An Evolving Algorithm to Select and Sequence Therapies in EGFR Mutation-positive NSCLC: A Strategic Approach

Barbara Melosky,[1] Sanjay Popat,[2] David R. Gandara[3]

Abstract

The optimal treatment sequence for patients with metastatic epidermal growth factor receptor (*EGFR*) mutation-positive (*EGFR*-M$^+$) non–small-cell lung cancer (NSCLC) continues to evolve, related largely to an increasing number of breakthroughs and studies in the field. The efficacy of tyrosine kinase inhibitors in the treatment of these patients is well established; however, the treatment decision-making process is becoming more complex as our knowledge of *EGFR* mutations and resistance pathways grows and more treatment options become available. Thus, treating physicians must consider an increasing number of factors. We present a stepwise approach to personalizing the treatment of patients with *EGFR*-M$^+$ NSCLC, emphasizing some of the real world challenges faced by treating physicians. We reviewed the decision criteria for selecting the best first-line therapy, highlighted the importance of repeat biopsy on disease progression to determine the most appropriate next-line therapy, and discussed the options for third-line therapy and beyond. We also present an algorithm designed to optimize the sequencing strategies for prolonging survival and maintaining quality of life in our patients with *EGFR*-M$^+$ NSCLC.

Clinical Lung Cancer, Vol. 19, No. 1, 42-50
Keywords: Afatinib, Del19, Gefitinib, L858R, T790M

Introduction

For many years, standard first-line systemic treatment of metastatic non–small-cell lung cancer (NSCLC) consisted of 2-drug platinum combination chemotherapy. The typical interval to progression for patients receiving mutation-unselected chemotherapy was 4 to 6 months and the median survival was 10 to 12 months. The discovery of driver mutations in genetically defined subsets of NSCLC has changed this paradigm.

First-line Treatment of Epidermal Growth Factor Receptor Mutation-positive NSCLC

When epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) were first introduced, clinicians observed that a small number of patients experienced a dramatic and prolonged response to this new therapeutic agent. Subsequent studies revealed that this patient subset had an activating mutation in the EGFR tyrosine kinase domain and that *EGFR* mutation status was a predictive biomarker for TKI efficacy.[1] Subsequently, the treatment paradigm changed, and, for the first time for NSCLC, care was dictated by the results of molecular testing. The typical first-line treatment schema is shown in Figure 1.

A number of treatment guidelines[2-4] have recommended universal *EGFR* mutation (*EGFR*-M) testing for patients with advanced-stage lung cancer of nonsquamous histologic features. Approximately 10% to 40% of patients with nonsquamous NSCLC will have a sensitizing *EGFR/HER1* gene mutation; the incidence might be as great as 60% in Asian NSCLC patients with adenocarcinoma histologic features and a history of never or light smoking.[5]

Randomized clinical trials have demonstrated superior response rates and progression-free survival (PFS) with EGFR TKIs compared with chemotherapy in *EGFR*-M$^+$ populations (Table 1).[6-15] These EGFR-targeted therapies are now the standard of care for first-line therapy. However, none of the individual randomized trials of EGFR TKIs for EGFR-mutant NSCLC have shown statistically significant improvement in overall survival (OS) for the overall population of *EGFR*-mutant patients. This might

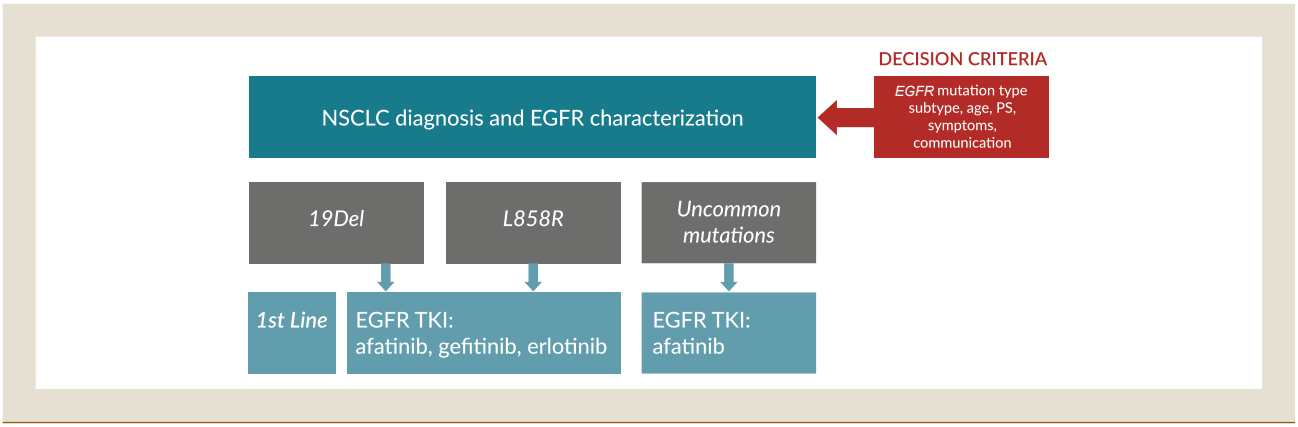
[1]Department of Medical Oncology, BC Cancer Agency, Vancouver Centre, Vancouver, BC, Canada
[2]Royal Marsden Hospital, London, UK
[3]UC Davis Comprehensive Cancer Center, Sacramento, CA

Submitted: Jan 24, 2017; Revised: May 24, 2017; Accepted: May 30, 2017; Epub: Jun 8, 2017

Address for correspondence: Barbara Melosky, MD, FRCPC, Department of Medical Oncology, BC Cancer Agency, Vancouver Centre, 600 10th Avenue West, Vancouver, BC V5Z 4E6, Canada
E-mail contact: bmelosky@bccancer.bc.ca

1525-7304/$ - see frontmatter
http://dx.doi.org/10.1016/j.clc.2017.05.019

Figure 1 First-line Therapy for Epidermal Growth Factor Receptor (*EGFR*) Mutation-positive Non–Small-cell Lung Cancer (NSCLC). Treatment and Care in the First Line Should Be Directed by the Results of Molecular Testing and Patient-related Factors Such as Age, Performance Status (PS), and Symptomatic Load



Abbreviations: *19Del* = deletion in exon 19; *L858R* = point mutations in exon 21; TKI = tyrosine kinase inhibitor.

have resulted from the high crossover rate from chemotherapy to an EGFR TKI, confounding the detection of any OS advantage.

Patient-related Factors and Side Effect Profiles in First-line Therapy Selection

Some treating oncologists believe that patient-related factors are important criteria for selecting first-line therapy. The patient's age, performance status, symptomatic load, and communication skills should be considered, because the therapeutic ratio of the different first- and second-generation EGFR TKIs vary. Thus, the TKI selected for 1 individual patient might differ from that selected for another patient. First-line TKIs bind reversibly and selectively to the EGFR. The most common toxicities of first-generation EGFR TKIs are rash and diarrhea. Although uncommon, EGFR TKIs can also lead to liver enzyme elevation and interstitial lung disease (ILD), predominantly in Asian patients. Second-generation, irreversible pan-HER inhibitors, such as afatinib, can result in an increased incidence of mucositis and grade 3 diarrhea. Patient and treating physician education are keys to improving compliance and quality of life with the use of these agents. Dose reductions according to patient tolerability are recommended for both erlotinib and afatinib, because the plasma levels achieved might exceed the inhibitory concentrations required. Preventative strategies such as prophylactic minocycline or loperamide are also options to improve TKI tolerance, without diminishing efficacy.[16] The PAN-Canadian Rash trial, although negative for its primary endpoint of the incidence of rash, showed a significant decrease in the severity of rash and delayed onset of rash with the use of prophylactic minocycline as exploratory endpoints.

EGFR Mutation Subtype in First-line Therapy Selection

The 2 most common *EGFR* mutation subtypes are a deletion in exon 19 (*Del19*) or point mutations in exon 21 (*L858R*). These constitute approximately 90% of activating mutations. Patients with advanced NSCLC whose tumors harbor different types of *EGFR* mutations experience variable responses to the currently available EGFR TKIs. Subgroup analysis from a number of the trials listed in Table 1 have shown that a *Del19* mutation is generally predictive of better efficacy than an *L858R* mutation.[17]

A preplanned subgroup analysis of the LUX-Lung 3 and 6 clinical trials demonstrated that afatinib-treated patients whose tumors had *Del19* mutations had statistically significant OS improvements compared with those receiving chemotherapy (Table 2), with balanced postprogression EGFR TKI use. For LUX-Lung 3, the hazard ratio (HR) was 0.54 (95% confidence interval [CI], 0.36-0.79; $P = .0015$). For LUX-Lung 6, the HR was 0.64 (95% CI, 0.44-0.94; $P = .023$).[18] The LUX-Lung 3 and 6 studies are the first randomized trials to show statistically significant OS improvements with first-line EGFR TKI use. *Del19* and *L858R* mutations, therefore, constitute different populations, and future trial designs should stratify patients for the different mutations. For the treating physician, the *EGFR*-mutation genotype is an additional factor to consider in the EGFR TKI selection process and might have implications for both initial drug selection and the sequencing of drug therapy.

First- Versus Second-Generation EGFR TKI for First-line Therapy

Previously, little information was available that directly compared first- and second-generation EGFR TKIs. LUX-Lung 7 is a randomized phase IIb trial that compared afatinib and gefitinib in the first-line treatment setting for advanced NSCLC with common EGFR mutations.[19,20] LUX-Lung 7 was powered for the co-primary endpoint of a HR of 0.75 for PFS. This endpoint was met for the superiority of afatinib (HR, 0.74; $P = .0178$). This observed PFS benefit for afatinib was independent of the mutation subtype. In the *L858R* mutation subgroup, the PFS HR was 0.71 (range, 0.48-1.06) and in the *Del19* subgroup, the HR was 0.76 (range, 0.55-1.06).[19] A secondary endpoint, the tumor response, was 73% versus 56% ($P = .002$) in favor of afatinib, with an improved response rate observed for both *L858R* and *Del19* genotypes.[20] No significant OS advantage was demonstrated in patients with exon 19 mutations. A 3-month OS improvement favored afatinib, although the difference was not statistically

Table 1 Randomized Trials Showing Efficacy (ORR and PFS) of EGFR TKIs Versus Chemotherapy for First-line Therapy for *EGFR* Mutation-positive NSCLC

Study; Agent	*EGFR*-M+ Subjects (n)	ORR (TKI vs. CT)	Common Mutations	
			PFS (TKI vs. CT; mo)	OS (TKI vs. CT; mo)
EURTAC[6]; erlotinib	174	58% vs. 15%	9.7 vs. 5.2; HR, 0.37 (0.25-0.54)	19.3 vs. 19.5; HR, 1.04 (0.65-1.68); $P = .8702$
OPTIMAL[7]; erlotinib	165	83% vs 36%; $P < .0001$	13.1 vs. 4.6; HR, 0.16 (0.10-0.26)	22.8 vs. 27.2; HR, 1.19 (0.83-1.71)
NEJGSG_002[8]; gefitinib	228	74% vs. 31%; $P < .001$	10.8 vs. 5.4; HR, 0.30 (0.22-0.41)	27.7 vs. 26.6; HR, 0.89 (0.63-1.24)
WJTOG 3405[9]; gefitinib	172	62% vs. 32%; $P < .0001$	9.2 vs. 6.3; HR, 0.50 (0.34-0.71)	34.8 vs. 37.3; HR, 1.25 (0.88-1.78)
IPASS[10,11]; gefitinib[a]	261	71% vs. 47%; $P < .001$	9.5 vs. 6.3; HR, 0.48 (0.36-0.64)	21.6 vs. 21.9; HR, 1.00 (0.76-1.33); $P = .990$
LUX-Lung 3[12,13]; afatinib	345	60.8% vs. 22.1%; $P < .0001$	13.6 vs. 6.9; HR, 0.47 (0.34-0.65); $P < .0001$	31.57 vs. 28.16; HR, 0.78 (0.58-1.06); $P = .1090$
LUX-Lung 6[13,14]; afatinib	364	67% vs. 23%	11.0 vs. 5.6; HR, NR	23.6 vs. 23.5; HR, 0.83 (0.62-1.09); $P = .1756$

Data in parentheses are 95% confidence intervals.
Abbreviations: CT = chemotherapy; EGFR-M+ = epidermal growth factor receptor mutation-positive; HR = hazard ratio; NR = not reached; NSCLC = non–small-cell lung cancer; ORR = overall response rate; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.
[a]EGFR-M+ subset only.

significant (27.9 vs. 24.5 months; $P = .2580$). The toxicities experienced were as expected, with a preponderance of diarrhea and rash for afatinib and liver transaminitis for gefitinib. Although these results suggest that irreversible pan-ErbB blockade might be superior to reversible EGFR inhibition in the treatment of *EGFR*-M+ NSCLC, the phase IIb study design limits definitive interpretation. Also, we do not have randomized data comparing erlotinib and afatinib. The results of the ARCHER 1050 study (A study of dacomitinib vs. gefitinib in 1st-line treatment of advanced NSCLC), a 452-patient phase III randomized trial of first-line treatment *EGFR*+ NSCLC comparing gefitinib with dacomitinib, another second-generation EGFR TKI, might shed light on this question.[21]

Dual Inhibition of EGFR and Angiogenesis Pathways

The results of a randomized phase II trial from Japan illustrated the benefit of the combination erlotinib plus bevacizumab compared with erlotinib alone for common *EGFR* mutations.[22] The median PFS for the combination was 16.0 months versus 9.0 months for erlotinib monotherapy, with no statistically significant difference in the response rate or OS.[23] Based principally on these results, in June 2016, the European Commission approved the combined use of erlotinib and bevacizumab for first-line treatment of NSCLC patients with *EGFR* mutations. A larger phase III trial of this EGFR TKI–bevacizumab combination would ideally confirm and quantify the benefit.[23] This rationale equally supports the combination of other EGFR TKIs and bevacizumab in this setting, although robust Phase III data are lacking.

Use of Third-generation EGFR Inhibitors in the First-line Setting

Although first- and second-generation TKIs currently dominate the first-line treatment algorithm, studies are ongoing to test the efficacy of third-generation inhibitors in this setting. Although the primary target of these drugs is the *T790M* resistance mutation, they are also active against the common activating *EGFR* mutations *Del19* and *L858R*. These agents are associated with a favorable toxicity profile owing to the relative sparing of wild-type EGFR. Multiple third-generation EGFR inhibitors are being developed, including AZD9291 (osimertinib)[24,25] and ASP8273.[26] Head-to-head trials in the first-line setting are ongoing. The FLAURA trial (AZD9291 vs. gefitinib or erlotinib in patients with locally advanced or metastatic non-small cell lung cancer) is randomizing treatment-naive patients with *EGFR*-mutated NSCLC to osimertinib or an EGFR TKI (gefitinib or erlotinib). The trial is closed to accrual, and we look forward to learning the results. In the phase I expansion cohorts of the AURA trial (AZD9291 first time in patients ascending dose study), 60 patients who were EGFR TKI-naive received osimertinib as first-line therapy. Their overall response rate was an impressive 77%, and the median PFS was 19.3

Table 2 Influence of EGFR Mutation Subtype on Survival When Treated With Afatinib

Mutation Subtype	LUX-Lung 3		LUX-Lung 6	
	Median OS (mo)	HR (95% CI); *P* Value	Median OS (mo)	HR (95% CI); *P* Value
Del19		0.54 (0.36-0.79); .0015		0.64 (0.44-0.94); .023
Afatinib	33.2 (26.8-41.5)		31.4 (24.2-35.3)	
CT	21.1 (16.3-30.7)		18.4 (14.6-25.6)	
L858R		1.30 (0.80-2.11); .29		1.22 (0.81-1.83); .34
Afatinib	27.6 (19.8-41.7)		19.6 (17.0-22.1)	
CT	40.3 (24.3-NE)		24.3 (19.0-27.0)	

Abbreviations: CI = confidence interval; CT = chemotherapy; *Del19* = deletion in exon 19; EGFR = epidermal growth factor receptor; HR = hazard ratio; *L858R* = point mutations in exon 21; NE = not estimable; OS = overall survival.

months for the 160-mg dose.[25] To replace both first- and second-generation EGFR inhibitors, the benefits in survival parameters must exceed those observed with sequential use of a first- and second-generation agent followed by a third-generation drug.

Uncommon Mutations

Although *Del19* and *L858R* mutations constitute 90% of *EGFR* mutations, a number of uncommon mutations account for the remaining 10%. An analysis of outcomes for the 75 patients with uncommon mutations identified from the LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 trials demonstrated that 31% had exon 20 insertions, 19% had de novo *T790M* mutations (usually with a concurrent sensitizing mutation), and 51% had other activating rare mutations, primarily point mutations and/or duplications in exons 18 to 21.[27] The response rate to afatinib in patients with de novo *T790M* mutations or exon 20 insertions was 14% and 9%, respectively. For patients with point mutations or duplications in exons 18 to 21, the response rate was 71%. These results are consistent with other data demonstrating that not all uncommon *EGFR* mutations are associated with poorer outcomes and might, indeed, predict a good outcome with erlotinib.[28]

EGFR Mutation-uncharacterized Patients

During regular practice, patients will occasionally present with a very aggressive disease that requires immediate therapy, but the results of *EGFR* mutation testing will not yet be available. If patients have received $\geq$ 1 cycles of chemotherapy, therapy can be switched to an EGFR TKI if the results of mutation testing confirm their *EGFR*-M$^+$ status. Lending some credence to this approach are the results from the EURTAC trial (erlotinib vs. standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non–small-cell lung cancer), which demonstrated that OS was equivalent whether patients were treated with an EGFR TKI as first-line therapy or second-line therapy after crossover.[6]

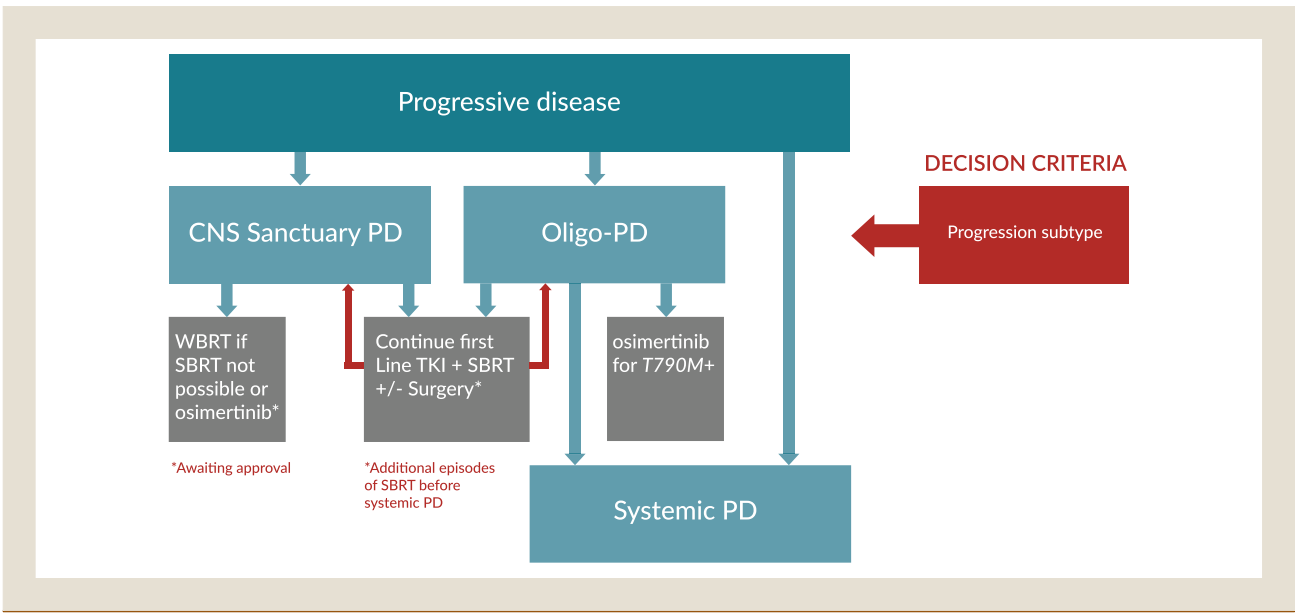
Progression After First-line Therapy

Although first- and second-generation EGFR TKIs have been proved highly effective, acquired resistance is almost universal, typically occurring within a 10- to 14-month period.[6,8-10] Patients with progressive disease will have 1 of 3 different progression subtypes: central nervous system (CNS) sanctuary progressive disease (PD), oligo-PD, and systemic PD.[29] The treatment paradigm varies for each of these types (Figure 2).

Oligo-PD

Some patients experience CNS sanctuary PD disease, characterized by isolated CNS failure in the absence of systemic progression. For these patients, the treatment strategy is to continue the initial TKI and apply local treatment to the brain with stereotactic radiosurgery and/or surgical resection. A retrospective trial showed that weekly treatment with high-dose erlotinib showed a partial CNS response in 67% of subjects.[30] This finding should be confirmed in a prospective trial. Although whole brain radiotherapy is sometimes necessary owing to lesion number or size, it will not improve OS after either stereotactic body radiotherapy or surgical resection and might lead to a decrease in cognitive function.[31,32] In the BLOOM trial, high-dose osimertinib was shown to be efficacious in patients with leptomeningeal disease.[33] This approach is not yet approved by the Food and Drug Administration or European Medicines Agency.

Figure 2 **Progression After First-line Therapy for Epidermal Growth Factor Receptor (EGFR) Mutation-positive Non–Small-cell Lung Cancer (NSCLC). Treatment for Patients With Progression After First-line Tyrosine Kinase Inhibitor (TKI) Depends on Progression Subtype: Central Nervous System (CNS) Sanctuary Progressive Disease (PD), Oligo-PD, or Systemic PD**



Abbreviations: SBRT = stereotactic body radiotherapy; WBRT = whole body radiotherapy.

Oligo-PD refers to progression in a limited number (≤ 4) of new or in previously responsive areas outside the CNS. Oligo-PD can be treated using the same principles as CNS sanctuary PD, by continuing the initial TKI and applying local treatment with stereotactic body radiotherapy and/or surgical resection. However, the magnitude of additional benefit gained by local therapy has yet to be prospectively evaluated in a randomized trial. To answer this question, a randomized trial is planned in Europe.[34] In most patients with EGFR-mutated lung cancer, acquired resistance will manifest as systemic PD, with multiple new lesions or regrowth in multiple areas not amenable to locoregional therapy. In these patients, new systemic therapy is needed. With the recent approval of the third-generation TKI osimertinib for *T790M*-positive recurrence, the practice of continuing first-line treatment beyond progression will change for a subset of these patients with more aggressive disease.

Leptomeningeal Disease

Leptomeningeal disease is often devastating to patients when it presents, and survival is often short. Neurologic abnormalities are common, and the local treatment options are few because the disease is often disseminated. Limited case reports and series have supported pulsed dosing of first- and second-generation TKIs.[35]

Other therapeutic options are currently being explored for leptomeningeal disease. BLOOM is a multicohort phase I study specifically designed to examine treatment of brain and leptomeningeal metastases with AZ3579, a reversible first-generation TKI designed for CNS permeability. When the osimertinib study data revealed responses in brain metastases, this indication was added as a cohort to the BLOOM study at a higher dose of 160 mg daily. Data from patients treated with both drugs were presented at the American Society of Clinical Oncology 2016 meeting.[33] In the cohort of 29 patients treated with AZ3579, all patients had received ≥ 1 line of an EGFR TKI plus chemotherapy, 22 had measurable brain metastases, and 5 had leptomeningeal disease. Among the 22 patients with measurable brain metastases, a response was seen in 6 (27%). Among the 5 patients with leptomeningeal disease, 4 had a > 50% tumor cell number decrease in the cerebrospinal fluid.[33] In the cohort of 20 patients treated with osimertinib, all patients had confirmed cerebrospinal fluid cytology. The data presented were exciting but preliminary, with activity in heavily pretreated patients demonstrated. Of the 12 patients evaluable at 12 weeks for imaging, 7 had had a radiologic response, and 7 showed improvement in their neurologic assessment.[36] Further evaluation of both AZ3579 and osimertinib in this difficult clinical scenario is anticipated.

T790M-acquired Mutation

All patients will eventually experience loss of clinical benefit from first-line EGFR TKI, with symptomatic multisite progressive disease. On repeat biopsy, an acquired mutation in *EGFR* exon 20, specifically *T790M*, can be found in ≤ 60% of patients.[37] Several other mechanisms of acquired resistance have been demonstrated, including the emergence of *MET* or *HER2* amplification or *BRAF* or *PI3K* mutation, among others. Testing for the *T790M* mutation is now recommended as routine practice in many guidelines, including the National Comprehensive Cancer Network.[38] Furthermore, it is becoming clear that the presence of the *T790M* mutation does not necessarily cause resistance in some patients. Determining when *T790M* is the cause of resistance versus an artifact is an area of increasing research interest, because the presence of *T790M* might identify a relatively more indolent tumor subtype.[39] Small-cell lung transformation can occur and can be identified when repeat biopsy is conducted.[40] In these patients, appropriate treatment should be considered.

Third-generation EGFR TKIs have demonstrated impressive response rates of > 60% and prolonged PFS in *T790M*-positive disease, resulting in the approval of osimertinib (AZD9291) in several countries. Recently, the results of 2 AURA studies of osimertinib conducted in patients with *T790M*-positive disease who had developed progression during previous EGFR TKI therapy were presented. Patients experienced a response rate of 71% and a PFS of 9.1 months in a phase I dose-expansion cohort of 63 patients and a response rate of 66% and a PFS of 11 months for 411 patients from a pooled result of 2 phase II studies.[41] The confirmatory phase III AURA 3 trial randomized 419 patients in whom first-line EGFR TKI had failed and who had a *T790M* mutation to either osimertinib or a platinum-pemetrexed doublet.[42] PFS favored osimertinib at 10.4 months versus 4.4 months for chemotherapy (HR, 0.3; 95% CI, 0.23-0.41; $P < .001$).

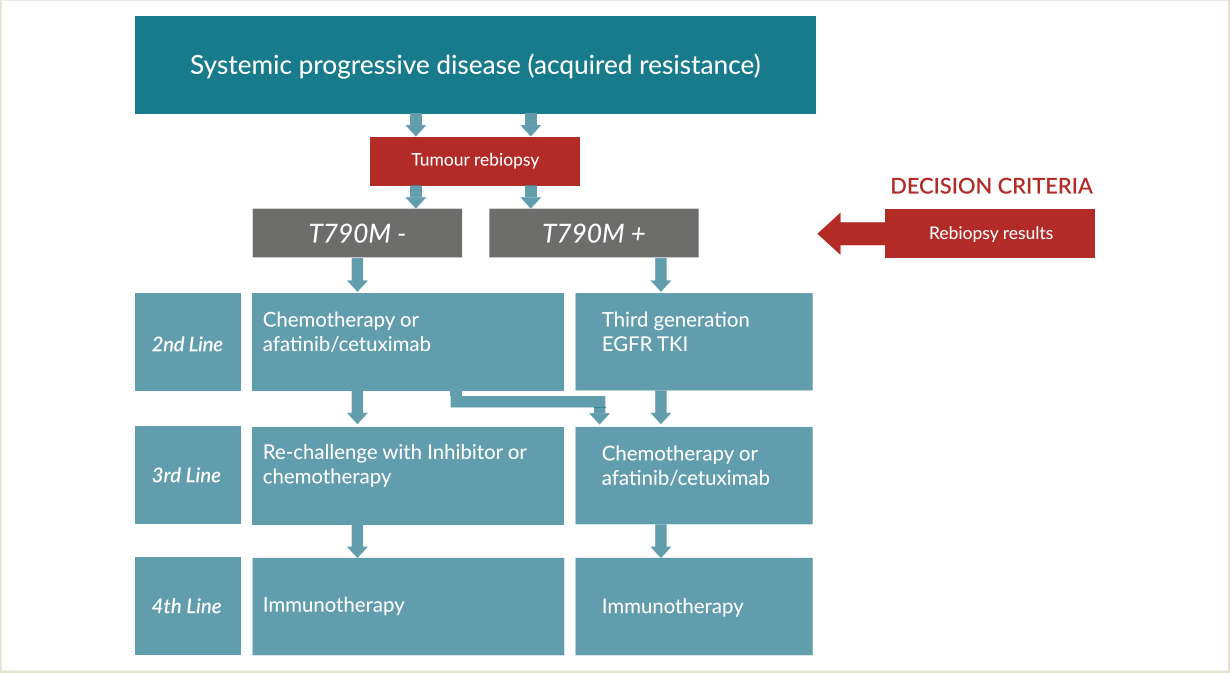
Another emerging third-generation EGFR TKI, olmutinib (BI 1482694), showed clinical activity in the second-line setting in *EGFR*-M+ NSCLC patients with an acquired *T790M* mutation. In that trial, 34 patients (54%) experienced a confirmed overall response, with a median duration of response of 8.3 months (range, 5.7-9.7 months). This drug has been approved only in Korea, and clinical development in other countries has stopped.

As promising as these results are, the side effect profiles of these third-generation agents should be considered. A history of ILD with first- or second-generation EGFR TKI is a contraindication for the use of third-line agents. However, of > 1200 patients across studies treated with osimertinib, only 35 patients (2.9%) experienced ILD.[41]

The influence of the *T790M*-resistance mutation highlights the importance of retesting for mutation status at each subsequent progression. An algorithm for a multidisciplinary approach to repeat biopsy is shown in Figure 3. In the algorithm, the biopsy results dictate the initial therapy, and on each determination of PD, a repeat biopsy is performed to inform the next treatment decision. Careful planning is required regarding repeat biopsy because molecular failures can occur in ≤ 40% of cases.

Most recently, the use of plasma cell-free DNA has been proposed as an alternative to repeat biopsy. Technological advances have resulted in single gene testing and next generation sequencing platforms for plasma, although this has low sensitivity and high specificity compared with paraffin-embedded tumor material.[43] These advances led to the European Medicines Agency label extension for gefitinib to include cell-free DNA in the first-line setting. Plasma samples from the AURA 2 study were tested using 4 different platforms, and high concordance was found between cell-free DNA and tumor tissue.[44] Using the cobas assay, the concordance between tumor and plasma determination of T790M was 70%.[45] The cobas EGFR mutation test recently obtained Food and Drug Administration approval to use a liquid biopsy specimen (plasma) for EGFR testing of NSCLC patients. Another study using

Figure 3 Current Paradigm: Rebiopsy. An Algorithm for a Multidisciplinary Approach to Rebiopsy in Which Biopsy Results Dictate Initial Therapy. On Each Determination of Progressive Disease, a Repeat Biopsy Is Performed to Inform the Next Treatment Decision



Abbreviations: EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor.

a more sensitive technique found that plasma cell-free DNA had 81% (155 of 192) concordance with the tissue analysis.[46] In addition, increasing evidence has shown that plasma cell-free DNA assessment of *T790M*, which reflects globally on tumor DNA shed into plasma, might be more accurate than tumor biopsy, which is fraught with the problems of tumor heterogeneity.[44] Clinicians are starting to accept cell-free DNA as the standard first test. However, repeat tissue biopsy is necessary if the plasma findings are negative owing to the relatively high rate of false-negative results with plasma testing. How the liquid biopsy approach might influence our treatment algorithm is shown in Figure 4.

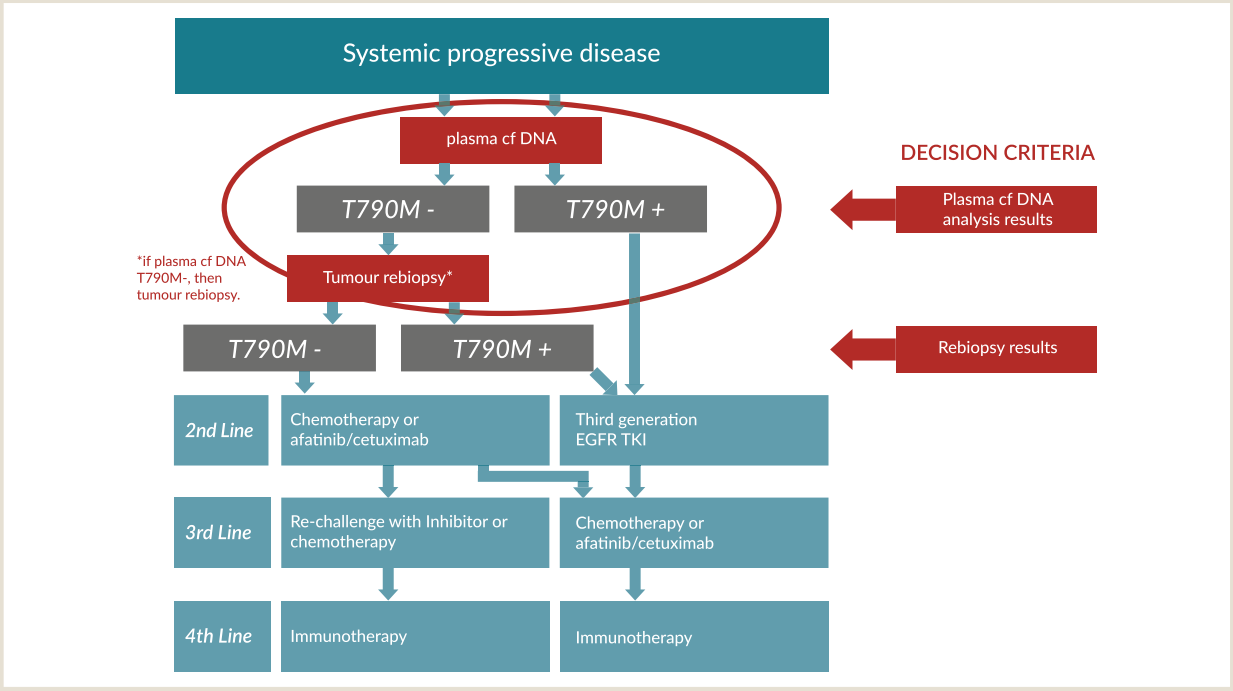
Treatment Beyond Progression

The concept of "treatment beyond PD" was based on the desire to have patients continue oral low-toxicity TKI therapy versus switching to chemotherapy. Anecdotal observational studies have supported this concept.[47,48] To evaluate this concept prospectively, the IMPRESS study (gefitinib plus chemotherapy vs. placebo plus chemotherapy in *EGFR*-mutation-positive non—small-cell lung cancer after progression on first-line gefitinib) randomized patients progressing with EGFR TKI therapy (gefitinib) to either switching to chemotherapy or adding chemotherapy to the TKI.[49] No benefit was seen in the primary PFS endpoint; however, a trend toward worsening OS was observed. Subsequent subset analysis revealed that continuing the EGFR TKI with chemotherapy provided a modest increase in PFS only in those patients with *T790M*-negative cancer, refuting the concept of treatment beyond PD.[49] The ASPIRATION study (first-line erlotinib therapy until and beyond response evaluation criteria in solid tumors progression in Asian patients with epidermal growth factor receptor mutation-positive non—small-cell lung cancer) was a single-arm phase II trial in which patients with *EGFR*-mutated cancer were either switched to chemotherapy or continued with TKI plus chemotherapy, at the physician's discretion. Despite the inherent biases in the study design, the trial demonstrated that many physicians decided to continue EGFR TKI therapy for patients with slow progression.[50] The IMPRESS and ASPIRATION studies were both conducted before the proved efficacy of third-generation EGFR TKIs, emphasizing the importance of repeat analysis for acquired EGFR mutations, as new effective therapy emerges.

Dual Blockade

In preclinical models, dual blockade of the EGFR pathway with afatinib (an EGFR TKI) and cetuximab (an anti-EGFR monoclonal antibody) might be a promising strategy for overcoming T790M-mediated resistance.[51] In a trial in the acquired resistance setting, combining cetuximab with afatinib in patients with progression during first-generation TKI therapy resulted in a response rate of 30% in the *T790M* mutation-positive tumors.[51] The response rate was equivalent for those with *T790M*-negative disease, implying that this approach might target other mechanisms of resistance such as those associated with bypass pathways, given the pan-HER kinase activity of afatinib. Studies are ongoing to determine whether this approach might circumvent or delay the onset of resistance when applied with first-line therapy for *EGFR*-mutated lung cancer.[52]

Figure 4 New Paradigm: Plasma Cell-free (cf) DNA Testing First Showing How the Treatment Algorithm Is Likely to Be Influenced by the Liquid Biopsy Approach in the Future



Abbreviations: EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor.

T790M Mutation Negative

For patients with progression during first-line EGFR TKI therapy, whose tumors do not demonstrate the *T790M* mutation, chemotherapy with a platinum-based doublet with or without bevacizumab remains the standard of care. Non-*T790M* resistance mechanisms are poorly understood and are the focus of much ongoing research. The limited, but positive, activity of the third-generation EGFR TKIs observed in patients with *T790M* wild-type cancer illustrates our limited understanding of the resistance mechanisms but might also reflect difficulties in truly identifying the *T790M* mutation using routine paraffin-embedded diagnostic biopsy material. This could be explained by the false-negative results, because any patient with *T790M*-negative tumor found by biopsy examination might actually have *T790M*-positive cancer by plasma analysis owing to tumor heterogeneity. Novel combinations of EGFR TKIs, immune checkpoint inhibitors, and new third-generation EGFR TKIs are other strategies being tested to overcome resistance mutations.

Third-line Treatment

Rechallenge

For patients with progression after multiple lines of therapy, rechallenge with an EGFR inhibitor might be an option, in particular, if the patient has had a "TKI-free" period in between the first and subsequent EGFR TKI treatment. The LUX-Lung 1 and 5 clinical trials revealed PFS advantages when gefitinib- and erlotinib-treated patients were rechallenged with afatinib, although neither of these studies were specific for *EGFR*+ patients.[53,54] Although common practice, rechallenge with TKI has still not shown an OS benefit in randomized trials. Also, the duration of benefit with rechallenge will never be as long as in the first-line setting.[53]

Immunotherapy

To date, no data are available to support the routine early use of immunotherapy for the subset of patients with *EGFR* mutations. The second- and third-line trials Checkmate 057 [study of BMS-936558 (nivolumab) compared to docetaxel in previously treated metastatic non-squamous NSCLC],[55] KEYNOTE 010 [study of two doses of pembrolizumab (MK-3475) versus docetaxel in previously treated participants with non-small cell lung cancer],[56] and OAK (atezolizumab vs. docetaxel in patients with previously treated non−small-cell lung cancer)[57] all favored docetaxel chemotherapy over checkpoint inhibitors for patients with EGFR mutations. Thus, subsequent first-line trials excluded lung cancer patients with *EGFR* mutations.[58,59] Because of a lack of superiority for immune checkpoint inhibitors compared with docetaxel chemotherapy, these should be used in later lines of therapy after failure of chemotherapy.

Conclusion

EGFR TKI therapy has emerged as the standard of care in the first-line setting for patients with NSCLC whose tumors harbor an *EGFR* mutation. Efficacy, safety profiles, and patient factors should be considered when selecting treatments, in addition to the specific *EGFR* mutation type. With impressive efficacy and very favorable toxicity profiles, the emergence of third-generation EGFR TKIs is

changing the treatment strategy and should be made available to appropriate patients. Other strategies when the third-generation inhibitors are not available or approved for patients with *T790M*-negative disease include local therapies, systemic chemotherapy, or total blockade of the EGFR pathway. This could also apply for patients who experienced ILD during first- or second-generation EGFR TKI therapy. Further prospective clinical trials are required to precisely define the optimal treatment sequences, with the goal of converting lung cancer to a chronic disease.

Acknowledgments

S.P. received National Health Service funding to the Royal Marsden Hospital/Institute of Cancer Research National Institute for Health Research—Biomedical Research Centre. The authors thank Chrystal Palaty for medical writing support and assistance with formatting, and Amanda Maxwell for assistance with submitting the manuscript. Dr Melosky paid both writers personally.

Disclosure

B.M. has received honoraria from Boehringer Ingelheim, Eli Lily, Pfizer, Roche, Merck, Bristol-Myers Squibb, Novartis, and AstraZeneca; is in a consulting/advisory role with Boehringer Ingelheim; and has received travel/accommodations/expenses from Boehringer Ingelheim, AstraZeneca, Novartis, and Pfizer and her institution has received research funding from Roche and Bayer. D.R.G. has received grants and other support from Genentech, AstraZeneca, Boehringer-Ingelheim, and Clovis, outside the submitted work. S.P. has been a consultant to AstraZeneca, Boehringer Ingelheim, Clovis Oncology, and Roche and has received honoraria from AstraZeneca and Boehringer Ingelheim.

References

1. Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. *Nat Rev Cancer* 2007; 7:169-81.
2. Lindeman NI, Cagle PT, Beasley MB, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Thorac Oncol* 2013; 8:823-59.
3. Leighl NB, Rekhtman N, Biermann WA, et al. Molecular testing for selection of patients with lung cancer for epidermal growth factor receptor and anaplastic lymphoma kinase tyrosine kinase inhibitors: American Society of Clinical Oncology endorsement of the College of American Pathologists/International Society for the Study of Lung Cancer/Association of Molecular Pathologists Guideline. *J Clin Oncol* 2014; 32:3673-9.
4. Kerr KM, Bubendorf L, Edelman MJ, et al. Second ESMO consensus conference on lung cancer: pathology and molecular biomarkers for non-small-cell lung cancer. *Ann Oncol* 2014; 25:1681-90.
5. Janku F, Garrido-Laguna I, Petruzelka LB, Stewart DJ, Kurzrock R. Novel therapeutic targets in non-small cell lung cancer. *J Thorac Oncol* 2011; 6:1601-12.
6. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012; 13:239-46.
7. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011; 12:735-42.
8. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non—small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010; 362: 2380-8.
9. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010; 11:121-8.
10. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin—paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; 361:947-57.
11. Fukuoka M, Wu Y-L, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non—small-cell lung cancer in Asia (IPASS). *J Clin Oncol* 2011; 29:2866-74.
12. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013; 31:3327-34.
13. Yang JC-H, Sequist LV, Schuler MH, et al. Overall survival (OS) in patients (pts) with advanced non-small cell lung cancer (NSCLC) harboring common (Del19/L858R) epidermal growth factor receptor mutations (EGFR mut): pooled analysis of two large open-label phase III studies (LUX-Lung 3 [LL3] and LUX-Lung 6 [LL6]) comparing afatinib with chemotherapy (CT). Study presented at the American Society of Clinical Oncolog 2014 Annual Meeting. Available at: http://meetinglibrary.asco.org/record/95362/abstract. Accessed: June 23, 2017.
14. Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol* 2014; 15:213-22.
15. Melosky B. Review of EGFR TKIs in metastatic NSCLC, including ongoing trials. *Front Oncol* 2014; 4:244.
16. Melosky B, Anderson H, Burkes RL, et al. Pan Canadian Rash trial: a randomized phase III trial evaluating the impact of a prophylactic skin treatment regimen on epidermal growth factor receptor-tyrosine kinase inhibitor—induced skin toxicities in patients with metastatic lung cancer. *J Clin Oncol* 2016; 34:810-5.
17. Lee C, Davies LC, Wu YL, et al. The impact on overall survival (OS) of first-line gefitinib (G) and erlotinib (E) and of clinical factors in advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor mutations (EGFR mut) based on meta-analysis of 1231 patients (pts) enrolled in 6 major randomized trials. *J Clin Oncol* 2015; 33(suppl) (abstract 8072).
18. Yang JC, Wu YL, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol* 2015; 16:141-51.
19. Park K, Tan E-H, Zhang L, et al. Afatinib versus gefitinib as first-line treatment for patients with advanced non-small cell lung cancer harboring activating EGFR mutations: LUX-Lung 7: a phase 2B, open-label, randomised controlled trial, Presented at European Society for Medical Oncology Asia 2015; Singapore. *Lancet Oncol* 2016; 17:577-89 (abstract LBA2_PR).
20. Paz-Ares L, Tan EH, O'Byrne K, et al. Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial [e-pub ahead of print]. *Ann Oncol* http://dx.doi.org/10.1093/annonc/mdw611, accessed February 7, 2017.
21. Mok T, Nakagawa K, Rosell R, et al. Phase III randomized, open label study (ARCHER 1050) of first-line dacomitinib (D) versus gefitinib (G) for advanced (adv) non-small cell lung cancer (NSCLC) in patients (pts) with epidermal growth factor receptor (EGFR) activating mutation(s), ASCO Annual Meeting 2013; Chicago, Illinois. *J Clin Oncol* 2013; 31(suppl) (abstract TPS8123).
22. Seto T, Kato T, Nishio M, et al. Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. *Lancet Oncol* 2014; 15:1236-44.
23. Gridelli C, Rossi A, Ciardiello F, et al. BEVERLY: rationale and design of a randomized open-label phase III trial comparing bevacizumab plus erlotinib versus erlotinib alone as first-line treatment of patients with EGFR-mutated advanced nonsquamous non-small-cell lung cancer. *Clin Lung Cancer* 2016; 17:461-5.
24. Janne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med* 2015; 372:1689-99.
25. Ramalingam S, Yang JCH, Lee CK, et al. LBA1_PR: Osimertinib as first-line treatment for EGFR mutation-positive advanced NSCLC: updated efficacy and safety results from two Phase I expansion cohorts. *J Thorac Oncol* 2016; 11(4 suppl):S152.
26. Yu HA, Spira AI, Horn L, et al. Antitumor activity of ASP8273 300 mg in subjects with EGFR mutation-positive non-small cell lung cancer: interim results from an ongoing phase 1 study, Presented at the 2016 American Society of Clinical Oncology, Chicago, Illinois. *J Clin Oncol* 2016; 34(suppl) (abstract 9050).
27. Yang JCH, Sequist LV, Geater SL, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *Lancet Oncol* 2015; 16:830-8.
28. Klughammer B, Brugger W, Cappuzzo F, et al. Examining treatment outcomes with erlotinib in patients with advanced non—small cell lung cancer whose tumors harbor uncommon *EGFR* mutations. *J Thorac Oncol* 2016; 11:545-55.
29. Gandara DR, Li T, Lara PN, et al. Acquired resistance to targeted therapies against oncogene-driven non-small-cell lung cancer: approach to subtyping progressive disease and clinical implications. *Clin Lung Cancer* 2014; 15:1-6.
30. Grommes C, Oxnard GR, Kris MG, et al. "Pulsatile" high-dose weekly erlotinib for CNS metastases from EGFR mutant non-small cell lung cancer. *Neuro Oncol* 2011; 13:1364-9.
31. Brown PD, Asher AL, Ballman KV, et al. NCCTG N0574 (Alliance): a phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases, Presented at the American Society of Clinial Oncology Annual Meeting, 2015, Chicago, Illinois. *J Clin Oncol* 2015; 33(suppl) (abstract LBA4).
32. Mulvenna PM, Nankivell MG, Barton R, et al. Whole brain radiotherapy for brain metastases from non-small lung cancer: quality of life (QoL) and overall survival

(OS) results from the UK Medical Research Council QUARTZ randomised clinical trial (ISRCTN 3826061), Presented at the American Society of Clinial Oncology Annual Meeting, 2015. *J Clin Oncol* 2015; 33(suppl) (abstract 8005).
33. Yang JC-H, Kim D-W, Kim S-W, et al. Osimertinib activity in patients (pts) with leptomeningeal (LM) disease from non-small cell lung cancer (NSCLC): updated results from BLOOM, a phase I study, Presented at the 2016 American Society of Clinical Oncology Annual Meeting, 2016, Chicago, Illinois. *J Clin Oncol* 2016; 34(suppl) (abstract 9002).
34. Bainbridge H, Toms C, Kilburn L, Popat S, Bliss J, McDonald F. 141 HALT trial: stereotactic radiotherapy for oligo-progressive disease (OPD) in oncogene-addicted lung tumours—results of a national trial feasibility questionnaire. *Lung Cancer* 2016; 91(suppl):S51.
35. Sacher AG, Janne PA, Oxnard GR. Management of acquired resistance to epidermal growth factor receptor kinase inhibitors in patients with advanced non-small cell lung cancer. *Cancer* 2014; 120:2289-98.
36. Ahn M-J, Kim D-W, Kim TM, et al. Phase I study of AZD3759, a CNS penetrable EGFR inhibitor, for the treatment of non-small-cell lung cancer (NSCLC) with brain metastasis (BM) and leptomeningeal metastasis (LM), Presented at the 2016 American Society of Clinical Oncology Annual Meeting, Chicago, Illinois. *J Clin Oncol* 2016; 34(suppl) (abstract 9003).
37. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res* 2013; 19:2240-7.
38. NCCN Guidelines Version 7.2017 — June 22, 2017. Non-Small Cell Lung Cancer. National Comprehensive Cancer Network; 2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed: June 3, 2017.
39. Oxnard GR, Arcila ME, Sima CS, et al. Acquired resistance to EGFR tyrosine kinase inhibitors in EGFR-mutant lung cancer: distinct natural history of patients with tumors harboring the T790M mutation. *Clin Cancer Res* 2011; 17:1616-22.
40. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med* 2011; 3:75ra26.
41. Yang JC, Ramalingam SS, Janne PA, Cantarini M, Mitsudomi T. LBA2_PR—osimertinib (AZD9291) in pre-treated patients with T790M-positive advanced NSCLC: updated phase 1 (P1) and pooled phase 2 (P2) results, Presented at the European Lung Cancer Conference, April 14, 2016, Geneva, Switzerland. *J Thorac Oncol* 2016; 11(4 suppl):S152-3.
42. Mok TS, Wu Y-L, Ahn M-J, et al. Osimertinib or platinum—pemetrexed in EGFR T790M—positive lung cancer. *N Engl J Med* 2017; 376:629-40.
43. Douillard JY, Ostoros G, Cobo M, et al. First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: a phase-IV, open-label, single-arm study. *Br J Cancer* 2014; 110:55-62.
44. Thress KS, Brant R, Carr TH, et al. EGFR mutation detection in ctDNA from NSCLC patient plasma: a cross-platform comparison of leading technologies to support the clinical development of AZD9291. *Lung Cancer* 2015; 90:509-15.
45. Jenkins S, Yang JC, Ramalingam SS, et al. 134O_PR: plasma ctDNA analysis for detection of EGFR T790M mutation in patients with EGFR mutation-positive advanced non-small cell lung cancer, Presented at the European Lung Cancer Conference, 2016, Geneva, Switzerland. *J Clin Oncol* 2016; 11(suppl):S153-4.
46. Sequist LV, Goldman JW, Wakelee HA, et al. Efficacy of rociletinib (CO-1686) in plasma-genotyped T790M-positive non-small cell lung cancer (NSCLC) patients (pts), Presented at the American Society of Clinical Oncology Annual Meeting, 2015, Chicago, Illinois. *J Clin Oncol* 2015; 33(suppl) (abstract 8001).
47. Neal JW. The SATURN trial: the value of maintenance erlotinib in patients with non-small-cell lung cancer. *Future Oncol* 2010; 6:1827-32.
48. Weickhardt AJ, Scheier B, Burke JM, et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene addicted non-small cell lung cancer. *J Thorac Oncol* 2012; 7:1807-14.
49. Soria JC, Wu YL, Nakagawa K, et al. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. *Lancet Oncol* 2015; 16:990-8.
50. Park K, Yu CJ, Kim SW, et al. First-line erlotinib therapy until and beyond response evaluation criteria in solid tumors progression in Asian patients with epidermal growth factor receptor mutation-positive non-small-cell lung cancer: the ASPIRATION study. *JAMA Oncol* 2015; 2:305-12.
51. Janjigian YY, Smit EF, Groen HJM, et al. Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor—resistant EGFR-mutant lung cancer with and without T790M mutations. *Cancer Discov* 2014; 4:1036-45.
52. Bökkerink G, de Graaf E, Punt C, et al. The CARTS study: chemoradiation therapy for rectal cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery. *BMC Surg* 2011; 11:1-7.
53. Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol* 2012; 13:528-38.
54. Schuler MH, Yang C-H, Park K, et al. Continuation of afatinib beyond progression: results of a randomized, open-label, phase III trial of afatinib plus paclitaxel versus investigator's choice chemotherapy in patients with metastatic non-small-cell lung cancer (NSCLC) progressed on erlotinib/gefitinib and afatinib: LUX-Lung 5, Presented at the American Society of Clinical Oncology, 2014, Chicago, Illinois. *J Clin Oncol* 2014; 32(suppl) (abstract 8019).
55. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non—small-cell lung cancer. *N Engl J Med* 2015; 373:1627-39.
56. Herbst RS, Baas P, Kim D-W, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016; 387:1540-50.
57. Barlesi F, Park K, Ciardiello F. Primary analysis from OAK: a randomized phase III study comparing atezolizumab with docetaxel in advanced NSCLC, Presented at the European Society for Medical Oncology, Copenhagen, Denmark, October 7-11, 2016. *Ann Oncol* 2016; 27(suppl 9):ix139-56.
58. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1—positive non—small-cell lung cancer. *N Engl J Med* 2016; 375:1823-33.
59. Socinski M, Creelan B, Horn L, et al. CheckMate 026: a phase 3 trial of nivolumab vs investigator's choice (IC) of platinum-based doublet chemotherapy (PT-DC) as first-line therapy for stage IV/recurrent programmed death ligand 1 (PD-L1)—positive NSCLC, Presented at the European Society for Medical Oncology 2016-2017. *Ann Oncol* 2016; 27(suppl 6) (abstract LBA7_PR).