Mechanisms of Acquired Osimertinib Resistance and Updated Clinical Outcomes in EGFR-Positive Non-Small Cell Lung Cancer

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ABSTRACT

BACKGROUND: Lung cancer is the leading cause of cancer-related deaths with 2.21 million cases and 1.80 million deaths worldwide in 2020. Within the United States alone, an estimated 235,760 new cases and 131,880 deaths are projected to occur in 2021. Osimertinib is an oral, third-generation tyrosine kinase inhibitor (TKI) that irreversibly binds EGFR-sensitizing and T790M mutations in non-small cell lung cancer (NSCLC) with encouraging results as first-line therapy in treatment-naïve patients and as a later-line agent in previously treated patients. Unfortunately, acquired resistance to osimertinib is inevitable. A previous retrospective study investigated the molecular alterations and outcomes of 92 patients with EGFR-positive NSCLC treated with osimertinib at the University of Colorado health system from 2008-2018. This project seeks to expand upon the original dataset of patients to a) provide a larger sample size, b) identify molecular alterations prior to and upon progression of osimertinib, and c) describe the survival benefit derived from treatment with targeted therapies following radiographic progression on osimertinib.

METHODS: This is a single-center, retrospective study of adult patients with EGFR-positive NSCLC treated with osimertinib who were evaluated at the University of Colorado health system from 2008-2021. Eligible patients were identified from an IRB-approved database of thoracic cancer patients treated at the University of Colorado. Eligibility criteria include histologically confirmed NSCLC; radiographic demonstration of disease progression after initiation of osimertinib; pretreatment and posttreatment molecular testing using validated tissue biopsy or ctDNA assays; and at least one instance of physician follow-up after disease progression. Patient demographics, clinicopathological features, molecular alterations, and treatment outcomes were collected. Survival curves were generated through the Kaplan-Meier method using a log-rank test to assess for differences in progression-free survival (PFS) and overall survival (OS).

RESULTS: The results of the expanded study are anticipated to remain similar to previous findings. The preliminary study found that TP53 co-mutation identified at the time of osimertinib initiation in 43 patients (57%) was associated with worse PFS (13 vs 9 months; $p = 0.013$, HR 0.32, 95% CI 0.01 – 0.67) and OS (44 vs. 33 months; $p = 0.03$, HR 0.43, 95% CI 0.21 – 0.92). Molecular testing via ctDNA assay or tissue biopsy was performed on 41 patients (44%), with 8 (19%) found to have acquired resistance mutations responsive to currently available targeted therapies. Osimertinib resistance in treatment naïve patients is likely to encompass more bypass signaling mechanisms (ex. MET amplification) while T790M-positive patients are likely to demonstrate EGFR-dependent resistance mechanisms (ex. C797S). Resistance testing at the onset of osimertinib resistance will identify targetable mutations in a subset of patients – particularly MET amplification and HER2 amplification. Finally, patients who received second-line, targeted treatment in conjunction with continued osimertinib achieved an additional median PFS of approximately 13.5 months.

CONCLUSION: Preliminary data suggest the following: detection of mutant TP53 prior to osimertinib initiation is associated with significantly worse progress free survival and overall survival; identification of T790M mutation at the time of osimertinib progression may drive the acquisition of EGFR-dependent resistance mechanisms; resistance testing at the time of progression may identify targetable resistance mutations; and targeted therapies in combination with osimertinib achieve longer progress free survival. By and large, the expansion of the participant population is anticipated to demonstrate the same overall findings; additional mechanisms of resistance and their prognostic value may be identified as the project expands. Nevertheless, a study of this kind of would benefit from expansion of the participant population and inclusion of multiple institutions.

CONFLICTS OF INTEREST: C.N. has no conflicts of interest to disclose. T.P. is on the advisory board at: Janssen, Mirati, Turning Point, Sanofi, Pfizer, Astrazeneca, and Takeda. He is involved in company sponsored studies at: EMD Soreno and Janssen.

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