

EDUCATIONAL OBJECTIVES

After participating in this activity pharmacists will be able to:

- DESCRIBE NSCLC's pathogenesis in nonsmokers
- LIST the abnormalities in growth stimulatory signaling pathways in NSCLC
- DESCRIBE the components of individualized treatment plans for EGFR mutation positive NSCLC
- REVIEW new and emerging treatment options in EGFR T790M mutation positive patients
- MAXIMIZE the pharmacist's contribution in improving treatment adherence and ongoing monitoring to attain therapeutic treatment goals

After participating in this activity pharmacy technicians will be able to:

- LIST the basic characteristics of NSCLC in nonsmokers
- RECALL oral TKIs used in EGFR mutation positive NSCLC
- IDENTIFY when to refer patients to the pharmacists for recommendations or referrals



The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in this application-based activity and will receive up to 0.2 CEU (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission.

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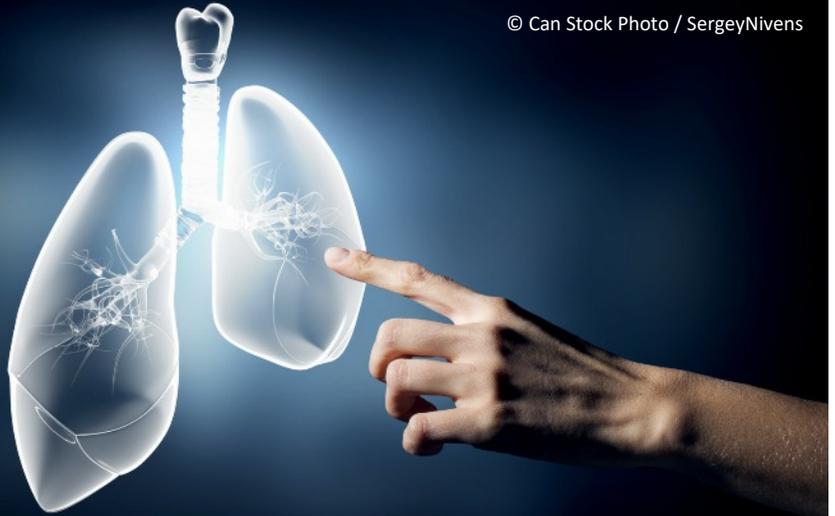
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Cancer in Non-Smokers: Who, What, Why and How to Treat

ABSTRACT: Lung cancer includes many different diseases in the pulmonary space. Increasingly, oncologists are diagnosing lung cancer in non- or never-smokers. Those lung cancers are often associated with a specific set of mutations. The tyrosine kinase inhibitors (TKIs) target mutations that are more likely to occur in lung cancer in non-smokers. Available in three generations, the reversible TKIs are often used as first line treatments. If patients develop resistance, TKIs from the second and third generations can be used. These drugs have unique adverse effect profiles. Pharmacy teams need to be aware of management strategies for the most common adverse effects, including cutaneous reactions and diarrhea. In addition, all TKIs have drug-drug interactions, and pharmacy teams need to screen carefully to ensure that patients avoid some medications, or have dose modifications if they need to take others. Informed pharmacists and pharmacy technicians can help patients manage adverse effects, understand their therapies, and avoid medical misadventure.

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INTRODUCTION

Often, when people hear that a friend or relative has lung cancer, their first question is, "Does he smoke?" Increasingly, the answer is, "No." This answer often surprises and confuses healthcare providers and lay people. Yet lung cancer includes many different diseases in the pulmonary space. Medical researchers consider patients who have smoked fewer than 100 cigarettes during their lifetime "never-smokers," while people who have smoked more than 100 as "ever-smokers."¹

Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancers.² Patients are often diagnosed at advanced stages, and median survival time is less than a year when oncologists use conventional chemotherapy. NSCLC occurs in two

common subtypes: pulmonary adenocarcinoma and pulmonary squamous cell carcinoma.³ Committed smoking cessation efforts have led to decreased lung cancer incidence in the US over the last several decades.⁴ But the proportion of never-smokers with lung cancer (LUNS) has grown at an alarming rate. Experts estimate roughly 25% of all lung cancers are unrelated to tobacco use, accounting for more than 300,000 deaths each year.⁵ LUNS ranges from 10% of lung cancers in men in Western countries to up to 40% of lung cancers in Asian women.^{1,2}

LUNS is a distinct entity with a different tumorigenic pattern, pathology, and natural history than smoking-related lung cancer. Adenocarcinoma is the most common histology observed in never-smokers.³ Smoking is strongly associated with squamous cell carcinoma and small cell lung cancer.

LUNS is more common in women and in East Asian countries.³ Never-smokers exposed to secondhand smoke, pollution, occupational carcinogens, and those who have inherited genetic susceptibility are at increased risk. Molecular profiling has shown a higher frequency of epidermal growth factor receptor (EGFR) mutations and echinoderm microtubule associated protein-like 4 (EML4) with anaplastic lymphoma kinase (ALK) translocations in this patient population. These unique mutations are biomarkers to classify the lung cancer and choose the most appropriate therapy. Pharmacy teams can actively help patients manage adverse effects, prevent drug interactions, and improve treatment adherence.

To understand how treatment targets LUNS, one has to drill down to the molecular level and the lengthy sidebar to the right explains the science. Although the science may seem heavy, reading slowly and making note of the abbreviations can help.

Gene Mutations Differences

Mutation patterns in lung cancer are distinct in never-smokers compared to smokers.⁵ A meta-analysis of epidemiologic studies showed smokers had increased odds of KRAS mutations and decreased odds of EGFR or ALK-EML4 rearrangements.¹¹ Smokers with smoking histories longer than 30 pack-years had decreased odds of EGFR mutations. EGFR prevalence was higher in Asian women than Caucasian/Mixed ethnicity women. Never-smokers had decreased odds of KRAS mutations compared to ever smokers. Tobacco carcinogens might specifically induce RAS signaling pathways through KRAS mutation, while in never-smokers, carcinogens might selectively target the upstream EGFR pathway through EGFR mutation.⁵ The tumor suppressor gene, p53 acts as a

SIDEBAR: Signaling Pathways and Gene Mutations in Lung Cancer

Epidermal Growth Factor Receptor

EGFR is a member of a family of four tyrosine kinase receptors: EGFR (ERB-B1 or HER1), ERB-B2 (HER2), ERB-B3 (HER3), and ERB-B4 (HER4).⁶ EGFR, found on epithelial cell surfaces, regulates cell proliferation, survival, migration, and angiogenesis. Ligand binding activates key intracellular signaling pathways: the mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt). Signaling molecules involved in the MAPK pathway include RAS/RAF, followed by mitogen activated extracellular signal-regulated kinase (MEK) and MAPK.

Implication in LUNS: The RAS/RAF/MAPK pathway regulates a variety of cellular functions important for tumor growth.⁷ Most NSCLC overexpresses EGFR. EGFR mutations are more likely in non-smokers, females, Asians and adenocarcinoma histology tumors. Smoking history correlates inversely with EGFR mutations; as pack-years increase, the probability of EGFR mutation decreases.¹

HER-2

HER-2 binds with other HER-2 or EGFR or HER-3 receptors activating downstream signaling pathways of PI3K/Akt/ mammalian target of rapamycin (mTOR) and RAS/RAF/MEK. The PI3K/Akt/mTOR signaling pathway is crucial for cell growth and survival in physiologic and pathologic conditions.⁸ Approximately 20% of NSCLC patients overexpress HER-2, while gene amplification and mutations occur in 2% of patients.

Implication in LUNS: HER-2 gene mutations are common in never-smokers, women, Asians, and adenocarcinoma histology.¹ HER-2 mutations often occur with EGFR or KRAS mutations.

ALK Rearrangements

ALK is a transmembrane tyrosine kinase receptor absent in normal lung tissue.⁹ In NSCLC, chromosomal rearrangements result in EML4-ALK fusion gene. EML4-ALK fusion activates downstream signaling proteins such as Akt, signal transducer and activator of transcription 3 (STAT3), and extracellular signal regulated kinase 1 and 2 (ERK1/2).

Implication in LUNS: In lung cancer, ALK rearrangements occur at a higher incidence in younger patients, never-smokers, and adenocarcinoma histology.¹ ALK rearrangements occur in about 3-7% of patients with NSCLC.

ROS1 Rearrangements

ROS1, a tyrosine kinase receptor occurs in low levels in normal adult lung tissue.¹⁰ Chromosomal rearrangements result in ROS1 gene fusions up-regulating the MAPK/ERK, PI3K/Akt and janus kinase (JAK) signaling pathway. About 1-2% of patients with NSCLC exhibit ROS1 rearrangement.

Implication in LUNS: Patients with ROS1 rearrangements are usually younger, and light or never-smokers with adenocarcinoma histology.¹⁰ ALK, EGFR, and ROS1 mutations usually occur together in NSCLC patients.

transcription factor for several target genes, and regulates downstream effects of apoptosis (programmed cell death) and DNA damage response. p53 mutations can occur in smokers and never-smokers, but occur less frequently in never-smokers.⁵

In summary, smokers and never-smokers develop different gene mutations:

- Smokers are more likely to have KRAS, RAS, or p53 mutations
- Never-smokers are more likely to have EGFR mutations (exon 19 deletions, L858R), EML4-ALK, and ROS1 rearrangements

Patient and tumor characteristics differ between smokers and never-smokers.¹²

- Never-smokers are more likely to seek medical care after symptom onset regardless of symptoms, histological type, or gender
- Pleural metastasis is more frequent in never-smokers regardless of histological type or sex
- Never-smokers have better survival rates than smokers, independent of stage, treatment, or co-morbidities
- Conventional chemotherapy's benefit in never-smokers is unclear. Studies have reported never-smokers with NSCLC responded to chemotherapy better than or similarly to smokers
- However, never-smokers treated with agents targeting EGFR and other gene mutations for lung adenocarcinoma have shown dramatic response rates

TYROSINE KINASE INHIBITORS CLASSIFICATION

The EGFR tyrosine kinase inhibitors (TKI) are small molecules that bind to EGFR through ATP binding sites and block activation of downstream signaling.¹³

First Generation TKIs

Oncologists use two first generation EGFR TKIs in clinical practice: erlotinib and gefitinib.

Erlotinib was the first EGFR-TKI approved for the first-line treatment of locally advanced or metastatic NSCLC with EGFR mutations.¹⁴ Erlotinib is rapidly absorbed, has poor bioavailability, and has a half-life exceeding 36 hours.¹⁵ The recommended daily dose is 150 mg. Erlotinib must be administered on an empty stomach. Food can modify drug absorption, delay gastric emptying, and increase bioavailability. Smoking can decrease erlotinib plasma concentrations. For concomitantly smoking patients, erlotinib's labeling recommends increasing the dose by 50 mg in two-week intervals to a maximum of 300 mg per day.

In 2015, the U.S. Food and Drug Administration (FDA) approved gefitinib for first-line treatment of patients with metastatic NSCLC with EGFR mutations.¹⁴ Its bioavailability is unaffected by food.¹⁶ The recommended dose is 250 mg daily. Gefitinib undergoes metabolism by the hepatic CYP450-enzyme system, predominantly CYP3A4.

PAUSE AND PONDER: How would you approach a non-smoking patient who tells you she has newly diagnosed lung cancer?

In EGFR mutation positive patients with NSCLC¹⁷⁻²²

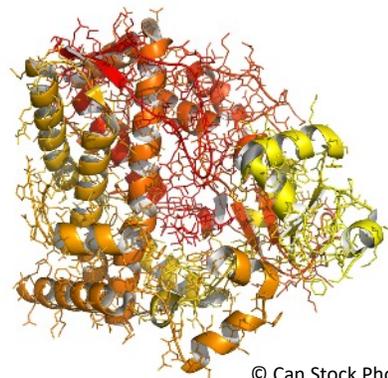
- Erlotinib conferred a significant progression-free survival (PFS) benefit in patients and favorable tolerability compared to conventional platinum-based chemotherapy
- Gefitinib improved PFS compared to first- and second-line chemotherapy
- Gefitinib following chemotherapy improved overall survival (OS) and PFS over placebo
- Never-smokers on erlotinib or gefitinib had longer PFS and improved OS compared to former or current smokers
- Three TKIs (afatinib [discussed below], erlotinib, gefitinib) confer significant PFS benefit over platinum-based chemotherapy regardless of smoking status, but PFS was significantly better in never-smokers

Second Generation TKIs

Patients treated with first and second generation TKIs show high initial response and disease control rates but eventually develop tumor progression due to emergence of therapeutic resistance. Patients on erlotinib and gefitinib usually develop resistance to treatment in nine to 13 months.²³ Researchers developed the second generation TKIs to address acquired resistance. Currently, the FDA has approved two second generation TKIs for NSCLC, afatinib and dacomitinib.

Afatinib, an irreversible TKI, binds to three of the tyrosine kinase receptors (EGFR, HER2, and HER4).¹⁴ (See the SIDEBAR on page 4 for a description of reversible and irreversible binding.) Afatinib receptor binding blocks the entire EGFR downstream signaling pathway related to growth and apoptosis suppression. Irreversible inhibition results in potent, prolonged suppression of receptor kinase activity compared to reversible first generation TKIs. Afatinib's bioavailability is unaffected by age, smoking status, or hepatic function.²⁴ Patients with low body weight and renal insufficiency require dose adjustments. The recommended dose is 40 mg daily, but may be adjusted to a maximum dose of 50 mg or minimum dose of 20 mg daily based on tolerability.

CYP3A4



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TECH TALK:

Reversible and Irreversible Binding

What is the difference between reversible TKIs like erlotinib and gefitinib, and irreversible TKIs, like the second and third generation TKIs? As described in this activity, the TKIs inhibit EGFR by binding to receptor sites. EGFR is a biologic catalyst; it increases or stimulates chemical reaction rates. The various TKI generations bind to EGFR differently.

In human physiology, chemical bonds hold substances the body needs for critical processes (e.g., signaling, and energy production) together. For example, EGFR regulates cell proliferation, survival, migration, and angiogenesis (blood vessel formation and differentiation)—important functions at a cellular level. In the body, substances are formed by bonds that may be ionic, covalent, or hydrogen bonds. Bonding occurs when atoms transfer or share electrons creating new, more complex substances. Here is a brief review.

- **Ionic bonds:** Atoms transfer electrons by donating or accepting them. This results in a positive ion (called a cation) and a negative (called an anion) which are then held together by electrostatic force. The force is very strong in the solid state but in biological fluids, the ions are often soluble and they separate. Many minerals, such as potassium, magnesium, and calcium are present in the body as cations because they have dissolved, or separated from their anion in biological fluid. Since many ionic substances can be dissolved in biological fluids, ionic bonds are considered reversible in this CE activity, meaning the bonds can form and un-form.
- **Covalent bonds:** These molecules are created when atoms share electrons creating stability within the molecule. The molecules formed might be soluble in biological fluids, but the bonds are not, so fluids cannot decompose the compound. It stays intact and these bonds appear to be stronger than ionic bonds in the body. These covalent molecules are considered irreversible in this CE activity.
- **Hydrogen bonds:** These are attractive forces between covalent molecules. The bonds form when covalent molecules have two regions: (1) regions where electrons are more prevalent and therefore partially negative and (2) regions where electrons are less prevalent and therefore partially positive. Neighboring molecules attract each other forming a weak and likely reversible bond.

The bottom line: The first generation TKIs use ionic or hydrogen bonding at the EGFR site. Those bonds are reversible, and various influences can encourage the TKI to detach from the site. The second and third generation TKIs bond covalently. Those bonds are strong.

A phase 3 clinical trial (N = 345) compared afatinib's efficacy to that of cisplatin plus pemetrexed in EGFR mutation positive lung adenocarcinoma patients.²⁵ Investigators observed a significant increase in PFS in the afatinib-treated group compared to chemotherapy at 16 months. When afatinib was compared with gemcitabine plus cisplatin, the results were similar.²⁶ Afatinib is approved for NSCLC tumors harboring uncommon EGFR mutations S768I, L861Q, and G719X in addition to gene alterations at exon 19 deletions or L858R.²⁷

Dacomitinib, an irreversible TKI, also inhibits the entire EGFR receptor family.²⁸ In a phase 3 clinical trial, first-line dacomitinib was superior to gefitinib in improving PFS and OS. In head-to-head trials in NSCLC patients with EGFR mutations, second generation TKIs improved PFS compared to gefitinib.²⁹ Dacomitinib also increased OS but the result was not statistically significant.

Irreversible binding of second generation TKIs leads to increased toxicity. Dose reductions are required in 39-52% and 66% of patients treated with afatinib and dacomitinib, respectively.²⁹ Afatinib and dacomitinib exhibit anti-EGFR T790M activity *in vitro*, but dose-limiting toxicity preclude their use in a clinical setting due to non-selective inhibition of wild type EGFR. (A gene in its natural, non-mutated form is termed as wild type.)

Third Generation TKIs

In approximately 50% of patients, a gatekeeper mutation of T790M mediates resistance to first and second generation TKIs.³⁰ (Genes that inhibit cell growth and induce apoptosis are called gatekeeper genes.) Osimertinib is an irreversible third-generation TKI that inhibits EGFR-sensitizing mutations at exon 19 deletions and L858R and inhibits mutated EGFR with T790M resistance mutation. It also has low activity against wild-type EGFR. Osimertinib is discussed in detail in the later section.

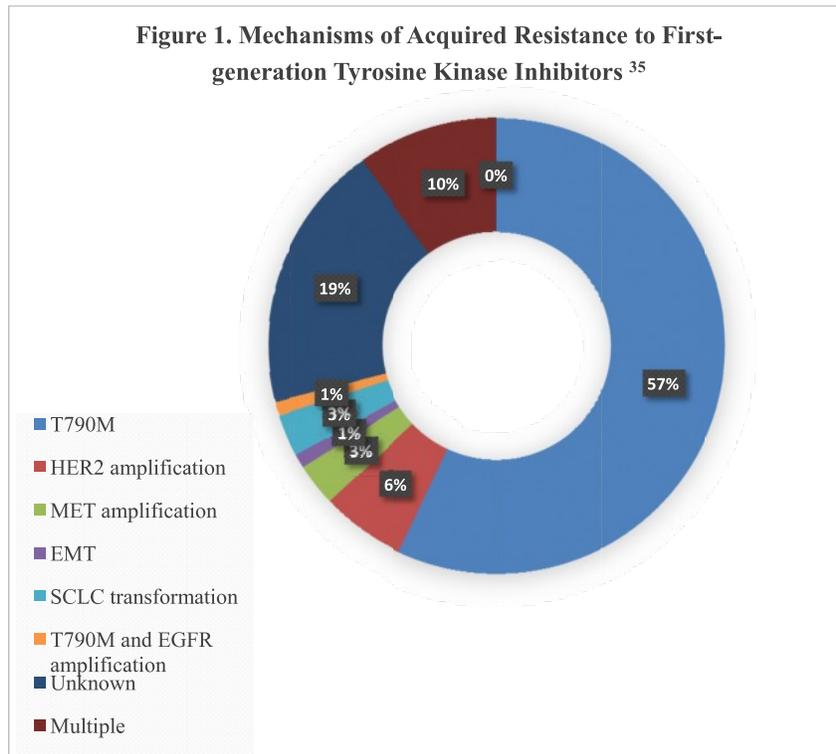
ALK Inhibitors

Crizotinib is a first generation TKI used in patients with NSCLC harboring ALK rearrangements.³¹ Secondary point mutations in the kinase domain are responsible for drug resistance to crizotinib in about 20% of patients. Ceritinib, alectinib, and brigatinib are second-generation ALK inhibitors with activity against mutations affecting the kinase domain. Lorlatinib is a third generation ALK inhibitor used after progression in treatment with first and second generation TKIs. Discussion of these drugs is beyond the scope of this article.

Molecular Markers for TKI Selection

Cancer cells harbor many mutations. Molecular cancer mutations are divided into driver and passenger mutations.³² Mutations in driver genes transform a benign cell to a malignant cell. Passenger mutations occur during somatic cell division, do not contribute to cancer development, and have no functional consequences. A transformed cell relies on driver mutation signaling for survival, a process called oncogene addiction. Driver mutations can stimulate multiple signaling pathways involved in

Figure 1. Mechanisms of Acquired Resistance to First-generation Tyrosine Kinase Inhibitors³⁵



growth and survival. Disrupting the driver mutation-signaling pathway in cancer cells will disrupt multiple signaling cascades, so driver mutations are good candidates for targeted therapy.

Useful genetic markers in clinical practice³²

- Indicate driver mutations
- Can be identified through a genetic test
- Are common in the affected population
- Involve an oncogenic pathway for which effective targeted therapy exists

Clinicians test for cancer cell mutations using polymerase chain reaction (PCR), immunohistochemistry (IHC), and fluorescence in situ hybridization (FISH).

The American Society of Clinical Oncology (ASCO) recommends testing for EGFR and ALK rearrangements to guide therapy in patients with advanced-stage lung adenocarcinoma irrespective of smoking history, sex, race, or other factors. ASCO updated its guidelines in 2018 to include ROS1 and BRAF genes.³³ Routine stand-alone testing for RET, HER2, MET, and KRAS are not recommended but may be performed as part of a larger testing panel or when EGFR, ALK, BRAF, and ROS1 testing is negative. In patients who harbor EGFR-sensitizing mutations and relapse after treatment with EGFR targeted TKI, ASCO guidelines recommend EGFR T790M mutation testing.

EGFR mutations at exon 19 and L858R account for 90% of EGFR mutations found in lung adenocarcinoma.³⁴ Mutations in EGFR predict sensitivity to first generation TKIs (gefitinib and erlotinib). EML4-ALK translocation predicts response to crizotinib, a first generation TKI. EGFR mutations occur at a higher rate than EML4-ALK translocation in lung adenocarcinoma. The two mutations are unlikely in the same tumor. Oncologists order EGFR

testing first since it is more likely to be positive. If it is negative, then they order FISH analysis for EML4-ALK translocation.

Resistance Mechanisms

Acquired resistance to first and second generation EGFR-TKIs develops through acquired mutations, activation of bypass signaling pathways, and phenotypic or histologic tumor transformation.³⁵ Figure 1 shows the relative frequency of mutations. EGFR T790M mutations are most common. EGFR-TKI treatment-naïve patients with EGFR mutation can exhibit T790M mutations. The T790M mutation structurally inhibits binding of first generation TKIs to the ATP binding sites, and downstream cell proliferation signaling is unaffected.

MET amplification can activate bypass signaling, which could activate the PI3-Akt pathway independent of HER-3 signaling pathway.³⁶ HER-2 amplification, PI3-Akt mutation and BRAF mutations can activate acquired resistance. Rare mechanisms of resistance include acquired receptor kinase fusions and BRAF kinase fusions. Patients with concurrent HER2 amplification, MET amplification, or p53 mutations have shorter time to progression and OS on EGFR TKI therapy. Early biomarker identification may help tailor individualized treatment plans and improve OS.

About 3% of patients undergo histological transformation of EGFR-mutant adenocarcinoma to small cell lung cancer (SCLC) after acquired resistance to TKIs.³⁶ Studies have shown that inactivation of retinoblastoma gene (Rb) and p53 facilitates transformation of EGFR-mutant adenocarcinoma to SCLC. In addition, about 1% undergo induction of epithelial-mesenchymal transition (EMT) which causes tumor invasion, metastasis, drug resistance, and stem cell properties.

TKI SIDE EFFECTS

Clinicians measure the severity of chemotherapy-induced adverse effects using the Common Terminology Criteria for Adverse Events (CTCAE).³⁷ The CTCAE scale uses a grading system: Grade 1—Mild, Grade 2—Moderate, Grade 3—Severe, Grade 4—Life threatening and Grade 5—Death. Patients generally tolerate TKIs better than conventional chemotherapy. The most common class effects are dermatologic or gastrointestinal (GI) in nature.

Dermatologic

TKI therapy's most common adverse effects are cutaneous.³⁸ EGFR-induced cutaneous side effects may indicate the therapy is working. Studies have shown EGFR-induced rash correlates to better PFS and OS. The most common dermatologic adverse events caused by EGFR inhibitors include characteristic papulopustular eruptions or acneiform rash (small raised pimples with pus), xerosis (dry, itchy skin), hair changes, nail changes, and photosensitivity.

Papulopustular Eruptions. EGFR are localized to basal cells of the epidermis, hair shaft, sebaceous glands, and hair follicle root sheath.³⁸ EGFR signaling helps maintain normal skin development and regeneration. When TKIs inhibit signaling, they alter skin integrity, weakening the stratum corneum leading to xerosis and skin fissuring. Inhibition of EGFR signaling pathway ultimately leads to inflammation that manifests as papulopustular eruptions and paronychia (nail infection).

In patients treated with TKIs, acneiform rash develops in stages³⁹

- Week 1—Patients experience sensory disturbance, erythema, and edema
- Week 2—Papulopustular eruptions
- Week 4—Crusting occurs
- Weeks 4 to 6 —If rash is treated successfully, erythema, and dry skin occurs in papulopustular eruptions

A majority of patients enrolled in phase 3 clinical trials of gefitinib, erlotinib, and afatinib reported Grade 1-2 skin toxicities.⁴⁰

- Patients treated with erlotinib reported fewer Grade 1-2 toxicities
- Patients treated with afatinib reported the highest percentage of Grade 3-4 toxicities
- Secondary infections due to skin barrier disruption can occur, and about 38% of patients with EGFR-induced skin eruptions developed bacterial or viral infections

Paronychia. A meta-analysis reported about 17.2% of patients developed nail changes from TKIs.³⁸ Nail changes include paronychia; brittle, thin nails that break easily; onycholysis (detachment of nails from nail bed); and discolored nails. Patients can experience significant discomfort and interference in normal activities. The big toe is usually the first area affected;

PAUSE AND PONDER: What over the counter medications would you recommend for a patient who develops a cutaneous side effect from a tyrosine kinase inhibitor?

Which types of gastrointestinal side effects may require over the counter medication?

pyogenic granuloma (benign vascular tumor) develops around the nail fold causing significant pain.

- In erlotinib and gefitinib clinical trials, paronychia was uncommon⁴⁰
- In afatinib clinical trials, the percentage of patients experiencing paronychia was significantly higher than first generation TKIs³⁹

Xerosis. EGFR inhibition can lead to abnormal keratinocyte differentiation, impairing the epidermal barrier.⁴¹ Xerosis resembles atopic dermatitis on any part of the body and can be complicated by secondary *Staphylococcus aureus* or herpes simplex viral infection. It manifests late in TKI therapy, after at least 30 to 60 days, with or after the appearance of the papulopustular eruptions.

Hair Changes. Hair changes can occur one to two months into treatment.⁴¹ Patients on TKI therapy can develop patchy hair loss (scarring or non-scarring alopecia), hair texture changes, and severe scalp inflammation. Non-scarring hair loss improves after therapy cessation. Eyelashes can lengthen and become coarse, curly, and thickened, and may cause blepharitis. Eyebrow or eyelash poliosis (loss of pigment) has also been reported. Hirsutism can appear one to two months after therapy.⁴¹

Gastrointestinal Adverse Effects

The squamous epithelium covers the tongue, esophagus and GI tract. EGFR pathway inhibition can affect the epithelial layer and manifest as GI adverse effects.⁴¹

Oral Mucositis. Oral mucositis and stomatitis are common.^{40,41} Patients may present with extensive erythema or aphthous-like stomatitis (inflammation of mouth/lips). Older patients and people with dentures or poor oral hygiene are more prone to mucositis. Most cases are mild, but make eating and drinking painful. Clinical trial data showed higher percentage of patients with Grade 3-4 mucositis with afatinib (5.4-6.8%) compared to gefitinib (0%) and erlotinib (1%).

Diarrhea. Diarrhea is also common. The mechanism underlying its development is poorly understood, but researchers suggest changes in gut motility, damage in the colonic crypt, and altered microflora as possible causes.⁴⁰ Clinical trial data showed fewer Grade 3-4 diarrhea in erlotinib (1-5%) and gefitinib (1%) compared to afatinib (5-14.4%).

TREATMENT OPTIONS IN EGFR T790M MUTATION POSITIVE PATIENTS

Among NSCLC patients with EGFR mutations, 50-70% respond to TKIs, but patients acquire resistance and tend to progress.³⁰ About 50% of patients develop the T790M gatekeeper mutation. Researchers developed a third generation TKI, osimertinib to target T790M and EGFR-sensitizing mutations.

Osimertinib in NSCLC Therapy

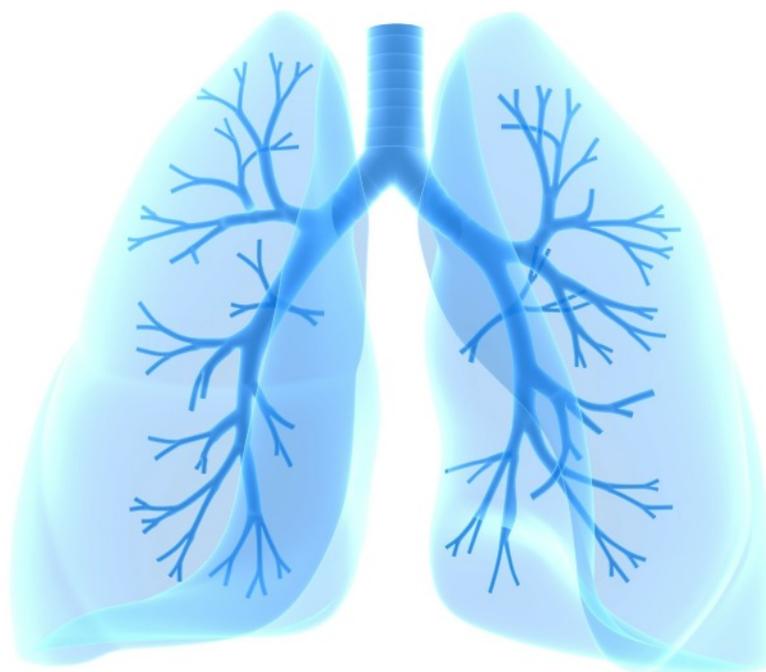
In two phase 2 trials, osimertinib-treated NSCLC patients with T790M mutation showed a prolonged median PFS of 12.3 and 9.9 months and high objective response rates of 62% and 70%.³⁰ Pooled analysis showed the median OS was 26.8 months (95% CI, 24.0-29.1 months); and the 12-month, 24-month, and 36-month survival rates were 80%, 55%, and 37%, respectively.

A phase 3 trial compared osimertinib to platinum-based therapy with pemetrexed in patients with EGFR T790M-positive NSCLC with prior TKI therapy.⁴² Patients received oral osimertinib (n=279) 80 mg once daily or intravenous pemetrexed plus carboplatin or cisplatin (n=140) every three weeks for up to six cycles. Osimertinib significantly prolonged PFS with a 70% reduction in the risk of disease progression or death. At six months, 69% of osimertinib patients and 37% of platinum-pemetrexed patients were alive; progression free rates at 12 months were 44% and 10%, respectively. This benefit was sustained in all subgroups (race, presence of CNS metastases, co-occurring EGFR T790M mutation at baseline, smoking history, sex, age, and previous duration of TKI therapy).

The FLAURA trial (N = 556) investigated osimertinib as first-line treatment for EGFR mutation positive NSCLC following impressive clinical results in other phase 3 trials.⁴³ It compared osimertinib to standard TKI therapy (gefitinib and erlotinib). The primary end point was investigator assessed PFS. Researchers randomized patients 1:1 to receive osimertinib 80 mg once daily or standard TKI-gefitinib 250 mg once daily or erlotinib 150 mg once daily. The median PFS was significantly longer in the osimertinib group compared to standard TKIs (18.9 months vs. 10.2 months). The median duration of response was also superior in osimertinib-treated patients compared to standard TKIs (17.2 months vs 8.5 months). As first line treatment for EGFR mutation positive advanced NSCLC, osimertinib was superior to standard TKIs.⁴³

Final data analysis at three-year follow-up was also favorable.⁴⁴ Median OS was 38.6 months for osimertinib compared to 31.8

PAUSE AND PONDER: What are the differences in adverse events among the three generations of tyrosine kinase inhibitors?



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months for standard TKIs (gefitinib and erlotinib).⁴⁴ The number of patients receiving the drug at three years was also higher in the osimertinib group (79 of 279 patients) compared to the TKI group (26 of 277 patients). The FLAURA trial supports use of osimertinib as first-line therapy for NSCLC.

Central nervous system (CNS) metastases is a poor prognostic factor in patients with advanced NSCLC with EGFR mutations.⁴⁵ About 30% of patients experience CNS metastases during TKI therapy. Subgroup analysis of a phase 3 trial showed PFS was 11.7 months for osimertinib (as second line therapy) compared to 5.6 months with chemotherapy. In the first line setting, the phase 3 FLAURA trial also revealed osimertinib possessed high CNS efficacy.⁴⁶ Patients in the osimertinib group developed fewer new brain lesions compared to the control group (12% vs 30%).

Osimertinib is approved in the United States⁴⁷

- For the treatment of metastatic EGFR T790M mutation positive NSCLC in patients who have progressed on or after TKI therapy
- For first line treatment of patients with metastatic NSCLC with exon 19 deletions or L858R mutations

PAUSE AND PONDER: How does treatment failure occur when patients are treated with TKIs?

Adverse Effects

Osimertinib's most common adverse effects ($\geq 20\%$) in the FLAURA trial were diarrhea, rash, dry skin, nail toxicity, stomatitis, fatigue, and decreased appetite.⁴³

Fewer patients reported Grade 3 or higher adverse effects in the osimertinib group than in the standard TKI group (34% vs 45%). A higher percentage of osimertinib patients experienced QT prolongation than those in the standard TKI group (10% vs 5%). Upper respiratory tract infections were also higher in the osimertinib group.

Interstitial lung disease (ILD) occurred in 3.9% of patients of the 1142 osimertinib-treated patients, and 0.4% of cases were fatal. The manufacturer recommends screening for ILD in patients who present with worsening respiratory symptoms (e.g., dyspnea, cough, and fever) and withholding therapy.⁴⁷ If ILD is confirmed, therapy must be discontinued. Cardiomyopathy, keratitis, and post-marketing cases of Stevens-Johnson syndrome and erythema multiforme major have also been reported with osimertinib.

Acquired Resistance to Osimertinib

Patients on osimertinib can also develop resistance pursuant to EGFR-dependent and EGFR-independent mechanisms.^{35,45} Repeated tumor biopsy and plasma genotyping are crucial steps in understanding the resistance mechanisms and guiding future therapy.

The most common mechanism of acquired resistance to osimertinib is the point mutation of C797S in exon 20 of EGFR.⁴⁵ C797S-mediated resistance to third generation TKIs develops within one year. Resistant cells may be sensitive to a combination of first and third generation TKIs if C797S and T790M are present on separate alleles (variant forms of a gene). If mutations occur on the same allele, the cells are resistant to all TKIs. Other EGFR mutations include L792X mutation, G796S mutation, L718Q mutation, and exon 20 insertion. EGFR independent mechanisms include MET gene amplification, HER2 amplification, RAS–MAPK pathway activation, PI3K pathway activation, oncogenic fusions, and histologic and phenotypic transformations.

The loss of T790M mutation during osimertinib therapy leads to treatment failure.⁴⁵ First generation TKIs are usually ineffective if T790M mutation is also accompanied by alternate mechanisms of resistance such as MET amplification and KRAS mutation. Since C797S mutation is common in T790M positive osimertinib resistant patients, fourth generation TKIs are being developed to overcome EGFR C797S mutation.



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Combination Protocols with Osimertinib

Currently, the FDA has not approved any drugs or therapeutic strategies for osimertinib-resistant patients. However, researchers are investigating the combination of osimertinib with other agents (conventional chemotherapy, first generation TKIs, MET inhibitors, Poly [ADP-ribose] polymerase [PARP] enzyme inhibitors, EGFR antibodies etc) in several clinical trials.⁴⁵ Researchers are also investigating the safety and efficacy of osimertinib combined with platinum-based chemotherapy in a small (n=24) randomized, open label phase 2 trial.⁴⁸ Preliminary results are promising. Patients receive osimertinib 80 mg once daily alone or in combination with carboplatin-pemetrexed therapy. A total of 24 patients are enrolled in the study with the following characteristics: 100% had adenocarcinoma; 58.3% had exon-19 deletion; and 41.7% L858R mutations of EGFR and 54.2% were never-smokers. After the first cycle, all patients had treatment-associated adverse effects, but the adverse event frequency in the combination arm was similar to rates reported previously for carboplatin-pemetrexed. Preliminary results show the combination therapy is safe in this small population.

Researchers designed the TATTON study to assess osimertinib's safety and tolerability with selumetinib (MEK1/2 inhibitor), savolitinib (MET-TKI), or durvalumab (anti-programmed cell death ligand 1 monoclonal antibody).⁴⁹ Patients with advanced EGFR mutation NSCLC with prior TKI therapy tolerated osimertinib with selumetinib or savolitinib. The combination with durvalumab was not feasible due to reports of ILD. Preliminary results show the combination of osimertinib and savolitinib has an acceptable risk/benefit profile in this population.

Table 1. Management of TKI-associated Acneiform Rash^{39,53}

CTCAE Grade Toxicity	Management Strategy
Mild—Grade 1 <i>Less than 10% of BSA is covered in papules or pustules (or both), with or without tenderness or pruritus</i>	Continue on current dose of TKI Hydrocortisone 2.5% cream or clindamycin 1% gel →Reassess in 2 weeks
Moderate—Grade 2 <i>Between 10% and 30% of BSA is covered in papules or pustules (or both), with or without tenderness or pruritus</i> <i>Associated with psychosocial impact</i> <i>Limits instrumental activities of daily living</i>	Continue current dose of TKI with minocycline 100 mg or doxycycline 100 mg orally twice daily for 4 weeks AND hydrocortisone 2.5% or desonide cream OR alcomethasone 0.05% cream topically to face and shoulders, or fluocinonide 0.05% cream to chest and back →Reassess in 2 weeks For prolonged Grade 2 rash, TKI can be temporarily discontinued until rash improves to Grade 1 or less. Reinitiate TKIs at a dose-based on physicians discretion
Severe—Grade 3 <i>More than 30% of BSA covered in papules or pustules (or both) with or without tenderness or pruritus</i> <i>Associated with local superinfection, with oral antibiotics indicated</i> <i>Limits self-care activities of daily living</i>	Minocycline 100 mg OR doxycycline 100 mg orally twice daily for 4 weeks AND hydrocortisone 2.5% or desonide cream OR alcomethasone 0.05% cream topically to face and shoulders, OR fluocinonide 0.05% cream to chest and back AND prednisone 0.5 mg/kg for seven days →Reassess after 2 weeks If symptoms do not improve, discontinue TKI for 2-4 weeks. If rash improves to Grade 2 or less, reinitiate TKI at a dose of physician’s discretion. If skin toxicity does not worsen, can increase the dose. If no improvement, discontinue the medication

Challenges to Oral Oncology Medications

Oral oncology medications (OOMs) account for 25-35% of the oncology pipeline.⁵⁰ Optimal medication adherence—the extent to which a patient’s behavior with respect to timing, dosage, and frequency corresponds with the healthcare provider’s recommendations—is vital for therapeutic success. Studies indicate OOM medication adherence ranges from 20% to 100%.⁵⁰

Patients prefer oral regimens because oral oncology regimens are associated with greater convenience, fewer clinic visits, reduced invasive procedures, and fewer missed workdays or social activities than intravenous therapy.⁵¹

In a multicenter prospective observational study, researchers followed patients taking erlotinib for four months to assess adherence.⁵² Adherence was measured using MEMS (SIMpill®, Evalan, Amsterdam, The Netherlands). An electronic processor in the pillbox records all time-points when the box is opened. MEMS data showed a mean adherence rates of 96.8 ± 4% from days 0 to 120. About one-third (19/55) of patients had an adherence rate of less than 95%. At one month, 21% of patients were not taking erlotinib on an empty stomach. Risk factors for non-adherence included older age, suboptimal adherence, experiencing ocular symptoms, and stomatitis.

OOMs create several challenges:

- OOMs have a high potential for toxicity. Potential adverse effects warrant ongoing assessment and monitoring
- OOMs require special handling

- OOM regimens can be complicated; adding medications to manage adverse effects and chronic conditions can complicate self-management
- Therapeutic dosing may require combinations of different strengths
- Food restrictions may be confusing
- Patients with poor literacy are at higher risk of self-medicating errors
- Medication costs of OOMs are very high

About 10% of patients with newly prescribed oral oncology medications do not pick up their medication.⁵⁰ Consequences of non-adherence include drug resistance, disease progression, increased burden for caregivers, and death.

ADVERSE EFFECT MANAGEMENT

Dermatologic Adverse Effects

Patients need to be followed closely during the first six weeks of treatment, and pharmacy staff should remind them to report skin changes immediately to prevent dose reduction or discontinuation of TKI. Pharmacists should tell patients initiating TKIs to apply alcohol-free and fragrance-free emollient cream to the entire body and sunscreen to sun-exposed areas, and avoid hot showers or products that dry the skin. Pharmacists and technicians can show patients how to look for alcohol content on product labeling. Acneiform rash dissipates once the TKI therapy is stopped. **Table 1** describes an algorithm to assess skin toxicity and find an appropriate management strategy.

Table 2. Management of Stomatitis and Paronychia with TKI³⁹

CTCAE Grade Toxicity	Stomatitis	Paronychia
Mild	Continue at current TKI dose Apply triamcinolone in dental paste 2-3 times daily as needed	Continue at current dose of TKI Apply betamethasone valerate cream 2-3 times daily as needed
Moderate	Continue at current TKI dose Apply triamcinolone in dental paste 2-3 times daily as needed AND Oral erythromycin 250-350 mg daily OR minocycline 50 mg daily	
Severe	Apply clobetasol ointment, 2-3 times daily as needed AND Oral erythromycin 500 mg daily OR minocycline 100 mg daily Discontinue TKI for 2-4 weeks. Upon improvement to Grade 2 or less, initiate at a dose of the physician’s discretion. If toxicities do not worsen, increase the dose. If no improvement, discontinue.	Apply clobetasol cream 2-3 times daily as needed Discontinue TKI for 2-4 weeks. Upon improvement to Grade 1 or less, reinstate TKI at a dose of the physician’s discretion. If toxicities do not worsen, increase the dose. If no improvement, discontinue.

Mucositis/Stomatitis and Paronychia

Professional evaluation of the oral cavity is recommended before starting TKIs, during, and after treatment completion.³⁹ Patients must avoid commercial mouthwashes containing alcohol, as these can dry and irritate the oral mucosa. They must also use soft-bristle toothbrushes, floss, and use normal saline rinses at least twice a day.

Patients can manage mild paronychia with emollients, cushioning of affected areas, trimming nails, and wearing gloves while cleaning to avoid skin irritants. Patients should avoid aggressive manicures. **Table 2** describes additional management strategies.

Gastrointestinal Adverse Effects

Most patients on TKIs develop diarrhea in the first four weeks of treatment initiation.⁵⁴ Afatinib-treated patients can develop diarrhea within seven days. Loperamide is the mainstay of therapy for management of TKI-induced diarrhea (See **Table 3**).

(Text continues on page 12)

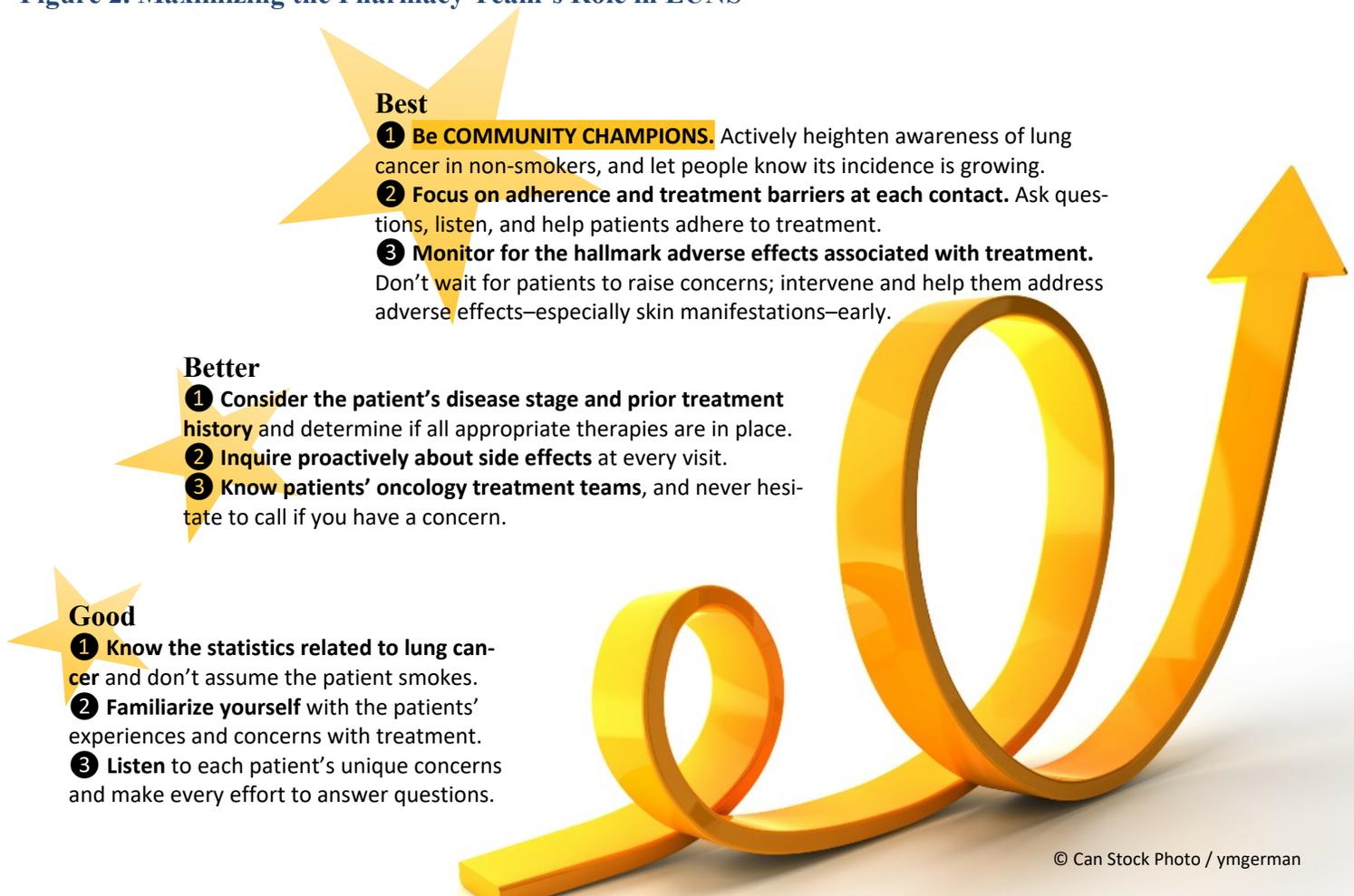
Table 3. Management of TKI-associated Diarrhea⁵⁴

CTCAE Grade Toxicity	Management Strategy
Mild—Grade 1 <i>Increase of fewer than 4 stools per day over baseline</i>	Continue current dose of TKI Hydration with 8-10 glasses of clear fluids Loperamide 4 mg followed by 2 mg after each loose stool until bowel movement stops for 12 hours (up to 20 mg per day)
Moderate—Grade 2 <i>Increase of 4-6 stools per day over baseline</i>	Continue loperamide. Assess for dehydration and electrolyte imbalance. Consider intravenous fluids and electrolyte replacement. If diarrhea does not improve after 48 hours, temporarily discontinue TKI. Upon improvement to Grade 1, restart TKI at a reduced dose (except gefitinib; restart at the original dose)
Severe—Grade 3 <i>Increase of 7 or more stools per day over baseline; incontinence; hospitalization indicated; limits self-care activities of daily living</i>	Intravenous fluid replacement for 24 hours or more. Temporarily discontinue TKI. Upon improvement to Grade 1, initiate TKI at a reduced dose (except gefitinib; restart at the original dose). Permanently discontinue TKI if diarrhea does not return to Grade 1 within 14 days despite treatment discontinuation and best supportive care

Table 4. Management of Ocular Side Effects^{55,56}

Agent	Ocular Effects	Management
Gefitinib	Conjunctivitis/blepharitis/dry eye (7%) and keratitis (0.1%)	External disorders: Wash eyelashes gently with diluted baby shampoo Antibiotic or combination antibiotic and steroid ointment can be used as a scrub along the lash line
Erlotinib	Decreased tear production, abnormal eye lash growth, keratitis leading to corneal, and ulceration (18%)	Mild dry eye: Use natural tear eye drops Severe dry eye: Short trial of topical corticosteroids or topical cyclosporine drops Contact lenses: Patients with significant dry eyes should be discouraged from wearing contact lenses. Dryness is a risk factor for ulceration and keratitis. Soft contact lenses with extended wear time can increase the risk of keratitis by five times compared to daily wear
Afatinib	Conjunctivitis (11%)	Conjunctivitis: Topical antibiotics/steroids may be required
Osimertinib	Dry eye, blurred vision, keratitis, cataract, eye irritation, blepharitis, eye pain, increased lacrimation, and vitreous floaters (18%)	Ocular complications: Refer to ophthalmologist May be necessary to discontinue TKI until symptoms improve

Figure 2. Maximizing the Pharmacy Team’s Role in LUNS



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Table 5. Common Drug Interactions with TKIs⁵⁷

Drug	Effect on TKI	Recommendations
PPI H-2 blockers Antacids	Decreased TKI exposure	Avoid concurrent PPI use with erlotinib/gefitinib and dacomitinib Administer erlotinib 10 hours after and at least 2 hours before the next H ₂ -receptor antagonist dose Administer gefitinib 6 hours before or after H ₂ -receptor antagonists and antacids
CYP inducers	Decreased TKI exposure	For concomitant use, increase erlotinib in 50-mg increments at 2-week intervals as tolerated (maximum 450 mg) For concomitant use, increase gefitinib to 500 mg as tolerated Avoid concomitant use with osimertinib where possible Dose reduction may be needed for dacomitinib when coadministered drugs are predominantly metabolized by CYP2D6
CYP inhibitors	Increased TKI exposure	Avoid concomitant use with erlotinib, gefitinib, or osimertinib where possible For severe reactions, decrease erlotinib in 50-mg decrements For concomitant use with gefitinib and osimertinib, monitor patients for adverse reactions
P-gp inducers	Decreased TKI exposure	Increase afatinib by 10 mg for concomitant use Resume previous dose 2-3 days after discontinuing P-gp inducer
P-gp inhibitors	Increased TKI exposure	Reduce afatinib by 10 mg for concomitant use Resume previous dose following discontinuation of P-gp inhibitor as tolerated
Cigarette smoking	Decreased TKI exposure	Increase erlotinib in 50-mg increments at 2-week intervals as tolerated for concurrent cigarette smoking (maximum 300 mg). Resume recommended dose upon smoking cessation
Anticoagulants	Increased INR and bleeding reactions	Erlotinib/gefitinib: Regularly monitor prothrombin time/INR. No dose modifications are recommended
Food	Increase erlotinib/afatinib plasma concentrations	Take erlotinib on an empty stomach one hour before or two hours after food Take afatinib on an empty stomach one hour before or two hours after food

Rare Ocular Side Effects

EGFR is expressed on corneal, limbal, and conjunctival epithelium. Inhibition of EGFR pathway affects the cell proliferation and stratification required for corneal wound repair.⁵⁵ [Table 4 \(previous page\)](#) lists strategies to manage ocular side effects.

Common Drug Interactions

The major determinant in TKI absorption is pH-dependent solubility. TKIs are weakly basic and optimal absorption requires an acidic environment. When intragastric pH is elevated (e.g., due to concurrent proton pump inhibitor [PPI] use), TKI solubility and bioavailability may decrease significantly.⁵⁷ Gefitinib and erlotinib share similar drug interaction profiles due to comparable structures and pharmacokinetic properties. Both undergo extensive metabolism by CYP450. Afatinib is a substrate and inhibitor of the P-glycoprotein drug transporter system. Hepatic enzymes minimally metabolize afatinib. (See [Table 5](#))

Conclusion

The rate of lung cancer in never-smokers is increasing steadily. It is a distinct entity with unique mutations and different tumorigenic pattern. NSCLC patients who have specific molecular alterations are candidates for TKI therapy, which often improves survival and quality of life. EGFR TKIs are integral to the treatment of NSCLC. TKIs have a wide range of adverse effects most of which can be successfully managed. Preventive adverse effect management strategies mitigate the need for dosage reduction or discontinuation of medication. Routine follow-up and assessment of patients helps to identify adverse effects and increase adherence and medication compliance. Pharmacists are an important resource to patients. Effective counseling can minimize TKI-induced toxicities and prevent avoidable hospitalizations.

[Figure 2](#) (previous page) offers suggestions to maximize your role in care for patients who are non- or never-smokers and who develop lung cancer.

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