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The International Association for the Study of Lung Cancer Consensus Statement on Optimizing Management of EGFR Mutation-Positive Non-Small Cell Lung Cancer: Status in 2016

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ABSTRACT

Mutations in the epidermal growth factor receptor gene (EGFR) represent one of the most frequent "actionable" alterations in non–small cell lung cancer (NSCLC). Typified by high response rates to targeted therapies, EGFR tyrosine kinase inhibitors (TKIs) are now established first-line treatment options and have transformed the treatment paradigm for NSCLC. With the recent breakthrough designation and approval of the third-generation EGFR TKI osimertinib, available systemic and local treatment options have expanded, requiring new clinical algorithms that take into account individual patient molecular and clinical profiles. In this International Association for the Study of Lung Cancer commissioned consensus statement, key pathologic, diagnostic, and therapeutic considerations, such as optimal choice of EGFR TKI and management of brain metastasis, are discussed. In addition, recommendations are made for clinical guidelines and research priorities, such as the role of repeat biopsies and use of circulating free DNA for molecular studies. With the rapid pace of progress in treating EGFR-mutant NSCLC, this statement provides a state-of-the-art review of the contemporary issues in managing this unique subgroup of patients.

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Keywords: Non–small cell lung cancer; EGFR mutation; Tyrosine kinase inhibitor; Therapy; Resistance; Brain metastases

Introduction

Since the seminal discovery of activating epidermal growth factor receptor gene (EGFR) mutations in 2004,1,2 the management paradigms and outcomes of lung cancer have changed dramatically. One of the key conceptual advances has been the identification of subsets of patients with non–small cell lung cancer (NSCLC) who exhibit differential responses to specific therapies. The significant impact of mutation-specific targeted therapies directed against an expanding list of "actionable" alterations has necessitated rapid integration of molecular profiling into clinical practice. One of the striking observations arising from molecular screening of patient populations globally has been the difference in prevalence of EGFR mutations across ethnicities.3,4 For example, the prevalence of EGFR mutations ranges from between 5% and 10% in whites to between 60% and 70% in never-smoking Asian patients with adenocarcinoma—notably leading to regional differences in molecular profiling algorithms, as well as to varying levels of feasibility in conducting biomarker-selected trials.5

As a classic oncogene-driven solid tumor, EGFR mutation–positive NSCLC has a unique disease course typified by high response rates to tyrosine kinase inhibitors (TKIs).6 Several phase III studies comparing first- and second-generation epidermal growth factor receptor (EGFR) TKIs with chemotherapy have demonstrated significantly higher response rates and longer progression-free survival (PFS), establishing EGFR TKIs as a first-line treatment of EGFR-mutant NSCLC.6–13 However, resistance to TKIs almost invariably occurs and several molecular mechanisms have been described, with the EGFR T790M somatic mutation being the most frequent alteration detected in approximately half of progressing tumors.14–16 Next-generation EGFR TKIs have since been developed specifically to target the T790M mutation,17,18 and they have demonstrated high and durable responses in patients with advanced EGFR-mutant NSCLC who have been previously treated and in whom first- or second-generation EGFR TKIs have failed. The median overall survival (OS) after first- or second-generation EGFR TKIs has reached 2 to 3 years and is likely to be extended further with the recent approval of
third-generation EGFR TKIs that demonstrated a median PFS of 9.6 months (for patients without central nervous system [CNS] metastases).\textsuperscript{18}

With an expanding array of biomarker-directed treatment approaches in NSCLC, there has been an increasing role for multiplexed clinical testing—both at the time of initial diagnosis and at the time of disease progression. New clinical paradigms such as repeat biopsies specifically for molecular profiling and novel efficacy end points, such as dynamic changes in plasma EGFR mutations, are starting to play a broader role in patient management. Furthermore, with improved delineation of the clinical sequelae of EGFR-mutant NSCLC (e.g., lifetime risk of CNS involvement), there has been a need to better coordinate multidisciplinary care with the expanding number of treatment options available. With further comprehensive genomic profiling studies on lung cancers, relevant cancer traits and putative therapeutically tractable targets have emerged.\textsuperscript{19–22} As a result, there has been significant enthusiasm for developing multiple novel agents and combinations in select patient populations, as well as an urgent need to develop and validate a broad repertoire of scalable laboratory techniques to screen patients with lung cancer for actionable biomarkers.

In 2013 the International Association for the Study of Lung Cancer published a consensus report on the management of NSCLC with EGFR inhibitors.\textsuperscript{23} Given the rapidly evolving clinical paradigms, the committee has found it timely to convene an expert panel to review the emerging data pertaining to contemporary management of this unique subgroup of patients, who may have the potential for a long-term “chronic” life perspective involving sequential treatment options. This consensus statement was the result of a 2-day expert meeting with participants from a multidisciplinary team comprising medical and radiation oncologists, thoracic surgeons, pathologists, pulmonologists, and radiologists. All members critically reviewed and discussed the available scientific data, with the specific aim of providing practitioners with contemporary guidance with regard to diagnostic algorithms and interdisciplinary clinical management, as well as prioritized research questions.

**Molecular Diagnostics**

**Methods for Ascertaining EGFR Mutation Status**

With the increased accessibility of EGFR TKIs, routine molecular testing for EGFR mutations has been increasingly adopted as the standard of care worldwide. In the seminal publication by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society,\textsuperscript{24} strong recommendations were made regarding the necessity to classify more accurately the histological types of NSCLC, and guidelines were proposed for optimal management of tissues to maximize their availability for molecular studies. Although EGFR testing is recommended for all patients in whom nonsquamous NSCLC has been diagnosed, it may also be considered in cases of squamous histological findings with unique clinical phenotypes (e.g., in never-smokers or in patients with mixed adenosquamous subtypes). In this process, the role of the pathologist is highly important to adequately integrate both routine histopathologic assessment and molecular testing into clinical pathology for proper tumor diagnosis and subsequent selection of the most appropriate therapy. The handling of the biopsy and cytologic specimens for histological examination and subsequent molecular testing requires thoughtful prioritization of sample use to prevent loss of tissue in lower-priority analysis relative to the molecular testing required for selection of therapy. The pathologist should determine whether the amount of malignant cells available in the specimen is adequate for nucleic acid extraction and also for histological section–based tests (e.g., diagnostic immunohistochemical analysis, fluorescence in situ hybridization, etc.).

Nevertheless, there is international variation in terms of who initiates molecular studies (i.e., the treating oncologist or the pathologist). Reflex testing ordered by the pathologist who makes the diagnosis can result in a significant reduction in waiting time for the oncologist making treatment decisions.\textsuperscript{25} However, this is largely determined by the reimbursement policy for molecular studies in the country or local health authority. From the standpoints of the pathologist and workflow, it is generally more efficient to obtain unstained sections sufficient to test for the necessary molecular markers relevant to clinical practice during the initial diagnostic workup of the tumor biopsy sample. In this respect, two critical considerations are the type of platform utilized for molecular studies and the source of DNA.

A range of techniques and platforms are currently available for evaluating EGFR mutation status and are summarized in Table 1. Although most have high specificity, they vary in terms of assay sensitivity, whether only known mutations are detected, and scalability for multiplex testing. In general, a sensitivity of 1% to 5% is considered acceptable and the procedure should be conducted in a clinically approved diagnostic laboratory. Although the Roche cobas 4800 system (Roche Molecular Systems, Inc.) is the only U.S. Food and Drug Administration (FDA)-approved companion diagnostic for erlotinib, a range of sensitive sequencing methods are typically implemented in many molecular pathology laboratories. Moreover, despite conferring high sensitivity, the Roche cobas 4800 assay covers only the 28
A further consideration is discordance among studies of biopsy and cytologic samples with respect to the extent of molecular testing. Importantly, molecular testing experiences have reported that 70% to 85% of cases of primary lung tumors, with the remainder from metastatic lesions and management of potential complications. Biopsies should be directed at progressing sites (i.e., a

mutations that comprise approximately 95% of known EGFR alterations, whereas Sanger sequencing may uncover known and novel mutations (e.g., C797S) in the context of resistance to third-generation EGFR TKIs.39

Although tissue specimens are preferable for molecular testing, cytologic samples with abundant malignant cells can also be successfully used for such analyses. Considering that two-thirds or more of patients with lung cancer present with advanced-stage disease, the most often available diagnostic samples are small biopsy specimens obtained through transthoracic or broncho-ne-needle aspiration.4,40

Thus, it is not surprising that large population-based testing experiences have reported that 70% to 85% of tested samples include core needle biopsy specimens, fine-needle aspiration samples, and fluid specimens.4,40

Approximately 60% of the specimens are from the primary lung tumor, with the remainder from metastatic sites. Importantly, the reported failure rates for testing are approximately 5% to 30%, mostly owing to inadequate sample materials or lower than the minimum required tumor cellularity.40–42 In addition, tissues samples obtained through transthoracic or bronchoscopic needle biopsies are usually formalin fixed and embedded in paraffin, which imposes some limitations on the extent of molecular testing. Importantly, molecular studies of biopsy and cytologic samples with adequate material have yielded similar failure rates.40,43,44 A further consideration is discordance in molecular status between primary and metastatic sites,45,46 which could be associated with tumor heterogeneity between the different sites of involvement.

Newer sequencing technologies can potentially offer greater breadth of detecting genetic mutations with high sensitivity—in both EGFR and other drivers. Targeted multiplexed hotspot panels (e.g., Agena Oncocarta [Agena Bioscience, San Diego, CA],47 SNaPshot [Applied Biosystems, Foster City, CA]),48 and next-generation sequencing (NGS) panels49,50 have already been developed and are available in College of American Pathologists (CAP)-accredited academic and commercial laboratories. Not only do they permit frequently occurring mutations to be detected simultaneously, but some NGS-based assays offer the possibility of detecting chromosomal rearrangements, copy number variations, and insertions or deletions, thus making a compelling case for NGS-based molecular prescreening because all classes of alterations—point mutations, rearrangements, copy number changes, and insertions or deletions—are therapeutically relevant in the management of NSCLC.

It is anticipated that the requirement for molecular testing will increasingly affect the way that biopsies are performed on suspicious or progressing lesions and how samples are processed for routine pathologic diagnosis. In particular, given the clinical impact of delineating mechanisms of resistance to EGFR TKIs (e.g., the T790M mutation), additional expertise is required to evaluate the suitability of acquiring biopsy specimens from posttreatment lesions—in terms of both selection of appropriate lesions and management of potential complications. Biopsies should be directed at progressing sites (i.e., a

<table>
<thead>
<tr>
<th>Technique</th>
<th>Sensitivity (% Mutant DNA)</th>
<th>Mutations Identified</th>
<th>Detection of Co-mutations</th>
<th>Potential Applications</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct sequencing</td>
<td>10%-25%</td>
<td>Known and new</td>
<td>No</td>
<td>Tissue</td>
<td>Multiple studies</td>
</tr>
<tr>
<td>Pyrosequencing</td>
<td>5%-10%</td>
<td>Known only</td>
<td>No</td>
<td>Tissue</td>
<td>Young et al., 2013</td>
</tr>
<tr>
<td>Multiplex PCR (Snaphot)</td>
<td>5%</td>
<td>Known only</td>
<td>Yes (hotspots)</td>
<td>Tissue</td>
<td>Dias-Santagata et al., 2010</td>
</tr>
<tr>
<td>cobas</td>
<td>3%-5%</td>
<td>Known only</td>
<td>No</td>
<td>Tissue, Plasma</td>
<td>Lopez-Rios et al., 2013</td>
</tr>
<tr>
<td>WAVE-surveyor</td>
<td>2%</td>
<td>Known only</td>
<td>No</td>
<td>Tissue, Plasma</td>
<td>Janne et al., 2006</td>
</tr>
<tr>
<td>Mass spectrometry based</td>
<td>1%-10%</td>
<td>Known only</td>
<td>Yes (hotspots)</td>
<td>Tissue, Plasma</td>
<td>Arcila et al., 2011; Sherwood et al., 2014</td>
</tr>
<tr>
<td>High-depth NGS (at least 200× depth)</td>
<td>1%-10% depending on error rates and sequencing depth</td>
<td>Known and new</td>
<td>Yes</td>
<td>Tissue, Plasma</td>
<td>Uchida et al., 2015</td>
</tr>
<tr>
<td>Therascreen</td>
<td>1%-5%</td>
<td>Known only</td>
<td>No</td>
<td>Tissue, Plasma</td>
<td>Lopez-Rios et al., 2013</td>
</tr>
<tr>
<td>Scorpions ARMS</td>
<td>1%</td>
<td>Known only</td>
<td>No</td>
<td>Tissue, Plasma</td>
<td>Chiu et al., 2014</td>
</tr>
<tr>
<td>Locked nucleic acid clamp</td>
<td>1%</td>
<td>Known only</td>
<td>No</td>
<td>Tissue, Plasma</td>
<td>Costa et al., 2014</td>
</tr>
<tr>
<td>TAm-Seq</td>
<td>2%</td>
<td>Known and new</td>
<td>Yes</td>
<td>Tissue, Plasma</td>
<td>Forshew et al., 2012</td>
</tr>
<tr>
<td>BEAMing</td>
<td>&lt;0.1%</td>
<td>Known only</td>
<td>No</td>
<td>Tissue, Plasma</td>
<td>Taniguchi et al., 2011</td>
</tr>
<tr>
<td>Digital droplet PCR</td>
<td>&lt;0.1%</td>
<td>Known only</td>
<td>No</td>
<td>Tissue, Plasma</td>
<td>Watanabe et al., 2015</td>
</tr>
<tr>
<td>CAPP-Seq</td>
<td>~0.02%</td>
<td>Known and new</td>
<td>Yes</td>
<td>Plasma</td>
<td>Newman et al., 2014</td>
</tr>
</tbody>
</table>

EGFR, epidermal growth factor receptor gene; PCR, polymerase chain reaction; NGS, next-generation sequencing; ARMS, amplification refractory mutation system; CAPP, cancer personalized profiling by deep sequencing.

Table 1. Methods for Detecting EGFR Mutations, Relative Performance, and Applications
growing lesion, a fluorodeoxyglucose F18–positron emission tomography–positive site, or a new lesion), and ideally on-site cytologic evaluation would be at hand to verify quality of tissue yield. The committee recommends that individual institutions establish a strategy or protocol for obtaining tissue samples adequate for both clinical and research studies, including additional tissue cores during biopsy procedures, implementing rapid on-site cytologic evaluation, and storage of frozen tissue for maximal yield of genomic material.

What Is the Current Role for Plasma-Based EGFR Testing?

Not all patients with advanced NSCLC are amenable to repeat biopsy. In a single-center series of 126 patients, repeat biopsy was feasible in 74.6% of patients, with 20% of patients with successful biopsies having inadequate tissue for mutational analysis, which highlights the need to explore noninvasive tools to detect common alterations. As such there has been significant enthusiasm for development of noninvasive methods for testing EGFR mutation status, such as circulating cell-free DNA (cfDNA).

To date, most studies have been retrospective. A meta-analysis reported a sensitivity of 0.62 and a specificity of 0.96 as compared with tissue genotyping as the standard, with higher sensitivity observed in patients with stage III and IV disease. This has led to increasing acceptance of noninvasive plasma-based testing for EGFR mutations as a standard test for patient selection, with the cobas platform having been approved in Europe and China. Nevertheless, there remains a significant chance of false negativity in ascertaining T790M in cfDNA at present, underscoring the continued role for traditional tissue-based molecular diagnosis.

Beyond providing a diagnostic tool, cfDNA status may also make it possible to prognosticate patients. In the EURTAC trial, a peptide nucleic acid–mediated 5′-nuclease real-time polymerase chain reaction (PCR) assay was used to detect cfDNA at baseline in 78% of patients (76 of 97), which suggested that the presence of L858R mutation in cfDNA is a negative prognostic factor. Similarly, cfDNA has been examined as a pharmacodynamic marker, where the failure of clearance of plasma EGFR mutations after three cycles of combined EGFR TKI treatment and chemotherapy (the FAST-ACT2 study) was found to be an independent predictor of shorter PFS and OS. Thus, it may provide a tool to further stratify patient subsets and provide an opportunity to identify “poor-risk” groups for escalation of therapy (e.g., combinatorial approaches).

These data underscore the promise of cfDNA in disease monitoring, although several issues remain to be elucidated before its widespread clinical application. These include the differences in performance among assay platforms (allele-specific PCR, emulsion PCR, and NGS) and standardization of the time points for disease monitoring, which will need to be prospectively validated to determine relevant cutoffs and clinical relevance.

Recommendations. (1) EGFR mutations should be evaluated routinely in nonsquamous NSCLC, and it is reasonable to consider testing lung cancer with other histological patterns, especially in patients with atypical clinical features (e.g., squamous cell carcinoma in a never-smoker). (2) EGFR mutation studies should be undertaken in College of American Pathologists/Clinical Laboratory Improvement Amendments–accredited laboratories on validated and sensitive platforms. Multiplexed testing should be explored to cover the breadth of actionable alterations in NSCLC. (3) Tissue-based molecular analysis remains the accepted standard for establishing initial diagnosis, as well as for evaluating resistance to TKIs. Repeat biopsies of accessible growing lesions in a safe manner after failure of EGFR TKIs should be considered a new standard of care. (5) At present, the clinical context in which genotyping cfDNA has gained approval in certain countries is at the time of initial diagnosis. (6) More research focused on assay performance and the analytical range of cfDNA is warranted to expand the potential clinical utility (such as in enhancing patient stratification), although prospective validation of this approach is required.

Optimal Selection of First-Line Therapy for EGFR Mutation-Positive NSCLC

With eight randomized phase III trials establishing the superior efficacy of first- and second-generation EGFR TKIs versus chemotherapy, patients with activating EGFR mutations should commence by receiving either a first or second-generation EGFR TKI or participate in ongoing clinical trials of EGFR inhibitors. There are few studies comparing the relative efficacy of gefitinib versus erlotinib, although retrospective studies suggest that there is no difference in efficacy. Although the incidence of adverse events such as rash and diarrhea is more pronounced with second-generation EGFR TKIs, there may be some patient subgroups that may especially benefit from afatinib. Combined analysis of LUX-3 and LUX-6 studies showed for the first time an OS benefit in the exon 19 deletion subgroup receiving afatinib compared with those treated with platinum doublet chemotherapy. However, a limitation in these trials is the low proportion of patients in the chemotherapy arms who crossed over to TKI.
Nevertheless, this underscores the importance of ensuring early access to an EGFR TKI during the disease course and highlights the limitation of adopting OS as an end point in clinical trials of EGFR-mutant NSCLC.

Given the potential for higher efficacy, second-generation inhibitors such as afatinib and dacomitinib are also being evaluated in the first-line setting. LUX Lung-7 was the first randomized study that compared a first-generation (gefitinib) to a second-generation (afatinib) EGFR TKI.57 This phase IIb study (n = 319) aimed to show difference in three coprimary end points, including PFS, OS, and time to treatment failure. Although the median PFS times for afatinib and gefitinib were 11.0 versus 10.9 months, respectively, the hazard ratio demonstrated a significant difference at 0.73 (95% confidence interval: 0.57–0.95, p = 0.017). In addition, the proportion of patients who achieved an objective tumor response was higher with afatinib (70% versus 56%, p = 0.0083) and this difference was observed in both the L858R mutation (66% versus 42%) and exon 19 deletion (73% versus 66%) subgroups. As anticipated, the increased rates of grade 3 or higher adverse events such as diarrhea (13% versus 1%), rash (9% versus 3%), and fatigue (6% versus 0%) resulted in more dose reductions in the afatinib arm compared with in the gefitinib arm (42% versus 2%). The OS results remain immature. The other study that compared dacomitinib with gefitinib (ARCHER 1050) completed accrual in March 2015 and data will likely be available in late 2016. First-line trials involving a third-generation EGFR TKI such as osimertinib have also been initiated against erlotinib or gefitinib (Table 2) on the premise that eradicating T790M-positive clones can forestall resistance to treatment. However, at present, clinical data do not convincingly support preferential use in the first-line setting. Nevertheless, given the differences in pharmacokinetics, dose intensity, and toxicity profiles, key considerations in determining the choice of agent include patient tolerability, mutation subtype, and access to therapies.

Patients who commence by receiving chemotherapy upfront (e.g., those whose EGFR mutation status had yet to be determined before initiation of therapy) should consider switching to an EGFR TKI after confirmation of activating mutations. Although most randomized clinical trials do not reveal differences in OS when comparing an upfront TKI versus chemotherapy, EGFR TKIs do have superior CNS disease control (discussed in a later section on management of CNS disease).58 However, if the initial response to chemotherapy is good, it is also reasonable to consider completing four to six cycles followed by maintenance TKI, an approach validated in a small subgroup of EGFR mutation-positive patients in the SATURN trial.59

### Table 2. Selected Randomized Late-Phase Trials for EGFR-Mutant NSCLC Comparing Experimental Arms against EGFR TKIs

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary End Point</th>
<th>Line of Therapy</th>
<th>Sample Size (Estimated Enrollment)</th>
<th>Study Start Date</th>
<th>Phase Selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUX Lung-7 NCT01466660</td>
<td>PFS</td>
<td>First</td>
<td>319</td>
<td>Dec 2011</td>
<td>L858R, exon 19 del</td>
</tr>
<tr>
<td>ARCHER 1050 NCT01774721</td>
<td>PFS</td>
<td>First</td>
<td>440</td>
<td>Apr 2013</td>
<td>L858R, exon 19 del</td>
</tr>
<tr>
<td>RELAY NCT02411448</td>
<td>PFS</td>
<td>First</td>
<td>462</td>
<td>May 2015</td>
<td>L858R, exon 19 del</td>
</tr>
<tr>
<td>NEJ026 UMIN000017069</td>
<td>PFS</td>
<td>First</td>
<td>214</td>
<td>Apr 2015</td>
<td>L858R, exon 19 del</td>
</tr>
<tr>
<td>BEVERLY NCT02633189</td>
<td>PFS</td>
<td>First</td>
<td>200</td>
<td>Dec 2015</td>
<td>L858R, exon 19 del</td>
</tr>
<tr>
<td>SWOG 1403 NCT02278051</td>
<td>PFS</td>
<td>First</td>
<td>605</td>
<td>Mar 2015</td>
<td>L858R, exon 19 del</td>
</tr>
<tr>
<td>FLAURA NCT02296225</td>
<td>PFS</td>
<td>First</td>
<td>530</td>
<td>May 2015</td>
<td>L858R, exon 19 del</td>
</tr>
<tr>
<td>SOLAR NCT02588261</td>
<td>PFS</td>
<td>First</td>
<td>540</td>
<td>Jul 2015</td>
<td>L858R, exon 19 del</td>
</tr>
</tbody>
</table>

EGFR, epidermal growth factor receptor gene; NSCLC, non–small cell lung cancer; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; del, deletion; PFS, progression-free survival; OS, overall survival.
There are fewer data regarding activity of EGFR TKIs for uncommon EGFR mutations, which are found in approximately 10% of patients.60–62 Most of the studies are retrospective, comprising individual case reports in patients treated with both first- and second-generation TKIs that highlight differential sensitivities based on mutation type.62,63 According to the largest pooled analysis to date, which pooled data from LUX Lung 2, LUX Lung 3, and LUX Lung 6, objective responses to afatinib were observed in patients with G719X (77.8% [14 of 18]), L861Q (56.3%, [nine of 16]), and S768I (100% [eight of eight]) mutations. Finally, not all exon 20 insertions or duplications are insensitive to EGFR TKIs, with the FQA insertion at position A763_Y764 (in the middle of the c-helix) conferring sensitivity to first- and second-generation EGFR TKIs.60,64

As EGFR TKIs generally do not cure patients, a range of combinatorial approaches with other active agents is very appealing. EGFR TKIs combined with chemotherapy have been evaluated in unselected NSCLC. In subgroup analysis, PFS benefit has been observed in patients with EGFR activating mutations; however, a clinically relevant OS advantage has not been demonstrated.65 Combinations with antiangiogenic therapy have yielded promising results. In a randomized phase II study examining the role of erlotinib-bevacizumab, median PFS reached an impressive 16.0 months, compared with 9.7 months for erlotinib alone.66 Another strategy with anti-EGFR antibodies is the combination of afatinib-cetuximab, which has demonstrated early evidence of efficacy in EGFR TKI-resistant NSCLC.67 Other approaches that are also being tested include targeting common escape pathways, such as MET proto-oncogene, receptor tyrosine kinase (MET) and insulin-like growth factor 1 receptor (IGF1R).68,69 Although these are rational combinations, their clinical efficacy is unproven and the outcome of ongoing clinical trials are eagerly awaited. Combinations with immune checkpoint inhibitors have shown durable responses,70 but they have not yet clearly shown better efficacy than TKI alone, and further studies are underway. Current ongoing prospective phase III studies of combinations examined in EGFR-mutant NSCLC are summarized in Table 2 and have yet to be reported.

**Recommendations.** (1) Optimal first-line treatment for EGFR-mutant NSCLC includes any of the approved EGFR TKIs, including gefitinib, erlotinib, and afatinib. The choice of agent should be based on factors such as performance status and access to therapies. (2) For patients with EGFR mutations whose treatment is initiated with chemotherapy up front, due consideration should be given to transitioning them to an EGFR TKI.

**EGFR TKI Resistance**

**Definitions of Resistance: Clinical, Imaging, or Emerging Biomarkers?**

A diagnosis of “acquired resistance” to EGFR TKI therapies is usually decided when lung cancer with a known sensitizing EGFR mutation develops systemic progression of disease (PD) (Response Evaluation Criteria in Solid Tumors [RECIST] or World Health Organization) while the patient is continuing to receive an EGFR TKI after a documented partial or complete response, or has had stable disease for more than 6 months, according to “Jackman’s criteria.”71 This clinical definition has been adopted as a patient selection criterion in many trials but does not take into account the molecular mechanisms of resistance or the clinical context of progression.

RECIST defines PD as an increase in the sum of diameters of target lesions by 20% usually on CT scans. Suppose that an original tumor is 10 cm in diameter and then shrinks to 3 cm. The diagnosis of PD would be made when the tumor diameter becomes 3.6 cm. These “progressing” patients may remain relatively asymptomatic from their disease and current targeted treatment. Therefore, a RECIST-based diagnosis of PD may not necessarily indicate a need for an immediate change of treatment. The ASPIRATION study showed that in selected patients whose tumor was judged to have slow growth, lack of symptoms, or a small number of lesions at PD, erlotinib beyond the point of PD according to RECIST could be continued at the investigators’ discretion. Approximately half of the cohort (54% [93 of 171]) were eligible to continue EGFR TKI beyond progression, and the median duration of postprogression erlotinib was 3.1 months.72 Patient characteristics in the postprogression treatment group included an Eastern Cooperative Oncology Group performance status of 0 to 1 at time of progression, longer median PFS, improved depth of response, and longer time from best objective response to RECIST-based progression.72 The overall consensus is that it is reasonable to maintain patients on an EGFR TKI even in the setting of low-volume disease progression, as long as there is perceived clinical benefit. In this setting, interval imaging assessments should be continued at consistent time points to monitor changes in tumor growth.

Nevertheless, given the deeper understanding of molecular mechanisms and clinical patterns of resistance, it will be increasingly important for trials to consistently and accurately delineate patterns of resistance or PD to reduce heterogeneity in patient cohorts, as well as to improve interpretation of treatment efficacy. Here the major challenge is identifying patients who may have continued benefit from existing EGFR TKIs with only low-volume disease progression. In this
respect, clinical studies should take into account the pace of tumor growth, as well as improve documentation of disease beyond RECIST-based criteria, including CNS versus extracranial progression and oligoprogression versus systemic progression (Fig. 1). This will be especially critical because PFS is increasingly being adopted as the primary end point in clinical trials and novel agents might have specific therapeutic niches (e.g., CNS-penetrant EGFR TKIs). A clinical pathway is proposed in Figure 1, together with an updated definition of primary and secondary EGFR TKI resistance described in Table 3.

**Molecular Mechanisms of EGFR TKI Resistance**

The emergence of the T790M mutation in exon 20 of EGFR is the most common mechanism of resistance to first- and second-generation EGFR TKIs (erlotinib, gefitinib, and afatinib). Although attributed to steric
Beyond genomic alterations, transcriptomic analysis has identified several key players in EGFR TKI resistance. For instance, the BRAF serine/threonine kinase gene (BRAF) and the PIK3CA gene (coding for the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene) with T790M mutations confer resistance. In the setting of clinical resistance to EGFR TKI, the extended phase I study (AURA) of the third-generation TKI, osimertinib (AZD9291) confers an objective response rate (ORR) of 70% to 77% in patients with T790M mutations confirmed in repeat tumor biopsies and 21% in T790M-negative tumors.18 With further robust data arising from the phase II trial of osimertinib (AURA2), the FDA granted accelerated approval to osimertinib in November 2015. Another third-generation EGFR TKI, rociletinib, was initially reported as having similarly high responses in the T790M-positive group (RR 59%).85 However the ORRs confirmed by independent radiological review in the cohorts of patients with T790M-positive tumors (centrally confirmed) who received 500 mg twice daily and 625 mg twice daily were updated and substantially lower (28% and 34%, respectively).86 Because the FDA’s Oncologic Drugs Advisory Committee recommended against accelerated approval of rociletinib, Clovis Oncology decided to stop further clinical development of rociletinib as part of its company strategy.

It is notable that responses have been observed among T790M-negative patients with both third-generation inhibitors. Possible reasons for tumor response in T790M-negative patients include EGFR TKI retreatment effect, intratumoral heterogeneity (in which case biopsies may have missed the detection of T790M), false-negative results and/or low detection rate, and possibly off-target effects of the active metabolites (e.g., IGF1R inhibition). At this time, patients with T790M-negative tumors should be screened for other therapeutically tractable resistance mechanisms under clinical evaluation, including MET amplification,86,87 AXL receptor tyrosine kinase gene (AXL) overexpression,88 and PIK3CA mutation.89 If there are no suitable clinical trials, then platinum-based chemotherapy would be a reasonable option. The question of whether a EGFR TKI should be continued beyond progression when switching to platinum-based chemotherapy was addressed in the IMPRESS study, in which patients received up to six cycles of pemetrexed-cisplatin, with or without gefitinib, after progression from a first-line EGFR TKI.90 No difference in response rates (32% versus 34%) or median PFS (5.4 months in both groups) was demonstrated. However, a subsequent subgroup analysis stratifying patients according to plasma T790M status at time of progression suggested a role for continuing gefitinib in those who are T790M negative. Thus, although the IMPRESS study suggested no difference associated with a TKI continued with chemotherapy, whether selected patient subgroups

Table 3. IASLC Definitions of EGFR TKI Resistance

<table>
<thead>
<tr>
<th>EGFR TKI Resistance</th>
<th>Clinical and Molecular Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Stable disease as best response after EGFR TKI monotherapy</td>
</tr>
<tr>
<td>Secondary</td>
<td>Partial response or stable disease for more than 6 mo with an enlarging extracranial target lesion(s)</td>
</tr>
<tr>
<td></td>
<td>Documented resistance mechanism (e.g., T790M mutation, MET amplification, or other emerging mechanism relevant to the TKI)</td>
</tr>
<tr>
<td></td>
<td><strong>To avoid retreatment effect or disease flare</strong></td>
</tr>
<tr>
<td></td>
<td>1. Patients can have minimal or no washout to EGFR TKI, especially in absence of grade 2 or higher toxicity</td>
</tr>
<tr>
<td></td>
<td>2. Patients should be receiving an EGFR TKI as the last line of therapy</td>
</tr>
</tbody>
</table>

Note: Patients who have a treatment-free interval from an EGFR TKI beyond 30 days may still be considered EGFR TKI resistant if (a) there has been no intervening alternative treatment or (b) there has been intervening therapy but no appreciable response was observed.
IASLC, International Association for the Study of Lung Cancer; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; MET, MET proto-oncogene, receptor tyrosine kinase.

Clinical Strategies for EGFR TKI Resistance

At present, numerous ongoing clinical trials are specifically addressing these resistance mechanisms; however, the only mature data are related to the T790M mutation. In the setting of clinical resistance to EGFR TKI, the extended phase I study (AURA) of the third-generation inhibitor osimertinib (AZD9291) confers an objective response rate (ORR) of up to 51% in patients with T790M mutations confirmed in repeat tumor biopsies and 21% in T790M-negative tumors.18 With further robust data arising from the phase II trial of osimertinib (AURA2), the FDA granted accelerated approval to osimertinib in November 2015. Another third-generation EGFR TKI, rociletinib, was initially reported as having similarly high responses in the T790M-positive group (RR 59%).85 However the ORRs confirmed by independent radiological review in the cohorts of patients with T790M-positive tumors (centrally confirmed) who received 500 mg twice daily and 625 mg twice daily were updated and substantially lower (28% and 34%, respectively).86 Because the FDA’s Oncologic Drugs Advisory Committee recommended against accelerated approval of rociletinib, Clovis Oncology decided to stop further clinical development of rociletinib as part of its company strategy.

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hindrance imposed by the methionine residue, the T790M mutation has also been shown in direct binding assays to increase adenosine triphosphate affinity.74 Other resistance mechanisms involve bypass pathways such as MET proto-oncogene, receptor tyrosine kinase gene (MET) amplification (5%–30% depending on thresholds), erb-b2 receptor tyrosine kinase 2 (HER2) amplification (12%), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene (PIK3CA) mutation (5%), and B-Raf proto- oncogene, serine/threonine kinase gene (BRAF) mutation (1%).14,16,75 Beyond genomic alterations, transcriptomic and proteomic perturbations such as AXL receptor tyrosine kinase overexpression, phosphatase and tension homolog loss, insulin-like growth factor 1/insulin-like growth factor 1 receptor (IGF1/IGF1R) activation, nuclear factor-kappa-B activation, and epithelial to mesenchymal transition have also been implicated, although these are less frequently reported on account of the lack of available robust assays. Histological transformation to both squamous cell cancer76 and small cell lung cancers16 has also been described, with the latter shown to be consistently associated with loss of retinoblastoma 1 gene (RB1).77 The common resistance mechanisms are summarized in Table 4.

Clinical Strategies for EGFR TKI Resistance

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(e.g., T790M-negative) may obtain additional benefit from this approach remains an open question.

Given the importance of establishing T790M status in the context of available third-generation EGFR TKIs, there are circumstances in which target lesions might not be amenable to tissue biopsies, such as in the case of multiple small pulmonary nodules or in patients who are at high risk for complications due to comorbidities, poor lung function, or ongoing hemoptysis. Like plasma-based EGFR mutation testing at time of diagnosis, the prospect of tailoring treatment according to plasma T790M status at the time of TKI resistance is appealing, although there remain several questions that need to be addressed.

**T790M as a Dynamic Biomarker**

The presence or absence of T790M in plasma and tumor can be due to biological and/or or technical reasons. Differences in preanalytic processing, platform performance characteristics and detection limits of cfDNA, and disease burden, can all have an impact on the test outcome. For example, determination of pretreatment T790M mutation status in formalin-fixed, paraffin-embedded tissue by using standard sequencing platforms has been classically described in less than 5% of treatment-naive tumors (Table 5), but with more sensitive techniques (e.g., droplet digital PCR), T790M can be detected in up to 80% of these tumors. On the other hand, recent in vitro data using cell line models have suggested that T790M mutation could also arise de novo as a new mutation in tumor cells that survive (referred to as a drug-tolerant population) during TKI therapy. Tumor heterogeneity can exist between different disease sites (e.g., primary lesion versus liver metastasis) and even within the same site, and sampling bias may inadvertently result in a missed T790M mutation. cfDNA may circumvent this by providing molecular portraits of the total burden of the disease and not just a single site, which is supported in studies in which pretreatment discordance between cfDNA and tumor biopsies was found to be T790M positive, to some extent illustrating the impact of biological heterogeneity and the complementary role of noninvasive genotyping.

The optimal management of patients who are plasma positive and not progressing according to imaging remains uncertain. In another prospective study evaluating serial samples using digital droplet PCR technology, plasma levels of EGFR sensitizing mutations were found to drop with tumor response, with the emergence of T790M mutations occurring in plasma up to 4 months before PD by imaging studies, presumably owing to an
emerging population of resistant clones. Prospective clinical trials will be required to establish the utility of an early switch from first- to third-generation inhibitors at "molecular progression" (i.e., the first appearance of T790M in plasma).

To date, the diagnosis of TKI resistance has been made by RECIST using imaging studies in clinical trials. Blood or serum biomarkers and other imaging techniques (e.g., positron emission tomography–CT) are encouraged in the framework of investigational studies and protocols, but their application in routine clinical management beyond more traditional size-based criteria remains to be established. In clinical practice, continuation of an initial EGFR TKI beyond RECIST-based PD, as long as the patient remains asymptomatic, can be an option in selected cases. In summary, noninvasive plasma-based testing is highly promising, with great potential for clinical utility in the clinic, although for technical and biological reasons it should not at this time replace tumor biopsies for ascertaining molecular status.

**Recommendations.** (1) In patients with minor disease progression, it is reasonable to continue an EGFR TKI beyond progression, especially if patients are asymptomatic. (2) Alternative end points beyond RECIST should be actively examined, particularly in the context of stratifying for novel combinations and agents directed toward specific therapeutic niches. (3) Third-generation T790M-specific, wild-type-sparing EGFR TKIs are recommended in patients harboring T790M mutations who progress while they are receiving a first- or second-generation TKI. (4) Numerous strategies to overcome resistance are currently being explored beyond T790M, and participation in clinical trials should be encouraged. Platinum-based chemotherapy is recommended for patients without targetable alterations. (5) At this time, the decision to switch to a third-generation EGFR TKI should be based on radiologically determined progression and not solely on the detection of T790M in cfDNA. This is especially true given the range of sensitivities of T790M detection currently available.

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**Table 5. Cohort-Based Studies Examining the Prevalence of the T790M Mutation**

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>Source</th>
<th>Technique</th>
<th>n</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment Naive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inukai et al., 2006</td>
<td>Unselected NSCLC</td>
<td>FFPE tissue</td>
<td>Sanger sequencing</td>
<td>1 of 280</td>
<td>0.36%</td>
</tr>
<tr>
<td>Jain et al., 2015</td>
<td>EGFR M+</td>
<td>FFPE tissue</td>
<td>Mutant-enriched PCR assay</td>
<td>10 of 280</td>
<td>3.5%</td>
</tr>
<tr>
<td>Costa et al., 2014</td>
<td>EGFR M+</td>
<td>FFPE tissue</td>
<td>Peptide-nucleic acid clamp PCR</td>
<td>62 of 95</td>
<td>65.26%</td>
</tr>
<tr>
<td>Rosell et al., 2011</td>
<td>EGFR M+</td>
<td>FFPE tissue</td>
<td>Peptide-nucleic acid TaqMan PCR</td>
<td>45 of 129</td>
<td>35%</td>
</tr>
<tr>
<td>Maheswaran et al., 2015</td>
<td>EGFR M+</td>
<td>Plasma</td>
<td>Scorpion ARMS</td>
<td>10 of 26</td>
<td>38%</td>
</tr>
<tr>
<td>Yu et al., 2014</td>
<td>EGFR M+</td>
<td>FFPE tissue</td>
<td>Mass spectrometry-based</td>
<td>11 of 579</td>
<td>2%</td>
</tr>
<tr>
<td>Su et al., 2012</td>
<td>EGFR M+</td>
<td>FFPE tissue</td>
<td>Mass spectrometry-based</td>
<td>27 of 107</td>
<td>25.2%</td>
</tr>
<tr>
<td>Watanabe et al., 2015</td>
<td>EGFR M+</td>
<td>FFPE tissue</td>
<td>Sanger sequencing</td>
<td>3 of 107</td>
<td>2.8%</td>
</tr>
<tr>
<td>Uchida et al., 2015</td>
<td>EGFR M+</td>
<td>Plasma</td>
<td>NGS (ion torrent PGM)</td>
<td>0 of 103</td>
<td>0%</td>
</tr>
<tr>
<td>Mok et al., 2015</td>
<td>Unselected NSCLC</td>
<td>FFPE tissue</td>
<td>cobas EGFR mutation</td>
<td>3 of 241</td>
<td>1.2%</td>
</tr>
<tr>
<td><strong>Post-TKI treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taniguchi et al., 2011</td>
<td>EGFR M+</td>
<td>Plasma</td>
<td>BEAMing</td>
<td>10 of 23</td>
<td>43.5%</td>
</tr>
<tr>
<td>Su et al., 2012</td>
<td>EGFR M+</td>
<td>FFPE tissue</td>
<td>Mass spectrometry</td>
<td>10 of 12</td>
<td>83.3%</td>
</tr>
<tr>
<td>Sequist et al., 2011</td>
<td>EGFR M+</td>
<td>FFPE tissue</td>
<td>Sanger sequencing</td>
<td>4 of 12</td>
<td>33%</td>
</tr>
<tr>
<td>Sakai et al., 2013</td>
<td>EGFR M+</td>
<td>Plasma</td>
<td>Multiplexed PCR</td>
<td>18 of 37</td>
<td>48%</td>
</tr>
<tr>
<td>Hata et al., 2013</td>
<td>EGFR M+</td>
<td>FFPE tissue</td>
<td>Mass spectrometry (SABER)</td>
<td>21 of 75</td>
<td>28%</td>
</tr>
<tr>
<td>Yu et al., 2013</td>
<td>EGFR M+</td>
<td>FFPE tissue</td>
<td>Not reported</td>
<td>22 of 54</td>
<td>41%</td>
</tr>
<tr>
<td>Oxnard et al., 2014</td>
<td>EGFR M+</td>
<td>Tissue</td>
<td>Mass spectrometry, Sanger sequencing, LNA</td>
<td>98 of 155</td>
<td>63.2%</td>
</tr>
<tr>
<td>Ishii et al., 2015</td>
<td>EGFR M+</td>
<td>Tissue</td>
<td>Digital PCR</td>
<td>11 of 18</td>
<td>61%</td>
</tr>
<tr>
<td>Sundaresan et al., 2015</td>
<td>EGFR M+</td>
<td>Tissue</td>
<td>Digital PCR</td>
<td>10 of 18</td>
<td>56%</td>
</tr>
</tbody>
</table>

FFPE, formalin-fixed, paraffin-embedded; PCR, polymerase chain reaction; EGFR M+, epidermal growth factor receptor gene mutation-positive; ARMS, amplification refractory mutation system; NGS, next-generation sequencing; PGM, Personal Genome Machine; NSCLC, non-small-cell lung cancer; SABER, single allele base extension reaction; LNA, locked nucleic acid.
Local Therapy for Unique Sites of Disease Involvement

CNS Metastases

Brain metastases will develop in at least 25% to 30% of patients with NSCLC. Whether EGFR-mutated NSCLC has a higher tropism to metastasize to the CNS is unclear, because the lifetime risk is confounded by this molecular subgroup’s longer survival. Because of the blood-brain barrier, systemic chemotherapy tends to be ineffective against brain metastases and palliative radiotherapy is frequently used. The traditionally cited prognosis is grim, with a median OS of less than 3 months without treatment and less than 6 months for most patients. Interestingly, patients with EGFR-mutant NSCLC who are harboring brain metastases have been reported as having median survival times as long as 2 to 3 years. However, although patients with EGFR-mutant NSCLC demonstrate high response rates to whole brain radiation therapy (WBRT) and WBRT improves the duration of intracranial disease control over TKIs or stereotactic radiosurgery (SRS), many practitioners seek to avoid the hair loss, fatigue, and other neurocognitive sequelae of WBRT in this population. If radiation therapy is to be performed, factors that may be considered in the decision between WBRT or SRS might include the degree of symptoms, size of metastatic tumor(s), presence of hemorrhage or peritumoral edema, brainstem involvement, and number of metastases. Consultation with a radiation oncologist to evaluate technical factors is highly encouraged. Rarely, in the context of oligometastasis, neurosurgery can be considered, particularly at first presentation and if there is low-volume extracranial disease. Furthermore, EGFR TKIs have independent activity in the CNS, with response rates ranging up to 86% in small series of patients treated exclusively with EGFR TKIs and raising the question as to whether small asymptomatic brain metastases may be treated with a TKI alone. Although it is unlikely that a complete response will be achieved with a TKI, TKIs frequently produce partial responses or stable disease and it has not been established in this clinical scenario that local therapy increases survival.

The combinatorial effect of TKIs with WBRT has been tested in two prospective trials. A multi-institutional phase II study combined erlotinib with WBRT in 40 patients with NSCLC. The ORR was 86% and the median survival was 11.8 months, but in patients with a known EGFR mutation, it was 19.1 months. The study established the feasibility and tolerability of this option for patients with EGFR-mutant NSCLC who have numerous or symptomatic brain metastases and require simultaneous urgent initiation of systemic therapy at the time of WBRT.

The Radiation Therapy Oncology Group conducted a phase III trial of WBRT and SRS, given alone or with either temozolamide or erlotinib, for patients with NSCLC with one to three brain metastases. The study closed early on account of poor accrual and because the three arms were not statistically different. Grade 3 to 5 toxicity rates were 41% to 49% in the two arms incorporating concurrent drug treatment. Patients were not tested for EGFR mutation in this study and the combination of both WBRT and SRS has now become less favored, especially in the EGFR-mutant population, thus limiting the impact of this study on practice.

EGFR TKIs have shown promising efficacy in the treatment of leptomeningeal disease. In particular, a high dose or pulsatile dosing may produce a higher response rate in this situation. More recently, newer-generation EGFR TKIs have been reported to show activity against leptomeningeal disease (e.g., osimertinib and the CNS-penetrant EGFR TKI AZD3759). Both agents are currently being evaluated in a larger cohort of patients with leptomeningeal disease and brain metastasis. TKIs may also be combined with focally directed SRS or partial brain radiotherapy for isolated leptomeningeal disease. For this challenging clinical situation, consideration may be given to intrathecal chemotherapy and/or WBRT, although there should be reservations about the morbidity unless the patient has an exceptional performance status.

Sites of Local Involvement Other Than the CNS

Locally directed therapy may take the form of SBRT, image-guided ablation (including cryotherapy, radiofrequency ablation, and microwave ablation), or even surgical resection. Some of the key considerations are summarized in Table 6. All of these therapies aim to completely ablate the local disease with the view that there will be overall benefit to the patient. The challenge in deciding among these different methods is one of balancing potential harms versus benefits.

One major limitation is that most of the data are derived from retrospective case series, with only a few series examining the management of oligometastases in patients with EGFR mutations. From a systematic review of patients with NSCLC with one to five metastases undergoing radiation or surgery, significant factors that predicted favorable outcomes include definitive treatment of the primary site of disease, nodal status, and a disease-free interval of 6 to 12 months. In a series cohort of 25 patients with oncogene-driven NSCLC (15 anaplastic lymphoma receptor tyrosine kinase gene [ALK] driven and 10 EGFR driven) treated with local
ablative therapy, the median time to first oligoprogressive disease was 9.8 months and median duration of targeted therapy beyond progression of 6.2 months (7.1 months in CNS-only progression and 4.0 in extracranial progression). Local therapy comprised radiation to the brain (SRS \( n = 7 \) and WBRT \( n = 6 \)) or SBRT to extracranial sites, except in one patient having an adrenalectomy.\(^{125}\) In another case series specifically in patients with \( \text{EGFR}^- \text{mutant NSCLC} \) progressing while receiving either gefitinib or erlotinib, aggressive local therapy was pursued in 18 patients (approximately 10% of examined cohort). The therapy included 11 thoracic procedures (seven lobectomies, one wedge resection, and three pneumonectomies) and two adrenalectomies, with five other patients receiving either radiofrequency ablation or radiation to lung lesions and/or nodal basins.\(^{126}\) From the time of local therapy, the median time to progression was 10 months and the median time to new systemic therapy was 22 months. The median OS from the time of local therapy was 41 months for these highly selected patients.

In summary, the role for surgery or locally ablative therapy (image-guided or stereotactic radiation) in oligometastatic or oligoprogressive disease is limited to highly selected cases and is to a certain degree dependent on the natural history of disease in each individual patient. This may include patients who, after treatment with the TKI, have had either (1) a complete response of all disease with the exception of the primary lung lesion, which starts to progress, or (2) a significant response in all sites followed by development of progression in four or fewer extracranial sites that are amenable to complete surgical resection or local therapy. In all cases, the magnitude of the proposed resection (especially if pulmonary), the patients’ underlying cardiopulmonary reserve, and whether postresection sequencing of the tumors may influence subsequent management must be considered carefully. Future comparative studies should be designed, whether in the context of direct comparisons or with the use of well-documented registries, so that the role of each local treatment modality may be better understood.

**Recommendations.** (1) For patients with a limited number and volume of brain metastases, SRS produces fewer neurologic sequelae than WBRT does, and it is a frequently preferred option if technically feasible. (2) Upfront TKIs may be considered for a limited number of small asymptomatic metastases, although intracranial disease control may be less robust in the absence of radiation therapy. (3) Local therapy for extracranial oligometastases can be considered on a case-by-case basis.

**Stage I to III \( \text{EGFR}^- \text{mutant NSCLC} \)**

In potentially curable earlier-stage disease, the addition of EGFR TKIs to curative-intent chemoradiation or surgery is attractive in theory but remains an unresolved area of research. In stage III disease, combination of EGFR TKI with curative-intent chemotherapy and radiation in unselected patients has been shown to be harmful,\(^{127}\) although there are currently ongoing studies such as RTOP 1306, which is exploring the role of

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**Table 6. Comparison of Methods to Treat Oligometastatic or Oligoprogressive Disease**

<table>
<thead>
<tr>
<th>Variable</th>
<th>SBRT</th>
<th>Image-Guided Ablation (Including Radiofrequency Ablation, Cryoablation, and Microwave Ablation)</th>
<th>Surgery</th>
</tr>
</thead>
</table>
| Key considerations     | • Patient fitness  
  • Lung function  
  • Size of tumor | • Size of tumor  
  • Location (proximity to major vessels)  
  • Tumor consistency  
  • Local expertise | • Patient fitness  
  • Burden of residual disease |
| Advantages             | • Noninvasive  
  • Able to encompass tumor volume  
  • Multiple lesions can be targeted | • Patient discharged the same day  
  • Multiple lesions can be targeted  
  • Preserves lung function  
  • Biopsy can be obtained for diagnostic purposes at same sitting | • Macroscopic removal of tumor  
  • Ample tissue for molecular analysis and heterogeneity studies |
| Disadvantages          | • Unable to obtain tissue for molecular studies | • May not achieve complete ablation  
  • Increasing use of general anesthesia | • Risk related to general anesthesia  
  • Outcomes dependent on careful patient selection and local expertise |
| Complications          | • Pneumonitis | • Pneumothorax, bronchopleural fistula, pulmonary embolism  
  • Risk related to general anesthesia (if indicated) | • Risk related to general anesthesia  
  • Surgical complications depending on location |

SBRT, stereotactic body radiation therapy.
induction EGFR TKI before chemoradiation in patients with activating EGFR mutations (NCT01822496). In the large prospective RADIANT trial of stage IB to IIIA resected NSCLC, the subset of patients harboring EGFR mutations had a prolongation of disease-free survival, albeit not a statistically significant prolongation.\textsuperscript{126} At present, the overall consensus is that there is a limited role for EGFR TKIs in stage I to III disease until further studies are completed. Several prospective adjuvant trials evaluating erlotinib (ALCHEMIST [NCT02193282]), and more recently osimertinib (NCT02511106), in patients with resected EGFR mutation NSCLC are ongoing.

**Recommendation.** (1) At present, there are no data supporting the use of EGFR TKIs in patients with stage I to III disease. Enrollment onto the ongoing randomized trials is highly encouraged to definitively address this subject.

**Concluding Remarks**

This consensus statement represents a distillation of more than a decade of bench-to-bedside research, during which time the clinical community has seen the transformation of metastatic NSCLC into a chronic disease. However, the median OS of patients with EGFR-mutant NSCLC still remains only approximately 2 to 3 years, notwithstanding the impact of highly promising therapeutic approaches being evaluated in current trials. We envision that the therapeutic landscape will evolve rapidly to become more complex with the advent of new combinations that incorporate immunotherapy and multidimensional biomarker testing on tissue from both traditional and nontraditional sources. As new therapies and combinations are introduced, it is anticipated that the genomic spectrum of resistance will shift depending on the selective pressures imposed by therapy (e.g., C797S mutations in resistance to third-generation EGFR TKIs).\textsuperscript{39} Careful integration of localized therapies, such as surgery and radiation, may provide assistance in maximizing the effects of systemic therapies. Integrating those therapeutic measures that are highly effective in the advanced stage into management of early-stage disease remains an important goal to reduce risk for disease relapse. An even more nascent research priority would be the identification of never smoker cohorts at risk for development of EGFR mutant NSCLC so as to implement screening programs for early detection. Continued progress will undoubtedly require additional resourcing of clinical and laboratory services to meet the demands of new patient management algorithms and the accelerated pace of drug and biomarker development—and increase the need to foster seamless interdisciplinary research and patient care to deliver high-precision next-generation therapeutics tailored to individual patients.

**References**


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