MET, Her2, and p53 alterations and Osimertinib resistance in EGFR mutant non-small cell lung cancer patients, a meta-analysis

Hannah Caldwell[1], Annie Le[1], Jun Wang[2]

[1]Osteopathic Medicine Student, DeBusk College of Osteopathic Medicine, Lincoln Memorial University, Harrogate, TN
[2]Department of Pathology, DeBusk College of Osteopathic Medicine, Lincoln Memorial University, Knoxville, TN

Introduction

Tyrosine kinase inhibitors (TKI) have become frequently used to treat epidermal growth factor receptor (EGFR) mutant NSCLCs. While remarkable improvement of clinical outcome is evident in many patients, resistance to first and second-generation TKIs has been reported and is commonly associated with acquired EGFR T790M mutation.

Osimertinib is a third generation TKI that selectively inhibits EGFR T790M. Its use has been approved for the treatment of NSCLC in patients with disease progression on first and second-generation TKIs, especially those with T790M mutations. However, resistance to osimertinib has been observed and appears to be associated with acquired genetic alterations in tumor genomes.

Tumor protein p53, referred to as p53, is a tumor suppressor gene that regulates cell proliferation. Human epithelial growth factor receptor 2 (Her2) and mesenchymal epithelial transition (MET) are tyrosine kinases that are involved in cell signaling and proliferation. Mutation of p53 and Her2, as well as amplification of MET, are frequently observed in osimertinib resistant patients.

Meta-analysis was performed using published clinical observations of EGFR mutant NSCLC patients treated with osimertinib to determine whether p53, Her2, and MET alterations are associated with resistance.

Materials & Methods

Published studies of the clinical efficacy of osimertinib on EGFR NSCLCs were gathered through PubMed. A variety of key words in the title and abstract such as lung, osimertinib, resistance, and sequencing were used. The abstracts obtained from the initial search results were manually reviewed. Only original studies with status of p53, Her2, MET alterations and osimertinib associated objective responses were included. Preclinical studies, case reports, and reviews were excluded. The full text of the included studies was reviewed. The prevalence of p53, Her2, and MET alterations in patients with or without osimertinib resistance was compared. Meta-analysis was conducted using RevMan 5.

Selection of Studies

Initial PubMed searching yielded 191 studies. After screening and reviewing abstracts, 29 studies were included for further analysis (Figure 1). These studies provide patient-specific information on the status of MET, Her2, and p53, as well as individual PFS values. MET, Her2, and p53 status are tested in 29 studies. Case reports, preclinical reports, reviews, NSCLC with CNS metastases, and studies lacking MET, Her2, or p53 associated clinical outcomes are excluded.

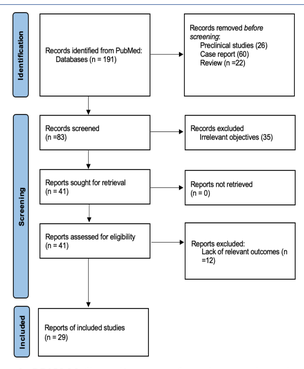

Figure 1. PRISMA flow diagram of study search and selection

Results

Publication ID	Total number of pt tested	Total number of MET mutation	Percentage
Kato 2021	20	6	30
Lee 2020	17	0	0
Mehlman 2019	61	8	13
Oxnard 2018	41	24	59
Suryavanshi 2022	15	2	13
Vendrell 2021	13	2	15
Yang 2018	93	7	8
Zugazagoitia 2019	15	2	13
Buttitta 2020	7	3	43
Chmielecki 2023	109	17	16
Hondelink 2021	148	18	12
Fernandes 2021	10	1	10
Lee 2021	29	5	17
Nie 2018	9	0	0
Nie 2022	21	6	29
Osoegawa 2021	19	6	32
Wang 2018	13	5	39
Schoenfeld 2020	28	3	11
Chen 2022	27	7	26
Jori 2021	41	4	10
Lim 2022	36	1	3
Roper 2020	13	7	54
Total	785	134	22

Table 1. Incidences of MET alteration in osimertinib resistant patients

Publication ID	Total number of pt tested	Total number of p53 mutation	Percentage
Ding 2019	9	4	44
Kato 2021	20	9	45
Mehlman 2019	61	3	5
Oxnard 2018	41	24	59
Suryavanshi 2022	15	1	7
Vendrell 2021	13	7	54
Yang 2018	93	56	60
Zugazagoitia 2019	15	7	47
Buttitta 2020	7	1	14
Lee 2021	29	19	66
Nie 2018	9	4	44
Nie 2022	21	14	67
Osoegawa 2021	19	11	58
Wang 2018	13	10	77
Shoenfeld 2020	28	15	54
Chen 2022	37	26	70
Jori 2021	41	22	54
Lim 2022	36	21	58
Vokes 2022	31	23	74
Roper 2020	13	2	15
Total	551	279	20

Table 2. Incidences of p53 alteration in osimertinib resistant patients

Publication ID	Total number of pt tested	Total number of Her2 mutation	Percentage
Guibert 2018	25	2	8
Kato 2021	20	4	20
Mehlman 2019	61	1	2
Suryavanshi 2022	15	0	0
Vendrell 2021	13	1	8
Yang 2018	93	4	4
Buttitta 2020	7	1	14
Hondelink 2021	148	3	2
Fernandes 2021	10	0	0
Lee 2021	29	1	3
Nie 2018	9	0	0
Nie 2022	21	2	10
Osoegawa 2021	19	2	11
Wang 2018	13	1	8
Schoenfeld 2020	28	1	4
Jori 2021	41	4	10
Lim 2022	36	1	3
Total	588	28	17

Table 3. Incidences of Her2 alteration in osimertinib resistant patients

Results

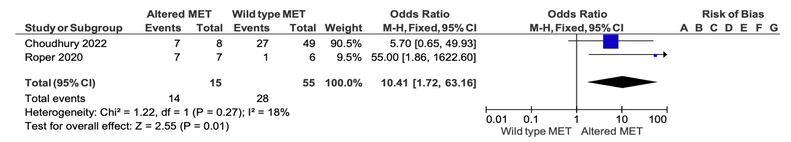

Figure 1. Probability of MET alteration associated with osimertinib resistance

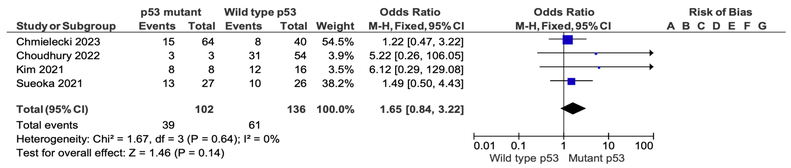

Figure 2. Probability of p53 alteration associated with osimertinib resistance

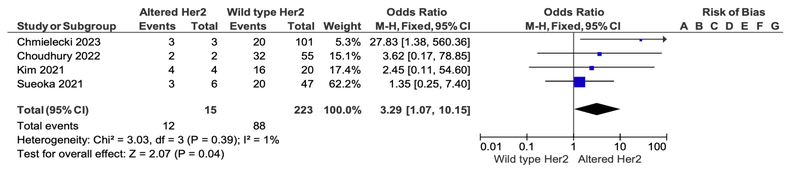

Figure 3. Probability of Her2 alteration associated with osimertinib resistance

Conclusions

1. Alterations of MET or p53 are commonly observed in patients treated with osimertinib but appear to be more frequent in osimertinib resistant patients. However, frequencies of Her2 are similar in groups with and without osimertinib resistance.
2. Her2 and MET alterations appear to be associated with shortened progression free survival, but mutation of p53 does not.
3. Patients with Her2 or MET alterations are more likely to develop osimertinib resistance.
4. Monitoring serum or tissue samples for MET gene and Her2 gene alterations in NSCLC patients treated with osimertinib may serve as an indication of osimertinib resistance, and the addition of a MET inhibitor or Her2 targeted therapy could potentially result in improved clinical outcomes in these patients.

References

1. Buttitta, F., et al., 2020. Early prediction of resistance to tyrosine kinase inhibitors by plasma monitoring of EGFR mutations in NSCLC: A new algorithm for patient selection and personalized treatment. Oncotarget, 11(11), 982–991. https://doi.org/10.18632/oncotarget.27517
2. Chen, J., et al., 2022. Single-cell DNA-seq depicts clonal evolution of multiple driver alterations in osimertinib-resistant patients. *Annals of Oncology*, *33*(4), 434–444.https://doi.org/10.1016/j.annonc.2022.01.004
3. Chmielecki, J., et al., 2023. Candidate mechanisms of acquired resistance to first-line osimertinib in EGFR-mutated advanced non-small cell lung cancer. *Nature Communications*, *14*(1). https://doi.org/10.1038/s41467-023-35961-y
4. Chmielecki, J., et al., 2023. Analysis of acquired resistance mechanisms to osimertinib in patients with EGFR-mutated advanced non-small cell lung cancer from the aura3 trial. *Nature Communications*, *14*(1). https://doi.org/10.1038/s41467-023-35962-x
5. Choudhury, N. et al., 2023. Molecular biomarkers of disease outcomes and mechanisms of acquired resistance to first-line osimertinib in advanced EGFR-Mutant Lung Cancers. *Journal of Thoracic Oncology*, *18*(4), 463–475. https://doi.org/10.1016/j.jtho.2022.11.022
6. Ding, P. N., et al., 2019. Plasma next-generation sequencing and droplet digital pcr-based detection of epidermal growth factor receptor (EGFR) mutations in patients with advanced lung cancer treated with subsequent-line osimertinib. *Thoracic Cancer*, *10*(10), 1879–1884. https://doi.org/10.1111/1759-7714.13154
7. Fernandes, M. G., et al., 2021. Resistance profile of osimertinib in pre-treated patients with EGFR T790M-mutated non-small cell lung cancer. *Frontiers in Oncology*, *11*. https://doi.org/10.3389/fonc.2021.602924
8. Fu, Y., et al., 2021. Advanced NSCLC patients with EGFR T790M harboring TP53 R273C or KRAS G12V cannot benefit from osimertinib based on a clinical multicentre study by tissue and liquid biopsy. *Frontiers in Oncology*, *11*. https://doi.org/10.3389/fonc.2021.621992
9. Guibert, N., et al., 2018. Amplicon-based next-generation sequencing of plasma cell-free DNA for detection of driver and resistance mutations in advanced non-small cell lung cancer. *Annals of Oncology*, *29*(4), 1049–1055. https://doi.org/10.1093/annonc/mdy005
10. Hondelink, L. M., et al., 2021. Real-world approach for molecular analysis of acquired EGFR tyrosine kinase inhibitor resistance mechanisms in NSCLC. *JTO Clinical and Research Reports*, *2*(12), 100252. https://doi.org/10.1016/j.jtocrr.2021.100252
11. Jori, B., et al., 2021. Comparison of resistance spectra after first and second line osimertinib treatment detected by liquid biopsy. *Cancers*, *13*(12), 2861. https://doi.org/10.3390/cancers13122861
12. Kato, R., et al., 2021. CAPP-Seq analysis of circulating tumor DNA from patients with EGFR T790M–positive lung cancer after osimertinib. *International Journal of Clinical Oncology*, *26*(9), 1628–1639. https://doi.org/10.1007/s10147-021-01947-3
13. Lee, J., et al., 2020. Genomic landscape of acquired resistance to third-generation EGFR tyrosine kinase inhibitors in EGFR T790M-mutant non-small cell lung cancer. *Cancer*, *126*(11), 2704–2712. https://doi.org/10.1002/cncr.32809
14. Lee, K., et al., 2021. Exploring the resistance mechanisms of second-line osimertinib and their prognostic implications using next-generation sequencing in patients with non-small-cell Lung Cancer. *European Journal of Cancer*, *148*, 202–210. https://doi.org/10.1016/j.ejca.2021.01.052
15. Lim, S. M., et al., 2022. Molecular landscape of osimertinib resistance in patients and patient-derived preclinical models. *Therapeutic Advances in Medical Oncology*, *14*, 17588359221079791. https://doi.org/10.1177/17588359221079125
16. Mehlman, C., et al., 2019. Resistance mechanisms to osimertinib in EGFR-mutated advanced non-small-cell lung cancer: A multicentric retrospective French study. *Lung Cancer*, *137*, 149–156. https://doi.org/10.1016/j.lungcan.2019.09.019
17. Nie, K., et al., 2018. Mutational profiling of non-small-cell lung cancer resistant to osimertinib using next-generation sequencing in Chinese patients. *BioMed Research International*, *2018*, 1–6. https://doi.org/10.1155/2018/9010353
18. Nie, N., et al., 2022. First-line osimertinib in patients with EGFR-mutated non-small cell lung cancer: Effectiveness, resistance mechanisms, and prognosis of different subsequent treatments. *Clinical Medicine Insights: Oncology*, *16*, 11795492211347. https://doi.org/10.1177/11795492211347
19. Osoegawa, A., et al., 2021. High incidence of c797s mutation in patients with long treatment history of EGFR tyrosine kinase inhibitors including osimertinib. *JTO Clinical and Research Reports*, *2*(7), 100191. https://doi.org/10.1016/j.jtocrr.2021.100191
20. Oxnard, G. R., et al., 2018. Assessment of resistance mechanisms and clinical implications in patients withegfr T790M–positive lung cancer and acquired resistance to osimertinib. *JAMA Oncology*, *4*(11), 1527. https://doi.org/10.1001/jamaoncol.2018.2969
21. Roper, N., et al., 2020. Clonal Evolution and Heterogeneity of Osimertinib Acquired Resistance Mechanisms in EGFR Mutant Lung Cancer. *Cell reports. Medicine*, *1*(1), 100007. https://doi.org/10.1016/j.xcrm.2020.100007
22. Schoenfeld, et al., 2020. Tumor analyses reveal squamous transformation and off-target alterations as early resistance mechanisms to first-line osimertinib in egfr-mutant lung cancer. *Clinical Cancer Research*, *26*(11), 2654–2663. https://doi.org/10.1158/1078-0432.ccr-19-3563
23. Sueoka-Aragane, N., et al., 2021. The role of comprehensive analysis with circulating tumor DNA in advanced non-small cell lung cancer patients considered for osimertinib treatment. *Cancer Medicine*, *10*(12), 3873–3885. https://doi.org/10.1002/cam4.3929
24. Suryavanshi, M., et al., 2022. Audit of molecular mechanisms of primary and secondary resistance to various generations of tyrosine kinase inhibitors in known epidermal growth factor receptor-mutant non-small cell lung cancer patients in a tertiary centre. *Clinical Oncology*, *34*(11). https://doi.org/10.1016/j.clon.2022.06.003
25. Vendrell, J. et al., 2021). EGFR-dependent mechanisms of resistance to osimertinib determined by ctdna NGS analysis identify patients with better outcome. *Translational Lung Cancer Research*, *10*(11), 4084–4094. https://doi.org/10.21037/tlcr-21-679
26. Vokes, N. et al., 2022. Concurrent TP53 mutations facilitate resistance evolution in EGFR-Mutant Lung Adenocarcinoma. *Journal of Thoracic Oncology*, *17*(6), 779–792. https://doi.org/10.1016/j.jtho.2022.02.011
27. Wang, Y., et al., 2018. Clinical analysis by next-generation sequencing for NSCLC patients with met amplification resistant to osimertinib. *Lung Cancer*, *118*, 105–110. https://doi.org/10.1016/j.lungcan.2018.02.007
28. Yang, Z., et al., 2018. Investigating Novel Resistance Mechanisms to Third-Generation EGFR Tyrosine Kinase Inhibitor Osimertinib in Non-Small Cell Lung Cancer Patients. *Clinical cancer research : an official journal of the American Association for Cancer Research*, *24*(13), 3097–3107. https://doi.org/10.1158/1078-0432.CCR-17-2310
29. Zugazagoitia, J., et al., 2019. Clinical utility of plasma-based digital next-generation sequencing in oncogene-driven non-small-cell lung cancer patients with tyrosine kinase inhibitor resistance. *Lung Cancer*, *134*, 72–78. https://doi.org/10.1016/j.lungcan.2019.05.032