The Importance of Retesting for EGFR Mutations at Disease Progression

Be aware of acquired resistance to first-line EGFR-TKI therapy

As previously discussed, testing is recommended in patients with metastatic non–small cell lung cancer (NSCLC) found to have an epidermal growth factor receptor (EGFR) sensitizing mutation who are receiving an EGFR tyrosine kinase inhibitor (EGFR-TKI) as a first-line treatment.[1]

Due to a phenomenon known as **acquired drug resistance**, the majority of patients who are treated with and respond to a first-line EGFR-TKI will eventually become unresponsive to the treatment, and their cancer will progress.[2]

The time it takes for a patient to develop drug resistance and for their cancer to progress is variable and involves many factors. Typically, time to drug resistance and disease progression falls between 9 and 13 months after first-line treatment with a first- or second-generation EGFR-TKI.[3-7]

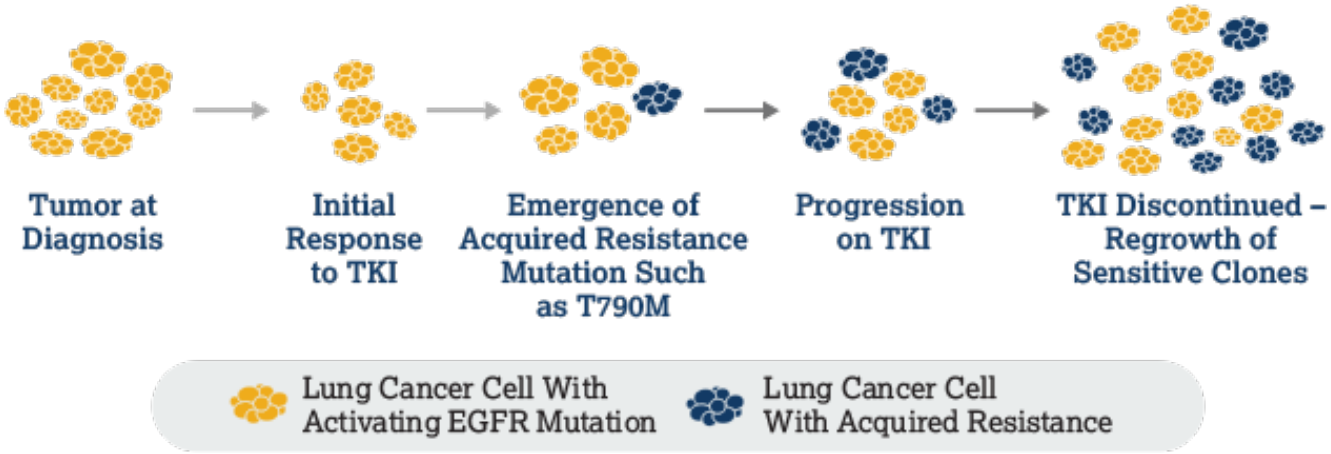
Acquired Drug Resistance to First-line Therapy With a First- or Second-generation EGFR-TKI

According to the NCCN Clinical Practice Guidelines in Oncology (NCCN® Guidelines), patients with NSCLC receiving a first-line EGFR-TKI should be monitored for progression.[1]

Did you know? Tumors have the ability to adapt

Acquired drug resistance to EGFR-TKI therapy is believed to occur due to selection pressure on the tumor. This means that the tumor adapts to the first-line treatment given to the patient, and the cancer cells develop a mechanism to survive despite treatment with a first-line EGFR-TKI.[8]

Resistance via Acquired Mutation Is the Most Common Mechanism of Disease Progression[8]



There are a number of ways that NSCLC cells may develop resistance to first- or second-generation EGFR-TKIs, but the most common is through the acquired resistance mutation in the EGFR gene, known as T790M.[8]

- In these instances, tumor cells with the acquired EGFR T790M mutation no longer respond to first-line EGFR-TKI treatment, and continue to grow

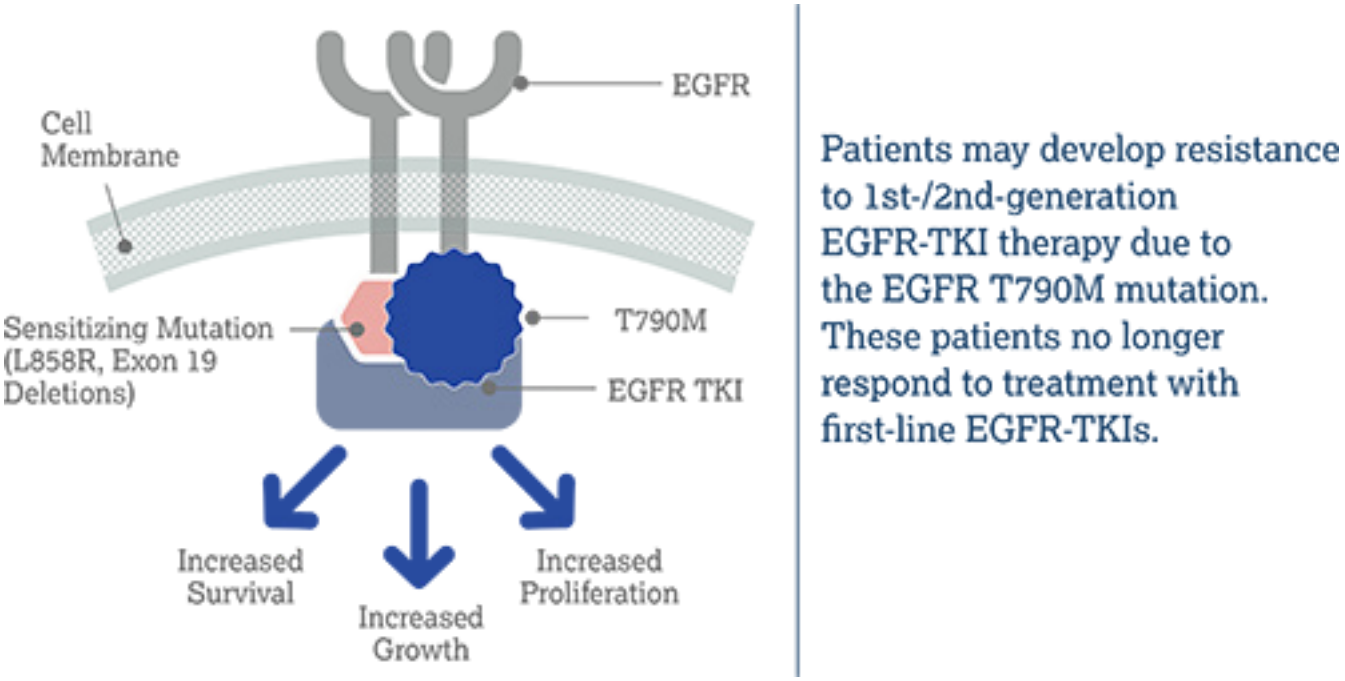
Reasons for Acquired Resistance to EGFR-TKIs[9]

T790M, a new EGFR mutation at progression

The T790M mutation is an EGFR point mutation, which means a specific part of the EGFR gene has changed.

- The EGFR T790M mutation is typically not present during initial diagnosis[8]
- The EGFR T790M mutation confers acquired drug resistance[9]

The EGFR T790M Mutation Confers Drug Resistance to First-generation EGFR-TKIs[8,9]



- Review EGFR sensitizing mutations in The Importance of Testing for EGFR Mutations at Initial Diagnosis in Metastatic NSCLC

Testing for mutations in patients with metastatic NSCLC who have progressed on a first-line EGFR-TKI can guide clinical decision-making.[1]

Recommendations for EGFR T790M mutation testing at progression

Knowing if a patient has an EGFR T790M mutation has implications for treatment decisions. Therefore numerous national organizations have recommended genetic testing at the time of progression, including[1,10]:

- National Comprehensive Cancer Network® (NCCN®)
- College of American Pathologists (CAP)
- International Association for the Study of Lung Cancer (IASLC)
- Association for Molecular Pathology (AMP)

Reminder: A new sample is required to test for EGFR T790M mutations at the time of progression.

In order to test for an EGFR mutation at progression, a new sample is necessary. If a repeat tissue biopsy is not feasible, a plasma sample should be considered. It is recommended that EGFR T790M mutation testing be conducted using an FDA-approved test or a validated laboratory-developed test (LDT) that adheres to the standards of the Clinical Laboratory Improvement Amendments (CLIA).[1,10] In the next module, we will discuss these testing options in greater detail.

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References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non–Small Cell Lung Cancer V3.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed January 26, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. **2.** Salgia R. Mutation testing for directing upfront targeted therapy and post-progression combination therapy strategies in lung adenocarcinoma. *Expert Rev Mol Diagn*. 2016;16(7):737-749. doi:10.1080/14737159.2016.1181545. **3.** 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(2):213-222. **4.** Rosell R, Carcereny E, Gervais R, et al; Spanish Lung Cancer Group; Groupe Français de Pneumo-Cancérologie; Associazione Italiana Oncologia Toracica. 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(3):239-246. **5.** Mitsudomi T, Morita S, Yatabe Y, et al; West Japan Oncology Group. 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(2):121-128. **6.** 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(27):3327-3334. **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(8):735-742. **8.** Sacher AG, Jänne 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(15):2289-2298. doi:10.1002/cncr.28723. **9.** 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(8):2240-2247. doi:10.1158/1078-0432.CCR-12-2246. **10.** Lindeman NI, Cagle PT, Aisner DL, et al. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: guideline from the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. *Arch Pathol Lab Med*. 2018;142(3):321-346. doi:10.5858/arpa.2017-0388-CP.

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