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## Management of *EGFR* Mutation–Positive Non–Small Cell Lung Cancer

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### Abstract

For appropriate treatment selection, the updated NCCN Guidelines for Non–Small Cell Lung Cancer (NSCLC) recommend broad molecular profiling for all patients with nonsquamous disease. Three different tyrosine kinase inhibitors (TKIs) are recommended as first-line treatment of *EGFR* mutation–positive NSCLC: gefitinib, erlotinib, and afatinib. Most patients whose disease responds will still experience progression, and the type of disease progression drives management. Systemic progression requires switching TKI treatment, whereas patients with oligoprogression and central nervous system progression may have their new lesions treated but continue on their TKI. A new third-generation TKI has been approved and others are currently under development, and new combinations of these drugs with a VEGFR inhibitor offer promise to improve outcomes.

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The identification of molecular targets and the development of agents to treat those targets has changed the paradigm for the management of non–small cell lung cancer (NSCLC).

“The progress in NSCLC has been absolutely amazing. *EGFR* and *KRAS* mutations are the most common genetic alterations, and *ALK*, *ROS1*, and *RET* rearrangements and *BRAF* mutations are also targetable. Less than half of NSCLCs of adenocarcinoma histology have no known alterable genotype,” explained Rogerio A. Lilenbaum, MD, Chief Medical Officer of Smilow Cancer Hospital.

The updated version of the NCCN Guidelines for NSCLC recommends that testing for *EGFR* and *ALK* mutations should be conducted as part of broad molecular profiling, which is now recommended for all patients with NSCLC (nonsquamous histology) to recognize rare actionable mutations. The results of the molecular profiling can be used to counsel patients and enroll them in clinical trials. “Broad molecular profiling is a key component of the improvement in care for patients with NSCLC,” the NCCN Guidelines state.

“Genotyping should be performed for every patient with nonsquamous NSCLC,” Dr. Lilenbaum told the audience. “Testing should not be limited to patients with a high

probability of *EGFR* mutations. It is critical that [physicians] perform genotyping, the same as you would check hormone receptor expression and HER2/neu in breast cancer.”

The best way to profile/sequence a tumor is still a work in progress. Dr. Lilenbaum said that at Yale Cancer Center/Smilow Cancer Hospital they use a tiered approach: tier 1 uses the TaqMan platform (Thermo Fisher Scientific, Waltham, MA; 8 genes, most actionable) with results available in less than 1 week; tier 2 uses the OncoPrint Comprehensive Assay (Thermo Fisher Scientific, Waltham, MA; 143 genes and >2,500 translocations/fusions), which takes up to 2 weeks to receive results; and tier 3 is whole-genome sequencing with future custom panels per organ system specification, with results available in 3 to 4 weeks.

Dr. Lilenbaum noted that patients with an *EGFR* mutation have better outcomes with gefitinib compared with chemotherapy, based on the results of the IPASS trial<sup>1</sup>, and that patients without the mutation experience a poor response on gefitinib. “If the *EGFR* mutation is not present, do not treat the patient with a tyrosine kinase inhibitor [TKI]. If you need to treat the patient before receiving the genomic profiling report, use chemotherapy first. You can always switch to gefitinib (or any 1 of the 3 TKIs) if the patient [has] the mutation,” Dr. Lilenbaum told listeners.

The updated NCCN Guidelines recommend gefitinib, erlotinib, and afatinib as appropriate first-line therapy options for *EGFR*-positive NSCLC. Afatinib is the only one of these agents to demonstrate an overall survival (OS) benefit in patients with del 19 mutations.<sup>2</sup> In the LUX-Lung 3 trial, OS with first-line afatinib was 31.7 months versus 20.7 with chemotherapy ( $P=.0001$ ). Patients with L858R mutations do not do as well as those with del 19, although these patients should still be treated with an EGFR inhibitor, he said.

The LUX-Lung 7 trial directly compared afatinib versus gefitinib in patients with *EGFR*-positive NSCLC and stratified them according to del 19 and L858R mutations.<sup>3</sup> Objective response rates and disease control rates favored afatinib (70% vs 56%, respectively). Survival data are immature, but progression-free survival curves split at 12 months, favoring afatinib. The analysis of the del 19 and L858R mutations is not yet available.

Thus, the efficacy of the 3 NCCN Guideline–recommended first-line TKIs is not exactly the same. At the recommended doses, afatinib has a higher rate of toxicity than gefitinib and erlotinib at the recommended doses. Toxicities should be considered when choosing among the available TKIs for first-line therapy, Dr. Lilenbaum said.

Combination erlotinib plus bevacizumab and afatinib plus cetuximab are currently being evaluated as first-line therapy. Studies thus far are promising, he said, but phase III results are awaited.

Currently, no TKI has been shown to be more effective than first-line chemotherapy for *EGFR*-positive NSCLC tumors that harbor the T790M and exon 20 insertions.

The third-generation TKI, osimertinib, is being evaluated in the FLAURA study as first-line therapy for patients with del 19 and other mutations. That trial has just completed accrual ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02296125) identifier: [NCT02296125](https://clinicaltrials.gov/ct2/show/study/NCT02296125)). Other third-generation TKIs are in

development, including rociletinib and ASP8273. The efficacy of the third-generation TKIS is currently being compared with first-line EGFR TKIs in the SOLAR trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02588261) identifier: [NCT02588261](https://clinicaltrials.gov/ct2/show/study/NCT02588261)).

## Acquired Resistance

Although 70% of patients with *EGFR*-positive NSCLC will experience response to first-line TKI therapy, most will develop disease progression after approximately 1 year.

“We know that these responding patients who progress have developed acquired resistance,” said Leora A. Horn, MD, MSc, FRCPC, Associate Professor of Medicine, Clinical Director of the Thoracic Oncology Program, Associate Vice-Chancellor for Faculty Development, Vanderbilt-Ingram Cancer Center.

Of note, the T790M mutation is present in approximately 50% of patients who experience disease progression. Other mutations have been described, but these are not yet targetable with therapy. “Not all patients who develop acquired resistance have a T790M mutation, multiple mechanisms of resistance exist including EMT, HER2, BRAF, etc,” Dr. Horn stated. In a small group of patients, NSCLC will transform to small cell lung cancer (SCLC); these patients have a poorer prognosis. A biopsy should be performed to identify disease transformation, and treatment should then be switched to that for SCLC, Dr. Horn said.

Dr. Horn also noted that the type of disease progression drives therapy. There are 3 subtypes of progressive disease: systemic progression, oligoprogression, and central nervous system progression. For patients who experience systemic progression, therapy should be switched. However, before switching therapy, all patients with systemic progression on a TKI should undergo biopsy to evaluate for T790M mutation. If a tissue biopsy is not possible, then a serum-based test for T790M is appropriate. For oligoprogression, the single site should be treated and treatment on a TKI should be continued. Finally, central nervous system lesions can be treated with radiation, and patients could be continued on a TKI, she advised.

For patients who discontinue use of an EGFR TKI before initiating a new study drug, disease flare is a concern. Dr. Horn noted that for these patients, shortening the washout period from 28 days to up to 3 days before initiating the new therapy has been implemented into many trial designs to help patients avoid experiencing disease flare. For patients switching to chemotherapy, the TKI can be continued up to the start date rather than stopping immediately on progression as the clinician arranges for a biopsy to determine next steps.

Another treatment concern is whether to continue patients on a TKI when they switch to chemotherapy after experiencing disease progression. The IM-PRESS trial,<sup>4</sup> suggested no benefit in PFS or OS when the TKI was continued with chemotherapy compared with chemotherapy alone. Therefore, continuing patients on TKI therapy is not recommended at this time.

Osimertinib is currently approved for patients on a first- or second-generation TKI who develop acquired resistance related to the presence of a T790M mutation. Additionally, Dr. Horn noted that “more agents are on the way.”

Toxicities are different with third-generation TKIs. Rash and diarrhea are no longer significant with the newer drugs, and they have lower rates of grades 3 and 4 toxicity.

Another third third-generation agent called ASP8273 is in development for *EGFR*-positive tumors with the T790M alteration. Unique toxicities thus far are hyponatremia and paresthesias.

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