Mechanisms of Acquired Osimertinib Resistance and Outcomes of Patients with Epidermal Growth Factor Receptor (EGFR) Positive Non-Small Cell Lung Cancer (NSCLC)

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Introduction
Lung cancer is the leading cause of cancer-related deaths worldwide. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases, most of which present with advanced disease at the time of diagnosis. A substantial proportion of patients with NSCLC demonstrate initial responses to epidermal growth factor receptor (EGFR) sensitizing mutations in exons 19 to 21 – about 10% in white patients and 50% in Asian patients – prompting the development of targeted therapies.

Osimertinib is an oral, third-generation tyrosine kinase inhibitor (TKI) that irreversibly binds EGFR-exon 20 mutations, including T790M (19q13.4) and acquired T790M resistance mutations with encouraging therapeutic effects. Mechanisms of acquired resistance to osimertinib have been described in recent years, but the prognostic value that these mutations confer is not well established. Additionally, outcomes following initiation of targeted therapies are still under investigation and remain a challenge in patients with EGFR-positive NSCLC.

To this end, a preliminary study investigated the molecular alterations and outcomes of 92 patients with EGFR-positive NSCLC treated at University of Colorado Health system from 2008-2018 (described here). This project seeks to expand upon the original database of patients to provide a larger sample size for molecular alterations prior to and upon progression of osimertinib, and to describe the survival benefit derived from treatment with targeted therapies following radiographic progression on osimertinib.

Methods
The current study is a single-center retrospective study of patients with EGFR-positive NSCLC treated with osimertinib who were evaluated at the University of Colorado health system from 2008 – 2021. Institutional Review Board (IRB) approval for the retrospective review of medical records was obtained through the University of Colorado Cancer Center. Adults of at least 18 years of age with histologically confirmed NSCLC are eligible for this study. Clinicopathological features, molecular alterations (both prior to and upon progression on osimertinib), and treatment outcomes are being collected. Progression free survival (PFS) and overall survival (OS) will be calculated. Survival curves will be generated through Kaplan-Meier method using a log-rank test for analysis for differences.

Results of Preliminary Study (2008-2018)

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Patients N (%)</th>
</tr>
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<tbody>
<tr>
<td>Race</td>
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<tr>
<td>Asian</td>
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<tr>
<td>White</td>
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<td>Stage IV</td>
<td>186</td>
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<tr>
<td>Prior chemotherapy and/or chemoimmunotherapy</td>
<td>186</td>
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</tbody>
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Figure 1. Resistance Testing at the Time of Progression on Osimertinib Identified Targetable Oncogenes

Osimertinib resistance mutations found in 30% of patients (44%) underwent resistance testing at time of progression on osimertinib with circulating tumor DNA (ctDNA) and tissue biopsy listed above. Among these 41 patients, 15 (37%) were found to have resistance mutations targetable with currently available therapies.

Figure 2. TP53 Mutation is a Prognostic Marker for Progress Free Survival and Overall Survival in Patients with EGFR NSCLC on Osimertinib

Forty-three patients (57%) harbored a TP53 mutation at the time of osimertinib resistance. A log-rank test was employed to compare PFS (hs) and OS (hs) between patients with the presence or absence of TP53 mutations prior to starting osimertinib. The presence of TP53 mutations is associated with significantly worse outcomes, with a median PFS of 8 months vs 10 months, p = 0.103, HR 0.32, 95% CI (0.01 – 0.67) and OS (33 months vs 44 months, p = 0.03, HR 0.43, 95% CI 0.21 – 0.92) irrespective of prior lines of therapy. A multivariate Cox proportional hazard model found no differences in PFS and OS when adjusted for age, prior lines of therapy, or brain metastases.

Figure 3. Acquired Resistance Mutations at the Time of Progression on Osimertinib

Mutations favored EGFR-dependent mechanisms (ex. C797S) when T790M was detected at the time of progression on osimertinib. Patients with undetectable levels of T790M demonstrated a tendency to acquire resistance mechanisms through EGFR-independent mechanisms such as MET amplification, HER2 amplification, ALK fusion. Similarly, a substantial proportion of cases in EGFR tyrosine kinase inhibitors (TKIs) demonstrated bypass resistance mechanisms. Mutations were detected using circulating tumor DNA (ctDNA) analysis, or tissue biopsy (invariant or variant assay). HER2 and MET amplification were detected using FISH with MET/CEP 7 ≥ 2 and HER2/CEP 2 ≥ 3.

Discussion

1. Presence of TP53 is associated with significantly worse progression free survival and overall survival in patients with EGFR-positive NSCLC.

2. Of the patients who underwent resistance testing for progression on osimertinib, 8 patients (19%) had oncogenes that were targetable with currently available agents. This demonstrates the value of resistance testing at the time of progression.

3. Resistance profiles differ between patients with detectable levels of T790M and those with undetectable levels of T790M mutation. The EGFR-dependent mutation C797S was the most common acquired resistance mechanism among patients with detectable T790M. Secondary drivers (i.e., bypass resistance mechanisms such as MET amplification) are more common among patients with undetectable T790M.

4. T790M was found to be a significant predictor of survival in patients with detectable T790M. Secondary resistance mechanisms (i.e., bypass resistance mechanisms such as MET amplification) were more common among patients with undetectable T790M.

5. The addition of osimertinib to patients with known T790M mutations has shown to improve progression free survival.

6. The presence of a detectable T790M mutation at progression is associated with worse outcomes. This indicates that patients with detectable T790M mutations at progression are less likely to benefit from treatment with chemotherapy, immunotherapy, or osimertinib.

Limitations

Limitations of this study reflect its small sample size at a single institution. As this project seeks to determine the correlation of specific genetic markers with clinical outcomes, further studies are necessary to meet the inclusion criteria, a study of this kind would benefit from expansion of the patient population to and aggregation of data from multiple institutions.

CONFLICTS OF INTEREST: C. N. has no conflicts of interest to declare. T.P. is on advisory boards for AstraZeneca, Novartis, Turing, Pfizer, Sorrento, Phase Acquisition, and Taiho. T. C. is involved in company sponsored studies at DANA/Onyx and janssen.

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