Medical Center and the University of Colorado to test the contribution of SABR to targeted therapies to enhance survival and allow patients to remain on effective systemic therapies.[95] Iyengar and colleagues[95] prospectively tested the use of SABR and concurrent erlotinib in 24 patients with 52 extracranial metastases from NSCLC who had experienced progression through at least one systemic regimen, including targeted therapies, in a limited metastatic fashion. SABR was delivered as salvage to all sites of oligoprogressive disease. The median survival and PFS were 20.4 months and 14.7 months, respectively. Only three local failures of 47 evaluable lesions were observed, and 10 patients experienced progression at distant sites. The use of SABR allowed patients to remain on one targeted therapy for longer periods of time than historical standards, changed/shifted the pattern of failure from local to distant sites first, and led to prolonged overall survival and PFS (when compared with historical outcomes). Interestingly, of the 12 patients who had marker evaluation, none harbored *EGFR* or *ALK* activating mutations.

In nonrandomized, prospective approaches, there is always a question of whether oligoprogressive disease represents a biologic entity with a more indolent disease course (i.e., fewer sites of progression or metastasis, resulting in improved survival independent of treatment management). To address this caveat, a multi-institutional Canadian phase II trial will assess local therapy in the form of SBRT for oligoprogression in a randomized setting (NCT02756793) with PFS as primary endpoint. Patients with targetable mutations will be eligible.

Ultimately, the limited data to date suggest that local therapies in the form of SABR can be completed quickly, are effective for local control, cause limited toxicity, and allow patients to continue to receive the same systemic therapy that probably is working to treat a majority

of the disease. Survival parameters also may be extended with local treatment, though these paradigms are actively being clarified in randomized studies. In oligoprogressive states, it appears best to combine SABR with systemic agents, not to use SABR alone. This thought comes from the evidence that suggests it is best to use the local therapy for the most resistant areas of disease but to use the systemic therapy for microscopic disease (i.e., disease that is not obvious on imaging), because it is accessible by all tissues. Finally, we should view and treat oligoprogressive NSCLC with targetable mutations potentially in the same fashion as limited metastatic colorectal cancer. Once metastasized, colorectal cancer is treated with a pragmatic approach that consists of intermittent aggressive local therapy and continued use of systemic therapies for as long as some benefit is manifest.

CONCLUSION

In summary, targeted therapies continue to reshape the management of NSCLC, particularly among patients with *EGFR* mutations and *ALK* rearrangements. Despite steady improvements in targeted therapies within these molecular subsets, however, acquired resistance to therapy is ever present. Recent preclinical models and translational efforts have provided critical insights into the molecular mechanisms of resistance. Such work has been complemented by recent advances in noninvasive tools, such as circulating free DNA assays, which have permitted additional insights into the temporal dynamics and heterogeneity of resistance. Collectively, these insights have helped inform strategies to overcome resistance. To date, these strategies have centered on the development of novel next-generation inhibitors, rationale combinations, and use of local ablative therapies. It is hoped that such approaches will continue to improve outcomes among patients who have NSCLC with targetable alterations.

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KEY POINTS

- Acquired drug resistance remains a critical barrier in the effort to maximize the efficacy of targeted therapies in lung cancer.
- Mechanisms of acquired drug resistance include target-dependent alterations, including acquired mutations or amplification of the drug target, and target-independent mechanisms, including activation of bypass signaling pathways and histologic transformation.
- Second- and third-generation EGFR and ALK TKIs have been developed to overcome target-dependent mechanisms of acquired drug resistance. These drugs have increased on-target potency; however, acquired resistance remains a significant problem, even with more potent inhibitors.
- Rational combination therapeutic approaches to overcome drug resistance, such as the addition of MEK blockade to EGFR and ALK inhibition, have been developed on the basis of preclinical modeling of the disease states.
- Treatment of oligoprogressive disease with local therapies may significantly improve outcomes in patients treated with targeted therapies.

TABLE 1.

EGFR TKIs Currently in Clinical Use for Patients With *EGFR-Mutant* NSCLC

EGFR TKI	Selectivity	Reversible/ Irreversible	Status in Lung Cancer	Select Clinical Trials
First Generation				
Erlotinib	Wild-type *EGFR*	Reversible	FDA approved	
Getitinib	Wild-type *EGFR*	Reversible	FDA approved	
Second Generation				
Afatinib	Wild-type *EGFR*	Irreversible	FDA approved	
Third Generation				
Osimertinib (AZD9291)	Mutant *EGFR*	Irreversible	FDA approved; T790M-positive only	NCT02296125 (phase III first line)
				NCT02511106 (phase III adjuvant)
Rociletinib (CO-1686)	Mutant *EGFR*	Irreversible	No longer in development	NCT02147990 (phase II)
Nazartinib (EGF816)	Mutant *EGFR*	Irreversible	Investigational	NCT02335944 (phase IB/II)
				NCT02108964 (phase IB/II)
Olmutinib (BI1482694/ HM61713)	Mutant *EGFR*	Irreversible	Investigational	NCT02485652 (phase II)
				NCT02444819 (phase II)
ASP8273	Mutant *EGFR*	Irreversible	Investigational	NCT02500927 (phase II)
				NCT02588261 (phase III first line)

Abbreviations: FDA, U.S Food and Drug Administration; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

TABLE 2.

Acquired Resistance Across the Spectrum of EGFR and ALK Inhibitors

TKI	Target-Dependent Mechanisms	Target-Independent Mechanisms
EGFR TKIs		
Wild-type selective EGFR TKIs	Acquisition of a secondary mutation, most commonly T790M	*HER2* amplification
		MET amplification
		PIK3CA mutation
		EMT
		Small cell transformation
Mutant-selective EGFR TKIs	Acquisition of a tertiary mutation, such as C797S or L718Q	*HER2* amplification
	Loss of T790M allele	*MET* amplification
	EGFR amplification	*KRAS* mutation
		Small cell transformation
ALK TKIs		
First-generation ALK TKIs (crizotinib)	Acquisition of secondary mutations (> 10 reported), most commonly L1196M and G1269A	EGFR activation
	ALK fusion gene amplification	MAPK pathway activation
		c-KIT amplification and SCF overexpression
		SRC activation
		IGF-1R activation
		Ligand-mediated HER2/3 activation
		Protein kinase C activation
		Small cell transformation (rare)
Second-generation ALK TKIs (ceritinib, alectinib, and brigatinib)	Acquisition of secondary mutations, most commonly *ALK* G1202R	MAPK reactivation
		SRC activation
		PIK3CA mutations
		MET amplification
		EMT

Abbreviations: ALK, anaplastic lymphoma kinase; EMT, epithelial-mesenchymal transition; IGF-1R, insulin-like growth factor 1 receptor; MAPK, mitogen-activated protein kinase; SCF, stem cell factor; SRC, SRC proto-oncogene, non-receptor tyrosine kinase; TKIs, tyrosine kinase inhibitors.

TABLE 3.

Select ALK TKIs Currently in Clinical Use and/or Under Investigation for Patients With *ALK*- Rearranged NSCLC

		Select Trial Details				
ALK TKIs	**Status in Lung Cancer**	**Trial/Name**	**Phase**	**No. of Patients***	**ORR (%)**	**Median PFS (Months)**
First Generation						
Crizotinib	FDA approved	PROFILE 1014	III	343	74	10.9
		PROFILE 1007	III	347	65	7.7
Second Generation						
Ceritinib	FDA approved	ASCEND-1	I	163	56	6.9
		ASCEND-2	II	140	38.6	5.7
		ASCEND-4**	III	376	72.5	16.6
Alectinib	FDA approved	NP28673	II	138	50	8.9
		NP28761	II	87	48	8.1
		J-ALEX**	III	207	85.4	NR (95% CI, 20.3 to NR)
Brigatinib	Breakthrough therapy designation	NCT01449461	I/II	79	62	13.2
		ALTA	II	222†	45–55	8.8–15.6
Ensartinib (X-396)	Investigational	NCT01625234	I/II	27‡	70	N/A
Third Generation						
Lorlatinib	Investigational	NCT01970865	I/II	41§	46	11.4

*Number of participants in the overall study population.

**Enrolled ALK inhibitor-naive patients.

†Participants were randomly assigned to either 90 or 180 mg of brigatinib.

‡Includes eight crizotinib-naive patients.

§Includes 26 patients previously treated with two or more ALK TKIs.

Abbreviations: ALK, anaplastic lymphoma kinase; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.