MET Alterations Are Associated With Osimertinib Resistance in EGFR Mutant Lung Cancers, a Meta-Analysis

Annie Le[1], Marissa Viola[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) targeting sensitive EGFR mutations (EGFRm) have been effective in treating non-small cell lung cancers (NSCLCs). While improved clinical courses are seen in most patients, resistance to first and second generation TKIs have been reported widely. Most of them are associated with acquired EGFR T790M mutation, or concurrent alterations of other tumor driver genes.

Osimertinib is a third generation TKI that selectively inhibits both EGFRm and T790M. Its use has been approved for lung cancers with EGFRm, and those progressing on first and second generation TKIs with T790M. Resistance to osimertinib has been reported and appears to be associated with acquired alterations of tumor genomes.

Mesenchymal Epithelial Transition (MET) is a receptor tyrosine kinase. Binding to hepatocyte growth factor results in its activation through autophosphorylation of its intracellular domain. Activation of MET regulates various cellular functions, including proliferation, morphogenesis and survival. Alterations of MET gene (*MET*), including amplification and point mutations, have been identified in approximately 5% NSCLCs.

To investigate whether *MET* alterations affect the clinical outcomes of EGFR mutant NSCLCs treated with osimertinib, a meta-analysis was performed using published clinical observations.

Materials & Methods

Published studies with clinical outcomes of EGFR mutant lung cancers treated with osimertinib are collected from PubMed. Combination of key words in title or abstract of lung, osimertinib, resistance, and sequencing were used. Abstracts of all the initial searching results were screened manually. Only original studies with status of *MET* alterations and osimertinib associated clinical outcomes are included. Case reports, reviews, and preclinical studies were excluded. Full texts of the included studies were reviewed. Incidences of *MET* alterations were compared in patients with or without osimertinib resistance. Meta-analysis was conducted using RevMan 5.

Selection of studies

Initial PubMed searching yielded 191 studies. After screening and reviewing abstracts, 16 studies were included for further analysis (Figure 1). Among these, *MET* status and PFSs from individual patients are available in 2 studies. *MET* status are only tested in osimertinib resistant patients in 14 studies. Case reports, preclinical investigations, reviews, NSCLC metastasis to CNS and studies without *MET* associated clinical outcomes are excluded. 5 studies were not included since the studies could not be retrieved.

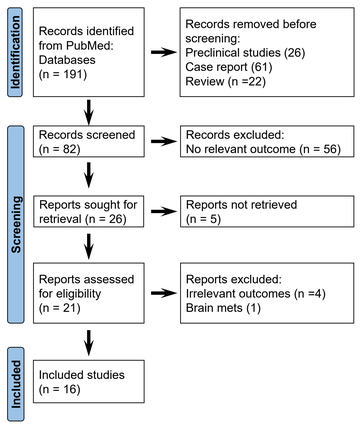

Figure 1. Study searching and selection

Results

MET alterations are common in Osimertinib resistant patients

MET status were assessed by direct sampling of the tumor, or serum tests. Alterations of *MET* are commonly seen following development of osimertinib resistance. Majority of these *MET* alterations are amplification. Rates of *MET* alterations shows great variation among studies, ranging from 0-43% (Table 1).

Table 1. Incidences of *MET* alterations in osimertinib resistant patients

Studies	Patients tested	*MET* alterations	Percentage
Buttitta 2020	7	3	43
Chmielecki 2023	78	14	18
Chmielecki 2023	109	17	16
Fernandes 2021	9	1	11
Hondelink 2021	142	17	12
Kim 2021	23	4	17
Lee 2021	29	5	17
Nie 2022	21	6	29
Nie 2018	9	0	0
Osoegawa 2021	19	6	32
Schoenfeld 2020	62	2	3
Wang 2018	13	5	38
Wu 2021	10	1	10
Yang 2018	93	7	8
Total	624	88	14

Majority of *MET* alterations are acquired

MET status were compared before and after osimertinib treatment in 7 studies. Majority of the *MET* alterations identified in post-treatment specimens are acquired (Table 2).

Table 2. Incidences of acquired *MET* alterations in patients after development of osimertinib resistant

Studies	Patients with paired tests	Total *MET* alterations	Acquired *MET* alterations	Percentage
Chmielecki 2023	78	14	14	100
Chmielecki 2023	109	17	17	100
Kim 2021	23	4	4	100
Nie 2022	21	6	6	100
Osoegawa 2021	19	6	6	100
Wang 2018	6	4	3	75
Yang 2018	12	2	2	100

MET alterations are associated with osimertinib resistance

Meta-analysis was performed using 2 studies with individual or grouped PFSs. Presence of *MET* alterations is associated osimertinib resistance, presented as PFS shorter than 12 months (p=0.01, Figure 1).

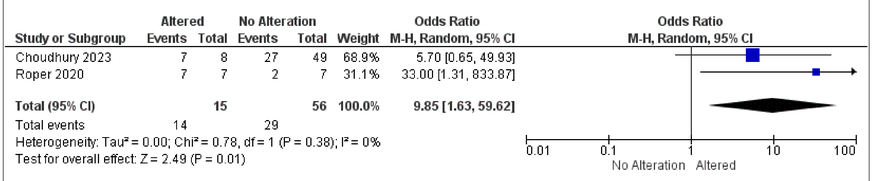

Figure 1. Meta-analysis of two studies with resistance defined as PFS shorter than 12 months

Conclusions

1. *MET* alterations are commonly seen in osimertinib resistant patients, but the rates of *MET* alterations vary greatly in different patient populations.
2. Majority of *MET* alterations associated with osimertinib resistance are acquired.
3. *MET* alterations appear to be associated with shortened PFS in patients treated with osimertinib.
4. By monitoring serum levels of altered *MET* in patients treated with osimertinib, resistance might be identified at early stages.
5. More favorable clinical courses might be achieved by combination therapy with osimertinib and MET inhibitor in patients.

1. Buttitta 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.
2. Chmielecki 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. Nat Commun. 14(1):1071.
3. Chmielecki et al., 2023. Candidate mechanisms of acquired resistance to first-line osimertinib in EGFR-mutated advanced non-small cell lung cancer. Nat Commun. 14(1):1070.
4. Choudhury et al. 2023. Molecular biomarkers of disease outcomes and mechanisms of acquired resistance to first-line osimertinib in advanced EGFR-mutant lung cancers. J Thorac Oncol. S1556-0864(22)01932-3.
5. Fernandes et al. 2021. Resistance profile of osimertinib in pre-treated patients with EGFR T790M-mutated non-small cell lung cancer. Front Oncol. 11:602924.
6. Hondelink et al., 2021. Real-world approach for molecular analysis of acquired EGFR tyrosine kinase inhibitor resistance mechanisms in NSCLC. JTO Clin Res Rep. 2(12):100252.
7. Kim et al., 2021. Longitudinal circulating tumor dna analysis in blood and saliva for prediction of response to osimertinib and disease progression in EGFR-mutant lung adenocarcinoma. Cancers (Basel). 13(13):3342.
8. Lee 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. Eur J Cancer. 148:202.
9. Nie et al., 2017. Mutational profiling of non-small-cell lung cancer resistant to osimertinib using next-generation sequencing in Chinese patients. Biomed Res Int. 2018:9010353
10. Nie 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. Clin Med Insights Oncol. 16:1.
11. Osoegawa et al., 2021. High incidence of C797S mutation in patients with long treatment history of EGFR tyrosine kinase inhibitors including osimertinib. JTO Clin Res Rep. 2(7):100191.
12. Roper et al., 2020. Clonal evolution and heterogeneity of osimertinib acquired resistance mechanisms in EGFR mutant lung cancer. Cell Rep Med. 1(1):100007.
13. 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. Clin Cancer Res. 26(11):2654.
14. Wang et al., 2018. Clinical analysis by next-generation sequencing for NSCLC patients with MET amplification resistant to osimertinib. Lung Cancer. 118:105.
15. Wu et al., 2021. Novel resistance mechanisms to osimertinib analysed by whole-exome sequencing in non-small cell lung cancer. Cancer Manag Res. 13:2025.
16. Yang et al., 2018. Investigating novel resistance mechanisms to third-generation EGFR tyrosine kinase inhibitor osimertinib in non-small cell lung cancer patients. Clin Cancer Res. 24(13):3097.