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Review Article

# Non-Small Cell Lung Cancer; Review of Mutations and Tyrosine Kinase Inhibitors

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ABSTRACT

Lung cancer is the leading cause of cancer-related death in the United States and the incidence of this in never smokers is about 15-20% in males and about 50% in females. Non-small cell lung carcinoma (NSCLC) constitutes about 75% to 80% of these cancers and is more common than small cell lung carcinoma (SCLC) in never smokers. Treatment of NSCLC has been rapidly evolving with the discovery of targetable mutations like EGFR, and ALK. Despite this, prognosis of NSCLC remains guarded given diagnosis at an advanced stage as well as patient factors like age and comorbidities. The standard of care should include therapy customized to suit the patient. In this review article we report the first known case of checkpoint mutation seen in a patient with NSCLC and summarize the common mutations along with targeted therapy with tyrosine kinase inhibitors.



## Description

We present a case report of a patient who was a lifetime non-smoker and was found to have a rare *CHEK2* mutation with non-small cell lung cancer. Hence, we present a short review of the common mutations and TKIs involved in non-small cell lung cancer.

## Introduction

Lung cancer occurred in approximately 2.1 million patients in 2018 and caused an estimated 1.7 million deaths. It is the commonest cancer in both sexes combined and is the leading cause of death; however, it is the 2nd leading cause of death in females after breast cancer [1]. In the United States, there are over 230,000 new cases of lung cancer and 130,000 deaths annually [2]. Histopathologic classification of lung cancer includes small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). In the past, treatment decisions were based on a simple distinction between SCLC and NSCLC however further classification of these cancers into adenocarcinoma vs squamous cell carcinoma has led to further optimization of therapy with better outcomes. Tremendous research has been dedicated over the last decade to improving the survival in these patients.

Non-small cell lung cancer is a broad term encompassing squamous cell cancer, adenocarcinoma and large cell cancer. NSCLC constitutes approximately 75-80% of all lung cancers [3]. Oncogenic mutations are mutations leading to transformation of non-cancerous tissue to cancerous tissue. The discovery of driver mutations has changed the face of management of lung cancers and led to the achievement of individually tailored therapy.

Some of the known oncogenic drivers in NSCLC include epidermal growth factor receptor (*EGFR*) mutations, anaplastic lymphoma kinase (ALK), and *ROS1* fusion genes among others. Increased detection of targetable mutations over the past 10 years has led to a better understanding of the biology and underlying genetic susceptibilities in patients with NSCLC.

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The primary risk factor for lung cancer is smoking, accounting for about 90% of all lung cancers; however, that leaves approximately 10-20% lung cancers that occur in non-smokers. Lung cancer in never smokers (defined as those who have had less than 100 cigarettes in their lifetime) has been recognized as having a distinct epidemiology and biology which is enough to support the notion that it can be considered a separate entity. The incidence is seen to be at 15-20% incidence in males and about 50% incidence in females however the incidence varies with different geographic locations [4]. Sun *et al*. reported that in Asia the incidence of lung cancer in female never smokers was about 60-80% [5]. In one analysis in the United States, an estimated 19 percent of women with lung cancer had never smoked, compared with approximately 9 percent of men with the disease [6]. The incidence of SCLC in never smokers is exceedingly small hence discussions regarding lung cancer in never smokers focus for the most part on NSCLC.

In recent years, an increasing number of lung cancers have been observed in people who have never smoked tobacco (LCINS). This phenomenon is more likely to be observed among women, especially those living in Southeast Asia. Environmental conditions, such as air pollution, secondhand smoke, exposure to radon, asbestos, heavy metals, human papillomavirus, and genetic conditions are the main causes [7].

It has been postulated that lung cancer in never smokers occurs at a younger age but this has not been validated in all cohorts in Western populations. In studies from Asia, however, a younger age at diagnosis is characteristic of lung cancer in never smokers [8]. The age-adjusted incidence rate for lung cancer in never smokers, in the United States, aged 40 to 79 years ranged from 11.2 to 13.7 per 100,000 person-years for men and from 15.2 to 20.8 per 100,000 person-years for women. These incidence rates are like those for myeloma in men or cervical cancer in women in this country. By contrast, the age-adjusted rates of lung cancer in current smokers in the same cohorts were approximately 12 to 30 times higher [9]. Subtype analysis of NSCLC has come full circle now that epidermal growth factor receptors (EGFR), anaplastic lymphoma kinase (ALK), and c-ROS oncogene 1 (*ROS1*) mutations are not only identifiable but their targeted treatment results in responses better than that with standard chemotherapy.

The incidence of the *EGFR* mutation in patients with adenocarcinoma varies with ethnicity and has been seen to be about 15 to 30% in non-Asian populations while it can be as high as 60% in Asian patients [10, 11]. The *ALK* mutation has been seen at an incidence of about 2 to 7% in the United States. The other mutations are not as common and incidences of these mutations in adenocarcinoma have been summarized in (Table 1) below. Given the improving response to tyrosine kinase inhibitors, it has been recommended that EGFR and ALK testing should be done in all advanced-stage adenocarcinoma, mixed cancers, and in those with NSCLC in whom adenocarcinoma cannot be excluded.

**Table 1:** Frequency of genetic mutations in NSCLC.

| Target | Mutation | Frequency (%) |
|---|---|---|
| *EGFR* | Exon 19 deletion and exon 21 point mutation | 30-60 |
| | *HER2* point mutation | 2-4 |
| | T790M (somatic) | 1-4 |
| *KRAS* | Mutations in codons 12, 13, and 61 | 15-25 |
| *ALK* | EML4-ALK | 2-8 |
| *NTRK1* | NTRK1 fusion | 3.3 |
| *c-MET* | Amplification | 2-4 |
| | Exon 14 skipping mutation | 3-4 |
| *BRAF* | V600E mutation | 1-4 |
| *ROS1* | ROS1 | 2 |
| *RET* | RET fusion | 1 |
| Co-mutations | | Upto 15 |

## EGFR

Epidermal growth factor receptor (EGFR, HER-1, ERBB1) is a member of the tyrosine kinase receptor family consisting of 3 additional receptors with a similar structure: EGFR2 / HER2 / HER-2-NEU / ERBB2, EGFR3 / HER-3 / ERBB3 and ERBB4 / HER4. Several studies have shown that *EGFR* mutations occur with a frequency of 30% to 60% in NSCLC. Overexpression of EGFR is the main factor maintaining self-sufficiency of proliferation and maintaining the tumor phenotype in some NSCLC. Mutations and atypical expression within EGFR have been shown to influence development, progression, and acquisition of NSCLC chemoresistance. Various mechanisms contribute to EGFR overexpression including increased number of gene copies, epigenetic modifications, and activation by oncogenic viruses. Two of the commonest *EGFR* mutations in NSCLC are deletion in exon 19 and specific point mutation in exon 21 of codon 858. Both of which account for about 80-90% of all detected *EGFR* mutations. As mentioned above, certain *EGFR* mutations like point mutation at position T790M can lead to resistance to therapy including insensitivity to first generation kinase inhibitors such as erlotinib and gefitinib. This may be a primary mutation or appear during treatment (secondary) and may also have oncogenic potential [12]. The other receptors in the EGFR family have not been studied as extensively though it has been seen in certain studies that *HER2-NEU* mutations could appear in about 1.6% NSCLC. From limited studies available, it is thought that higher expression of HER2-NEU and other receptors in the family promote resistance to TKIs [12].

**ALK**

Genetic alterations of the anaplastic lymphoma kinase (*ALK*) gene have been reported in 2-7% of the patients with NSCLC, and the most common alteration of ALK is the fusion of the *ALK* gene with the Echinoderm microtubule-associated protein-like 4 (*EML4*) gene and occur more frequently in non-smokers and younger patients [13-16]. Anaplastic lymphoma kinase (ALK) is a transmembrane receptor tyrosine kinase from the insulin receptor superfamily. *ALK* gene activation occurs by rearrangement of the chromosomes and binding the promoter region, resulting in increased transcription and protein expression. The EML4-ALK protein contains the N-terminal EML4 domain and the ALK intracellular catalytic domain. EML4 region causes constitutive dimerization of the ALK kinase domain, leading to incorrect activation of signal transduction and causing tumor cell proliferation and causing tumor cell proliferation [12].

Many rearrangement variants encode the EML4-ALK protein such as assembly of exon 13 EML4 to exon 20 ALK (E13, A20) which exist in 33% patients with this mutation in NSCLC patients while 29% of the patients were found to have the addition of exon 6 EML4 to exon 20 ALK (E6a/b, A20) [12].

The overall frequency of *ALK* oncogene mutation in general NSCLC patients is low, however the knowledge of clinicopathologic features enables easy identification and targeted management of these patients. Shaw *et al*. conducted a study in which patients were selected for genetic testing based on clinical features, including never/light smoking status and adenocarcinoma histology [16]. Thirteen percent of the overall patients had the *ALK* fusion gene. Among the light or never smokers, the incidence of this oncogene was 22% while the frequency was as high as 33% if the patients did not have an *EGFR* mutation [16].

Patients with ALK-positive lung cancer are relatively younger at onset than those without this abnormality. The two studies that were used to support the approval of crizotinib included 255 patients whose tumors contained an *ALK* fusion oncogene; in this database, the median age was 52 years (range, 21 to 82 years) [17, 18]. The *ALK* fusion oncogene in patients with NSCLC is associated with a history of never or light smoking (<10 pack-years) [19]. In the crizotinib study database of 255 patients, never-smokers and former smokers comprised 70 and 28 percent of cases, respectively [17, 18]. ALK-mediated signaling plays a role in development and progression of several cancers as is evidenced by the presence of *ALK* gene rearrangements in other malignancies other than NSCLC, for example, large cell anaplastic lymphoma (ALCL) and myofibroblastic tumors [12].

**ROS**

ROS1 is a receptor tyrosine kinase (RTK) that belongs to the same insulin receptor superfamily as ALK. The role of ROS1 is unknown however, some studies suggest that it participates in epithelial cell differentiation [12]. There is no identifiable ligand however, it has been noted that ROS1 fusion protein expression results in activation of cellular pathways involved in proliferation of cells. *ROS1* gene rearrangements were originally found in glioblastomas and later discovered in NSCLC and cholangiocarcinoma alike [12].

About 2% of NSCLC has been reported to have *ROS1* gene fusions and like the *ALK* mutations, these have been seen in younger patients and those without a history of smoking. They also seem to be mutually exclusive with other oncogenic driver genes [12].

**KRAS**

The four different Ras proteins, H-RAS, N-RAS, K-RAS-4A and K-RAS-4B, are encoded by three genes. *RAS* gene mutations are found in almost one-third of human cancers. Mutated RAS proteins preferentially bind GTP keeping the proteins active and increasing proliferation and differentiation. Other mechanisms can also activate the Ras protein, for example receptors with tyrosine kinase activity, such as EGFR and other growth factor receptors, such as PDGFR and IGFR. Continuous RAS pathway activity not only plays a role in cell proliferation but also in development of resistance to cancer therapy [13].

*KRAS* mutations are found in about 15% to 25% of NSCLC patients, of which 97% have exon 2 and 3 alterations (G12, G13 and Q61) [13]. Most of these mutations involve codons 12 and 13 and are mutually exclusive with EGFR or ALK alterations. *KRAS* mutations may be seen in never smokers but are more frequently associated with smoking [12]. Despite being a very frequent mutation in several cancers, targeted therapy towards Ras proteins have not been developed yet [13].

**BRAF**

BRAF is a serine–threonine protein kinase that belongs to the RAF family. BRAF signaling activates ERK and its downstream effectors which in turn control cell differentiation, proliferation, growth, and apoptosis. *BRAF* mutations therefore allow for autonomous cell growth via activation of MEK/ERK signaling [12].

*BRAF* mutations were originally described in malignant melanomas and are found in about 30% of human cancers. In NSCLC they occur at a frequency of about 1% to 4% and are more common in current or former smokers, which is unlike *ALK* or *EGFR* mutations. Just like *ROS1* they are also typically mutually exclusive of other driver oncogenes and unfortunately patients with these mutations have a shorter overall survival [12]. *BRAF* mutations in lung cancer can be either V600E or non-V600E with prevalence of approximately 50% each. The most common non-V600E mutations include G469A, T599_V600insT, D594N, and V600_K601delinsE mutations [12].

**RET**

RET fusions occur in about 1% of NSCLC and the commonest histological subtype is adenocarcinoma. Like *ALK* mutations, *RET* mutations are associated with never-smoking status however they are usually mutually exclusive. 90% of *RET* mutations are KIF5B-RET fusion with fusion partners CCDC6 and NCOA4 representing the remaining 10% [12].

*NRTK1* fusion mutations are seen in about 3.3% of lung adenocarcinomas. Two in-frame gene fusions characterized by rearrangements between the myosin phosphatase Rho-interacting protein gene (*MPRIP-NTRK1*) and *CD74* gene (*CD74-NTRK1*) have

been seen in female never smokers. NRTK1 genetic alterations are also being targeted as therapeutic targets [12].

**MET**

c-MET is a receptor tyrosine kinase in the MET/RON family with hepatocyte growth factor as its ligand. MET dimerization and phosphorylation occur after ligand binding, eventually recruiting signaling protein complexes including SRC, GRB2, SHC, and the p85 regulatory unit of the phosphoinositide 3-kinase, for the activation of several downstream signaling cascades [12].

Several cancers such as renal cell carcinoma and lung cancer have demonstrated aberrant c-MET signaling. Majority of lung cancers demonstrate MET exon 14 skipping mutations with and without gene amplification (3% to 4% of lung adenocarcinoma). *MET* gene amplification has been reported to occur in 2% to 4% of NSCLC. Increased MET expression is seen with more aggressive tumor biology and is a negative prognostic factor. Given the high frequency with which *MET* mutations are seen, there has been increasing interest in developing potential targets for this pathway [12].

**CHEK Mutation**

The role for immunotherapy in treatment of advanced-stage lung cancer is promising and rapidly evolving. Checkpoint inhibitors promote recognition of cancer cells as foreign cells by the immune system and reverse the tumor-driven inhibition of the immune system that promotes tumor growth. Clinical trials using antibodies to programmed death receptor 1 and programmed death ligand 1 have shown significant survival benefit in advanced NSCLC. The activity of the checkpoint inhibitors can be predicted to some extent by programmed death-ligand 1 (PD-L1) expression levels, but other factors play a key role as well.

In a specific analysis of patients with KRAS-mutated NSCLC, investigators found that patients with a smoking history were more likely to express PD-L1 (44 percent) versus former (20 percent) or never smokers (13 percent). Though PD-L1 expression is not the only marker of programmed cell death protein 1 checkpoint inhibitor efficacy, this does add to the data supporting mechanisms of resistance to checkpoint inhibitor therapy in those who are never smokers [20].

New immunotherapy strategies are emerging in advanced non-small cell lung cancer (NSCLC). In EMPOWER-Lung 1, among over 560 patients with advanced NSCLC with programmed death-ligand 1 (PD-L1) expression of ≥50 percent, the immune checkpoint inhibitor cemiplimab improved overall survival (OS) relative to platinum-doublet chemotherapy (median five-year OS rates of 32 versus 16 percent, respectively). Grade ≥3 toxicities were 28 percent with cemiplimab and 39 percent with chemotherapy. This data led to approval by the United States (US) Food and Drug Administration (FDA) for patients with PD-L1 high, advanced NSCLC lacking a genetic aberration in *ALK*, *EGFR*, or *ROS1* [21].

In IMpower 110, in the subset of over 200 patients with advanced NSCLC and PD-L1 expression ≥50 percent, atezolizumab improved overall survival relative to platinum based chemotherapy (20 versus 13 months). Grade ≥3 adverse events occurred in approximately 30 percent of patients assigned to atezolizumab and 53 percent assigned to chemotherapy. These results led to approval by the US FDA of atezolizumab for the front-line treatment of those with advanced PD-L1 high NSCLC (PD-L1-stained ≥50 percent of tumor cells or PD-L1-stained tumor-infiltrating immune cells covering ≥10 percent of the tumor area), with no EGFR or ALK genomic alterations [22].

Duration of checkpoint inhibitor treatment in advanced non-small cell lung cancer is the subject of active study. In the CheckMate 153 trial, patients with previously treated advanced NSCLC were treated with nivolumab. Among 174 patients with stable or responding disease after one year of nivolumab, those assigned to continued treatment experienced an improvement in both median progression free survival (25 versus 9 months) and overall survival (not reached versus 33 months) relative to those assigned to observation [23]. Other preliminary data, however, suggest that discontinuation of pembrolizumab after two years may be an appropriate strategy [24]. In general, in patients with advanced NSCLC receiving a checkpoint inhibitor, we continue it until progression or unacceptable toxicity occurs, although discontinuation after two years of treatment may be a reasonable alternative.

Germline *CHEK2* mutations are associated with a wide variety of cancer risks, including early-onset cancer and multiple primaries. Confirmation of the patient's carrier status could be beneficial for the patient's family members. The National Comprehensive Cancer Network recommends that germline *CHEK2* mutation carriers undergo increased surveillance for breast and colorectal cancers. Follow-up testing should be performed on blood or saliva.

**Case Presentation**

Our patient is a 37 y/o female with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), asthma, depression, and seizure disorder, who is a lifetime non-smoker and presented with chest pain. Imaging revealed no demonstrated pulmonary embolism or arterial dissection. Mildly enlarged bilateral axillary nodes, unchanged per mediastinal lymphadenopathy with the largest lymph node measuring 1.7 cm, mildly progressed. Increase in size of the cavitary nodule in the right upper lobe measuring 2.3 cm on the current exam. Increase in size of pulmonary nodules in the right upper lobe and the right middle lobe the largest measuring 0.8 cm. Computed Tomography guided biopsy of the right lung mass showed well to moderately differentiated adenocarcinoma, consistent with pulmonary primary, acinar predominant with mild focal micropapillary features.

Caris next generation sequencing panel–ALK IHC 3+, RNA tumor fusion detected. Genetic testing profile showed a pathogenic variant in CHEK2: c.1100delC (p.T367fs) that is frequently germline. It is present in 39% of the tissue sample. *BRAF*-Mutation not detected. *EGFR* mutation not detected. ROS 1 fusion not detected. NTRK 1/2/3–fusion not detected. Tumor mutation burden is low. MET DNA tumor amplification not detected. RET RNA tumor fusion not detected.

She was diagnosed with Stage IIIB (cT3N2M0) lung adenocarcinoma based on PET-CT results and completed chemoradiation and 2 cycles of adjuvant chemotherapy. It is important to note that she had SLE and RA

and was on immunosuppression which made maintenance immunotherapy with durvalumab an inconsiderable option. Restaging imaging showed no evidence of progression and it was decided that she would have continued close follow-up and in case of progression, a TKI would be considered.

## Discussion

### I What are the Mutations in Non-Smokers in NSCLC?

Much as the environmental and genetic risk factors for NSCLC in non-smokers are unclear, it is known that there are characteristic mutations associated with this entity. NSCLC in never-smokers has a distinct biology marked by an increased incidence of mutations in oncogenes that are now specifically targetable. Multiple studies have shown an association between lung cancer in never smokers and a family history of lung cancer, suggesting a role for genetic factors.

In a case-control study of 257 cases (including both smokers and never smokers), lung cancer was more common in those with a positive family history (OR 7.2) while in another case-control study of 316 never-smokers (including 2400 of their relatives), there was a 25 percent greater risk of lung cancer among first-degree relatives [25, 26]. Ying *et al*. noted that the relative risk (RR) of lung cancer associated with a positive family history, adjusted for age, gender, residence, education, and smoking, was 1.57 (95% CI 1.25-1.98) [27].

Specific mutations are noted to run in families of never smokers and the best understood so far are germline mutations in EGFR. An uncommon germline mutation was noted in a Japanese family where nine patients with lung cancer were seen over three generations. The proband was a 53-year-old woman with only 1.2 pack-years of smoking history whose mother did not have a smoking history. Both had HER2 G660D germline mutation in lung adenocarcinomas [28]. *EGFR* mutations represent the commonest mutations in never smokers with NSCLC and carry a higher frequency in never smokers compared to smokers.

Sonobe *et al*. reported an incidence of *EGFR* mutations in non-smokers as 83% versus 50% in smokers (p 0.008) [29]. Though they found absence of smoking to be an independent factor affecting EGFR incidence, they did not find sex to be an independent factor. This is unlike Marchetti *et al*. who found sex to be an independent factor affecting incidence of *EGFR* mutations [30].

Much as *KRAS* mutations are seen more commonly in smokers, an analysis of 482 lung adenocarcinomas, found that the rate of *KRAS* mutations was not significantly different in never smokers compared with former smokers, and current smokers (15 vs 22 vs 25 percent respectively). There was however a difference in the type of mutation as never smokers were seen to have a transition mutation (G-->A) rather than the transversion mutations known to be smoking-related (G-->T or G-->C; $P < 0.0001$) [31]. The EML4-ALK fusion is seen with a higher frequency in never smokers and is nearly always mutually exclusive with *EGFR* and *KRAS* mutations. Shaw *et al*. found that 74% of never smokers had *ALK* mutation compared to 26% light smokers (defined as those with 10 or less pack year history of smoking) and none in smokers [16].

Differences are also seen in the expression of several other mutations and genes in never smokers compared to smokers. As an example, *TP53* mutations were found to be more common in smokers and the specific mutations were different based on smoking status. G:C to T:A transversions and A:T to G:C transitions were associated with smoking while G:C to A:T transitions were associated with never smoking. In the same study they noted no significant differences in Cox-2 expression based on smoking, and higher levels of nitrotyrosine (a marker of nitric oxide associated protein damage) in never smokers compared to smokers [32].

### II Do Patients with *ALK* Mutations have Other Somatic or Germline Mutations?

Guidelines recommend routine testing for *ALK* mutation in all patients with stage IV lung adenocarcinoma, mixed tumors or those with NSCLC in whom adenocarcinoma cannot be excluded. *ALK* mutation testing can be performed on plasma or tissue specimens however, if not detected in plasma specimens, then tumor tissue should be tested [33].

The Lung Cancer Mutation Consortium reported 2.7% dual-positive mutations in over 1000 specimens analysed. The majority of these involved one or more of the following: ALK, MET or PIK3CA [34]. Several other retrospective analyses have demonstrated a co-occurence rate of upto 1% for EGFR and ALK. Yang *et al*. identified concomitant *EGFR* and *ALK* mutations at an overall frequency of 1.3% [35]. As per another large series, the frequency of dual mutations in *ALK* translocated NSCLC was about 4.4% when using direct sequencing and fluorescence in situ hybridization (FISH). However, this number increased to as high as 15.4% when using mutant-enriched next-generation sequencing (NGS) assays [36]. Given such variation in incidence with different assays and since the newer assays like NGS are becoming more available and the cost is going down, then it is likely that the rate of concurrent mutations is going to increase in the future [37].

The etiology behind concurrent mutations is unknown and it is also unclear as to whether these mutations arise within the same cell or if they occur in different cells due to intratumoral heterogeneity [37]. The idea behind heterogeneity within the tumor is backed by support from Bai *et al*. who microdissected NSCLC samples to look for intratumoral heterogeneity. They reported that upto 32.9% of the samples had a combination of EGFR-mutated and wild-type cells. The clinical significance of this was that it affected resistance to TKIs hence single point biopsies may not be optimal in deciding personalized TKI therapy [38].

### III Tyrosine Kinase Inhibitors

Targeted therapy against specific proteins, that play a part in signaling transduction and metabolic pathways in cancer cells, have become an important part of treatment. They can be used alone in lung cancer however may have more effectiveness in combination with chemotherapy and/or radiotherapy, as well as immunotherapy [12].

*EGFR, ALK* and *ROS-1* mutations contribute to about 20% of mutations in NSCLC and are the most common targets for TKIs. According to a multicenter center trial, the median survival in those patients who

received targeted therapy against a driver alteration was about 3.5 years compared to 2.4 years in those who had an identifiable target but did not get targeted therapy and 2.1 years in those with no identifiable target [39].

Examples of these drugs include:
EGFR TKIs: Eerlotinib, gefitinib, afatinib, dacomitinib, osimertinib. Table 2 below summarizes information about these TKIs.
ALK TKIs: Crizotinib, ceritinib, alectinib, lorlatinib, brigatinib
VEGFR and PDGFR TKIs: Sunitinib
Raf inhibitor: Sorafenib
MET receptor TKI: Trametinib

**Table 2:** Below shows a summarized detail of the approved EGFR TKIs.

| TKI | Generation (Gen) | Study | Finding | S/E |
|---|---|---|---|---|
| Erlotinib | 1st gen | OPTIMAL trial: Erlotinib versus gemcitabine + carboplatin [42]<br><br>EURTAC trial: Erlotinib vs platinum-based chemotherapy doublet [43]<br><br>ENSURE trial: Erlotinib or gemcitabine and cisplatin [44] | PFS 13.1 versus 4.6 months (HR 0.46, 95% CI 0.37-0.57)<br>Response Rate 83 vs 36%<br><br>PFS 9.7 versus 5.2 months (HR 0.16, 95% CI 0.10-0.26)<br><br>PFS 11.0 versus 5.5 months (HR 0.34, 95% CI 0.22-0.51) | Rash, Diarrhea, LFT elevation, Nausea and vomiting |
| Gefitinib | 1st gen | IPASS trial: gefitinib or carboplatin plus paclitaxel [45] | 12-month progression-free rate 25 versus 7 percent, HR for progression 0.74<br><br>Patients with *EGFR* mutation had better PFS with gefitinib however those without *EGFR* mutation, PFS was shorter with gefitinib | Acne-like rash, diarrhea, stomatitis, elevation of liver enzymes, interstitial lung disease |
| Afatinib (Irreversible) | 2nd gen | Phase III Lux-Lung 3 trial: Afatinib or cisplatin plus pemetrexed [46]<br><br>Phase III trial Lux-Lung 6: afatinib or gemcitabine plus cisplatin [47] | 12 month progression-free rate 51 versus 21 percent, HR for progression 0.58, 95% CI 0.43-0.78<br><br>PFS 11.0 versus 5.6 months | Diarrhea, rash, stomatitis, paronychia, and dry skin |
| Dacomitinib | 2nd gen | Phase III trial ARCHER 1050: Dacomitinib versus gefitinib [48]<br><br>Mok *et al*. [49] | At 22 months PFS was 14.7 versus 9.2 months; HR 0.59, 95% CI 0.47-0.74<br><br>At 31 months OS was 34 versus 27 months; HR 0.76, 95% CI 0.58-0.99 | Grade 3-4 dermatitis, grade 3-4 diarrhea |
| Osimertinib | 3rd gen | Phase III FLAURA trial: Osimertinib versus standard of care [50] | PFS 18.9 versus 10.2 months<br><br>Response Rate 80 versus 76% | QT prolongation, reduction in EF |

*ALK-EML4* gene fusion positive NSCLC is highly sensitive to TKI therapy and is recommended for all patients whose tumors contain this mutation as confirmed by either fluorescence in situ hybridization (FISH), next-generation sequencing (NGS), or immunohistochemistry (IHC).

Li *et al*. systematically reviewed phase I, II, and III clinical studies and discovered that ALK-inhibitors significantly improved the overall survival (OS) and progression-free survival (PFS) of non-small cell lung cancer patients. Treatment with ALK-inhibitors was specifically favoured in the patients that were positive for fusion of *ALK* or *ROS1* genes [40].

Various phase III trials comparing ALK inhibition with first generation ALK TKI crizotinib versus chemotherapy showed prolonged progression-free survival (PFS), improved response rate and quality of life. Shaw *et al*. demonstrated PFS of 7.7 months versus 3.0 months for crizotinib versus pemetrexed or docetaxel (hazard ratio, 0.49; $p < 0.0001$) and Solomon *et al*. showed median survival 10.9 months versus 7.0 months for crizotinib versus pemetrexed plus either cisplatin or carboplatin (hazard ratio, 0.45; 95% confidence interval, 0.35 to 0.60; $p<0.001$). Subsequent trials showed PFS benefits with second-generation TKIs as well including alectinib, brigatinib and ensartinib over crizotinib [18, 41].

## IV Any Role for Concurrent Targeted Therapy with Radiation?

For stage I and II disease, radiation therapy is indicated only for those with positive surgical margins after resection or for those who are not candidates for surgery [51]. About 25% to 30% cases of NSCLC are stage IIIA/B, locally advanced and with inoperable disease [52]. Adjuvant chemotherapy along with radiotherapy (RT) is recommended

for better regional and systemic control of disease and is specifically indicated for those with lymph node involvement or positive margins post resection. The most common cause of mortality in patients with stage III unresectable NSCLC is distant recurrent disease. Chemo-radiation therapy (CRT) can be concurrent (cCRT), as was the case with our patient, or it could be sequential (sCRT) [52]. The median progression-free survival among patients who have been treated by CRT is around 8 months and only 20% of patients are alive at 5 years after NSCLC diagnosis [53, 54].

A greater survival benefit is seen with cCRT as compared to sCRT however, it is also associated with more side effects.
Concurrent delivery of cisplatin-based chemotherapy with thoracic radiotherapy (TRT) confers a long-term survival benefit compared with the sequential delivery of these therapies. As per this phase III trial, five-year survival was statistically significantly higher for patients treated with the concurrent regimen with once-daily TRT compared with the sequential treatment (sequential arm using cisplatin and vinblastine had 10% five-year survival [confidence interval 7 to 15%]; concurrent arm with cisplatin and vinblastine had 16% five-year survival [confidence interval 11 to 22%], concurrent arm using cisplatin and etoposide had 13% five-year survival [confidence interval 9 to 18%] [53].

In another phase III randomized study, the cCRT arm was associated with an improved response rate (84% vs. 66%), median OS (16.5 vs. 13.3 months) and 2- and 5-year survival rates (34.6% vs. 27.4% and 15.8% vs. 8.9%, respectively) compared with the sCRT arm. In this study they used cisplatin, mitomycin and vindesine as the chemotherapy regimen [55].

However, cCRT comes at the cost of increased toxicities which can lead to missed doses of chemotherapy which eventually is associated with worse outcomes. cCRT increases esophageal toxicities over sCRT or one modality alone and is also associated with higher incidence of hematologic toxicities. Rates of, grade 3 and above, thrombocytopenia, leukopenia and granulocytopenia can reach 10%, 70% and 71% of patients, respectively [56].

A study by Deek *et al*. reported a median OS of 9.6 months in patients with missed chemotherapy versus 24.3 months in those without missed chemotherapy. The main reasons to miss chemotherapy were reported to be hematologic toxicities (59%), esophagitis (17%), decline in performance status (12%) and allergic reaction (5%) [57]. Sequential CRT (sCRT) could be less toxic but OS is 6–7% less when compared to cCRT and sCRT has been used as an alternative option in elderly or low-performance patients or with severe comorbidities [53].

## V Prognosis

The 5-year survival for NSCLC is reported to be about 25% which reflects the fact that most lung cancers are diagnosed at an advanced stage and that effective treatment of NSCLC is often limited by the advanced age of patients and numerous comorbidities [58]. Furthermore, advanced NSCLC treatment is often hindered by resistance to classic cytotoxic drugs.

There is no clear evidence as to whether patients with NSCLC who are never smokers have a better outcome than those with a positive smoking history. Several observational studies have been performed and the results have mixed results though most do favour better overall survival in patients who are never smokers.

A study from California included 12,000 patients and showed that smokers had a shorter survival as compared to never smokers, with hazard ratio [HR] for death 1.09, 95% CI 1.00-1.18 [59]. Another study comparing 132 never smokers with 522 current smokers, found that the five-year survival was significantly better among never smokers, even on multivariate analysis (23 versus 16 percent) [60].

A large lung cancer registry trial, which included over 15,000 Japanese and over 13,000 Caucasian patients from Southern California, demonstrated statistically significant improvement in survival for the patients with no smoking history and this was supported by another study from Japan that analysed 26,957 NSCLC patients [61]. This study from Japan reported that median overall survival was significantly longer for never smokers compared with ever smokers (30 versus 19 months) [62]. Interestingly, a study of 254 lung cancer patients showed that the five-year survival was not significantly different in never smokers compared to smokers (27 versus 31 percent, respectively) [63].

## Conclusion

NSCLC is complex and has been increasing in incidence in never smokers. The use of targeted therapy has changed the treatment of NSCLC dramatically. Questions regarding choice of therapy remain intact especially in patients with rare mutations and hence we recommend customization of therapy for each patient based on age, comorbidities, and mutations.

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## Abbreviation

**NSCLC:** Non-Small Cell Lung Cancer
**SCLC:** Small Cell Lung Cancer
**TKI:** Tyrosine Kinase Inhibitor
**EGFR:** Epidermal Growth Factor Receptor
**ALK:** Anaplastic Lymphoma Kinase
**ROS1:** C-Ros Oncogene 1
**LCINS:** Lung Cancer in Never Smokers
**ELM4:** Echinoderm Microtubule-Associated Protein-like 4
**ALCL:** Anaplastic Large Cell Lymphoma
**RTK:** Receptor Tyrosine Kinase
**Ras:** Rat Sarcoma Virus
**KRAS:** Kirsten Rat Sarcoma Virus
**HRAS:** Harvey Rat Sarcoma Virus
**N-ras:** Neuroblastoma RAS Viral Oncogene Homolog

**GTP:** Guanosine-5'-Triphosphate
**PDGFR:** Platelet-Derived Growth Factor Receptor
**IGFR:** Insulin-like Growth Factor Receptor
**RAF:** Rapidly Accelerated Fibrosarcoma
**MEK/MAP2K:** Mitogen-Activated Protein Kinase
**ERK:** Extracellular-Signal-Regulated Kinase
**ROS1:** Reactive Oxygen Species 1
**RET:** Rearranged during Transfection
**NRTK:** Neurotrophic Receptor Tyrosine Kinase
**MET:** Mesenchymal-Epithelial Transition
**RON:** Recepteur d'Origine Nantais
**SRC:** Sarcoma
**GRB2:** Growth Factor Receptor Bound Protein 2
**CHEK:** Checkpoint Kinase
**PD-L1:** Programmed Death-Ligand 1
**OS:** Overall Survival
**PET-CT:** Positron Emission Tomography - Computed Tomography
**RR:** Relative Risk
**TP53:** Tumor Protein p53
**Cox2:** Cyclooxygenase-2
**PIK3CA:** Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha
**FISH:** Fluorescence In Situ Hybridization
**NGS:** Next Generation Sequencing
**VEGFR:** Vascular Endothelial Growth Factor Receptor
**IHC:** Immunohistochemistry
**PFS:** Progression Free Survival
**RT:** Radiotherapy
**CRT:** Chemo-radiation Therapy
**cCRT:** Concurrent Chemo-radiation Therapy
**sCRT:** Sequential Chemo-radiation Therapy
**TRT:** Thoracic Radiotherapy
**HR:** Hazard Ratio
**CI:** Confidence Interval

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