



Oncology Oral, Lung Cancer Therapeutic Class Review (TCR)

April 14, 2020

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MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
Anaplastic Lymphoma Kinase (ALK) Tyrosine Kinase Inhibitors		
allectinib (Alecensa®) ¹	Genentech	<ul style="list-style-type: none"> Treatment of patients with ALK-positive, metastatic non-small cell lung cancer (NSCLC) as detected by an FDA approved test*
brigatinib (Alunbrig®) ²	Millenium	<ul style="list-style-type: none"> Treatment of ALK-positive metastatic NSCLC in patients who have progressed on or are intolerant to crizotinib[†]
ceritinib (Zykadia®) ³	Novartis	<ul style="list-style-type: none"> Treatment of ALK-positive metastatic NSCLC as detected by an FDA-approved test*
crizotinib (Xalkori®) ⁴	Pfizer	<ul style="list-style-type: none"> Treatment of metastatic NSCLC in patients whose tumors are ALK-positive or ROS1-positive as detected by an FDA-approved test*
entrectinib (Rozlytrek®) ⁵	Genentech	<ul style="list-style-type: none"> Treatment of metastatic NSCLC in adults patients whose tumors are ROS1-positive Treatment of adult and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have either progressed following treatment or have no satisfactory alternative therapy[†]
lorlatinib (Lorbrena®) ⁶	Pfizer	<ul style="list-style-type: none"> Treatment of ALK-positive metastatic NSCLC whose disease has progressed on crizotinib and ≥ 1 other ALK inhibitor for metastatic disease; alectinib as the first ALK inhibitor therapy for metastatic disease; or ceritinib as the first ALK inhibitor therapy for metastatic disease[†]
Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitors		
afatinib (Gilotrif®) ⁷	Boehringer Ingelheim	<ul style="list-style-type: none"> First-line treatment of metastatic NSCLC with nonresistant EGFR mutations as detected by an FDA-approved test*[‡] Treatment of metastatic, squamous NSCLC progressing after platinum-based therapy
dacomitinib (Vizimpro®) ⁸	Pfizer	<ul style="list-style-type: none"> First-line treatment of metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test
erlotinib (Tarceva®) ⁹	Genentech	<ul style="list-style-type: none"> Treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test who are receiving first-line, maintenance, or second- or greater-line treatment after progression following ≥ 1 prior chemotherapy regimen*[§] First-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer, in combination with gemcitabine
gefitinib (Iressa®) ¹⁰	AstraZeneca	<ul style="list-style-type: none"> First-line treatment of patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test*[¶]
osimertinib (Tagrisso™) ¹¹	AstraZeneca	<ul style="list-style-type: none"> First-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test* Treatment of patients with metastatic EGFR T790M mutation-positive NSCLC as detected by an FDA-approved test, whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy**
Non-targeted Agents		
topotecan (Hycamtin®) ¹²	GlaxoSmithKline	<ul style="list-style-type: none"> Treatment of relapsed small cell lung cancer

* Information on FDA-approved tests for the detection of various mutations found in NSCLC tumors is available at <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm>.

† Approved under Accelerated Approval based on tumor response rate and/or duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

‡ Afatinib limitation of use: safety and efficacy have not been established in patients whose tumors have resistant EGFR mutations.

§ Erlotinib limitations of use include (1) it is not recommended for use in combination with platinum-based chemotherapy and (2) safety and efficacy of erlotinib have not been evaluated in patients with metastatic NSCLC whose tumors have other EGFR mutations. Patient selection for the use of erlotinib is based on the presence of exon 19 deletions or exon 21 (L858R) substitution mutations in tumor or plasma specimens. If these mutations are not detected in the plasma specimen, test tumor tissue if available.

¶ Gefitinib limitation of use: safety and efficacy have not been established in patients whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations. Patient selection for the use of gefitinib for first-line treatment of metastatic NSCLC is based on the presence of EGFR exon 19 deletions or exon 21 (L858R) substitution mutations in tumor or plasma specimens. If these mutations are not detected in the plasma specimen, test tumor tissue if available.

|| Confirmation of the presence of T790M EGFR mutation in tumor or plasma prior to initiation of therapy with osimertinib is needed. Testing for the mutation in plasma is recommended in patients only when a tumor biopsy cannot be obtained. If not detected in plasma specimen, re-evaluate the feasibility of tumor testing.

OVERVIEW

Lung cancer is the leading cause of cancer death in both men and women in the United States (US). In 2020, an estimated 228,820 new cases of lung cancer will be diagnosed and 135,720 deaths are estimated to occur.¹³ Currently, 5-year survival is estimated to be 20.5%, an increase from 18.6% reported in 2019.¹⁴ Historical rates of 5-year overall survival (OS) in patients with advanced NSCLC have rarely been reported in the context of clinical trials; however, in 2016 the International Association for the Study of Lung Cancer reported a historical 5-year OS of 6%. Declines in lung cancer mortality in the US have been accelerating in recent years. From 2008 through 2013, lung cancer mortality declined 3%, and from 2013 through 2017, there was a 5% decline in cancer mortality for men and a 4% decline in women. The latest figures to be reported are from 2017, which reflect a drop in overall lung cancer mortality of 2.2% from 2016 to 2017, the largest ever single-year drop in lung cancer mortality. Despite this decline in lung cancer deaths, there are still more US lung cancer deaths annually than deaths from breast cancer, prostate cancer, colorectal cancer, and brain cancers combined.¹⁵

The primary risk factor for the development of lung cancer is smoking tobacco, accounting for approximately 85% to 90% of all cases of lung cancer. The carcinogenic chemicals in cigarette smoke are responsible for most lung cancer-related deaths, while exposure to second-hand smoke also results in an increased relative risk of developing lung cancer.¹⁶ While chemoprevention agents are not yet established, lung cancer screening using low-dose computerized tomography (LDCT) is recommended by the US Preventive Services Task Force in current smokers aged 55 to 80 years who have a 30-pack year smoking history and former smokers who quit within the past 15 years and meet this criteria (grade B).¹⁷ This recommendation is based on the results of the National Lung Cancer Screening Trial; it reported a 20% relative reduction in lung cancer-specific death associated with LDCT in this population compared to chest radiography.^{18,19}

Depending on the stage of the disease at diagnosis and the histologic subtype, the treatment of lung cancer may involve surgery, radiation, chemotherapy, targeted therapy, immunotherapy, or a combination of these approaches. This review will focus on oral therapies to treat lung cancer, the majority of which are targeted agents. The use of targeted therapies represents an overall trend in the treatment of cancer which is based on identifying and targeting specific molecular mutations resulting in a more precise, personalized approach to treatment.

Lung cancer is divided into 2 major classes: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). These 2 types of lung cancer differ in their biology, treatment, and overall prognosis.

NSCLC accounts for more than 80% of all lung cancer cases. There are 2 major histologic subtypes of NSCLC, squamous cell and nonsquamous cell. Nonsquamous cell includes adenocarcinoma, which is the most common type of lung cancer diagnosed in the US and is also the most common subtype occurring in non-smokers.²⁰

Technologic advances in genomic profiling have identified ways to further classify NSCLC based on the presence of specific oncogenes. Drug therapy targets that function as tyrosine kinase inhibitors (TKIs) aimed at these specific oncogenes are FDA-approved for use in the treatment of lung cancer. These oral drugs target gene mutations in epidermal growth factor receptor (EGFR), B-Raf proto-oncogene (BRAF) V600E, or translocations in the genes encoding for anaplastic lymphoma kinase (ALK) and ROS proto-oncogene (ROS) 1, and neurotrophic tyrosine receptor kinase (NTRK) gene fusions. Unfortunately, these targeted therapies are appropriate for only a small percentage of advanced lung cancer patients. EGFR sensitizing mutations are the most commonly detected oncogenic alterations and are found in approximately 10% of Caucasian patients but may be present in as many as 50% of patients from East Asian descent. Anaplastic lymphoma kinase (ALK) is found in approximately 2% to 7% of advanced lung cancers and ROS1 gene rearrangement is found in only 1% to 2% of advanced lung cancers.^{21,22} NTRK gene fusions are estimated to occur in 0.2% of NSCLC cases.²³ EGFR, ALK, and ROS1 alterations are found most commonly in never smokers, while BRAF is seen more frequently in patients with a history of smoking.²⁴ As a general rule, these genetic alterations occur in singular fashion and are non-overlapping, although 1% to 3% of NSCLC patients may harbor concurrent alterations.²⁵ EGFR and BRAF mutations, as well as ALK or ROS1 gene rearrangements, occur almost exclusively in patients with adenocarcinoma, a nonsquamous NSCLC histology. However, testing should also be considered in certain patients with squamous cell carcinoma (never smokers, small biopsy specimens, or mixed histology; category 2A). NCCN also strongly advises broader molecular profiling for all patients with advanced or metastatic NSCLC, including testing for neurotrophic receptor tyrosine kinase (NTRK) gene fusion. Broad molecular profiling ensures that rare predictive biomarkers might be identified to appropriately counsel patients regarding the availability of clinical trials.

In the first-line setting of metastatic disease where an EGFR mutation is discovered prior to initiating cytotoxic chemotherapy, NCCN guidelines recommend targeted therapy with afatinib (Gilotrif), dacomitinib (Vizimpro), erlotinib (Tarceva), gefitinib (Iressa), or osimertinib (Tagrisso) (all category 1), while osimertinib is preferred.²⁶ Listed combination options include erlotinib plus either ramucirumab (Cyramza) (category 2A) or erlotinib plus bevacizumab (category 2B). Randomized clinical trials have demonstrated that progression-free survival (PFS) is improved with the use of these targeted agents when compared to standard first-line cytotoxic chemotherapy in patients with sensitizing EGFR mutations. If traditional cytotoxic therapy has already begun, the cytotoxic therapy may be completed or interrupted, followed by afatinib, dacomitinib, erlotinib, gefitinib, erlotinib + ramucirumab, or osimertinib (all category 2A); osimertinib is again preferred, and erlotinib plus bevacizumab is a category 2B recommendation. Unfortunately, most patients with sensitizing EGFR mutations develop resistance to first-line TKI therapy, as evidenced by progressive disease within 9 to 13 months after starting initial TKI therapy. The EGFR T790M mutation is associated with acquired resistance to TKI therapy in approximately 60% of patients who had an initial response to erlotinib gefitinib, or afatinib. Upon disease progression, patients who were treated with afatinib, dacomitinib, erlotinib alone or in combination with ramucirumab or bevacizumab, or gefitinib may continue to receive the same therapy (category 2A) or may be switched to osimertinib if the EGFR T790M mutation is present (category 1). For patients with advanced for metastatic lung cancer who are found to have a BRAF V600E mutation, a combination of dabrafenib (Tafinlar) plus trametinib (Mekinist) is recommended as preferred first-line therapy by the NCCN guidelines (category 2A), while single agent vemurafenib or dabrafenib may

be useful treatment options if the combination of dabrafenib plus trametinib is not tolerated (category 2A).

A smaller percentage of patients with NSCLC have ALK or ROS1 gene rearrangements.²⁷ However, certain subsets of patients, including younger patients and those who were never smokers, may have an incidence of ALK gene rearrangement as high as 30%. Regarding ROS1 rearrangement, both crizotinib (Xalkori) and entrectinib (Rozlytrek) are preferred in the NCCN guidelines for first-line use in patients with metastatic disease who have a ROS1 rearrangement, while ceritinib (Zykadia) is listed as an option as well but is no longer listed as preferred. Lorlatinib (Lorbrena) is recommended upon disease progression in this setting (category 2A). If a patient is discovered to have an ALK-rearrangement prior to beginning traditional cytotoxic therapy, crizotinib, alectinib, brigatinib, and ceritinib are recommended by NCCN (all category 1); however, alectinib is identified by NCCN as being the preferred agent. Similar to the recommendation for EGFR discovery, if cytotoxic therapy has already begun, the cytotoxic therapy may be completed or interrupted, followed by alectinib (preferred), brigatinib, ceritinib, or crizotinib. At the time of disease progression, patients with ALK-positive disease who received crizotinib may continue crizotinib or switch to alectinib, brigatinib, or ceritinib depending on the degree of symptomatology and location of disease progression (category 2A). For patients who progressed on first-line alectinib, brigatinib, or ceritinib, those drugs may be continued, or if the patient has symptomatic, systemic disease with multiple lesions, lorlatinib in either the second-line or third-line setting is recommended (category 2A). If the disease progression involves multiple central nervous system (CNS) lesions, brigatinib may be utilized, or ceritinib or alectinib could be used if the patient has not previously received those agents (all category 2A).

The American Society of Clinical Oncology (ASCO) guideline regarding molecular testing of lung cancer patients for treatment with targeted TKIs endorses the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association of Molecular Pathologists (AMP) guideline update with minor modifications²⁸ This guideline addresses appropriate genes for testing in patients with lung cancer as well as methods used to perform the molecular testing. New 2018 modifications by ASCO include a recommendation that BRAF testing be performed on all patients with advanced lung adenocarcinoma, regardless of clinical characteristics, and a recommendation that molecular biomarker testing be performed in all tumors with an adenocarcinoma component, nonsquamous, non-small cell histology, or any non-small cell histology when clinical features indicate a higher probability of an oncogenic driver such as young age (< 50 years) or light or absent tobacco exposure. The ASCO guidelines regarding systemic therapy for Stage 4 NSCLC published in 2017 were partially updated in 2020 to focus specifically on therapy in patients without driver mutations.^{29,30} ASCO notes in this 2020 update that they are working on a separate update for patients with identified targeted driver alterations and will address the therapy-relevant areas in the full clinical practice guideline update.

Topotecan (Hycamtin) is the only agent in this review that is not a targeted therapy. Rather, it is a classic cytotoxic agent, specifically a topoisomerase inhibitor. It is also the only agent in this review approved for use in small cell lung cancer (SCLC) rather than NSCLC. Nearly all cases of SCLC are attributable to cigarette smoking.³¹ SCLC is a rapidly growing cancer that is characterized by early development of widespread metastases. A more chemo-sensitive disease than NSCLC, SCLC usually responds well to chemotherapy initially, but nearly all patients experience relapse and long-term survival is rare. Topotecan is FDA-approved for use in the relapse setting of SCLC. For second-line therapy of SCLC in patients who relapse 6 months or less from their original therapy and have a performance status of 0 to 2, the NCCN guidelines state that either enrollment in a clinical trial or topotecan is preferred.

PHARMACOLOGY^{32,33,34,35,36,37,38,39,40,41,42,43}

All of the agents included in this review, with the exception of topotecan (Hycamtin), are tyrosine kinase inhibitors (TKIs). TKIs are small molecules that bind to extracellular receptors. This binding causes receptor dimerization and stimulates the protein kinase activity of the intracellular domain, leading to activation of multiple downstream signaling pathways. These pathways regulate proliferation, metabolism, survival, and apoptosis of the malignant cells.⁴⁴

Afatinib (Gilotrif), dacomitinib (Vizimpro), erlotinib (Tarceva), gefitinib (Iressa), and osimertinib (Tagrisso) all bind to the kinase domain of EGFR. Up-regulation or overexpression of EGFR in cancer cells has been associated with increased cell proliferation, cell survival by blocking apoptosis, increased invasive capacity for metastasis, and promotion of angiogenesis.⁴⁵ Gefitinib and erlotinib are considered first-generation EGFR TKIs as they bind reversibly to the receptor, while second-generation EGFR-TKIs, including afatinib and dacomitinib, irreversibly bind to the receptor. Gefitinib reversibly inhibits the kinase activity of wild-type and certain activating mutations of EGFR, preventing autophosphorylation of tyrosine residues associated with the receptor, thereby inhibiting further downstream signaling and blocking EGFR-dependent proliferation. Erlotinib reversibly binds to the adenosine tri-phosphate (ATP)-binding site and completely inhibits autophosphorylation by EGFR. Erlotinib and gefitinib have binding affinity for EGFR exon 19 deletions or exon 21 (L858R) mutations that is higher than their binding affinity for the wild-type receptor. Afatinib irreversibly inhibits tyrosine kinase autophosphorylation by covalently binding to the kinase domains of EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4). This results in blockage of downstream EGFR signal transduction pathways, cell cycle arrest, and inhibition of angiogenesis. Dacomitinib irreversibly inhibits EGFR kinase activity of EGFR/HER1, HER2, and HER4, and certain EGFR-activating mutations, such as exon 19 deletion or the exon 21 L858R substitution mutation; *in vitro* activity also inhibited DDR1, EPHA6, LCK, DDR2, and MNK1. Osimertinib (Tagrisso), a third generation EGFR TKI binds irreversibly to the EGFR mutations T790M, L858R, and exon 19 deletion and, to a lesser extent, wild-type EGFR amplifications.

Alectinib (Alecensa) targets anaplastic lymphoma kinase (ALK) and RET and inhibits ALK phosphorylation and ALK-mediated activation of the downstream signaling proteins STAT3 and AKT. Alectinib decreases tumor cell viability in multiple cell lines harboring ALK fusions, amplifications, or activating mutations.

Brigatinib (Alunbrig) demonstrates *in vitro* activity at clinically achievable concentrations against ALK, the proto-oncogene tyrosine-protein kinase ROS1 (ROS1), insulin-like growth factor-1 receptor (IGF-1R), FLT-3, and EGFR deletion and point mutations. It inhibits ALK phosphorylation and ALK-mediated activation of the downstream signaling proteins STAT3, AKT, ERK1/2, S6, and proliferation of cell lines expressing EML-ALK and NPM-ALF fusion proteins.

Crizotinib (Xalkori) is an inhibitor of receptor tyrosine kinases including ALK, Hepatocyte Growth Factor Receptor (HGFR, c-Met), ROS1 (c-ros), and Recepteur d'Origine Nantais (RON). The formation of ALK fusion proteins results in activation and dysregulation of the gene's expression and signaling which can contribute to increased cell proliferation and survival in tumors expressing these proteins.

Targets of ceritinib (Zykadia) kinase inhibition include ALK, insulin-like growth factor 1 receptor (IGF-1R), insulin receptor (InsR), and ROS1; of these, ceritinib is most active against ALK. By inhibiting ALK, ceritinib inhibits autophosphorylation, downstream signaling, and proliferation of ALK-dependent cancer cells.

Lorlatinib (Lorbrena) is a kinase inhibitor with *in vitro* activity against ALK and ROS1 as well as TYK1, FER, FPS, tropomyosin receptor tyrosine kinases (TRK)-A (TRKA), TRKB, TRKC, FAK, FAK2, and ACK.

Lorlatinib demonstrated *in vitro* activity against multiple mutant forms of the ALK enzyme, including some mutations detected in tumors at the time of disease progression on crizotinib and other ALK inhibitors.

Entrectinib (Rozlytrek) is a kinase inhibitor with inhibitory activity against TRKA, TRKB, and TRKC, as well as ROS1 and ALK. TRKs are encoded by the neurotrophic tyrosine receptor kinase (NTRK) genes. Other inhibitory activity of entrectinib includes inhibition of JAK2 and TNK2. The active metabolite of entrectinib also demonstrates similar inhibitory effects on TRK, ROS1, and ALK. *In vitro* and *in vivo*, entrectinib has been found to inhibit cancer cell proliferation of tumors with NTRK, ROS1, and ALK fusion genes.

Topotecan, a camptothecin analog, is a classic cytotoxic agent that works by inhibiting topoisomerase I, an enzyme involved in cleavage and repair of DNA strand breaks during DNA replication.

PHARMACOKINETICS^{46,47,48,49,50,51,52,53,54,55,56,57}

Drug	Half-Life (hr)	Metabolism	Elimination (%)	Effect of High Fat Meal (%)
ALK Tyrosine Kinase Inhibitors				
alectinib (Alecensa)	33	CYP3A4	Feces: 98 Urine: < 0.5	AUC: ▲ 90
brigatinib (Alunbrig)	25	CYP2C8 and CYP3A4; N-demethylation and cysteine conjugation	Feces: 65 Urine: 25	AUC: unchanged Cmax: ▼ 13
ceritinib (Zykadia)	41	CYP3A4	Feces: 92 Urine: 1.3	AUC: ▲ 73 Cmax: ▲ 41
crizotinib (Xalkori)	42	CYP3A4/5; oxidation, O-dealkylation and phase 2 conjugation	Feces: 63 Urine: 22	AUC: ▼ 14 Cmax: ▼ 14
entrectinib (Rozlytrek)	20	CYP3A4	Feces: 83 Urine: 3	No clinical impact
lorlatinib (Lorbrena)	24	CYP3A4 and UGT1A4 (major); CYP2C8, CYP2C19, CYP3A5, and UGT1A3 (minor)	Feces: 41 Urine: 48	No clinical impact
EGFR Tyrosine Kinase Inhibitors				
afatinib (Gilotrif)	37	Enzymatic metabolism is minimal	Feces: 85 Urine: 4	AUC: ▲ 39 Cmax: ▲ 50
dacomitinib (Vizimpro)	70	Oxidation (CYP2D6) and glutathione conjugation	Feces: 79 Urine: 3	No clinical impact
erlotinib (Tarceva)	36.2	CYP3A4: major CYP1A2, 1A1: minor	Feces: 83 Urine: 8	Bioavailability: ▲ 167
gefitinib (Iressa)	48	CYP3A4: major CYP2D6: minor	Feces: 86 Urine: < 4	Food does not alter gefitinib bioavailability to a clinically meaningful extent
osimertinib (Tagrisso)	48	CYP3A	Feces: 68 Urine: 14	AUC: ▲ 19 Cmax: ▲ 14

hr = hours

Pharmacokinetics (continued)

Drug	Half-Life (hr)	Metabolism	Elimination (%)	Effect of High Fat Meal (%)
Non-targeted Agents				
topotecan (Hycamtin)	3-6	Hydrolysis	Feces: 33 Urine: 20	Cmax: unchanged Tmax: ▲ 25

hr = hours

CONTRAINDICATIONS/WARNINGS^{58,59,60,61,62,63,64,65,66,67,68,69}

Contraindications

Except for lorlatinib, which is contraindicated in patients taking a strong CYP3A4 inducer due to potential serious hepatotoxicity, there are no contraindications, other than hypersensitivity to the drug, with any of the agents included in this review.

Warnings

Atrioventricular Block

Atrioventricular (AV) block and PR interval prolongation can occur in patients receiving lorlatinib. AV block was seen in 1% of patients on lorlatinib with 0.3% experiencing grade 3 AV block and undergoing pacemaker placement. An electrocardiogram (ECG) should be conducted prior to initiating lorlatinib and periodically thereafter.

Bone Marrow Suppression

Topotecan (Hycamtin) carries a boxed warning regarding severe myelosuppression and should only be administered to patients with baseline neutrophil counts $\geq 1,500$ cells/mm³ and platelet counts $\geq 100,000$ cells/mm³. Grade 4 neutropenia occurred in 32% of patients in clinical studies, most commonly during Cycle 1 (20% of patients). Grade 4 neutropenia associated with infection occurred in 17% of patients and febrile neutropenia occurred in 4%. Grade 4 thrombocytopenia occurred in 6% of patients and grade 3 or 4 anemia occurred in 25% of patients. When used in combination with cisplatin, grade 4 neutropenia occurred in 48%, grade 4 thrombocytopenia occurred in 7%, and grade 3 or 4 anemia occurred in 25% of patients. Peripheral blood cell counts should be monitored frequently.

Bradycardia

Bradycardia has been reported in patients receiving alectinib (Alecensa), brigatinib (Alunbrig), ceritinib (Zykadia), and crizotinib (Xalkori). The use of brigatinib, ceritinib, or crizotinib in combination with other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) should be avoided to the extent possible.

Dose modification of alectinib is not required for asymptomatic bradycardia. In cases of symptomatic bradycardia that is not life-threatening, withhold alectinib, brigatinib, and crizotinib until patient is asymptomatic or until the heart rate returns to at least 60 beats per minute (bpm). If the patient is receiving concomitant therapy that may decrease heart rate, resume alectinib, brigatinib, and crizotinib at a reduced dose. If the concomitant drug known to decrease heart rate is stopped or dose adjusted, then alectinib, brigatinib, and crizotinib may be restarted at their previous dosages. Permanently discontinue alectinib, brigatinib, and crizotinib in case of recurrence or life-threatening bradycardia if no contributing concomitant medication is identified.

Heart rate and blood pressure should be monitored regularly in patients receiving alectinib, brigatinib, ceritinib, and crizotinib. Increase frequency of monitoring if these agents are used with drugs known to cause bradycardia.

Central Nervous System Effects

Patients receiving lorlatinib may experience a broad range of central nervous system (CNS) effects including seizures, hallucinations, and changes in cognitive function, mood (including suicidal ideation), speech, mental status, and sleep. Overall, CNS effects occurred in 54% of patients receiving lorlatinib, and the median time to first onset of any CNS effect was 1.2 months. Cognitive effects occurred in 29% of patients with 2.1% being severe (grade 3 or 4), mood effects occurred in 24% with 1.8% being severe, speech effects occurred in 14% with 0.3% being severe, and sleep effects occurred in 10% of patients. Additionally, hallucinations occurred in 7% with 0.6% being severe, mental status changes occurred in 2.1% with 1.8% being severe, and seizures occurred in 3% of patients.

CNS adverse effects have been reported in patients receiving entrectinib (Rozlytrek). A total of 27% of patients exhibited cognitive impairment, 10% had mood disorders, 38% of patients experienced dizziness, and 14% reported sleep disturbances. Patients should be advised not to drive or operate machinery if exhibiting CNS adverse effects. Therapy may need to be withheld, require a dose reduction, or be permanently discontinued depending on the severity or worsening of CNS effects.

Cardiomyopathy

Cardiomyopathy, defined as chronic cardiac failure, congestive heart failure (CHF), pulmonary edema, or decreased ejection fraction, occurred in 2.6% of patients in clinical trials with osimertinib (Tagrisso), with 0.1% of cases being fatal. Left ventricular ejection fraction (LVEF) decline of greater than 10% and a drop to less than 50% occurred in 3.9% of patients in clinical trials with osimertinib (Tagrisso). LVEF should be assessed before initiation of osimertinib and then at 3-month intervals while on treatment in patients with cardiac risk factors. For symptomatic CHF, permanently discontinue osimertinib.

Across entrectinib (Rozlytrek) clinical trials, CHF occurred in 3.4% of patients, with 2.3% considered grade 3 severity. LVEF should be evaluated before starting entrectinib in patients with symptoms or risk factors for CHF. Patients should be monitored for signs/symptoms of CHF (e.g., shortness of breath, edema). Entrectinib may need to be withheld, reduced, or be permanently discontinued depending on the severity or worsening of CHF.

Dermatologic

The overall incidence of cutaneous reactions (rash, erythema, acneiform rash) with afatinib (Gilotrif) in clinical trials was 90%. A small percentage (< 1%) developed bullous, blistering, or exfoliating lesions. Patients who develop grade 2 cutaneous adverse reactions lasting more than 7 days, intolerable grade 2, or grade 3 cutaneous reactions should have afatinib withheld and resumed with an appropriate dose reduction upon resolution of toxicity. Patients with life-threatening bullous, blistering, or exfoliating lesions should have afatinib discontinued. Post-marketing cases consistent with toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (SJS) have been reported; the drug should be discontinued if TEN or SJS is suspected.

Rash was reported in 78% of dacomitinib-treated patients in clinical trials; 21% of cases were grade 3 or 4. Exfoliative skin reactions were reported in 7% of patients, with 1.8% grade 3 or 4; sun exposure may increase risk. Withhold dacomitinib if persistent grade 2 rash occurs or any grade 3 or 4 skin reaction. The patient may resume therapy when severity is grade 1 or less. Topical therapy with

moisturizers, antibiotics, and steroids should be started upon the development of grade 1 rash; initiate oral antibiotics for grade 2 or worse skin reactions.

Bullous, blistering, and exfoliative skin conditions, including cases suggestive of SJS or TEN, have occurred both with erlotinib (Tarceva) and gefitinib (Iressa).

Osimertinib (Tagrisso) should be withheld if SJS or erythema multiforme major (EMM) is suspected in patients as postmarketing cases of SJS and EMM have been reported. If SJS or EMM is confirmed, osimertinib should be permanently discontinued.

Embryo-fetal toxicity

Based on the mechanism of action, all agents in this review can cause fetal harm when administered to pregnant women. Pregnancy assessment prior to initiation is prudent. Patients should be made aware of the potential hazard to a fetus and both males and females should be counseled to use highly effective contraception while receiving any of these medications. The length of time to continue contraception after discontinuing the drugs varies, and individual product labeling should be consulted.

Gastrointestinal (GI)

Diarrhea occurred in 96% of patients treated with afatinib during 1 clinical trial. The severity was grade 3 in 15% of those patients and occurred within the first 6 weeks. Dehydration and renal impairment as a consequence of diarrhea were also reported. Patients should be provided with an anti-diarrheal agent for self-administration at the onset of diarrhea and instructed to continue therapy until 12 hours after the last loose bowel movement. Patients who develop grade 3 diarrhea or grade 2 diarrhea lasting more than 48 hours should have the afatinib dose held and an appropriate dose reduction should be undertaken when therapy is resumed.

Seventy-six percent of clinical trial participants experienced diarrhea, nausea, vomiting, or abdominal pain when taking ceritinib 450 mg once daily with food. This is significantly less than the 96% of patients that experienced these GI adverse events with the originally recommended dosage (750 mg daily on an empty stomach). Monitoring for GI toxicities, appropriate care, and dose modification, as needed, are recommended in patients receiving ceritinib.

Diarrhea occurred in 86% of patients treated with dacomitinib; 11% of cases were grade 3 and 0.3% were fatal. Initiate anti-diarrheal treatment (e.g., loperamide, diphenoxylate) and withhold dacomitinib treatment if grade 2 or greater diarrhea occurs. The patient may resume treatment at the same or lower dosage after recovery to grade 1 or less, depending on severity.

Grade 3 or 4 diarrhea occurred in 3% of gefitinib-treated patients across the clinical trials.

Diarrhea, including severe and life-threatening diarrhea, can occur with topotecan. Across 4 lung cancer trials, the incidence of diarrhea was 22%, with 4% of patients experiencing grade 3 diarrhea. The median time to onset was 9 days; diarrhea should be managed aggressively and the drug should be dose reduced after recovery from grade 3 to 4 diarrhea. Diarrhea can occur at the same time as topotecan-induced neutropenia.

Gastrointestinal (GI) Perforation

GI perforation has occurred in patients receiving erlotinib. Patients receiving concomitant anti-angiogenic agents, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), or taxane-based chemotherapy, or who have a prior history of peptic ulceration or diverticular disease, may be at an increased risk of perforation.

GI perforation occurred in 0.1% of gefitinib-treated patients across the clinical trials. Gefitinib should be discontinued in patients who develop GI perforation.

GI perforation, including fatal cases, occurred in 0.2% of afatinib-treated patients across clinical trials. Afatinib should be permanently discontinued in patients who develop GI perforation.

Hepatotoxicity

Hepatotoxicity has occurred in patients receiving afatinib and some of these cases were fatal. Liver function testing should be done periodically in patients receiving afatinib.

Elevations of alanine aminotransferase (ALT) greater than 5 times the upper limit of normal (ULN) occurred in 28% of patients treated in 1 clinical trial of ceritinib. Liver function tests, including ALT, aspartate aminotransferase (AST), and total bilirubin should be monitored monthly and as clinically indicated in patients receiving ceritinib. In patients who experience hepatotoxicity, the decision of whether to resume ceritinib at a reduced dose or permanently discontinue ceritinib should be based on the severity of the adverse drug reaction.

Crizotinib has been associated with hepatotoxicity, including fatal hepatotoxicity. Patients receiving crizotinib should have liver function tests, including ALT and total bilirubin, monitored every 2 weeks during the first 2 months of treatment, then once a month, and as clinically indicated.

Hepatic failure and hepatorenal syndrome can occur during treatment with erlotinib in patients with normal hepatic function; the risk of hepatic toxicity is increased in patients with baseline hepatic impairment. Liver function testing, including AST, ALT, bilirubin, and alkaline phosphatase, should be monitored during treatment with erlotinib. The frequency of liver function test monitoring should be increased in patients with pre-existing hepatic impairment or biliary obstruction. Erlotinib should be held in patients without pre-existing hepatic impairment if total bilirubin exceeding 3 times the ULN or if AST/ALT greater than 5 times the ULN develops. Any patient who has pre-existing hepatic impairment should have erlotinib therapy held for a doubling of bilirubin or a tripling of AST/ALT over their baseline levels. If liver function tests do not improve significantly or resolve within 3 weeks, erlotinib should be discontinued.

Patients receiving gefitinib across the clinical trials had an 11.4% incidence of increased ALT, 7.9% incidence of increased AST, and a 2.7% increase of increased bilirubin. The incidence of grade 3 hepatotoxicity with gefitinib ranged from 0.7% (increased bilirubin) up to 5.1% (increased ALT). Periodic liver function testing is recommended and gefitinib should be withheld in patients with worsening liver function or discontinued in patients with severe hepatic impairment.

Elevations of AST and ALT greater than 5 times the ULN occurred in 4.6% and 5.3% of alectinib-treated patients, respectively. Elevation of bilirubin greater than 3 times the ULN occurred in 3.7% of patients. The majority of these elevations occurred during the first 3 months of treatment. AST, ALT, and total bilirubin should be monitored every 2 weeks for the first 3 months of treatment then once per month as clinically indicated, with more frequent monitoring in patients who develop any degree of hepatotoxicity.

Concomitant use of lorlatinib and strong CYP3A4 inducers is contraindicated, and concomitant use with moderate CYP3A4 inducers should be avoided due to the risk of hepatotoxicity. Severe hepatotoxicity occurred in 10 of 12 healthy subjects receiving a single dose of lorlatinib with multiple daily doses of rifampin, a strong CYP3A inducer. Concomitant use resulted in grade 4 ALT or AST elevations in 50% of subjects, grade 3 ALT or AST elevations in 33%, and grade 2 ALT or AST elevations in 8%. These

elevations occurred within 3 days and returned to normal limits after a median of 15 days (range, 7 to 34 days).

In clinical trials of patients who received entrectinib (Rozlytrek), an increased AST and ALT of any grade occurred in 42% and 36% of patients, respectively. The incidence may be underestimated as 4.5% of patients had no post-treatment liver function tests. Increased AST or ALT leading to dose interruptions or reductions occurred in 0.8% and 0.8% of patients, respectively. Entrectinib was discontinued due to increased AST or ALT in 0.8% patients. AST and ALT should be monitored every 2 weeks during the first month of therapy and then on a monthly basis thereafter, unless clinically indicated. Entrectinib should be withheld or permanently discontinued based on severity of hepatotoxicity. If withheld, entrectinib should only be resumed at the same or reduced dose.

Hyperglycemia

Hyperglycemia can occur in patients receiving ceritinib and is more common in patients with diabetes or glucose intolerance or patients receiving corticosteroids. Monitor fasting serum glucoses prior to the start of ceritinib and as clinically indicated. Initiate or optimize anti-hyperglycemic therapy as indicated. In patients who experience hyperglycemia, ceritinib should be withheld until the hyperglycemia is controlled and then the drug should be resumed at a reduced dose. If hyperglycemic control cannot be achieved with optimal medical management, ceritinib should be permanently discontinued.

In clinical trials, 43% of patients treated with brigatinib developed new or worsening hyperglycemia. Fasting serum glucose should be evaluated prior to and during brigatinib therapy. Hyperglycemia should be treated with anti-hyperglycemic medications as needed. If glycemic control cannot be achieved, then a dose reduction or permanent discontinuation of brigatinib should be considered.

Hyperlipidemia

Increases in serum cholesterol and triglycerides can occur in patients receiving lorlatinib, with grade 3 or 4 elevations in total cholesterol occurring in 17% and grade 3 or 4 elevations in triglycerides occurring in 17% of the patients who received lorlatinib. These elevations had a median time to onset of 15 days. Eighty percent of patients required initiation of lipid-lowering medications, 7% required temporary discontinuation of lorlatinib, and 3% required dose reduction of lorlatinib for elevations in cholesterol and in triglycerides. Monitor serum cholesterol and triglycerides before initiating lorlatinib, 1 and 2 months after initiation, and periodically thereafter. Lipid-lowering agents should be initiated or increased in patients with hyperlipidemia. Dose adjustments are detailed in the labeling.

Hypertension

Hypertension was reported in clinical trials in patients treated with brigatinib, including grade 3 hypertension. Blood pressure should be monitored after 2 weeks of starting therapy and at least monthly thereafter while on therapy. Brigatinib should be withheld for grade 3 hypertension, even if the patient is on optimal antihypertensive therapy; brigatinib may be resumed at a reduced dose once blood pressure control resumes to grade 1 severity. If grade 4 hypertension occurs, consider permanent discontinuation of brigatinib.

Hyperuricemia

Hyperuricemia was reported in 9% of patients in entrectinib (Rozlytrek) clinical studies, with grade 4 hyperuricemia occurring in 1.7% of patients. In the majority of cases, urate-lowering medications resulted in resolution of the hyperuricemia. Serum uric acid levels should be measured prior to therapy and regularly during treatment; patients should be monitored for signs and symptoms of

hyperuricemia as urate-lowering medications and/or withholding of entrectinib may be required. A dose reduction may be necessary upon improvement in hyperuricemia.

Interstitial Lung Disease (ILD)/Pneumonitis

ILD or ILD-like adverse reactions (e.g., lung infiltration, pneumonitis, acute respiratory distress syndrome [ARDS], or alveolitis allergic) occurred in 1.5% of afatinib patients across the clinical trials and some of these cases were fatal. The incidence of ILD appears to be higher in patients of Asian ethnicity compared to non-Asians. Afatinib should be withheld in patients with suspected ILD and discontinued in confirmed cases of ILD.

Severe, life-threatening, or fatal ILD can occur in patients taking ceritinib or topotecan. Patients should be monitored for pulmonary symptoms indicative of ILD (e.g., cough, fever, dyspnea, hypoxia). Ceritinib and topotecan should be permanently discontinued if ILD is confirmed.

Likewise, severe, life-threatening, or fatal ILD has been reported with brigatinib. Adverse reactions consistent with possible ILD/pneumonitis occurred within 9 days of initiation (median onset, 2 days) in 6.4% of patients.

In clinical studies, severe and fatal ILD/pneumonitis was reported in 0.5% of patients treated with dacomitinib (Vizimpro), and 0.3% of cases were fatal. Withhold dacomitinib if ILD/pneumonitis is suspected (e.g., patient experiences dyspnea, cough, fever) and permanently discontinue if confirmed.

Cases of ILD associated with crizotinib have occurred and generally were within 2 months after the initiation of treatment. Pulmonary symptoms of patients receiving crizotinib should be monitored.

In patients receiving erlotinib that developed ILD, the onset of symptoms was between 5 days to more than 9 months (median, 39 days) after initiating erlotinib. Withhold erlotinib for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough, and fever. If ILD is confirmed, erlotinib should be permanently discontinued.

ILD or ILD-like adverse drug reactions occurred in 1.3% of the patients treated across gefitinib clinical trials. Grade 3 or higher cases were experienced by 0.7% of the patients and 3 cases were fatal.

ILD occurred in 1.5% of the patients treated with lorlatinib, with 1.2% of patients experiencing grade 3 or 4 ILD/pneumonitis and 1 patient (0.3%) discontinuing as a result. Investigate any patient who presents with worsening of respiratory symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Lorlatinib should be immediately withheld in patients with suspected ILD/pneumonitis; permanently discontinued for treatment-related ILD/pneumonitis of any severity.

Severe ILD (grade 3) occurred in 0.7% of alectinib patients treated during clinical trials. Patients should be monitored for symptoms of ILD including dyspnea, cough, and fever. Alectinib should be discontinued in any patient who develops ILD if no other potential causes can be identified.

ILD occurred in 3.9% of osimertinib clinical trial patients. Osimertinib should be permanently discontinued in any patient with confirmed ILD.

Ocular Disorders

Keratitis, characterized as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain, and /or red eye, has occurred in patients receiving afatinib. Contact lens use is a risk factor for keratitis and ulceration. If keratitis is diagnosed, the benefits and risks of continuing treatment with afatinib should be carefully considered.

Decreased tear production, abnormal eyelash growth, keratoconjunctivitis sicca, or keratitis can occur with erlotinib therapy and can lead to corneal perforation or ulceration. Interruption or discontinuation of erlotinib therapy is recommended if patients develop acute or worsening ocular disorders, such as eye pain.

Keratitis (0.1%); corneal erosion and aberrant eyelash growth (0.2%); and conjunctivitis, blepharitis, and dry eye (6.7%) have occurred in patients treated with gefitinib. The incidence of grade 3 ocular disorders was 0.1%.

In clinical trials, keratitis was reported in 0.7% of patients treated with osimertinib. Refer patients with symptoms consistent with keratitis to an ophthalmologist.

Optic atrophy and optic nerve disorder have been reported as possible causes of severe visual loss that has occurred in patients receiving crizotinib. Ophthalmological evaluation should be performed in patients with new onset of severe visual loss. A decision to resume therapy with crizotinib should consider the potential benefits versus the unknown risks of resuming crizotinib therapy.

In clinical trials, blurred vision, diplopia, reduced visual acuity, cataract, and macular degeneration were reported in patients receiving brigatinib. If new or worsening visual symptoms of at least grade 2 occur, withhold brigatinib and refer patient for ophthalmologic assessment. Brigatinib may be resumed at a reduced dose if symptom severity improves to grade 1 or less; however, it should be permanently discontinued if grade 4 severity occurs.

A total of 21% of patients in entrectinib (Rozlytrek) clinical studies experienced vision changes (e.g., blurred vision, photophobia, diplopia, visual impairment, photopsia, cataract, vitreous floaters), with the majority of these being grade 1 in severity. Vision changes may require withholding of therapy, ophthalmological evaluation, and/or dose reduction.

Pancreatitis

Elevations of lipase and/or amylase occurred in 14% of patients receiving ceritinib during clinical trials and there was 1 fatality attributed to pancreatitis. Serum lipase and amylase should be monitored prior to the start of ceritinib and as clinically indicated. If the serum lipase or amylase exceeds 2 times the ULN, Ceritinib should be withheld and resumed at a reduced dose after recovery of serum lipase or amylase to less than 1.5 times the ULN.

Elevations in amylase and/or lipase have occurred in patients treated with brigatinib, including grade 3 or 4 severity. Amylase and lipase should be monitored during treatment. Brigatinib should be withheld for grade 3 or 4 elevations and may be resumed at a dose described in the product labeling if levels return to grade 1 or better.

QT Prolongation

Ceritinib causes concentration-dependent increases in the corrected QT (QTc) interval. The use of ceritinib, as well as crizotinib, should be avoided in patients with congenital long QT syndrome, when possible. In patients receiving ceritinib, alectinib, osimertinib, or crizotinib, periodic monitoring of ECGs and electrolytes should be done in patients with congestive heart failure (CHF), bradyarrhythmias, electrolyte abnormalities, or those taking medications that are known to prolong the QTc interval. Ceritinib, crizotinib, and osimertinib should be withheld in patients who develop a QTc interval < 500 msec on at least 2 separate ECGs until the QTc interval is < 480 msec or recovery to baseline, and then treatment should be resumed at a reduced dose. Ceritinib, alectinib, osimertinib, and crizotinib should be permanently discontinued in patients who develop QTc interval prolongation in combination with

torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia.

Entrectinib (Rozlytrek) has the potential to prolong the QT interval as demonstrated in a small proportion of patients in clinical trials; 3.1% of patients had a QTc interval prolongation of > 60 msec and 0.6% exhibited a QTc interval > 500 msec. Patients who currently have or who have a strong likelihood of experiencing QTc interval prolongation should be monitored. The QT interval and serum electrolytes should be measured at baseline and regularly during therapy. Therapy may need to be withheld, require a dose reduction, or be permanently discontinued depending on the severity.

Renal Dysfunction

Hepatorenal syndrome, severe acute renal failure, and renal insufficiency can occur with erlotinib therapy. Periodic monitoring of renal function and serum electrolytes is recommended during treatment with erlotinib.

Renal impairment occurred in 8% of patients in clinical trials with alectinib. Impairment was classified as grade 3 or above in 1.7% of participants and resulted in death in 0.5% of patients who experienced grade 3 or higher toxicity. Therefore, it is recommended to discontinue alectinib in the presence of grade 4 renal toxicity. If the patient recovers to 1.5 times the ULN, after grade 3 renal toxicity, treatment may be resumed at a reduced dose.

Microangiopathic Hemolytic Anemia with Thrombocytopenia

Microangiopathic hemolytic anemia with thrombocytopenia was not seen in patients receiving erlotinib in the 3 monotherapy lung cancer studies, but there was a 1.4% incidence in the erlotinib/gemcitabine arm of the pancreatic cancer trial compared to no incidence in the placebo/gemcitabine arm.

Myocardial Infarction/Cerebrovascular Accident (CVA)

There was an approximate 2% incidence of myocardial infarction/ischemia in the erlotinib/gemcitabine arm of the pancreatic cancer trial compared to an approximate 1% incidence in the placebo/gemcitabine arm. The incidence of CVA in the erlotinib/gemcitabine arm was 2.5% compared to no incidences of CVA in the placebo/gemcitabine arm.

Severe Myalgia and Creatine Phosphokinase (CPK) Elevation

Myalgia occurred in 26% and CPK elevations occurred in 41% of alectinib clinical trial patients. Grade 3 events occurred in 0.7% of patients. Patients receiving alectinib should be advised to report any unexplained muscle pain, tenderness, or weakness. CPK levels should be assessed every 2 weeks for the first month of treatment and as clinically indicated based on symptoms.

CPK elevations were reported in patients treated with brigatinib (27% with 90 mg and 48% with 180 mg); incidence of grade 3 to 4 CPK increases occurred in 2.8% and 12% with 90 mg and the 180 mg doses, respectively. CPK levels should be monitored during brigatinib therapy. Withhold brigatinib if grade 3 or 4 elevations occur; if CPK improves to grade 1 or less, brigatinib may be restarted at a dosage as described in the product labeling.

Skeletal Fractures

Entrectinib (Rozlytrek) may increase the risk of fractures as these events occurred in 5% of adult subjects and 23% of pediatric patients. In adults, some fractures occurred as a result of a fall or other trauma to the affected area, whereas in the pediatric population, these fractures occurred with

minimal to no trauma. The majority of fractures occurred in the hip or lower extremity (femoral or tibial shaft). Patients with pain, changes in mobility, or deformity should be evaluated for fractures.

DRUG INTERACTIONS^{70,71,72,73,74,75,76,77,78,79,80,81}

Co-administration of CYP3A4 Inhibitors

When co-administered with potent inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, ritonavir, saquinavir, telithromycin), plasma concentrations of brigatinib (Alunbrig), ceritinib (Zykadia), crizotinib (Xalkori), **entrectinib (Rozlytrek)**, erlotinib (Tarceva), gefitinib (Iressa), lorlatinib (Lorbrena), and osimertinib (Tagrisso) can increase. Avoid concomitant administration of osimertinib and **entrectinib** with strong CYP3A inhibitors unless no other alternative exists and then patients should be monitored more closely for adverse reactions. Brigatinib, ceritinib, crizotinib, and lorlatinib should not be used concurrently with strong CYP3A inhibitors. If concomitant administration of brigatinib, ceritinib, or lorlatinib with strong CYP3A inhibitors is unavoidable, the brigatinib dose should be reduced by approximately one-half, ceritinib dose by approximately one-third, and the lorlatinib dose by 25%. If concomitant administration of brigatinib with moderate CYP3A4 inhibitors is unavoidable, reduce the dose of brigatinib by approximately 40%. The original dose should be resumed if the strong CYP3A4 inhibitor is discontinued, except for lorlatinib where the original dose should resume after 3 plasma half-lives have passed. **If concomitant administration of entrectinib with a strong or moderate CYP3A inhibitor must occur, the dose for adults and pediatric patients 12 years and older with body surface area (BSA) greater than 1.5 m² should be reduced to 100 mg and 200 mg, respectively.** The use of crizotinib with concomitant moderate CYP3A inhibitors should be done with caution. Avoid grapefruit or grapefruit juice with the use of brigatinib, ceritinib, crizotinib, and **entrectinib**. Monitor adverse reactions when administering strong CYP3A4 inhibitors with gefitinib.

Co-administration of CYP3A4 Inducers

Brigatinib, ceritinib, crizotinib, **entrectinib**, erlotinib, gefitinib, lorlatinib, and osimertinib concentrations may be decreased when administered with a CYP3A4 inducer (e.g. phenytoin, phenobarbital, carbamazepine, rifampin, rifabutin). If concomitant administration of brigatinib with moderate CYP3A4 inducer is unavoidable, then increase the brigatinib daily dose in 30 mg increments after 7 days of treatment or as tolerated, up to a maximum of twice the brigatinib dose that was tolerated prior to concomitant therapy. After discontinuation of a moderate CYP3A inducer, resume the brigatinib dose that was tolerated prior to initiating the moderate CYP3A inducer. The use of osimertinib with concomitant administration of a strong CYP3A inducer should be avoided, but if unavoidable, increase osimertinib dose to 160 mg daily during coadministration. Resume osimertinib at 80 mg 3 weeks after discontinuation of a strong CYP3A4 inducer. Ceritinib and crizotinib should not be used if concomitant use of strong CYP3A4 inducers cannot be avoided. The dose of gefitinib should be increased to 500 mg daily in patients receiving a concomitant strong CYP3A4 inducer and the dose of 250 mg daily should be resumed 7 days after discontinuation of the strong CYP3A4 inducer. Lorlatinib is contraindicated in patients taking strong CYP3A4 inducers. Discontinue strong CYP3A4 inducer for 3 plasma half-lives of the strong CYP3A4 inducer prior to initiating lorlatinib. Concomitant use of lorlatinib with a moderate CYP3A4 inducer has not been studied and, therefore, should be avoided. If concomitant use of moderate CYP3A4 is unavoidable, monitor ALT, AST and bilirubin.

Substrates of CYP3A4/CYP2C9/CYP1A2/BCRP/P-glycoprotein (P-gp)

Caution is advised when using crizotinib with CYP3A4 substrates that have a narrow therapeutic index (e.g., alfentanil, cyclosporine, ergot alkaloids, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus). Avoid coadministration of ceritinib with CYP3A4 and CYP2C9 substrates (e.g., phenytoin, warfarin) with narrow therapeutic indices; if unavoidable, a dose reduction of the substrate may be needed. Osimertinib may also affect plasma concentrations of sensitive substrates of breast cancer resistance protein (BCRP) or CYP1A2. Topotecan is also a substrate of BCRP, and systemic exposure may be increased in the presence of BCRP inhibitors (e.g., cyclosporine, eltrombopag). Coadministration of brigatinib with sensitive CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of CYP3A substrates.

Concurrent use of dacomitinib (Vizimpro) may increase the concentration of CYP2D6 substrates leading to increased risk of toxicity; avoid concomitant use.

Concomitant use of lorlatinib decreases the concentration of CYP3A4 substrates and should be avoided. If concomitant use is unavoidable, increase the CYP3A4 substrate dosage in accordance with approved product labeling. Osimertinib can affect exposure of P-gp substrates; monitor for adverse reactions.

P-glycoprotein (P-gp) Inhibitors

Concomitant use of P-gp inhibitors (e.g., ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, amiodarone) can increase exposure to afatinib, as well as oral topotecan (Hycamtin). Afatinib dose should be reduced by 10 mg per day if not tolerated. The concomitant use of P-gp inhibitors and topotecan should be avoided.

P-glycoprotein (P-gp) Inducers

Concomitant use of P-gp inducers (e.g., carbamazepine, phenytoin, phenobarbital, St. John's wort) can decrease exposure to afatinib. Afatinib dose may be increased by 10 mg per day if tolerated.

Warfarin

Severe and fatal hemorrhage associated with International Normalized Ratio (INR) elevations can occur when erlotinib and warfarin are administered concurrently. Increased INR elevations and/or hemorrhage have been reported in some patients taking warfarin while on gefitinib therapy. Regularly monitor prothrombin time and INR during erlotinib or gefitinib treatment in patients taking warfarin.

Drugs Affecting Gastric pH

H₂-receptor blockers and proton pump inhibitors are associated with long-term suppression of gastric acid secretion that may result in reduced systemic exposure of dacomitinib and erlotinib. Concomitant use of proton pump inhibitors with erlotinib is not recommended and erlotinib should be given 10 hours after or 2 hours before any dose of a histamine-2 (H₂) receptor antagonist. Dacomitinib should be taken at least 6 hours before or 10 hours after an H₂-receptor antagonist.

Proton pump inhibitors, H₂-receptor antagonists, and antacids may reduce plasma concentrations of gefitinib. Avoid concomitant use of gefitinib with proton pump inhibitors, if possible. If a proton pump inhibitor is required, gefitinib should be taken 12 hours after the last dose or 12 hours before the next dose of the proton pump inhibitor. Gefitinib should be taken 6 hours after or 6 hours before an H₂-receptor antagonist or an antacid.

Cigarette Smoking

Cigarette smoking has been shown to reduce the erlotinib area-under-curve concentration (AUC). Patients should be advised to stop smoking; however, if they continue to smoke, a cautious increase in the dose of erlotinib may be considered, while monitoring the patient's safety. If the erlotinib dose is adjusted upward, the dose should be reduced immediately to the indicated starting dose upon cessation of smoking.

Other

In an early interim analysis of a randomized, phase 3 trial in HER2 positive metastatic breast cancer, the combination of afatinib and vinorelbine was associated with a higher rate of adverse events (e.g., diarrhea, rash) and fatal events related to infections and cancer progression. Afatinib combined with vinorelbine should not be used in patients with HER2 positive metastatic breast cancer.

The use of ceritinib and crizotinib in combination with other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) should be avoided to the extent possible. Crizotinib and **entrectinib (Rozlytrek)** can prolong the QT interval and should be avoided with other QT-prolongating agents.

No pharmacokinetic interactions with alectinib requiring dosage adjustments have been identified.

The effect of coadministration of QTc interval-prolonging medications with osimertinib is unknown; avoid coadministration when possible or conduct periodic ECG monitoring.

ADVERSE EFFECTS^{82,83,84,85,86,87,88,89,90,91,92,93}

Drug	Diarrhea	Rash	Stomatitis	Nausea/Vomiting	Vision Problems	Conjunctivitis	Bradycardia
ALK Tyrosine Kinase Inhibitors							
alectinib (Alecensa)	16	18	nr	18	10	nr	nr
brigatinib (Alunbrig)	19-38 (0)	15-24 (1.8-3.6)	nr	23-40 (0.9-1.8)	7.3-10 (0-0.9)	nr	5.7-7.6
ceritinib (Zykadia)	86	16	nr	20	9	nr	3
crizotinib (Xalkori) versus pemetrexed or docetaxel	60 (19)	9	nr	57 (37)	60 (9)	nr	5 (0)
entrectinib (Rozlytrek)	35	11	nr	24-34	21	nr	nr
lorlatinib (Lorbrena)	22	14	nr	12-18	15	nr	nr
EGFR Tyrosine Kinase Inhibitors							
afatinib (Gilotrif) versus pemetrexed/cisplatin	96 (23)	90 (11)	71 (15)	nr (nr)	nr	11 (3)	nr
erlotinib (Tarceva) 2 nd /3 rd line therapy NSCLC versus platinum based doublet chemotherapy	54 (18)	75 (17)	17 (3)	33 (24)	nr	12 (2)	nr
erlotinib (Tarceva) 100 mg + IV gemcitabine versus gemcitabine pancreatic cancer	48 (36)	70 (30)	22 (12)	nr	nr	nr	nr
dacomitinib (Vizimpro) versus gefitinib	87 (56)	69 (47)	45 (19)	19 (22)	nr	19 (4)	nr
gefitinib (Iressa)	29 (10)	47 (17)	7 (4)	14 (10)	nr	6 (3.2)	nr
osimertinib (Tagrisso)	42	41	12	17	18	nr	nr
Non-targeted Agents							
topotecan (Hycamtin)	22	nr	nr	21-33	nr	nr	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for placebo or control arm groups are reported in parentheses. nr = not reported.

The most frequently reported serious adverse reactions occurring with alectinib were pulmonary embolism (1.2%), dyspnea (1.2%), and hyperbilirubinemia (1.2%). Fatal adverse reactions occurred in 2.8% of patients in clinical trials and included hemorrhage (0.8%), intestinal perforation (0.4%), dyspnea (0.4%), pulmonary embolism (0.4%), and endocarditis (0.4%). Photosensitivity occurred in 9.9% of patients exposed to alectinib. Patients were advised to avoid sun exposure and use broad-spectrum sunscreen.

In brigatinib clinical trials, serious adverse reactions occurred in 38% of patients treated with 90 mg group and 40% treated with 180 mg. The most common serious adverse reactions were pneumonia (5.5% overall) and ILD/pneumonitis (4.6% overall). Adverse reactions led to more patients in the 180 mg group needing a dose reduction (7.3% for 90 mg and 20% for 180 mg) or therapy discontinuation (2.8% for 90 mg, 8.2% for 180 mg). Discontinuation was most often due to ILD/pneumonitis and pneumonia.

Dose reductions due to adverse reactions occurred in 59% of patients treated with ceritinib in clinical trials. The most common adverse reactions that led to dose reductions or interruptions were increased ALT (29%), nausea (20%), increased AST (16%), diarrhea (16%), and vomiting (16%). Serious reported adverse drug reactions included convulsion, pneumonia, ILD/pneumonitis, dyspnea, dehydration, hyperglycemia and nausea. Fatal adverse reactions occurred with ceritinib in 5% of patients and included pneumonia, respiratory failure, ILD/pneumonitis, pneumothorax, gastric hemorrhage, general physical health deterioration, pulmonary tuberculosis, cardiac tamponade and sepsis.

Other common adverse reactions reported in clinical trials with dacomitinib (incidence > 20%) were paronychia (64%), decreased appetite (31%), dry skin (30%), decreased weight (26%), alopecia (23%), cough (21%), and pruritus (21%).

The most common adverse reactions with erlotinib are rash (70%) and diarrhea (42%), usually with onset during the first month of treatment.

Serious adverse effects of osimertinib reported in at least 2% of patients were pneumonia and pulmonary embolus. Fatal adverse reactions that occurred in at least 1 patient included ILD/pneumonitis, pneumonia, and CVA/cerebral hemorrhage.

Dose reductions due to adverse reactions were required in 57% of afatinib-treated patients in clinical trials. The most common adverse reactions leading to dose reductions included diarrhea, rash, paronychia, and stomatitis. Serious adverse reactions were reported in 29% of afatinib patients while fatal adverse reactions that occurred in at least 1 patient included pulmonary toxicity/ILD, sepsis, and pneumonia.

Approximately 5% of gefitinib-treated patients discontinued treatment due to an adverse event. The most frequent adverse reactions that led to discontinuation of gefitinib were nausea, vomiting, and diarrhea. The most frequent fatal adverse reactions were respiratory failure (0.9%), pneumonia (0.8%), and pulmonary embolism (0.5%)

A total of 34% of crizotinib-treated patients in clinical trials experienced serious adverse events. The most frequent serious adverse events included dyspnea (4.1%) and pulmonary embolism (2.9%). Fatal adverse events occurred in 2.3% of crizotinib patients during clinical trials. These included septic shock, acute respiratory failure, and diabetic ketoacidosis.

The most common ($\geq 20\%$) adverse reactions with lorlatinib were edema, peripheral neuropathy, cognitive effects, dyspnea, fatigue, weight gain, arthralgia, mood effects, and diarrhea. Serious adverse reactions occurred in 32% of lorlatinib treated patients in clinical trials, including pneumonia (3.4%),

dyspnea (2.7%), pyrexia (2%), mental status changes (1.4%), and respiratory failure (1.4%). The most common lab value abnormalities ($\geq 20\%$) with lorlatinib were hypercholesterolemia, hypertriglyceridemia, anemia, hyperglycemia, increased AST, hypoalbuminemia, increased ALT, increased lipase, and increased alkaline phosphatase. Fatal adverse reactions occurred in 2.7% of patients and included pneumonia (0.7%), myocardial infarction (0.7%), acute pulmonary edema (0.3%), embolism (0.3%), peripheral artery occlusion (0.3%), and respiratory distress (0.3%). Adverse effects resulting in permanent discontinuation of lorlatinib occurred in 8% of patients.

Other common ($\geq 30\%$) adverse reactions with entrectinib (Rozlytrek) include fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, dysesthesia, and dyspnea. Serious adverse effects occurred in 39% of patients. The most frequent serious adverse reactions ($\geq 2\%$) were pneumonia (3.9%), dyspnea (3.7%), pleural effusion (3.4%), sepsis (2.5%), pulmonary embolism (2.3%), respiratory failure (2%), and pyrexia (2%). Permanent discontinuation due to an adverse reaction occurred in 9% of patients.

The most frequently occurring adverse reactions with topotecan (Hycamtin) were hematologic, including a 98% incidence of anemia, an 83% incidence of neutropenia, and an 81% incidence of thrombocytopenia. Other adverse effects occurring in $> 10\%$ of patients included alopecia, fatigue, and anorexia.

SPECIAL POPULATIONS^{94,95,96,97,98,99,100,101,102,103,104,105}

Pediatrics

With the exception of entrectinib (Rozlytrek), none of the products included in this review have established safety and efficacy in patients less than 18 years old. The safety and efficacy of entrectinib in pediatric patients 12 years of age and older with solid tumors that have an NTRK gene fusion have been established. The safety and effectiveness of entrectinib in pediatric patients with ROS1-positive NSCLC have not been established.

Pregnancy

All of the agents included in this review are Pregnancy category D except alectinib (Alecensa), brigatinib (Alunbrig), entrectinib (Rozlytrek), gefitinib (Iressa), lorlatinib (Lorbrena), and osimertinib (Tagrisso) which were approved after the change in FDA pregnancy category determinations. However, all agents in this review can cause fetal harm when administered to a pregnant woman based on animal data. Female patients of reproductive potential and male patients with female partners of reproductive potential should be counseled to use highly-effective contraception during treatment and for varying lengths of time after treatment discontinuation; individual drug labeling should be consulted. Verify pregnancy status of females of reproductive potential prior to starting therapy.

Geriatrics

No overall differences in safety or efficacy were seen in patients 65 years and older during clinical trials with afatinib (Gilotrif), gefitinib, erlotinib (Tarceva), topotecan (Hycamtin), crizotinib (Xalkori), or lorlatinib.

Clinical trials with alectinib, brigatinib (Alunbrig), ceritinib (Zykadia) and entrectinib (Rozlytrek) did not include sufficient numbers of geriatric subjects to determine whether they respond differently than younger subjects.

Data on dacomitinib (Vizimpro) suggests patients 65 years and older may be at greater risk of grade 3 and 4 adverse reactions and may require more frequent dose interruptions/discontinuations compared to younger patients.

No overall differences in effectiveness were observed in osimertinib treated patients who were 65 years of age or older. However, exploratory analysis did suggest a higher incidence of grade 3 and 4 adverse reactions and more frequent dose modifications for adverse reactions in patients over 65 years of age as compared to patients who were younger than 65 years of age.

Renal Impairment

Adjustments to the starting dose of afatinib are not considered necessary in patients with mild or moderate renal impairment. The afatinib starting dose of 30 mg orally once daily is recommended for patients with severe renal impairment. Dosing recommendations for patients with estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m² or on dialysis cannot be provided as afatinib has not been studied in these patient populations.

No dose adjustment of brigatinib is recommended for patients with mild and moderate renal impairment (creatinine clearance [CrCl], 30 to 89 mL/min). In patients with severe renal impairment (CrCl, 15 to 29 mL/min), the daily dose of brigatinib should be reduced by approximately 50%.

The starting doses of crizotinib and alectinib do not need to be adjusted for patients with mild (CrCl, 60 to 89 mL/min) or moderate (CrCl, 30 to 59 mL/min) renal impairment. The dose of crizotinib should be decreased to 250 mg taken orally once daily in patients with severe renal impairment (CrCl < 30 mL/min) not undergoing dialysis. The safety of alectinib in patients with severe renal impairment (CrCl < 30 mL/min) or end stage renal disease (ESRD) has not been studied.

No dose adjustment of dacomitinib is recommended in patients with mild or moderate renal impairment (CrCl, 30 to 89 mL/min). The recommended dose of dacomitinib in patients with severe renal impairment (CrCl < 30 mL/min) is not established.

No clinical studies with erlotinib or gefitinib have been conducted in patients with compromised renal function.

No dose adjustment of lorlatinib is recommended for patients with mild to moderate renal impairment (CrCl, 30 to 89 mL/min); however, the recommended dose has not been established for patients with severe renal impairment.

No dose adjustment is recommended for osimertinib in patients with an estimated CrCl ≥ 15 mL/min. There is no recommended dose of osimertinib for patients with ESRD (CrCl < 15 mL/min).

No dose adjustment of topotecan (Hycamtin) is needed for patients with CrCl ≥ 50 mL/min; however, the dose should be reduced in patients with a CrCl ≤ 49 mL/min.

No dose adjustment of entrectinib is recommended for patients with mild to moderate renal impairment (CrCl, 30 to 89 mL/min). Entrectinib has not been studied in patients with severe renal impairment.

Hepatic Impairment

Dosing adjustments of afatinib are not considered necessary in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. Afatinib has not been studied in patients with severe (Child Pugh C) hepatic impairment. Closely monitor patients with severe hepatic impairment and adjust afatinib dose if not tolerated.

Dose adjustment of brigatinib or ceritinib is not recommended for patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. In patients with severe hepatic impairment (Child Pugh C), the daily dose of brigatinib should be reduced by 40%, and the daily dose of ceritinib should be reduced by one-third, rounded to the nearest multiple of the 150 mg dosage strength.

Dosing recommendations of crizotinib for patients with pre-existing hepatic impairment are dependent on severity. Patients with moderate impairment (any AST and total bilirubin > 1.5 times the ULN and ≤ 3 times ULN) are recommended to take 200 mg orally twice daily, while patients with severe impairment (any AST and total bilirubin > 3 times ULN) are recommended to take 250 mg daily.

No dose adjustment of dacomitinib is recommended in patients with mild or moderate hepatic impairment. The recommended dose of dacomitinib in patients with severe hepatic impairment is not established.

Patients with hepatic impairment (total bilirubin greater than the ULN or Child-Pugh A, B, and C) should be closely monitored during therapy with erlotinib. Treatment with erlotinib should be used with extra caution in patients with total bilirubin greater than 3 times ULN.

Systemic exposure of gefitinib has been shown to be increased by 40% in mild hepatic impairment (Child Pugh A), 263% in moderate impairment (Child Pugh B), and 166% in severe hepatic impairment (Child Pugh C). Monitor adverse reactions when gefitinib is administered to patients with moderate and severe hepatic impairment.

No dose adjustment of osimertinib (Tagrisso) is recommended in patients with mild or moderate hepatic impairment (Child Pugh A or B or total bilirubin ≤ ULN and AST > ULN or total bilirubin 1 to 3 times ULN and any AST). There is no recommended dose for osimertinib in patients with severe hepatic impairment (total bilirubin between 3 to 10 times ULN and any AST).

No dose adjustment is recommended for alectinib in patients with mild or moderate (Child Pugh A or B) hepatic impairment. The exposure of alectinib in patients with severe hepatic impairment (Child Pugh C) may be increased, and a dose reduction of 450 mg twice daily is recommended.

No dose adjustment of lorlatinib is recommended for patients with mild hepatic impairment (total bilirubin ≤ ULN with AST > ULN or total bilirubin > 1 to 1.5 ULN with any AST); however, the recommended dose has not been established for patients with moderate to severe hepatic impairment.

No dose adjustment of entrectinib (Rozlytrek) is recommended in patients with mild hepatic impairment (total bilirubin ≤ 1.5 times ULN). Entrectinib has not been studied in patients with moderate or severe hepatic impairment.

DOSAGES^{106,107,108,109,110,111,112,113,114,115,116,117}

Drug	Dose	Administration	Available Strengths
ALK Tyrosine Kinase Inhibitors			
alectinib (Alecensa)	600 mg twice daily	Take with food; do not open or dissolve capsules	150 mg capsules
brigatinib (Alunbrig)	90 mg once daily for 7 days; may increase to 180 mg once daily as tolerated	Take with or without food; swallow tablets whole If therapy is interrupted for ≥ 14 days for reasons other than adverse reactions, resume treatment at 90 mg once daily for 7 days before increasing to the previously tolerated dose	30 mg, 90 mg, 180 mg tablets 90 mg/180 mg tablet pack
ceritinib (Zykadia)	450 mg once daily	Take once daily with food	150 mg capsules 150 mg tablets
crizotinib (Xalkori)	250 mg twice daily	Take with or without food; swallow capsules whole	200 mg, 250 mg capsules
entrectinib (Rozlytrek)	NSCLC: 600 mg once daily NTRK gene fusion-positive solid tumors <ul style="list-style-type: none"> ▪ Adults: 600 mg once daily ▪ Pediatric patients ≥ 12 years old <ul style="list-style-type: none"> – BSA > 1.5 m²: 600 mg once daily – BSA 1.11 to 1.5 m²: 500 mg once daily – BSA 0.91 to 1.1 m²: 400 mg once daily 	Take with or without food; swallow capsules whole	100 mg, 200 mg capsules
lorlatinib (Lorbrena)	100 mg once daily	Take with or without food; swallow tablets whole and do not ingest if tablets are broken, cracked, or otherwise not intact	25 mg, 100 mg tablets
afatinib (Gilotrif)	40 mg once daily	Take at least 1 hour before or 2 hours after a meal	20 mg, 30 mg, 40 mg tablets
dacomitinib (Vizimpro)	45 mg orally once daily	Take with or without food	15 mg, 30 mg, 45 mg tablets

NSCLC = non-small cell lung cancer; Consult package insert for each individual medication for additional detailed information related to dosing and dose modifications.

Information on FDA-approved tests for the detection of EGFR and ALK mutations in NSCLC is available at: <http://www.fda.gov/CompanionDiagnostics>.

Dosages (continued)

Drug	Dose	Administration	Available Strengths
EGFR Tyrosine Kinase Inhibitors			
erlotinib (Tarceva)	NSCLC: 150 mg daily Pancreatic cancer: 100 mg daily in combination with IV gemcitabine	Take on empty stomach 1 hour before or 2 hours after a meal	25 mg, 100 mg, 150 mg tablets
gefitinib (Iressa)	250 mg once daily	Take with or without food; For patients who have difficulty swallowing solids, tablets may be immersed in 4 to 8 ounces of water and stirred for approximately 15 minutes; The patient should drink the mixture immediately or it may be administered through a naso-gastric (NG) tube immediately; The container should be rinsed with 4 to 8 ounces of water and readministered	250 mg tablets
osimertinib (Tagrisso)	80 mg once daily	Take with or without food; For patients who have difficulty swallowing solids, the tablet may be dispersed in approximately 60 mL of non-carbonated water only; stir until tablet is completely dispersed; rinse the container with 4 to 8 ounces of water and immediately drink Do not crush, heat, or ultrasonicate during preparation; For administration through a nasogastric tube (NG), disperse tablet in 15 mL of non-carbonated water and then use an additional 15 mL of water to transfer any residues to the syringe; the resulting 30 mL should be administered per NG tube with appropriate water flushes (approximately 30 mL)	40 mg, 80 mg tablets
Non-targeted Agents			
topotecan (Hycamtin)	2.3 mg/m ² /day for 5 consecutive days (cycle repeated every 21 days); round dose to nearest 0.25 mg	Take with or without food, swallow capsules whole, do not chew, crush, or divide the capsules	0.25 mg, 1 mg capsules

NSCLC = non-small cell lung cancer; Consult package insert for each individual medication for additional detailed information related to dosing and dose modifications.

Information on FDA-approved tests for the detection of EGFR and ALK mutations in NSCLC is available at: <http://www.fda.gov/CompanionDiagnostics>.

CLINICAL TRIALS

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials for FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Due to a paucity of data in the literature, clinical trials that are open-label have been included in this therapeutic class review. In addition, where published phase 3 data for the FDA-approved indications is lacking, phase 1 or phase 2 studies cited in the package insert are included in this therapeutic class review.

ALK-mutated NSCLC

alectinib (Alecensa) – ALK-positive NSCLC after disease progression on crizotinib (Xalkori)

A multicenter, open label, phase 2 study conducted at 27 centers in North America enrolled 87 patients who had advanced ALK-positive NSCLC and who had progressed on previous crizotinib.¹¹⁸ All patients received 600 mg alectinib orally twice daily. The primary outcome measure was objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by an Independent Review Committee (IRC). At the time of analysis (median follow-up of 4.8 months), ORR occurred in 48% (95% confidence interval [CI], 36 to 60) of patients. Adverse events included constipation (36%), fatigue (33%), myalgia (24%), and peripheral edema (23%) and were predominantly grade 2 or lower.

A multicenter, open-label trial enrolled 138 patients with ALK-positive NSCLC who had progressed on previous crizotinib therapy; patients were allowed to have received prior platinum-based chemotherapy as well or be chemotherapy-naïve.¹¹⁹ The primary outcome was ORR as assessed by an independent review. All patients were treated with alectinib 600 mg twice daily and continued therapy until disease progression, unacceptable toxicity, or withdrawal of consent. The majority of patients (61%) had CNS metastases at the time of study enrollment. The median time from last dose of crizotinib to first dose of alectinib was 15 days (range, 7 to 676 days). At 47 weeks, 50% of patients had met the endpoint of an objective response. Among the patients who experienced an objective response, the median duration of response was 11.2 months. Of the patients who had baseline CNS metastases, the overall CNS disease control rate was 83% and 27% of patients achieved a CNS complete response (CR). The duration of CNS response in this group was 10.3 months (95% CI, 7.6 to 11.2 months). The most commonly reported adverse events were constipation (33%), fatigue (36%), and peripheral edema (25%).

alectinib (Alecensa) versus crizotinib (Xalkori) – ALK-positive advanced NSCLC – first-line

ALEX: A randomized, multicenter, open-label phase 3 trial analyzed the efficacy and safety of alectinib versus crizotinib in previously untreated patients with ALK-positive NSCLC.¹²⁰ The trial included patients with asymptomatic CNS disease at baseline. Patients were randomized 1:1 to receive either alectinib 600 mg twice daily (n=152) or crizotinib 250 mg twice daily (n=151). Treatment groups had a median follow up of 18.6 months and 17.9 months, respectively. The primary endpoint (investigator-assessed progression free survival [PFS]) was greater with alectinib treated participants than with those treated with crizotinib (12-month event-free survival rate, 68.4% [95% CI, 61 to 75.9] with alectinib versus 48.7% [95% CI, 40.4 to 56.9] with crizotinib; hazard ratio [HR] for disease progression or death, 0.47 [95% CI, 0.34 to 0.65; p<0.001]). A secondary endpoint was time to CNS progression. The authors suggest that alectinib may improve management of CNS disease due to CNS progression occurring in only 12% of patients taking alectinib and in 45% of patients taking crizotinib (cause-specific HR, 0.16; 95% CI, 0.1 to 0.28; p<0.001). Alectinib also displayed lower toxicity than crizotinib. Fewer patients discontinued the medication, experienced grade 3 to 5 adverse effects, or needed to reduce their dose due to adverse effects.

brigatinib (Alunbrig) – ALK-positive NSCLC after disease progression on crizotinib (Xalkori)

ALTA:^{121,122} A phase 2, open-label, 2-arm, multicenter trial evaluated brigatinib in patients (n=222) with localized advanced or metastatic ALK-positive NSCLC (as determined by an FDA-approved test) who had progressed on crizotinib therapy. The study excluded patients with interstitial lung disease or drug-related pneumonitis or who received crizotinib within 3 days of the first study dose. The median age was 54 years, 95% of patient were not current smokers, 98% had stage IV disease, 69% of patients had metastases to the brain, and 64% had prior response to crizotinib. The primary efficacy endpoint was ORR as measured by RECIST v1.1. Patients were randomized 1:1 to brigatinib 90 mg once daily (Group A) or brigatinib 90 mg daily for 7 days, then 180 mg daily thereafter (Group B). Treatment continued until disease progression requiring alternative systemic therapy, intolerable toxicity, or consent withdrawal. Patients were stratified by presence or absence of brain metastases and if the patient had a prior response to crizotinib (complete/partial response versus other response or unevaluable). Patients were assessed every 8 weeks for fifteen 28-day cycles, and then every 12 weeks until disease progression. Median follow-up was 8 months. Patients were assessed by the investigators and by an IRC. The investigators reported a confirmed ORR of 45% (97.5% CI, 34 to 56) in Group A and 54% (95% CI, 43 to 65) in Group B. CR rates were 0.9% and 3.6% in Groups A and B, respectively, and partial response (PR) rates were 44% and 50% in Groups A and B, respectively. The investigator findings of median duration of response (DOR) for each group was 13.8 months (95% CI, 5.6 to 13.8) and 11.1 months (95% CI, 9.2 to 13.8) in Groups A and B, respectively, and PFS was 9.2 months (95% CI, 7.4 to 15.6) and 12.9 months in Groups A and B (95% CI, 11.1 to not reached), respectively. The IRC assessment reported similar findings: ORR of 48% and 53%, respectively; CR rates of 3.6% and 4.5% respectively; PR rates of 45% and 48%, respectively; median DOR of 13.8 months for both groups; and PFS of 9.2 and 15.6 months, respectively. The IRC assessment also confirmed ORR and PFS in patients with active brain metastases. At total of 217 patients had an IRC-evaluated brain magnetic resonance image (MRI) at baseline, of which 153 had baseline brain metastases and 44 had measurable lesions. The ORR in patients with measurable lesions (n=44) was 42% (95% CI, 23 to 63) in Group A and 67% (95% CI, 41 to 87) in Group B. The most common adverse reaction of any severity were gastrointestinal in nature, followed by headache and cough. Grade 3 adverse effects included hypertension and CPK elevation.

ceritinib (Zykadia) versus single agent chemotherapy – ALK-positive NSCLC-progression on or intolerance to prior therapy including crizotinib (Xalkori)

ASCEND-5: A randomized, multicenter, controlled, open-label, phase 3 trial examined the efficacy and safety of ceritinib in patients with disease progression after 1 or 2 lines of therapy which included both a platinum-based doublet chemotherapy and crizotinib.¹²³ Eligible patients (n=231) were 18 years of age or older with stage 3B or 4 ALK-positive NSCLC and had a minimum life expectancy of 12 weeks. Randomization occurred at a 1:1 ratio to the following treatment arms: ceritinib 750 mg per day (n=115) or single-agent chemotherapy (n=116). Investigators were able to select chemotherapy treatment with intravenous pemetrexed (500 mg/m²; n=40) or docetaxel (75 mg/m²; n=63). Intracranial and whole body tumor response was observed in patients every 6 weeks until month 18. The ceritinib group demonstrated significant improvement in median PFS, when compared to the chemotherapy treatment arm (ceritinib: 5.4 months [95% CI, 4.1 to 6.9] versus chemotherapy: 1.6 months [95% CI, 1.4 to 2.8]; HR, 0.49 [95% CI, 0.36 to 0.67]; p<0.0001). The median follow-up time was 16.5 months. Frequent grade 3 to 4 adverse events experienced in the ceritinib group included increased alanine aminotransferase (ALT) concentration (21%), increased gamma-glutamyltransferase (GGT) concentration (21%) and increased AST concentration (14%). Discontinuation due to an adverse event occurred in 13% of patient taking ceritinib and 7% of patient taking chemotherapy.

ceritinib (Zykadia) versus standard chemotherapy in ALK-rearranged NSCLC – first-line

ASCEND-4: A randomized, international, open-label, phase 3 trial randomized 376 patients with stage 3B/4 ALK-rearranged NSCLC who had received no prior therapy for their metastatic disease to receive either oral ceritinib 750 mg/day (n=189) or platinum-based doublet chemotherapy (n=187). The primary endpoint of BIRC-assessed PFS was 16.6 months (95% CI, 12.6 to 27.2) in the ceritinib group and 8.1 months (95% CI, 5.8 to 11.1) in the chemotherapy group (HR, 0.55; 95% CI, 0.42 to 0.73; p<0.00001). The most common adverse events in the ceritinib-treated group were diarrhea (85%), nausea (69%), vomiting (66%), and an increase in ALT (60%), while nausea (55%), vomiting (36%), and anemia (35%) occurred most commonly in the group who received chemotherapy.

ceritinib (Zykadia) – dosing regimen

ASCEND-8: A multicenter, randomized, open-label phase 1 trial examined the steady-state pharmacokinetics and safety of 3 different dosing schedules of ceritinib.¹²⁴ A total of 137 patients with ALK-rearranged NSCLC previously treated with crizotinib were randomized to receive either ceritinib 450 mg or ceritinib 600 mg, taken with a low-fat meal versus ceritinib 750 mg taken while fasting. Pharmacokinetic analysis revealed that at steady-state, the maximum concentrations and area under the curve for plasma concentration from hour zero to 24 were comparable for the ceritinib 450 mg with food dose and the ceritinib 750 mg fasting dose. The ceritinib 600 mg with food dosing schedule had an approximately 25% higher exposure. Compared to the ceritinib 750 mg fasting dose, the ceritinib 450 mg with food dose was associated with a lower proportion of patients with GI toxicities, mostly grade 1 diarrhea, nausea, and vomiting. The authors concluded that ceritinib 450 mg taken with food had a similar exposure and more favorable GI safety profile compared to ceritinib 750 mg taken in fasting state.

crizotinib (Xalkori) versus standard chemotherapy – second-line (ALK-positive)

A phase 3, open-label trial comparing crizotinib with chemotherapy in 347 patients with locally advanced or metastatic ALK-positive lung cancer was conducted. All patients had progressive disease after 1 prior platinum-based regimen.¹²⁵ Patients were randomly assigned to receive oral treatment with crizotinib (250 mg) twice daily or intravenous chemotherapy with either pemetrexed (500 mg per

square meter of body-surface area) or docetaxel (75 mg per square meter) every 3 weeks. Median PFS (the primary outcome measure) was 7.7 months in the crizotinib group and 3 months in the chemotherapy group (HR, 0.49; 95% CI, 0.37 to 0.64; $p < 0.001$). The incidence of serious adverse events was similar in the crizotinib and chemotherapy groups, although significantly more adverse events of any cause were observed in the crizotinib group. Despite this finding, patients reported greater reductions in symptoms of lung cancer and greater improvement in global quality of life with crizotinib than with chemotherapy.

crizotinib (Xalkori) versus chemotherapy – first-line (ALK-positive)

PROFILE 1014: Patients with ALK-positive nonsquamous NSCLC ($n=343$) who had received no previous systemic treatment for their advanced disease were evaluated in a multicenter, randomized, open-label, phase 3 trial.¹²⁶ Patients were randomized to receive either crizotinib 250 mg twice daily or standard intravenous chemotherapy (pemetrexed plus a platinum agent) every 3 weeks for up to 6 cycles. The primary endpoint was PFS as assessed by independent radiologic review. Secondary endpoints included ORR, overall survival (OS), safety, and patient-reported outcomes. Patients in the chemotherapy group who had disease progression were allowed to cross over to crizotinib treatment. With a median duration of follow-up of 17.4 months in the crizotinib arm and 16.7 months in the chemotherapy arm, the median PFS was 10.9 months compared to 7 months for crizotinib and chemotherapy arms, respectively (HR, 0.45; 95% CI, 0.35 to 0.6; $p < 0.001$). The ORR was significantly higher with crizotinib than with chemotherapy (74% versus 45%; $p < 0.001$). The median DOR was 11.3 months with crizotinib and 5.3 months with chemotherapy. There was no significant difference in OS between patients in the crizotinib group and those in the chemotherapy group at the time of the PFS analysis. The probability of 1-year survival was 84% (95% CI, 77 to 89) in the crizotinib group and 79% (95% CI, 71 to 84) in the chemotherapy group. In the final OS results, there continued to be no difference in OS (HR, 0.76; 95% CI, 0.548 to 1.053; $p=0.978$). However, patients were allowed to crossover to crizotinib from the chemotherapy arm after disease progression. After a crossover adjustment was included, there was an improvement in OS that favored crizotinib (HR=0.346, 95% bootstrap CI 0.081 to 0.718).¹²⁷ Patients in the crizotinib group had a higher incidence of vision disorder (71%), diarrhea (61%), and edema (49%) while patients in the chemotherapy group had a higher incidence of fatigue (38%), anemia (32%), and neutropenia (30%). Two patients in the crizotinib group developed interstitial lung disease, resulting in permanent discontinuation of crizotinib treatment. Adverse events from any cause that were associated with permanent discontinuation of treatment occurred in 12% of crizotinib-treated patients and 14% of patients who received chemotherapy. There was a significantly greater overall improvement from baseline in global quality of life among patients who received crizotinib compared to those who received chemotherapy ($p < 0.001$). There was a significantly greater overall reduction from baseline with crizotinib than with chemotherapy in the symptoms of pain, dyspnea, insomnia, cough, and chest pain. Patients treated with crizotinib had a significantly greater delay in the worsening of lung cancer symptoms (cough, dyspnea, or pain in the chest).

crizotinib (Xalkori) – ROS1-positive

Fifty patients from a phase 1 expansion cohort trial of crizotinib were determined to have histologically confirmed metastatic NSCLC with a ROS1 rearrangement.¹²⁸ Patients were treated with crizotinib 250 mg twice daily. The majority of patients were female (56%) and never smokers (78%). Asian patients comprised 42% of the study population while Caucasian patients accounted for 54% of the study population. The majority of patients (80%) had received prior platinum-based chemotherapy for metastatic disease while 14% had received no prior therapy for metastatic disease. The efficacy

outcome measures were ORR and DOR. The ORR was 72% (95% CI, 58 to 84). The median DOR was 17.6 months (95% CI, 14.5 months to not reached). Median PFS was 19.2 months (95% CI, 14.4 months to not reached). The most common treatment-related adverse events were visual impairment (82%), diarrhea (44%), nausea (40%), peripheral edema (40%), constipation (34%), vomiting (34%), elevated aspartate aminotransferase level (22%), fatigue (20%), dysgeusia (18%), and dizziness (16%). Of all treatment-related adverse events that were reported, 94% were grade 1 or 2 events.

entrectinib (Rozlytrek) – ROS1-positive

A pooled subgroup of patients with ROS1-positive metastatic NSCLC were enrolled in 1 of 3 multicenter, single-arm, open-label, clinical trials (ALKA, STARTRK-1, STARTRK-2).¹²⁹ The included patients had histologically confirmed, recurrent or metastatic, ROS1-positive NSCLC, ECOG performance status ≤ 2 , measurable disease per RECIST v1.1, ≥ 12 months of follow-up from first post-treatment tumor assessment, and no prior therapy with a ROS1 inhibitor (n=51). ROS1 gene fusion in tumor specimens was determined using either in situ hybridization (FISH) or next-generation sequencing (NGS) test. All patients were assessed for CNS lesions at baseline. While patients received entrectinib at various doses and schedules, 90% of patients received entrectinib 600 mg orally once daily. Major efficacy endpoints were ORR and DOR according to RECIST v1.1. The ORR was 78% (95% CI, 65 to 89) with 6% achieving a CR and 73% with PR. The range for duration of response was 1.8 to > 36.8 months with 70% of patients achieving DOR ≥ 9 months, 55% achieving DOR ≥ 12 months, and 30% achieving DOR ≥ 18 months. At baseline, 7 patients had measurable CNS metastases and had not received radiation therapy to the brain within 2 months of the trial. Responses in intracranial lesions were observed in 5 of these 7 patients.

lorlatinib (Lorbrena) – ALK-positive metastatic NSCLC progression previously treated with ALK kinase inhibitor

An open label, non-randomized, multi-cohort, multicenter, dose-ranging, and activity-estimating study examined patients with ALK-positive metastatic NSCLC with ≥ 1 measurable lesion who were previously treated with one or more ALK kinase inhibitors (n=215).¹³⁰ Asymptomatic CNS metastases patients, including patients with stable or decreasing steroid use within 2 weeks before the beginning of the study, were eligible to participate. Patients received 100 mg lorlatinib once daily. The study excluded patients with severe, acute, or chronic psychiatric conditions. Efficacy was determined based on a total of 215 patients belonging to 5 subgroups. These subgroups included patients with prior crizotinib and no prior chemotherapy (n=29), prior crizotinib and 1 or 2 lines of prior chemotherapy (n=35), prior ALK inhibitor (not crizotinib) with or without prior chemotherapy (n=28), 2 prior ALK inhibitors with or without prior chemotherapy (n=75), and 3 prior ALK inhibitors with or without prior chemotherapy (n=48). Brain metastases were present in 69% of the patients. Efficacy endpoints included ORR, intracranial ORR, duration of response, and intracranial duration of response. The ORR was 48% (95% CI, 42 to 55) with 4% achieving a CR and 44% having a PR. The median duration of response was 12.5 months (95% CI, 8.4 to 23.7). Intracranial response in patients with measurable brain lesions was 60% (95% CI, 49 to 70) with 21% CR and 38% with PR. The median duration of intracranial response was 19.5 months (95% CI, 12.4 to not reached).

EGFR-mutated NSCLC

afatinib (Gilotrif) versus chemotherapy (cisplatin/pemetrexed)

LUX-Lung 3 was a randomized, open-label, phase 3 trial comparing the efficacy and safety of afatinib as first-line treatment versus chemotherapy in 345 previously untreated patients with advanced (stage

IIIB/IV) NSCLC and proven EGFR mutations.¹³¹ Patients were randomized to afatinib 40 mg orally once daily (n=230) or up to 6 cycles of cisplatin plus pemetrexed (n=115) at standard doses every 21 days. Patients were stratified according to type of EGFR mutation (exon 19 deletion, L858R, or other) and race (Asian versus non-Asian). The majority of patients had a tumor sample with an EGFR mutation of exon 19 deletion (49%) or L858R substitution (40%), and 11% had other mutations. Seventy-two percent of study participants were of East Asian descent, 68% were never-smokers, and 65% were women. The primary efficacy outcome was PFS as assessed by an IRC. Secondary endpoints included ORR and OS. Median PFS was significantly increased for afatinib versus chemotherapy (11.1 months versus 6.9 months, respectively (HR, 0.58; 95% CI, 0.43 to 0.78; p=0.001). Median PFS among those with exon 19 deletions and L858R EGFR substitution mutations (n=308) was 13.6 months for afatinib versus 6.9 months for chemotherapy (HR, 0.47; 95% CI, 0.34 to 0.65; p=0.001). The overall response rate as assessed by independent reviewers was significantly increased with afatinib versus chemotherapy (56% versus 23%; p=0.001). Patient-reported outcomes (better control of cough, dyspnea, and pain) favored afatinib. In a subsequent follow-up after a median of 41 months, the subgroup of patients who had exon 19 deletions had a median OS of 33.3 months (26.8 to 41.5) in the afatinib group versus 21.1 months (16.3 to 30.7) in the chemotherapy group (HR, 0.54; 95% CI, 0.44 to 0.94; p=0.023).¹³² In contrast, there was no difference in OS for the entire study population or for the subgroup of patients who had L858R substitutions. A prespecified subgroup analysis examined patients in this trial who had asymptomatic brain metastases at baseline (n=81).¹³³ PFS was significantly improved with afatinib (8.2 months) versus chemotherapy (5.4 months) in this subgroup of patients as well (HR, 0.5; p=0.0297).

The most common treatment-related adverse events were diarrhea (96%), rash/acne (90%), and stomatitis (72%) for afatinib and nausea (66%), fatigue (47%), and decreased appetite (59%) for patients treated on the chemotherapy arm.¹³⁴ Grade 3 or higher treatment-related adverse events occurred in 49% of patients receiving afatinib and 48% of patients receiving chemotherapy. Overall, 8% of patients treated with afatinib discontinued therapy due to adverse reactions while 12% of chemotherapy patients discontinued treatment due to adverse effects.

afatinib (Gilotrif) versus gefitinib (Iressa)

LUX-Lung 7 was a phase 2B, randomized, open-label trial comparing afatinib to gefitinib in treatment naïve patients with EGFR mutation-positive advanced NSCLC. Patients were randomized 1:1 to either afatinib 40 mg orally once daily (n=146) or gefitinib 250 mg orally once daily (n=151). Co-primary endpoints were PFS by independent central review, time to treatment failure (TTF) and OS. At a median follow up of 27.3 months, PFS was 11 months (95% CI 10.6-12.9) for afatinib and 10.9 months (95% CI 9.1-11.5) for gefitinib HR=0.73 (95% CI 0.57-0.95), p=0.017. Median TTF was 13.7 months (95% CI 11.9-15 months) with afatinib compared to 11.5 months (95% CI 10.1-13.1) for gefitinib, HR 0.73 (95% CI 0.58-0.92, p=0.0073) After a median follow up of 42.6 months, median OS was 27.9 months in the afatinib arm and 24.5 months in the gefitinib arm (HR=0.86, 95% CI 0.66-1.12, p=0.2580).^{135,136}

Phase 3 trials, LUX-Lung 3 and LUX-Lung 6 demonstrated that afatinib significantly improved progression-free survival (PFS) and objective response compared to platinum-doublet chemotherapy.¹³⁷ A phase 2b trial, LUX-Lung 7, further illustrated that afatinib significantly improved PFS and time to treatment failure and also showed objective response compared to gefitinib. *Post-hoc* analyses of efficacy safety and patient-reported outcomes (PRO) in long term responders (LTR) were reported for LUX-Lung 3, 6 and 7 clinical trials. Patients who had been treated with afatinib for at least 3 years were considered LTRs. In the LUX-Lung 3, LUX-Lung 6 and LUX-Lung 7 trials, 10%, 10% and 12%

of afatinib-treated patients respectively were LTRs. Long term treatment with afatinib was independent of tolerability-guided dose adjustment and had no negative impact on safety or PROs.

dacomitinib (Vizimpro) versus gefitinib (Iressa) first-line treatment

The ARCHER 1050 trial, a randomized, multicenter, multinational, open-label trial, enrolled 452 adults with newly diagnosed advanced NSCLC and 1 *EGFR* mutation (exon 19 deletion or Leu858Arg).¹³⁸ Patients were randomized (1:1) to oral dacomitinib 45 mg/day (in 28-day cycles) or oral gefitinib 250 mg/day (in 28-day cycles) until disease progression or another discontinuation criterion was met. The primary endpoint of PFS was assessed by an independent review committee. After a median duration of 22.1 months, the median PFS was 14.7 months (95% CI, 11.1 to 16.6) with dacomitinib and 9.2 months (95% CI, 9.1 to 11) with gefitinib (HR, 0.59; 95% CI, 0.47 to 0.74; $p < 0.0001$). The most common grade 3/4 adverse events were dermatitis acneiform (14% with dacomitinib and 0% with gefitinib), diarrhea (8% versus 1%, respectively), and elevated ALT (1% versus 8%, respectively). Two treatment-related deaths occurred in the dacomitinib group and 1 occurred in the gefitinib group. The final reported OS data indicated the OS was 34.1 months with dacomitinib versus 26.8 months with gefitinib (HR=0.76, 95% CI 0.582 to 0.993; $p=0.44$).¹³⁹

erlotinib (Tarceva) versus standard first-line platinum-based doublet chemotherapy

The open-label EURTAC trial randomized 174 patients with metastatic NSCLC and *EGFR* mutations (exon 19 deletion or L858R mutation in exon 21) with no prior history of chemotherapy for metastatic disease to either standard platinum based doublet therapy (3 different combination regimens) given every 3 weeks or oral erlotinib 150 mg daily.¹⁴⁰ Patients were stratified by *EGFR* mutation and performance status. The primary endpoint was PFS. At the time of preplanned interim analysis, median PFS was 9.7 months in the erlotinib group compared with 5.2 months in the standard chemotherapy group (HR, 0.37; 95% CI, 0.25 to 0.54; $p < 0.0001$). Overall survival was not significantly different between the groups. The most common grade 3 or 4 toxicity with erlotinib was rash, and was neutropenia in the standard chemotherapy arm. Five patients on erlotinib had treatment-related severe adverse events compared with 16 patients on standard chemotherapy.

erlotinib (Tarceva) versus placebo – maintenance therapy

SATURN: A placebo-controlled, multicenter, phase 3 study assessed the use of erlotinib as maintenance therapy in patients with non-progressive advanced NSCLC following first-line platinum-doublet chemotherapy.¹⁴¹ At the end of the run-in phase (4 cycles of platinum-based chemotherapy), 889 patients who did not have progressive disease were entered into the main study, and were randomly assigned to erlotinib 150 mg/day or placebo until progression or unacceptable toxicity was observed. Primary endpoints were PFS in all analyzable patients regardless of epidermal growth factor receptor (*EGFR*) status, and PFS in patients whose tumors had *EGFR* protein over expression. After a median follow-up of 11.4 months for the erlotinib group and 11.5 months for the placebo group, median PFS was significantly longer with erlotinib compared with placebo (12.3 weeks for erlotinib and 11.1 weeks placebo; HR, 0.71; 95% CI, 0.62 to 0.82; $p < 0.0001$). PFS was also significantly longer in patients with *EGFR*-positive immunohistochemistry who were treated with erlotinib ($n=307$) compared with *EGFR*-positive patients on placebo ($n=311$; median PFS 12.3 weeks for erlotinib group and 11.1 weeks for placebo; HR, 0.69; 95% CI, 0.58 to 0.82; $p < 0.0001$). The most common grade 3 or higher adverse events included rash (9% for erlotinib and none for placebo), as well as diarrhea (2% versus none for erlotinib and placebo, respectively). Serious adverse events were reported in 11% and 8% of patients on erlotinib and placebo, respectively. Pneumonia was the most common serious adverse event (2% for erlotinib less than 1% for placebo).

erlotinib (Tarceva) versus placebo – previously treated with chemotherapy

A randomized, double-blind, placebo-controlled trial enrolled 371 patients with advanced NSCLC who had previously received ≥ 1 chemotherapy regimen(s).¹⁴² Platinum-based chemotherapy had been received previously by 93% of enrolled patients and 49% of enrolled patients had received 2 prior chemotherapy regimens. The PFS and OS were 2.2 months and 6.7 months for erlotinib compared to 1.8 months and 4.7 months for placebo (for PFS: HR=0.61; $p<0.001$) (for OS: HR=0.7; $p<0.001$). The discontinuation rate for toxicity associated with erlotinib was 5%, and rash, anorexia, and diarrhea being the most common toxicities.

gefitinib (Iressa) – first-line therapy

A multicenter, single-arm, open-label clinical trial involving 106 patients with metastatic NSCLC and EGFR exon 19 deletions (65%) or L858R (31%) substitution mutations was conducted.¹⁴³ Two patients each had tumors harboring L861Q or G719X substitutions. Patients were required to have no T790M or S768I mutations or exon 20 insertions in the tumor specimen that was prospectively evaluated prior to trial enrollment. None of the patients had received prior systemic treatment for their metastatic NSCLC. Patients received gefitinib 250 mg once daily until disease progression or unacceptable toxicity. The major efficacy outcome was ORR according to RECIST v.1.1 as evaluated by both the investigators and a blinded independent central review (BICR). Duration of response was a secondary outcome measure. The median duration of treatment was 8 months. The majority of study participants were female (71%) never smokers (64%). All patients in the study were Caucasian. The ORR was 50% (95% CI, 41 to 59) and the median duration of response was 6 months (95% CI, 5.6 to 11.1) according to the BICR assessment. The response rates were similar in patients who had EGFR exon 19 deletions and exon 21 L858R substitution mutations.

gefitinib (Iressa) versus carboplatin/paclitaxel – first-line therapy

Patients ($n=1,217$) with adenocarcinoma histology were randomized 1:1 to either gefitinib 250 mg once daily or carboplatin/paclitaxel for up to 6 cycles. A subset analysis of this population involved 186 patients (15%) who were determined to be EGFR positive.¹⁴⁴ In this subset, 83% of patients were female, 100% were Asian, and 96% were never smokers. The PFS was 10.9 months for the gefitinib group compared to 7.4 months in the carboplatin/paclitaxel group as assessed by the BICR (HR, 0.54; 95% CI, 0.38 to 0.79). The ORR was 67% for the gefitinib group compared to 41% for the carboplatin/paclitaxel group. The median duration of response was 9.6 months for the gefitinib group and 5.5 months for the carboplatin/paclitaxel group. In the reported final OS results of this trial, there was no significant difference in OS between the 2 treatments for EGFR mutation-positive patients (HR, 1; 95% CI, 0.76 to 1.33, $p=0.99$).¹⁴⁵ However, a high proportion (64.3%) of the patients randomly assigned to carboplatin/paclitaxel subsequently received an EGFR inhibitor, making interpretation of the OS data difficult.

osimertinib (Tagrisso) – second-line for EGFR T790M mutation-positive NSCLC

An international, randomized, open-label, phase 3 trial involving 419 patients with metastatic NSCLC and confirmed T790M EGFR mutations was conducted.¹⁴⁶ The trial compared oral osimertinib 80 mg daily to an intravenous regimen of pemetrexed plus either carboplatin or cisplatin every 3 weeks for up to 6 cycles and then maintenance pemetrexed, if appropriate. All patients had experienced progressive disease after first-line EGFR-TKI therapy. Treatment continued until disease progression or unacceptable toxicity. The primary endpoint was investigator-assessed PFS as measured by RECIST v1.1. A subsequent protocol amendment allowed patients with progressive disease on the pemetrexed-platinum arm to cross over to osimertinib. At the time of data analysis, the median follow-up was 8.3 months and 50% of

patients in the osimertinib treatment group had experienced disease progression compared to 79% of pemetrexed-platinum treatment group. The median duration of PFS was significantly longer in the osimertinib group compared to the pemetrexed-platinum group (10.1 months versus 4.4 months; HR, 0.3; 95% CI, 0.23 to 0.41; $p < 0.001$). PFS favored osimertinib in all subgroups analyzed including Asian versus non-Asian patients and those with CNS metastases. Adverse events occurred in 98% of osimertinib-treated patients and 99% of patients who received pemetrexed-platinum therapy. The incidence of grade 3 or higher adverse effects was lower in the osimertinib group (23%) compared to the pemetrexed-platinum group (47%). The most commonly reported adverse events in the osimertinib-treated patients included diarrhea (41%), rash (34%), dry skin (23%), and paronychia (22%), while the most commonly reported adverse events in the pemetrexed-platinum group were nausea (49%), decreased appetite (36%), constipation (35%), and anemia (30%).

osimertinib (Tagrisso) – first-line

FLAURA was a phase 3, randomized, double-blind trial that studied 556 patients with previously untreated, EGFR mutation-positive (exon 19 deletion or L858R) advanced NSCLC.¹⁴⁷ Patients were randomized 1:1 to receive either osimertinib 80 mg daily or a standard EGFR-TKI (gefitinib 250 mg daily or erlotinib 150 mg daily). The primary endpoint was investigator-assessed PFS which favored osimertinib (18.9 months) compared to standard EGFR-TKI therapy (10.2 months) (HR, 0.46; 95% CI, 0.37 to 0.57; $p < 0.001$). The median duration of response was 17.2 months (95% CI, 13.8 to 22) for osimertinib versus 8.5 months (95% CI, 7.3 to 9.8) for standard EGFR-TKI therapy. OS was a secondary endpoint, data on OS were immature at the interim analysis, but the survival rate at 18 months was 83% (95% CI, 78 to 87) for osimertinib compared to 71% (95% CI, 65 to 76) with standard EGFR-TKI therapy (HR, 0.63; 95% CI, 0.45 to 0.88; $p = 0.007$ which was nonsignificant for the interim analysis). Grade 3 or higher adverse events occurred in 34% of osimertinib-treated patients compared to 45% of patients who received standard EGFR-TKI therapy. At a median duration of follow up of 35.8 months in the osimertinib group and 27 months in the comparator group (gefitinib or erlotinib recipients), 321 deaths had occurred and a final analysis of OS was conducted. The median overall survival was 38.6 months (95% CI, 34.5 to 41.8) in the osimertinib group and 31.8 months (95% CI, 26.6 to 36.0) in the comparator (gefitinib or erlotinib) group (hazard ratio for death, 0.8; 95.05% CI, 0.64 to 1; $p = 0.046$). After 3 years, 28% of patients in the osimertinib group and 9% in the comparator group were still receiving a trial regimen. The safety profile between osimertinib and the comparator drugs was similar.¹⁴⁸

Metastatic Squamous Cell NSCLC

afatinib (Gilotrif) versus erlotinib (Tarceva) – subsequent-line therapy metastatic squamous cell NSCLC

LUX-Lung 8 was phase 3, open-label, multicenter, randomized trial examined 795 patients with metastatic squamous cell NSCLC who experienced disease progression following a minimum of 4 cycles of platinum-based doublet chemotherapy and were randomized to either afatinib 40 mg daily or erlotinib 150 mg daily.^{149,150} The major efficacy outcome, PFS, was statistically significantly improved for afatinib (2.4 months) compared to erlotinib (1.9 months) (HR, 0.82; 95% CI, 0.69 to 0.95; $p = 0.427$). With a median follow up of 18.4 months, overall survival also favored afatinib (7.9 months) compared to erlotinib (6.8 months) (HR, 0.81; 95% CI, 0.69 to 0.95; $p = 0.008$).

Recurrent SCLC

topotecan (oral) (Hycamtin) versus best supportive care

Patients (n=141) with relapsed small-cell lung cancer (SCLC) who were not considered candidates for further intravenous chemotherapy were randomized 1:1 to either oral topotecan (2.3 mg/m²/day, days 1 to 5, every 21 days) plus best supportive care (BSC) or BSC alone.¹⁵¹ Patients were required to be a minimum of 45 days out from their last dose of chemotherapy at the time of randomization. The primary endpoint was OS; the study also assessed ORR, quality of life (QOL) information, and safety data. Median OS was significantly longer in the topotecan group (25.9 weeks; 95% CI, 18.3 weeks to 31.6 weeks) compared to BSC (13.9 weeks; 95% CI, 11.1 weeks to 18.6 weeks). At 6 months, 49% of the topotecan-treated patients were alive versus 26% of patients who received BSC. Measures of QOL as assessed by the EuroQol-5 Dimensions of Health Questionnaire (EQ-5D) favored the topotecan arm with measurements for shortness of breath, sleep interference, and fatigue being statistically superior to those scores for patients receiving BSC alone. Patients receiving topotecan experienced greater toxicity, predominantly hematologic toxicity.

Pancreatic Cancer

gemcitabine plus erlotinib (Tarceva) versus gemcitabine plus placebo

A randomized, double-blind placebo-controlled trial in 569 patients compared standard gemcitabine therapy with or without the addition of oral erlotinib 100 mg daily.¹⁵² The primary endpoint was survival. Secondary endpoints included response rate and PFS. Overall survival was 6.4 months on the erlotinib arm compared with 6 months on the gemcitabine alone arm (HR, 0.81; 95% CI, 0.68 to 0.97; p<0.028). The response rate (CR plus PR) was 8.6% in the erlotinib/gemcitabine arm and 7.9% in the placebo/gemcitabine arm (p=0.87). Median PFS was 3.8 months in the erlotinib plus gemcitabine arm compared to 3.5 months in the gemcitabine plus placebo arm (HR, 0.76; 95% CI, 0.64 to 0.92, p<0.006).

Solid Tumors

entrectinib (Rozlytrek) – NTRK gene fusion-positive

A pooled subgroup of adult patients with unresectable or metastatic solid tumors with a NTRK gene fusion were enrolled in 1 of 3 multicenter, single-arm, open-label clinical trials (ALKA, STARTRK-1, STARTRK-2).¹⁵³ Included patients had previously received systemic therapy, if available, or would have required surgery causing significant morbidity for locally advanced disease, had measurable disease per RECIST v1.1, had ≥ 6 months of follow-up after the initial dose of entrectinib, and no prior therapy with a TRK inhibitor (n=54). While patients received entrectinib at various doses and schedules, 94% of patients received entrectinib 600 mg orally once daily until unacceptable toxicity or disease progression. The most common cancers were sarcoma (24%), lung cancer (19%), salivary gland tumors (13%), breast cancer (11%), thyroid cancer (9%), and colorectal cancer (7%). The ORR was 57% (95% CI, 43 to 71) with 7.4% achieving a CR and 50% with PR. The range for duration of response (DOR) was 2.8 to > 26 months, with 68% of patients achieving DOR ≥ 6 months, 61% achieving DOR ≥ 9 months, and 45% achieving DOR ≥ 12 months. For the patients who had received prior systemic therapy for metastatic disease, the ORR was 53%. At baseline, 4 patients had measurable CNS metastases and had not received radiation therapy to the brain within 2 months of the trial. Responses in intracranial lesions were observed in 3 of these 4 patients.

META-ANALYSIS

A meta-analysis was conducted to examine the effect of EGFR-TKIs on PFS and OS in patients with NSCLC.¹⁵⁴ The meta-analysis included 23 eligible trials that treated patients with gefitinib (Iressa), erlotinib (Tarceva), or afatinib (Gilotrif). Thirteen of these trials used EGFR-TKIs in the first-line setting, 7 trials included the use of EGFR-TKIs in the second-line setting, and 3 trials used EGFR-TKIs as maintenance therapy in patients with non-progressive disease after front-line chemotherapy. A total of 14,570 patients were enrolled in these 23 trials and EGFR mutation status was known for at least 31% (n=4,473) of the trial patients. The analysis was limited to those 4,473 patients with either known EGFR mutations (EGFRmut+) or those patients known to be without EGFR mutations (EGFRmut-). The results indicated that treatment with EGFR-TKIs was associated with a 57% reduction in the risk of disease progression in EGFRmut+ patients in the first-line setting (HR, 0.43; 95% CI, 0.38 to 0.49; p<0.001) and a 66% reduction in EGFRmut+ patients in the second-line setting (HR, 0.34; 95% CI, 0.2 to 0.6; p<0.001). There was no benefit seen in PFS in the same scenarios for EGFRmut- patients (front-line therapy: (HR, 1.06; 95% CI, 0.94 to 1.19; p=0.35), second- or subsequent-line therapy: (HR, 1.23; 95% CI, 1.05 to 1.46; p=0.01). However, this meta-analysis did not demonstrate any advantage in OS for either the EGFRmut+ or EGFRmut- groups. This lack of benefit on OS is likely confounded by standard protocols allowing post-progression therapy in both cohorts of patients. This meta-analysis also addressed the question of whether EGFR-TKIs should be given alone or in combination with traditional chemotherapy in different groups and different settings. Indirect comparison of trial arms suggested that combined EGFR-TKI treatment and chemotherapy is not more effective than EGFR-TKI therapy alone in reducing the risk of disease progression in EGFRmut+ patients in the first-line setting (HR, 1.42; 95% CI, 0.8 to 2.53; p=0.23). EGFR-TKIs, compared with chemotherapy in second-line or subsequent therapy, was associated with a 66% reduction in risk of disease progression in the EGFRmut+ subgroup. However, EGFR-TKI treatment compared with chemotherapy was 23% inferior in delaying disease progression in EGFRmut- patients. The meta-analysis concluded that EGFR-TKIs produce statistically significant delays in disease progression in EGFRmut+ patients in first- and second- or subsequent lines of therapy, but have no demonstrable impact on OS in either EGFRmut+ or EGFRmut- patients.

A meta-analysis involving 2,962 patients from 8 studies evaluated the benefit of EGFR-TKIs compared to standard platinum-based chemotherapy as first-line treatment for patients with metastatic NSCLC presenting with EGFR mutations.¹⁵⁵ Patients receiving EGFR-TKI therapy showed significantly longer PFS (HR, 0.266; 95% CI, 0.2 to 0.35; p<0.0001). No significant difference in OS was found (HR, 0.946; 95% CI, 0.35 to 2.53; p=0.912). The grade 3 or higher toxicities experienced by patients receiving EGFR-TKI therapy included skin rash, diarrhea, and increased aminotransferase. The authors concluded EGFR-TKIs should be considered as the first choice in the first-line treatment of patients with advanced NSCLC and EGFR mutation.

The overall risk of treatment-related toxicities from the EGFR TKI class as well as the individual comparison of toxicities between gefitinib, erlotinib, and afatinib were examined in a meta-analysis of 16 randomized trials that included 2,535 NSCLC patients.¹⁵⁶ The findings indicated that discontinuation of treatment related to adverse events was 7.7% overall and there was no difference between the individual EGFR TKIs. The most common cause of toxic death from this class of drugs was pneumonitis; however, it occurred rarely (1.7%) and there was also no difference between any of the individual drugs regarding toxic deaths. Overall, 40% of patients experienced grades 3 or 4 toxicities and the risk for grades 3 or 4 toxicities were lower with gefitinib (29%) compared with erlotinib (54.1%) or afatinib (42.1%) (p<0.01). The risk for rash and diarrhea (84.8% and 91.7%, respectively) were both higher with afatinib compared with erlotinib or gefitinib (62% and 42.4% for erlotinib; 62% and 44.4% for gefitinib).

In addition, the risk for increased liver enzyme levels was higher with gefitinib (61.7%) compared with erlotinib (17.8%) or afatinib (20.1%).

A total of 11 trials with 3,145 patients who were receiving 1 of 5 different EGFR-TKIs (gefitinib, erlotinib, afatinib, dacomitinib, and osimertinib) for first-line treatment of EGFR-positive NSCLC were selected for a meta-analysis to compare rates of PFS.¹⁵⁷ The 3 drugs with the best improvement in PFS were osimertinib (HR, 0.71), dacomitinib (HR, 0.8), and afatinib (HR, 0.96). The authors concluded that osimertinib given in the first-line setting achieved the longest PFS in EGFR-positive NSCLC patients.

A meta-analysis examined data from 5 phase 3 trials and 7 phase 2 trials to assess the incidence and risk of ALK inhibitor-induced hepatic toxicity in patients with NSCLC.¹⁵⁸ The 12 trials included data from 2,418 patients (1,873 who received an ALK inhibitor and 545 control patients). The incidence of any grade ALT and AST elevations were 26% (95% CI, 17.4 to 37) and 23.2% (95% CI, 16.7 to 31.4), respectively. High-grade ALT and AST elevations occurred in 8.4% (95% CI, 5.1 to 13.4) and 7% (95% CI, 5.4 to 9), respectively. A subgroup analysis found a significantly higher risk of ALT elevation with ceritinib (56.4%, 95% CI, 38.9 to 72.5) as compared to crizotinib (28.4%; 95% CI, 18.8 to 40.5) and alectinib (13.3%; 95% CI, 9.9 to 17.7).

SUMMARY

Lung cancer continues to be the number 1 cause of cancer death in the US with more than 135,000 deaths predicted to occur in 2020. Lung cancer is divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC is the most common type, representing approximately 80% of all cases. Within NSCLC, subtypes include squamous cell carcinoma or nonsquamous cell carcinoma. Adenocarcinoma, one type of nonsquamous cell NSCLC, is the most commonly occurring type of lung cancer.

Advances in precision medicine have identified various actionable targets for treating lung cancer. The frequency of occurrence of these mutations amenable to various oral tyrosine kinase inhibitors (TKIs) varies depending on several factors. Generally, these mutations occur in $\leq 10\%$ of all cases of NSCLC but may be higher in individual groups such as nonsmokers and patients of East Asian descent. Clinically actionable oncogenic drivers identified to date include mutations in the epidermal growth factor receptor (EGFR) and B-Raf proto-oncogene (BRAF) and gene rearrangements or fusions of anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), and neurotrophic tyrosine receptor kinase (NTRK). Testing for these genetic alterations in patients with advanced NSCLC prior to initiating treatment is now recommended as the standard of care for all patients with nonsquamous cell NSCLC and may be considered in some patients with squamous cell NSCLC.

If an EGFR sensitizing mutation is detected, afatinib (Gilotrif), dacomitinib (Vizimpro), erlotinib (Tarceva), gefitinib (Iressa), and osimertinib (Tagrisso) are all category 1 recommendations in the National Comprehensive Cancer Network (NCCN) guidelines, with preference to osimertinib. Likewise, if the tumor is found to be ALK-positive upon initial testing, alectinib (Alecensa), brigatinib (Alunbrig), ceritinib (Zykadia), or crizotinib (Xalkori) are recommended as a first-line agents by the NCCN guidelines (all category 1 with alectinib being listed as preferred). For patients found to be ROS1 positive, crizotinib, entrectinib or ceritinib are options with crizotinib or entrectinib being listed as preferred. Patients with BRAF V600E mutations may be treated with dabrafenib (Tafinlar) plus trametinib (Mekinist) (category 2A). If patients with BRAF V600E mutations are unable to tolerate combination therapy, single agent dabrafenib or vemurafenib (Zelboraf) are treatment options (category 2A).

Unfortunately, most patients with identified driver mutations develop resistance within 9 to 13 months after beginning first-line TKI therapy. Resistance to EGFR-TKIs has been associated with a T790M mutation in approximately 60% of patients who become resistant to first-line afatinib, erlotinib or gefitinib. Osimertinib (Tagrisso) is approved for use in patients displaying the EGFR T790M mutation who have progressed on or after initial EGFR-TKI therapy; use of osimertinib is a category 1 NCCN recommendation in this setting. Second-line options for ALK-positive NSCLC listed by the NCCN include all the first-line agents as well as lorlatinib (Lorbrena).

While the discovery of oncogenic driver mutations and the subsequent development of various TKIs has changed the treatment landscape for NSCLC, therapeutic progress has been slower with small-cell lung cancer (SCLC). SCLC is a more chemotherapy-sensitive disease initially, but responses are often of short duration. Oral topotecan (Hycamtin), approved by the FDA in 2007, has been shown to prolong survival as compared to best supportive care in patients with relapsed SCLC.

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