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 epidermal growth factor receptor (EGFR) sensitizing mutations in exons 18 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 and selectively binds EGFR-sensitizing mutations (such as exon 19 deletion and L858R) and acquired T790M resistance mutations with encouraging therapeutic effects. Mechanisms of acquired osimertinib resistance have been described in recent years, but the prognostic value that these mutations confer are 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 the University of Colorado health system from 2008-2018 (described here). This project seeks to expand upon the original dataset of patients to provide a larger sample size; identify molecular alterations prior to and upon progression of osimertinib; and 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. Clinicopathologic 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 assess for differences.

Results of Preliminary Study (2008-2018)

Table 1: Patient Demographics

Characteristics	Patients N = 92 (%)
Age (years)	
Median	61
Range	38 - 81
Sex	
Male	30 (33)
Female	62 (67)
Race	
White	69 (75)
Black	3 (3)
Hispanic	7 (8)
Asian	11 (12)
Other	2 (2)
Smoking Status	
Never / Light (≤ 10 pack years)	80 (87)
Heavy (>10 pack years)	12 (13)
Histology	
Adenocarcinoma	90 (98)
Adenosquamous	2 (2)
Stage at diagnosis	
Stage I	1 (1)
Stage II	7 (8)
Stage III	3 (3)
Stage IV	81 (88)
Brain metastases (at stage IV disease)	
Yes	33 (36)
No	59 (64)
Prior EGFR TKI therapy	
0	19 (21)
1	55 (60)
2 or greater	18 (19)
Prior chemotherapy and/or chemoimmunotherapy	
Yes	29 (32)
No	63 (68)

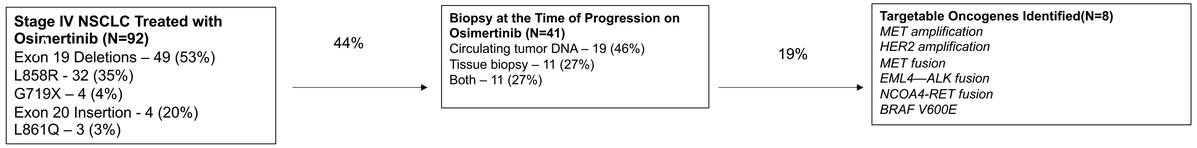
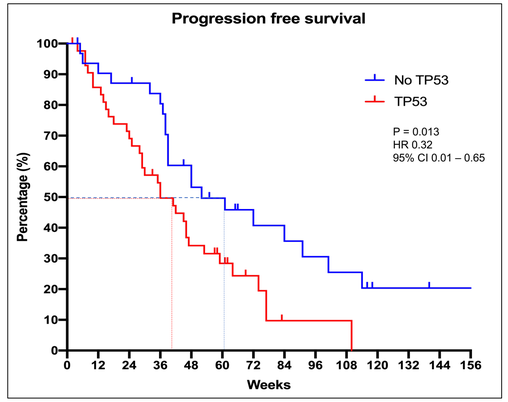
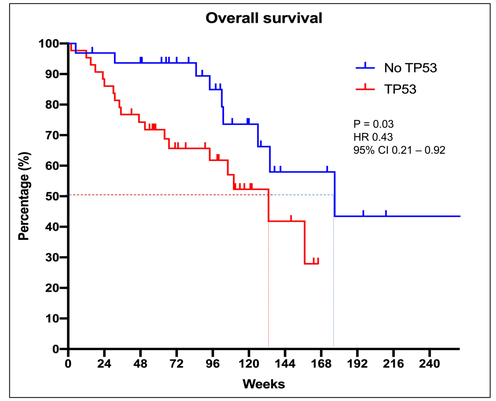


Figure 1. Resistance Testing at the time of Progression on Osimertinib Identified Targetable Oncogenes
Of the 92 patients included in this study, 41 patients (44%) underwent resistance testing at time of progression on osimertinib with circulating tumor DNA (Guardant®) and tissue biopsy listed above. Among these 41 patients, 19% (8 patients) were found to have resistance mutations targetable with currently available TKIs.



No TP53	32	29	28	25	17	14	9	8	6	6	4	2	1	1
TP53	43	38	33	22	14	10	6	2	2	1	1	1	1	1



No TP53	32	31	29	24	18	11	6	5	3	2	1	1		
TP53	43	38	31	21	17	8	5	1	1	1	1	1		

Figure 2. TP53 Comutation 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 comutation at the time of osimertinib initiation. A log-rank test was employed to compare PFS (left) and OS (right) between participants with the presence or absence of TP53 mutations prior to starting osimertinib. The presence of TP53 mutations was associated with significantly worse PFS (13 months vs 9 months; p = 0.013, 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.

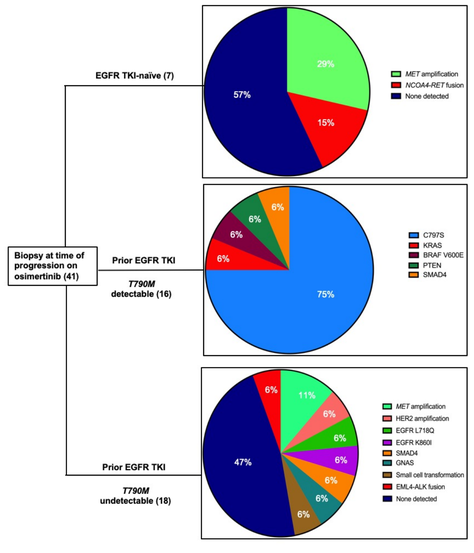


Figure 3. Acquired Resistance Mutations at the Time of Progression on Osimertinib
Mutations favored EGFR-dependent mechanisms (ex. C797S) when T790M was detected at the time of progression on osimertinib. Patients with undetectable levels of T790M demonstrated a tendency to acquire resistance mutations through EGFR-independent mechanisms such as MET amplification, HER2 amplification, AML4-ALK fusion. Similarly, a substantial proportion of cases in EGFR tyrosine kinase inhibitor naïve patients demonstrated bypass resistance mechanisms. Mutations were detected using circulating tumor DNA (Guardant® assay) or tissue biopsy (Archer Variant/Fusion Plex ® assay). HER2 and MET amplification were detected using FISH with MET/CEP7 ≥ 3 and HER2/CEP7 ≥ 3.

EGFR-Dependent Resistance Mutations	EGFR-Independent Resistance Mutations
C797S L718Q K860I	MET amplification NCOA4-RET fusion KRAS BRAF V600E PTEN SMAD4 Small cell transformation

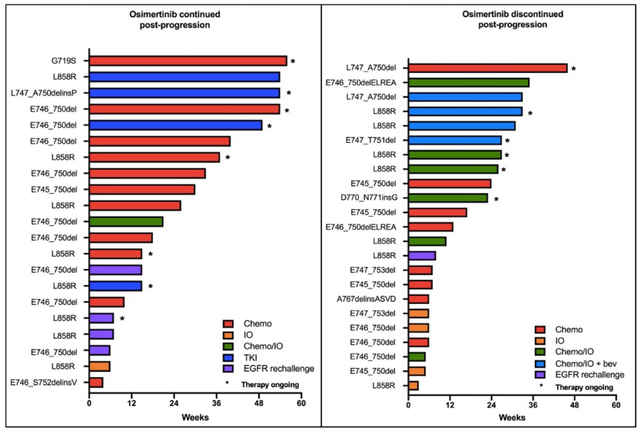


Figure 5. Outcomes Following Progression on Osimertinib in EGFR+ NSCLC
Comparison of PFS in patients that continued osimertinib versus those that discontinued osimertinib after progression. All chemotherapy agents consistent of a platinum doublet backbone. Immune checkpoint inhibitors (IO) included pembrolizumab, nibolumab, and atezolizumab. *Outcomes of Combined Osimertinib-Targeted Therapy (Not Pictured)*: Patients with targetable acquired resistance mutations (e.g. MET amplification, gene fusion) who received appropriate targeted therapy in combination with osimertinib achieved a median PFS of 13.5 months with a median follow up of 13 months. *Outcomes of Patients Treated with EGFR-TKI and Osimertinib (Left):* Patients who received EGFR rechallenge (e.g. erlotinib, cetuximab, panintumumab) in combination with osimertinib had median PFS of 3 months. *Outcomes Following Discontinuation of Osimertinib (Right)*: Patients achieved the following median PFS: 8 months with chemoimmunotherapy with bevacizumab, 5 months with chemoimmunotherapy, and 1.4 months with immunotherapy monotherapy. Median duration of follow up was 21 months.

Discussion

1. Presence of TP53 is associated with significantly worse progress free survival and overall survival in patients with EGFR-positive NSCLC.
2. Of the patients who underwent biopsy at the time of 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 mutation among patients with detectable T790M. Secondary drivers (ex. bypass resistance mechanisms such as MET amplification) are more common among patients with undetectable T790M. This suggests that T790M preferentially drives acquisition of EGFR-dependent resistance mechanisms.
4. Targeted therapies combined with osimertinib achieved a median PFS of 13.5 months with a median follow up of 13 months. If a targetable resistance oncogene is identified at the time of progression on osimertinib, combining therapies is a viable course of action.
5. EGFR rechallenge combined with osimertinib demonstrated a median PFS of 3 months; this response likely reflects an off-target mechanism of resistance.
6. Patients that discontinued osimertinib but continued to receive treatment with chemotherapy, immunotherapy, or both achieved modest median PFS with a median follow up of 21 months. This suggests that there may be a benefit to continuing osimertinib with these agents.
7. These findings are likely to remain unchanged as the patient population expands.

Limitations

Limitations of this study reflect its small sample size at a single institution. As this project seeks to expand significantly on previously obtained data and relatively few patients 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 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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