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.

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.

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.

**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.**

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

[Diagram showing treatment response, with 0 months, 9 months marked as acquired drug resistance, and 13 months]
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 Progression8

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-TKIs8

As many as 2 out of 3 patients who become resistant to 1st-/2nd-generation EGFR-TKIs do so because of T790M, an acquired mutation in the EGFR gene.8
**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.
- The EGFR T790M mutation confers acquired drug resistance.

**The EGFR T790M Mutation Confers Drug Resistance to First-generation EGFR-TKIs**

Testing for mutations in patients with metastatic NSCLC who have progressed on a first-line EGFR-TKI can guide clinical decision-making.
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:\textsuperscript{1,10}:

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

\textbf{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).\textsuperscript{1,10}

In the next module, we will discuss these testing options in greater detail.