



# Large Cell Neuroendocrine Carcinoma of Lung with Synchronous Dual Activating EGFR Mutation and ALK Rearrangement - A Case Report

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## Abstract

Lung cancer is responsible for 12.9% of all new cancer cases diagnosed globally and is responsible for 19.5% of all cancer-related deaths. The percentage of patients presenting as stage IV disease increased from 38.7% between 1994 and 1998 to 47.2% between 1999 and 2004 to 54.8% between 2008 to 2017. Histology has been found to be prognostic for survival in stage 4 lung cancer. Large Cell Neuroendocrine Carcinoma (LCNEC) is a subtype of Non-Small Cell Lung Cancer (NSCLC) and accounts for approximately 1.6% to 3.1% of all lung cancer. LCNEC is now recognized as a histologically high-grade non-small cell carcinoma by WHO, categorized as a variant of large cell carcinoma. It has a distant metastasis rate of 65% and poor prognosis even in early stages, with survival rates similar to Small-Cell Lung Carcinomas (SCCs). The life expectancy of stage IV LCNEC with distant metastasis was estimated at around 6 months.

We report a case of 49 years old male with carcinoma lung harboring LCNEC histology, who responded very well to Anti-EGFR TKI Gefitinib with a PFS of 14 months and ongoing with a partial response to disease.

**Keywords:** LCNEC; NSCLC; EGFR; TKI

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## Abbreviations

LCNEC: Large Cell Neuroendocrine Carcinoma; NSCLC: Non-Small Cell Lung Carcinoma; EGFR: Epidermal Growth Factor Receptor; TKI: Tyrosine Kinase Inhibitor

## Key Messages

Large Cell Neuroendocrine Carcinoma (LCNEC) of the lung is an aggressive and rare neoplasm and one of the most challenging diseases to treat with metastasis rate of 65% and poor prognosis even in early stages. We report a case of 49 years old male with carcinoma lung harboring LCNEC histology, who responded very well to Anti-EGFR TKI Gefitinib with a PFS of 14 months and ongoing with a partial response to disease.

## Introduction

Lung cancer is responsible for 12.9% of all new cancer cases diagnosed globally and is responsible for 19.5% of all cancer-related deaths [1]. The percentage of patients presenting as stage IV disease increased from 38.7% between 1994 and 1998 to 47.2% between 1999 and 2004 to 54.8% between 2008 to 2017 [2]. Histology has been found to be prognostic for survival in stage 4 lung cancer. Large Cell Neuroendocrine Carcinoma (LCNEC) of the lung is a rare disease, considered challenging to treat and an aggressive neoplasm. It is a subtype of Non-Small Cell Lung Cancer (NSCLC) comprising 1.6% to 3.1% of all lung cancers [3,4]. LCNEC by histology is considered as a high-grade non-small cell carcinoma by WHO, categorized as a variant of large cell carcinoma. It is known to spread at distant sites in 65% cases which makes it a poor prognosis subset with a median OS reported to be 6 months. Also, in the early stages survival rates are poor alike small cell carcinomas [5]. The optimal therapy for advanced LCNEC has not been defined yet. The standard of care is generally palliative chemotherapy, a position endorsed by most professional guidelines. Most patients diagnosed with LCNEC are treated with chemotherapy regimens similar to those used for Small Cell Lung Cancer (SCLC) which generally obtains short-lasting responses.

Much of the work done in NSCLC the last decade has been focused on mutations of the Epidermal Growth Factor Receptor (EGFR) and on the abnormal fusion of the Anaplastic Lymphoma Kinase (ALK) being inhibited successfully with Tyrosine Kinase Inhibitors (TKIs) [6]. In fact, current guidelines recommend upfront molecular testing of NSCLC to determine patients who possess predictive mutations so that they may be treated upfront with targeted therapy instead of chemotherapy. These drugs are not only more efficacious than chemotherapy, but also less toxic [7]. Newer generations of TKIs have shown better efficacy and lower toxicity. EGFR and ALK translocations are generally never found coexisting [8,9]. Co-existence of both mutations has been documented in literature in rare circumstances. In a systematic analysis looking at known EGFR positive tissue samples, ALK mutations were found to co-exist in 1.3% of samples [10].

LCNEC patients, unfortunately, have not shared in the recent bounty of targeted agents. In contrast to the prevalence in adenocarcinomas which may be as high as 25% to 30% in Asian populations, the prevalence of EGFR mutations in LCNEC is only reported as 2.8% while LCNEC with ALK mutations consists of isolated case reports only despite extensive literature review, we could not find any case of LCNEC with both activating EGFR mutations and ALK rearrangement [11-13]. Here we describe our experience with one such patient and implications of the same for clinical practice.

## Case History

A 59 years old male patient, non-smoker, presented with chief complaints of cough with left sided chest and back pain for 8 months. Chest X-ray done was showing a left sided lung opacity. A Contrast Enhanced CT scan of his chest revealed a dominant mass in left lower lobe with nodules in bilateral lung parenchyma, with enlarged mediastinal nodes and erosive lesions in ribs. EBUS-TBNA from mediastinal lymph nodes was suggestive of metastatic large cell neuroendocrine carcinoma. Whole body FDG-PET-CT scan was suggestive of a FDG-avid heterogeneously enhancing speculated mass lesion in the left lung lower lobe with focal pleural abutment, with multiple metastatic nodules in bilateral lung fields, multiple metastatic lymph nodes in the mediastinum and supraclavicular fossa, as well as multiple FDG-avid metastatic skeletal lesions. On molecular analysis, an activating mutation in EGFR L858R was identified in the sample by multiplex PCR. The sample was also found to be positive for ALK translocation by Fluorescent *In-Situ* Hybridization (FISH) with 76% nuclei positive for ALK gene rearrangement.

In view of good performance status, the patient received 3 cycles of combination chemotherapy with etoposide and cisplatin resulting in a partial response on subsequent PET-CT. Thereafter he received 3 more cycles which radiologically and clinically lead to a stable disease. In view of ALK rearrangement, it was decided to initiate treatment with crizotinib at a dose of 250 mg twice daily. Treatment was well tolerated. However, 4 months later, PET-CT showed disease progression with multiple new bilateral lung nodules, left pleural effusion and pleural thickening. As the patient had previously had a good response to chemotherapy, second line therapy was planned as a combination of carboplatin and irinotecan, on which he had the best response. Post this, he was put on maintenance Gefitinib (Anti-EGFR TKI), which continues till date with a progression free survival of 14 months and ongoing with a partial response of disease.

## Discussion

LCNEC is a rare subtype of NSCLC with poor prognosis and limited treatment options. Current evidence-based guidelines for the management of advanced lung adenocarcinoma suggest upfront evaluation of EGFR mutation and found positive recommends EGFR-TKI as first-line therapy with exons 19 and 21 mutated [13,14]. EGFR mutation in lung neuroendocrine carcinoma is uncommon and has been reported only in isolated case reports (0% to 3%) [9-12,15]. Most of these occur after TKI therapy as a result of transformation [8,15]. The response of EGFR-mutant LCNEC to anti-EGFR TKIs is bleak and is controversial where some reports suggesting a placebo effect, although no therapy is available as of now than chemotherapy in these subsets. NSCLC patients with both EML4-ALK rearrangements and EGFR mutations, available data is again lacking to prove any benefits with therapy. Yang et al. [16] and Ulivi et al. [17] in their trials report rate of 1.3% and 1.65% respectively, whilst Lee et al. described only 6 cases [17]. In some cases of ALK mutated NSCLCs, presence of EGFR mutations occurs as a result of acquired mutation to ALK inhibitors, whereas the vice versa is also true although rare [18,19]. Some authors suggest, they could be present concomitantly since the beginning in varying percentages with cellular clones expressing the heterogeneity of those tumors [17,19].

It is likely that there are fundamental molecular differences between LCNEC and other histologies which leads to resistance to TKIs even in the presence of activating mutations. It is possible that the complexity of the molecular pathogenesis introduces bypass pathways as a result of which intrinsic resistance to TKIs exists. Therefore, most of the EGFR mutated lung neuroendocrine carcinomas, even with sensitizing EGFR mutation, may restrict the efficacy of EGFR-TKI [19].

The coexistence of ALK and EGFR mutations in same tumor makes it less responsive to standard treatment [20]. Some authors suggesting good response in only the ones treated with first line ALK-TKIs, whereas the response with first line EGFR-TKIs being unsatisfactory [21,22]. In spite of these coexisting case reports and data available till date there is no guideline suggesting the standard line of care or sequencing.

ALK-TKIs seem to be marginally more effective than EGFR-TKIs with coexisting mutations with RR of 69.8% and 43.4% vs. 79.5% and 51.3% of reviewed cases treated with EGFR and ALK-TKIs respectively with no available data on standard of line cytotoxic chemotherapy [23].

In conclusion, an accurate bio-molecular characterization is crucial to drive the therapeutic strategy of NSCLC with multiple driver alterations. Perhaps the allelic alteration's fraction in NGS or the liquid biopsies could be useful in defining the best therapeutic choice [23]. All available clinical data should be shared and analyzed in order to increase our experiences and correctly manage these patients.

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