Title:

Acquired KRAS Co-Mutations on Osimertinib in EGFR-mutant Lung Cancer: A Case Series

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Introduction:

EGFR mutations are a common oncogenic driver in lung cancer.[1] Osimertinib provides durable responses,[2,3] however resistance inevitably develops. KRAS mutations are considered mutually exclusive with EGFR, but can rarely emerge as an acquired resistance mechanism.[4,5] The significance of EGFR-KRAS co-mutations remain poorly understood, although literature suggests reduced EGFR TKI sensitivity and worse prognosis.[4–6] This case series describes three patients with EGFR-mutated lung adenocarcinoma who developed acquired KRAS mutations at progression on osimertinib.

Methods:

We queried our thoracic oncology precision medicine database (n=2701) to identify patients with lung cancer and tissue NGS demonstrating concomitant EGFR and KRAS mutations. Of 19 total patients identified,15 had variants classified as VUS through ClinVar and/or COSMIC databases and were excluded. One patient had EGFR L858R/KRAS Q61H early stage disease at time of diagnosis and remained disease-free after lobectomy. Three patients with EGFR mutations and acquired activating KRAS mutations at progression were included.

Results:

A: 53-year-old never-smoker with EGFR L858R and TP53-mutated lung adenocarcinoma with metastases to the brain achieved 26.5 months of disease control on first-line osimertinib. At progression with worsening brain metastases, NGS demonstrated persistent EGFR and TP53 mutations with new KRAS Q61H mutation. She received carboplatin/paclitaxel/bevacizumab/atezolizumab with initial partial response before progression; survival was 14.2 months post-progression.

B: 67-year-old never-smoker metastatic EGFR exon 19 deletion and SMARCA4-mutated lung adenocarcinoma derived 25.6 months of benefit with osimertinib and received radiation for oligoprogression. At systemic progression, biopsy revealed persistent EGFR and SMARCA4 and new KRAS G12V mutations. He received one cycle of carboplatin/pemetrexed/osimertinib but deteriorated rapidly and died 0.4 months later.

C: 67-year-old never-smoker with stage III EGFR exon 19 deletion and SMARCA4-mutated lung adenocarcinoma deferred definitive chemoradiation and progressed after 5.7 months of osimertinib with small-cell transformation. Repeat pathology demonstrated Ki-67 95%, persistent EGFR and SMARCA4, and new KRAS A146T mutations. She received chemoradiation, but transitioned to hospice after two cycles.

	Stage (metastatic sites, if applicable)	Histology	Age	Sex	Smoking Status	PD-L1 TPS	NGS at time of diagnosis (VAF%)	NGS at time of progression (VAF%)	1L Treatment	PFS (mo)	OS (mo)	2L Treatment	PFS (mo)	OS (mo)
A	IV (brain bone, pericardium, pleura)	Adenocarcinoma	53	Female	Never	1-5	EGFR p.L858R (unknown) TP53p.G245S (unknown)	EGFR p.L858R (45.54%) TP53 p.G245S (78.63%) KRAS p.Q61H (7.68%)	Osimertinib	26.5	41.3	Carboplatin Paclitaxel Bevacizumab Atezolizumab RT to brain	9.5	14.2
B	IV (bone)	Adenocarcinoma	67	Male	Never	<1	EGFR p.E746_A750del (19.64%) SMARCA4 p.Q1512* (13.24%)	EGFR p.E746_A750del (15.51%) SMARCA4 p.Q1512* (23.74%) KRAS p.G12V (17.72%)	Osimertinib	25.6	49.1	Carboplatin Pemetrexed Osimertinib RT to bone	0.4	0.4
C	III	Adenocarcinoma with small cell transformation at time of progression	67	Female	Never	90-100	EGFR E746_A750del (11.31%) SMARCA4 p.F1102L (31.52%)	EGFR E746_A750del (11.31%) SMARCA4 p.F1102L (29.87%) KRAS p.A146T (2.84%)	Osimertinib	5.7	13.6	Cisplatin Etoposide RT to lung	7.1	7.1

Table 1. Summary of patients' histopathologic characteristics and treatment.

Conclusion:

Although typically mutually exclusive, acquired KRAS mutations can emerge as a resistance mechanism to osimertinib. In these cases, activating KRAS mutations appeared at progression with persistent EGFR driver alterations, suggesting clonal evolution and MAPK pathway reactivation. Their emergence coincided with aggressive disease behavior and limited benefit from subsequent therapies. All had co-mutations in either TP53 or SMARCA4, associated with poor prognosis, genomic instability and dedifferentiation,[7,8] which may have facilitated KRAS-driven resistance. These cases highlight the importance of repeat molecular profiling at progression and the need for improved combinatorial therapeutic strategies following osimertinib resistance.

References:

1. Tan, A. C. & Tan, D. S. W. Special Series: Thoracic Oncology: Current and Future Therapy review articles Targeted Therapies for Lung Cancer Patients With Oncogenic Driver Molecular Alterations. *J Clin Oncol* 40, 611–625 (2022).

2. Planchard, D. *et al.* Osimertinib with or without Chemotherapy in EGFR -Mutated Advanced NSCLC . *New England Journal of Medicine* 389, 1935–1948 (2023).

3. Soria, J.-C. *et al.* Osimertinib in Untreated EGFR -Mutated Advanced Non–Small-Cell Lung Cancer . *New England Journal of Medicine* 378, 113–125 (2018).

4. Zheng, J. *et al.* Overall signature of acquired KRAS gene changes in advanced non-small cell lung cancer patient with EGFR-TKI resistance. *Jpn J Clin Oncol* 54, 89–96 (2024).

5. Linardou, H. *et al.* Assessment of somatic k-RAS mutations as a mechanism associated with resistance to EGFR-targeted agents: a systematic review and meta-analysis of studies in advanced non-small-cell lung cancer and metastatic colorectal cancer. *www.thelancet.com/oncology* 9, (2008).

6. Sun, J. M., Hwang, D. W., Ahn, J. S., Ahn, M. J. & Park, K. Prognostic and Predictive Value of KRAS Mutations in Advanced Non-Small Cell Lung Cancer. *PLoS One* 8, (2013).

7. Baliakas, P. & Soussi, T. The TP53 tumor suppressor gene: From molecular biology to clinical investigations. *Journal of Internal Medicine* vol. 298 78–96 Preprint at https://doi.org/10.1111/joim.20106 (2025).

8. Ye, W., An, D. & Ou, W. Bin. SMARCA4: Promises and challenges in the treatment of cancers. *Cancer Letters* vol. 625 Preprint at https://doi.org/10.1016/j.canlet.2025.217811 (2025).