Non-Invasive Molecular Testing for Osimertinib Acquired Resistance in T790M Positive Advanced Non-Small Cell Lung Cancer

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Background: In Asia, there is limited knowledge about resistant mechanisms after treatment with osimertinib in T790M+ve non-small cell lung cancer (NSCLC). Non-invasive molecular testing (NIMT) was used to explore acquired resistance mechanisms and clinical relevance.

Methods: Cohort study in EGFR-T790M+ve advanced-NSCLC patients who received osimertinib after 1st/2nd generation EGFR-TKI treatment from January 2016 to December 2019 at Ramathibodi Hospital were included. Paired plasma samples were collected at baseline and progression for analysis by Next generation sequencing (NGS). Clinical data were collected from electronic medical records and analyzed clinical relevance.

Results: Fifty patients were included, and the response rates were 52% partial response, 34%stable disease, and 14% disease progression. A total of 19 patients had more than one resistant alteration; T790M-loss was most common (50%), followed by PIK3CA (14%) and so on. The OS for all patients was 16.4 months, and the time to treatment failure (TTF) for osimertinib was 9.3 months. Patients with T790M-loss tended to had a shorter TTF than T790M-maintained patients (6.0 vs 10.1 mo, P=0.21). Patients with T790M-maintained with C797S had a shorter OS compared to those with T790M-maintained without C797S (11.0 vs 15.2 mo). Patients with T790M-loss together with other co-mutations had a shorter TTF than patients with T790M-loss without other co-mutations (4.1 vs. 10.6 mo, P=0.07). Patients who had brain metastasis prior to using osimertinib were significantly more likely to have T790M-loss and patients who developed brain progression related to BRAF mutation.

Conclusions: The mechanisms of acquired resistance to osimertinib are heterogeneous in T790M+ve NSCLC. Patients with T790M-loss tended to have poorer TTF, while C797S and T790M-loss with other co-mutations affect the survival outcome.