J Current Biomed Report
ISSN: 2717-1906
2025, Volume 6, Number 2
Letters to Editor

Concurrent EGFR and KRAS mutations in non-small cell lung cancer: Challenging the paradigm of linear targeted therapy

Mohsen Farrokhpour[1], Seyedeh Hatameh Asadinejad Tahergourabi[1], Niloofar Keikhaei[2], Hamed Hekmat Nejad[3]*

1. *Firouzgar Hospital, Department of Internal Medicine, School of Medicine, Iran University of Medical Sciences, Tehran, Iran*
2. *Sayad Shirazi Hospital, Department of Internal Medicine, School of Medicine, Golestan University of Medical Sciences, Gorgan, Iran*
3. *Department of Basic Sciences, Sari Agricultural Sciences and Natural Resources University, Sari, Iran*

To the Editor

Article info:
Received: 27 May 2025
Accepted: 11 Jun 2025

Keywords:
Non-small lung cancer
KRAS
EGFR
Mutation
Targeted therapy

Non-small cell lung cancer (NSCLC) is the most common subtype of lung cancer, and its high prevalence has increased its attention. In recent years, extensive genomic studies have identified key driver mutations in NSCLC, paving the way for the development of targeted therapies. Among the most clinically significant mutations are those in the epidermal growth factor receptor (EGFR) and kirsten rat sarcoma virus (KRAS) genes, occurring in approximately 15–50% and 25–35% of patients, respectively, depending on racial and geographic factors [1,2]. Patients harboring activating EGFR mutations are eligible for treatment with EGFR tyrosine kinase inhibitors (TKIs), which are considered first-line therapy. Likewise, patients with KRAS mutations, particularly the G12C variant may benefit from specific inhibitors such as sotorasib or adagrasib [3,4]. While EGFR and KRAS mutations both activate key pathways involved in cell proliferation and survival, such as the MAPK/ERK signaling cascade, they are typically regarded as mutually exclusive. However, recent reports have documented rare instances of concurrent EGFR and KRAS mutations in NSCLC, challenging this long-standing assumption. The coexistence of these mutations has important clinical implications, particularly in predicting therapeutic response and resistance to TKIs [5].

In a report by Ma et al., a 71-year-old man with multiple primary lung adenocarcinomas was studied. CT scan and biopsy findings revealed multiple discrete foci in the lung, each of which was considered a separate primary tumor. Molecular analysis identified two mutations in distinct foci: an exon 19 deletion in the EGFR gene and a KRAS G12C mutation. The patient with primary lung adenocarcinoma received multimodality therapy. The initial step involved thoracoscopic surgery to remove the lesions, followed by a course of systemic chemotherapy combined with immunosuppressive therapy. With this combined treatment approach, progression-free survival (PFS) lasted for approximately one year. The disease subsequently progressed to the mediastinal lymph nodes and brain, and the patient ultimately died due to increased metastasis [6].

Corresponding Author(s):
Hamed Hekmat Nejad, MSc
Address: *Department of Basic Sciences, Sari Agricultural Sciences and Natural Resources University, Sari, Iran*
Tel: +98 911 9915699
E-mail: hamedhekmatnejad@yahoo.com

In this case, the use of targeted therapies such as third-generation EGFR inhibitors (e.g., Osimertinib) and KRAS inhibitors (e.g., Sotorasib or Adagrasib) was theoretically possible. However, the lack of sufficient clinical data and concerns about cumulative toxicity made this combination therapy questionable. Therefore, this approach may be considered a potential treatment for resistant or relapsed cases in the context of clinical trials [7]. In cases of concurrent EGFR and KRAS mutations, monotherapy with a single targeted agent may be insufficient due to persistent downstream signaling through pathways such as MAPK/ERK and PI3K/AKT, primarily driven by KRAS [8,9]. Limited evidence suggests that patients with co-mutations tend to exhibit poorer responses to targeted therapies compared to those with isolated EGFR mutations [10]. Therefore, extensive molecular testing is necessary to select the most effective treatment strategy.

These findings suggest that the traditional linear therapeutic approach based solely on the presence of a dominant mutation may require reconsideration in cases with concurrent mutations. It is therefore recommended that larger-scale clinical studies be conducted to evaluate the efficacy and safety of combination therapies in patients harboring both EGFR and KRAS mutations. A deeper understanding of the molecular complexities involved could guide more precise and effective treatment strategies for NSCLC.

Authors' contributions

Study design, Project administration, Supervision: MF, HH. Data curation, Investigation, Resources: MF, SHA, NK. Writing original draft, Review and Editing: SHA, NK, HH. All authors read and approved the final version of manuscript.

Conflict of interest

No potential conflict of interest was reported by the authors.

Ethical declarations

Not applicable.

Financial support

Self-funded.

References

1. Tan AC, Tan DSW. Targeted Therapies for Lung Cancer Patients With Oncogenic Driver Molecular Alterations. J Clin Oncol. 2022;40(6):611-625. DOI: 10.1200/JCO.21.01626 PMID: 34985916
2. Rotow J, Bivona TG. Understanding and targeting resistance mechanisms in NSCLC. Nat Rev Cancer. 2017;17(11):637-658. DOI: 10.1038/nrc.2017.84 PMID: 29068003
3. Skoulidis F, Li BT, Dy GK, Price TJ, Falchook GS, Wolf J, et al. Sotorasib for Lung Cancers with KRAS p.G12C Mutation. N Engl J Med. 2021;384(25):2371-2381. DOI: 10.1056/NEJMoa2103695 PMID: 34096690
4. Jänne PA, Riely GJ, Gadgeel SM, Heist RS, Ou SI, Pacheco JM, et al. Adagrasib in Non-Small-Cell Lung Cancer Harboring a KRASG12C Mutation. N Engl J Med. 2022;387(2):120-131. DOI: 10.1056/NEJMoa2204619 PMID: 35658005
5. Takamochi K, Oh S, Suzuki K. Differences in EGFR and KRAS mutation spectra in lung adenocarcinoma of never and heavy smokers. Oncol Lett. 2013;6(5):1207-1212. DOI: 10.3892/ol.2013.1551 PMID: 24179496
6. Ma JW, Fu YL, Miao L, Li M. Imaging of synchronous multiple primary lung adenocarcinoma with concomitant EGFR and KRAS mutations: a case report and review of the literature. Transl Cancer Res. 2021;10(5):2509-2515. DOI: 10.21037/tcr-20-3258 PMID: 35116566
7. Ernst SM, Uzun S, Paats MS, van Marion R, Atmodimedjo PN, de Jonge E, et al. Efficacy and Tolerability of Osimertinib and Sotorasib Combination Treatment for Osimertinib Resistance Caused by KRAS G12C Mutation: A Report of Two Cases. JCO Precis Oncol. 2023;7:e2300451. DOI: 10.1200/PO.23.00451 PMID: 38096473
8. Fu K, Xie F, Wang F, Fu L. Therapeutic strategies for EGFR-mutated non-small cell lung cancer patients with osimertinib resistance. J Hematol Oncol. 2022;15(1):173. DOI: 10.1186/s13045-022-01391-4 PMID: 36482474
9. Laface C, Maselli FM, Santoro AN, Iaia ML, Ambrogio F, Laterza M, et al. The Resistance to EGFR-TKIs in Non-Small Cell Lung Cancer: From Molecular Mechanisms to Clinical Application of New Therapeutic Strategies. Pharmaceutics. 2023;15(6):1604. DOI: 10.3390/pharmaceutics15061604 PMID: 37376053
10. Ou X, Gao G, Habaz IA, Wang Y. Mechanisms of resistance to tyrosine kinase inhibitor-targeted therapy and overcoming strategies. MedComm (2020). 2024;5(9):e694. DOI: 10.1002/mco2.694 PMID: 39184861