Oncology Oral, Lung Cancer
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
Anaplastic Lymphoma Kinase (ALK) Tyrosine Kinase Inhibitors		
alectinib (Alecensa®)[1]	Genentech	▪ Treatment of patients with ALK-positive, metastatic non-small cell lung cancer (NSCLC) as detected by an FDA approved test*
brigatinib (Alunbrig®)[2]	Millennium	▪ Treatment of adult patients with ALK-positive metastatic NSCLC, as detected by an FDA-approved test*
ceritinib (Zykadia®)[3]	Novartis	▪ Treatment of ALK-positive metastatic NSCLC as detected by an FDA-approved test*
crizotinib (Xalkori®)[4]	Pfizer	▪ Treatment of metastatic NSCLC in patients whose tumors are ALK-positive or ROS1-positive as detected by an FDA-approved test* ▪ Treatment of pediatric patients ≥ 1 year of age and young adults with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL) that is ALK-positive† ▪ Treatment of adult and pediatric patients ≥ 1 year of age with unresectable, recurrent, or refractory inflammatory myofibroblastic tumor (IMT) that is ALK-positive
entrectinib (Rozlytrek®)[5]	Genentech	▪ Treatment of metastatic NSCLC in adult patients whose tumors are ROS1-positive, as detected by an FDA-approved test ▪ Treatment of adult and pediatric patients ≥ 12 years of age with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, as detected by an FDA-approved test, 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	▪ Treatment of adult patients with metastatic NSCLC whose tumors are ALK-positive, as detected by an FDA-approved test*
Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitors		
afatinib (Gilotrif®)[7]	Boehringer Ingelheim	▪ 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	▪ 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]	generic, Genentech	▪ 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	▪ 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*,¶
mobocertinib (Exkivity™)[11]	Takeda	▪ Treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion (ex20ins) mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy*,‡,**

FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitors *(continued)*		
osimertinib (Tagrisso®) [12]	AstraZeneca	▪ 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* ▪ Adjuvant therapy after tumor resection in adult patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test*
Mesenchymal-Epithelial Transition (MET) Oral Kinase Inhibitors		
capmatinib (Tabrecta®) [13]	Novartis	▪ Treatment of adult patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping as detected by an FDA-approved test*,‡,††
tepotinib (Tepmetko®) [14]	EMD Serono	▪ Treatment of adult patients with metastatic NSCLC harboring MET exon 14 skipping alterations‡,‡‡
Rearranged During Transfection (RET) Kinase Inhibitors		
pralsetinib (Gavreto®) [15]	Genentech	▪ Treatment of adults with metastatic RET fusion-positive NSCLC, as detected by an FDA approved test*,‡ ▪ Treatment of adult and pediatric patients ≥ 12 years of age with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy‡ ▪ Treatment of adult and pediatric patients ≥ 12 years of age with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)‡
selpercatinib (Retevmo®) [16]	Eli Lily	▪ Treatment of adults with locally advanced or metastatic NSCLC with a RET gene fusion, as detected by an FDA-approved test* ▪ Treatment of patients ≥ 12 years of age with advanced or metastatic MTC with a RET mutation, as detected by an FDA-approved test, who require systemic therapy*,‡ ▪ Treatment of patients ≥ 12 years of age with advanced or metastatic thyroid cancer with a RET gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)*,‡ ▪ Adult patients with locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options‡
Kirsten Rat Sarcoma (KRAS) Protein Inhibitors		
sotorasib (Lumakras™) [17]	Amgen	▪ Treatment of adults with Kirsten rat sarcoma viral oncogene homologue (KRAS) G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least 1 prior systemic therapy*,‡,§§
Non-Targeted Agents		
topotecan (Hycamtin®) [18]	Novartis	▪ Treatment of relapsed small cell lung cancer (SCLC)

* 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.

† The safety and efficacy of crizotinib have not been established in older adults with relapsed or refractory, systemic, ALK-positive ALCL

‡ Approved under Accelerated Approval based on overall response rate, 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.

** Patient selection for the use of mobocertinib is based on the presence of EGFR exon 20 insertion mutations.

†† Patient selection for the use of capmatinib is based on the presence of MET exon 14 skipping in tumor or plasma specimens. If these mutations are not detected in the plasma specimen, test tumor tissue if available.

‡‡ Based on the presence of MET exon 14 skipping alterations in plasma (in patients for whom a tumor biopsy cannot be obtained) or tumor specimens.

§§ Patient selection for the use of sotorasib is based on the presence of KRAS G12C mutation in tumor or plasma specimens. If no mutation is detected in a plasma specimen, test tumor tissue.

OVERVIEW

Lung cancer is the leading cause of cancer death in both men and women in the United States (US). In 2022, an estimated 236,740 new cases of lung cancer will be diagnosed, and 130,180 deaths are estimated to occur.[19] Currently, 5-year survival is estimated to be 22.9%, an increase from 18.6% reported in 2019. Declines in lung cancer mortality in the US have been accelerating in recent years. From 2005 through 2014, lung cancer mortality declined 2.4%, but from 2014 through 2019, this decline more than doubled, resulting in a 4.9% decline in lung cancer mortality over that period. Additionally, there has been a steady decline in the incidence of lung cancer diagnoses in the US; the number of diagnoses declined from 2009 to 2018 by almost 3% annually in men and 1% annually in women. Despite these encouraging trends, there are still more US lung cancer deaths annually than deaths from breast cancer, prostate cancer, and colorectal cancer combined.[20]

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.[21] 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.[22] 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 (USPSTF), who expanded their lung cancer screening guidelines in 2021. The USPSTF guidelines now recommend annual screening with LDCT for patients 50 to 80 years of age who are current smokers with at least a 20 pack-year smoking history and former smokers who have quit within the past 15 years. (grade B).[23] This recommendation is based on the results of the National Lung Cancer Screening Trial, which reported a 20% relative reduction in lung cancer-specific death associated with LDCT compared to chest radiography.[24]

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).[25] 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 NCSLC, 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.

Technologic advances in genomic profiling have identified ways to further classify some NSCLC cases based on the presence of specific genomic mutations. A variety of oral tyrosine kinase inhibitor (TKI) drugs are now available to target many of these genomic mutations, including mutations in sensitizing epidermal growth factor receptor (EGFR), mesenchymal epithelial transition (MET) exon 14 skipping mutations, B-Raf proto-oncogene (BRAF) V600E point mutations, and Kirsten Rat Sarcoma (KRAS) point mutations. Other actionable targets with FDA approved therapies include anaplastic lymphoma kinase (ALK) rearrangements, ROS proto-oncogene (ROS) 1 rearrangements, and rearranged during transfection (RET) gene rearrangements. Finally, neurotrophic tyrosine receptor kinase (NTRK) gene fusions are also an actionable target with available drug therapy options. 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.[26] Anaplastic lymphoma kinase (ALK) gene rearrangements are found in approximately 5% of NSCLC, while ROS1 and RET gene rearrangements are found in only 1% to 2% of NSCLC. MET exon 14 skipping mutations are found in approximately 3% to 4% of patients with adenocarcinoma NSCLC and 1% to 2% of patients with other NSCLC histologies, and NTRK gene fusions are estimated to occur in 0.2% of NSCLC cases. 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. EGFR, ALK, and ROS1 alterations are found most commonly in never smokers, while BRAF and KRAS are seen more frequently in patients with a history of smoking. EGFR, BRAF, and KRAS mutations as well as ALK or ROS1 gene rearrangements occur almost exclusively in patients with adenocarcinoma, a nonsquamous NSCLC histology. KRAS mutations account for 25% of adenocarcinomas in North America. The National Comprehensive Cancer Network (NCCN) notes that these factors (histology, smoking status, ethnicity) should not be used to select patients for testing and instead strongly advises broad molecular profiling for all patients with advanced or metastatic NSCLC. Broad molecular profiling ensures that rare predictive biomarkers might be identified to appropriately counsel patients regarding the availability of clinical trials.

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 modifications.[27] This guideline addresses appropriate genes for testing in patients with lung cancer as well as methods used to perform the molecular testing. Modifications made to the guidelines in 2018 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. Furthermore, the 2021 ASCO guideline update regarding therapy for stage 4 NSCLC with driver mutations recommends that all patients with

nonsquamous NSCLC should have the results of testing for potentially targetable mutations reviewed before therapy is implemented, regardless of smoking status.[28]

Targeted Therapy

EGFR sensitizing mutations

NCCN guidelines incorporate the use of osimertinib (Tagrisso) in the adjuvant setting of earlier stage NSCLC.[29] They recommend the use of osimertinib for patients with stage 1B to 3A disease who have undergone complete resection, EGFR exon 19 deletions and L858R mutation disease who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy. For patients with EGFR exon 20 insertion positive metastatic disease with disease progression, NCCN recommends mobocertinib (Exkivity) as an option for subsequent therapy.

In the first-line setting of advanced or metastatic disease where an EGFR sensitizing mutation is discovered prior to initiating cytotoxic chemotherapy, NCCN category 1 targeted therapy options include afatinib (Gilotrif), dacomitinib (Vizimpro), erlotinib (Tarceva), and gefitinib (Iressa).[30] Osimertinib is recommended as category 1, preferred, in those with EGFR exon 19 deletion or L858R mutations. Listed combination options include erlotinib plus either ramucirumab (Cyramza) (category 2A) or bevacizumab (category 2A). If traditional cytotoxic therapy has already begun, the cytotoxic therapy may be completed or interrupted, followed by the same options as listed (with all options listed as category 2A, other than osimertinib, listed as preferred). 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, gefitinib, dacomitinib, erlotinib alone or in combination with ramucirumab or bevacizumab, may continue to receive the same therapy (category 2A) or may be switched to osimertinib if the EGFR T790M mutation is present (category 1). Osimertinib and afatinib are preferred first-line treatment in patients with EGFR S768I, L861Q, and/or G719X mutations. Other recommended agents (category 2A) include erlotinib, gefitinib, and dacomitinib.

ASCO/Ontario Health (Cancer Care Ontario) guidelines regarding stage 4 NSCLC with driver mutations, updated in 2021, indicate that osimertinib should be offered in the first-line setting for patients with T790M, L858R, or exon 19 deletion EGFR mutations (evidence quality: high; strength of recommendation: strong).[31] If osimertinib is not available in the first-line setting, gefitinib with chemotherapy or dacomitinib may be offered (evidence quality: high; strength of recommendation: moderate). Other options listed by the ASCO guidelines include afatinib or erlotinib/bevacizumab; erlotinib/ramucirumab; or gefitinib, erlotinib, or icotinib (not available in the US) as single agents (evidence quality: intermediate; strength of recommendation: moderate).

BRAF V600E point mutations

For patients with advanced or 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 NCCN (category 2A), while single agents vemurafenib (Zelboraf) or dabrafenib may be options if the combination of dabrafenib plus trametinib is not tolerated (category 2A).[32] According to ASCO guidelines, patients with stage 4 NSCLC and BRAF V600E mutations should be offered dabrafenib/trametinib in the first-line setting (type: informal consensus; evidence quality: low; strength of recommendation: moderate). For patients who receive targeted therapy in the first-line

setting, second-line therapy should consist of standard nondriver mutation guideline recommendations.[33]

MET exon 14 skipping mutations

Both capmatinib (Tabrecta) and tepotinib (Tepmetko) are listed as NCCN category 2A, preferred options, while crizotinib (Xalkori) is classified as a category 2A, useful in certain circumstances recommendation. ASCO guidelines recommend offering capmatinib or tepotinib in the first-line setting (type: informal consensus; evidence quality: low; strength of recommendation: moderate); if the patient does not receive one of these therapies in the first-line setting, it may be offered in the second-line setting (type: informal consensus; evidence quality: low; strength of recommendation: moderate).[34]

ALK rearrangements

A small percentage of patients with NSCLC have ALK gene rearrangements.[35] 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%. If a patient is discovered to have an ALK rearrangement prior to beginning traditional cytotoxic therapy, crizotinib, alectinib (Alecensa), brigatinib (Alunbrig), ceritinib (Zykadia), and lorlatinib (Lorbrena) are all classified as NCCN category 1 recommendations; however, alectinib, brigatinib, and lorlatinib are designated by NCCN as the preferred agents, while ceritinib is categorized as other recommended and crizotinib is categorized as useful in certain circumstances. Similar to the recommendation for EGFR discovery, if cytotoxic therapy has already begun, the cytotoxic therapy may be completed or interrupted, followed the same agents (category 2A) with alectinib, brigatinib, and lorlatinib still being the preferred options. 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 ALK G1202R-positive metastatic NSCLC or symptomatic, systemic disease with multiple lesions, lorlatinib in either the second-line or third-line setting is recommended (category 2A).

ASCO 2021 updated guidelines regarding patients with stage 4 NSCLC who harbor an ALK rearrangement recommend that alectinib or brigatinib be offered in the first-line setting (evidence quality: high; strength of recommendation: strong).[36] The guidelines recommend that if alectinib and brigatinib are not available, patients should be offered ceritinib or crizotinib (evidence quality: high; strength of recommendation: strong). The ASCO guidelines also outline drug choices for the second-line setting. Lorlatinib in the second-line setting is recommended if the patient received alectinib or brigatinib in the first-line setting (type: informal consensus; evidence quality: low). If the patient received crizotinib in the first-line setting, then alectinib, brigatinib, or ceritinib should be offered (evidence quality: low; strength of recommendation: weak). In the third-line setting, lorlatinib may be offered (type: informal consensus; evidence quality: low; strength of recommendation: moderate).

ROS1 rearrangements

Both crizotinib and entrectinib (Rozlytrek) are preferred (category 2A) in the NCCN guidelines for first-line use in patients with metastatic disease who have a ROS1 rearrangement, while ceritinib is categorized as a 2A, other recommended option.[37] Upon disease progression, entrectinib, crizotinib, ceritinib, or lorlatinib are category 2A recommendations. ASCO guidelines recommend crizotinib or entrectinib in the first-line setting (type: informal consensus; evidence quality: low; strength of recommendation: moderate).[38] Other options include ceritinib or lorlatinib (type: informal consensus;

evidence quality: low; strength of recommendation: weak). If targeted therapy was given in the first-line setting, then ASCO guidelines recommend that the standard treatment based on nondriver mutation guidelines should be followed (type: informal consensus; evidence quality: low; strength of recommendation: moderate).

RET rearrangements

Both pralsetinib (Gavreto) and selpercatinib (Retevmo) are listed as NCCN category 2A, preferred first-line options, while cabozantinib (Cabometyx) is recommended as useful in certain situations (category 2A).[39] ASCO guidelines state that selpercatinib or standard therapy based on nondriver mutation guidelines may be offered in the first-line setting (type: informal consensus; evidence quality: low; strength of recommendation: weak).[40] At the time of the ASCO publication, the pralsetinib recommendation in the first-line setting was provisional, pending confirmatory data (type: informal consensus; evidence quality: low; strength of recommendation: weak). Recommendations for second-line setting for *RET* rearrangements are dependent on the therapy received in the first-line; if targeted therapy with pralsetinib or selpercatinib were not given in the first-line setting, they may be offered as second-line therapy.

NTRK fusions

Both entrectinib (Rozlytrek) and larotrectinib (Vitrakvi) are NCCN category 2A preferred options in the first-line setting and subsequent therapy settings (category 2A).[41] ASCO guidelines also recommend entrectinib or larotrectinib in this setting, and these drugs may also be offered in the second-line setting for patients with NTRK gene fusions who did not receive them in the first-line setting.[42]

KRAS mutations

NCCN guidelines recommend sotorasib (Lumakras) for patients with KRAS G12C mutation disease with progression following platinum-based chemotherapy (category 2A).[43]

Non-targeting Therapy

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.[44] 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, lurbinectedin, or topotecan is preferred. Topotecan and lurbinectedin are also alternative treatment options (category 2A) in patients who relapse more than 6 months from their original therapy and have a performance status of 0 to 2.

PHARMACOLOGY[45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62]

All of the agents included in this review, with the exception of topotecan (Hycamtin) and sotorasib (Lumakras), 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.[63]

Afatinib (Gilotrif), dacomitinib (Vizimpro), erlotinib (Tarceva), gefitinib (Iressa), mobocertinib (Exkivity), 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.[64] 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. Mobocertinib (Exkivity) is an EGFR TKI that irreversibly binds to and inhibits EGFR exon 20 insertion mutations.

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.

Capmatinib (Tabrecta) and tepotinib (Tepmetko) are oral kinase inhibitors targeting MET, including the mutant variant produced by exon 14 skipping.

Pralsetinib (Gavreto) and selpercatinib (Retevmo) are oral kinase inhibitors of *RET*, including the RET-fusion and RET-mutants.

Sotorasib (Lumakras) is a protein inhibitor of the rat sarcoma proto-oncogene guanosine triphosphatase (RAS GTPase) family. By blocking KRAS signaling, it inhibits cell growth, and promotes apoptosis only in KRAS G12C tumor cell lines.

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[65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82]

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 UGTI1A3 (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

Pharmacokinetics (continued)

Drug	Half-Life (hr)	Metabolism	Elimination (%)	Effect of High Fat Meal (%)
EGFR Tyrosine Kinase Inhibitors *(continued)*				
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	No clinical impact
mobocertinib (Exkivity)	18	CYP3A	Feces: 76 Urine: 4	No clinical impact
osimertinib (Tagrisso)	48	CYP3A	Feces: 68 Urine: 14	AUC: ▲ 19 Cmax: ▲ 14
MET Kinase Inhibitors				
capmatinib (Tabrecta)	6.5	CYP3A4	Feces: 78 Urine: 22	AUC: ▲ 46 Cmax: unchanged
tepotinib (Tepmetko)	32	CYP3A4 CYP2C8	Feces: 85 Urine: 13.6	AUC: ▲1.6-fold Cmax: ▲ 2-fold
RET Kinase Inhibitors				
pralsetinib (Gavreto)	15.7 (single dose); 20	CYP3A4: major CYP2D6, CYP1A2: minor	Feces: 73 Urine: 6	AUC: ▲122 Cmax: ▲104
selpercatinib (Retevmo)	32	CYP3A4	Feces: 69 Urine: 24	AUC: unchanged Cmax: unchanged
KRAS Protein Inhibitors				
sotorasib (Lumakras)	5	non-enzymatic conjugation oxidation (CYP3A)	Feces: 74 Urine: 6	AUC: ▲ 25
Non-targeted Agents				
topotecan (Hycamtin)	3-6	hydrolysis	Feces: 33 Urine: 20	Cmax: unchanged Tmax: ▲ 25

hr = hours

CONTRAINDICATIONS/WARNINGS[83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100]

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. Hypersensitivity reactions can occur with several agents within this class.

Warnings

Atrioventricular Block

Atrioventricular (AV) block and PR interval prolongation can occur in patients receiving lorlatinib. AV block was seen in 1.9% of patients on lorlatinib 100 mg once daily, with 0.2% 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 ≥ 1,500 cells/mm^3 and platelet counts ≥ 100,000 cells/mm^3. 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, ceritinib, 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, ceritinib, and crizotinib at a reduced dose. If the concomitant drug known to decrease heart rate is stopped or dose adjusted, then alectinib, brigatinib, ceritinib, and crizotinib may be restarted at their previous dosages. Permanently discontinue alectinib, brigatinib, ceritinib, 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, psychotic effects, and changes in cognitive function, mood (including suicidal ideation), speech, mental status, and sleep. Overall, CNS effects occurred in 52% of patients receiving lorlatinib 100 mg once daily, and the median time to first onset of any CNS effect was 1.2 months. Cognitive effects occurred in 28% of patients, with 2.9% being severe (grade 3 or 4); mood effects occurred in 21%, with 1.7% being severe; speech effects occurred in 11%, with 0.6% being severe, and sleep effects occurred in 12% of patients. Additionally, psychotic effects occurred in 7%, with 0.6% being severe, mental status changes occurred in 1.3%, with 1.1% being severe, and seizures occurred in 1.9% 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 3% 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 3.2% 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.

Cardiac toxicity, including decreased ejection fraction, cardiomyopathy, and congestive heart failure can occur with mobocertinib, which can be fatal. In a safety analysis, heart failure occurred in 2.7% of patients taking mobocertinib, with 1.2% grade 3 reactions, 0.4% grade 4 reactions, and 0.4% fatal (1 case). Torsades de pointes caused by QTc prolongation also occurred with mobocertinib. Atrial fibrillation (1.6%), ventricular tachycardia (0.4%), first degree atrioventricular block (0.4%), second degree atrioventricular block (0.4%), left bundle branch block (0.4%), supraventricular extrasystoles (0.4%), and ventricular extrasystoles (0.4%) were reported. Cardiac function, including left ventricular ejection fraction, should be monitored at baseline and during treatment. Doses of mobocertinib should be withheld, reduced, or permanently discontinued depending on severity of cardiac dysfunction.

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.

Cutaneous vasculitis, including leukocytoclastic vasculitis, urticarial vasculitis, and IgA vasculitis, have occurred with osimertinib. If cutaneous vasculitis is suspected, hold osimertinib, evaluate systemic

involvement, and consider dermatology consultation. If confirmed and no other etiology is found, discontinuation of osimertinib may be required.

There is a risk of photosensitivity reactions with brigatinib, capmatinib, and crizotinib. It is recommended that patients wear sunscreen or protective clothing and limit direct ultraviolet exposure during treatment with these agents. Photosensitivity was reported in clinical trials with brigatinib, including grade 3 or 4 photosensitivity. Patients should also be advised to limit sun exposure during treatment with brigatinib and for at least 5 days following treatment. Patients who experience photosensitivity during brigatinib should withhold therapy, then resume at the same dose, reduce the dose, or permanently discontinue therapy depending on severity as described in the package insert.

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-nine 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 95% 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. Treatment with ceritinib should be held if GI events are severe, intolerable, or not responsive to standard treatment.

In clinical trials of patients with ALCL, GI toxicity occurred in 100% of patients treated with crizotinib; 27% of cases were grade 3. In clinical trials of pediatric patients with IMT, 93% of patients experienced vomiting, 86% experienced nausea, and 64% experienced diarrhea. Severe GI toxicity can occur in pediatric and young adults with ALCL or pediatric patients with IMT. Antiemetic prophylactic therapy and anti-diarrheal treatment is recommended for all patients receiving crizotinib for treatment of pediatric and young adults with ALCL and for pediatric patients with IMT. Antiemetics should be given prior to and during crizotinib therapy. Supportive care, including hydration, electrolyte supplementation, and nutritional support should be initiated as needed. If grade 3 nausea persists for 3 days or grade 3 or 4 diarrhea or vomiting develop despite medical management, withhold crizotinib and resume at lower dose once resolved.

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 can occur with mobocertinib and can be severe. In a safety analysis, diarrhea occurred in 93% of patients taking mobocertinib (grade 3 [20%] and grade 4 [0.4%]). The median time to first onset of diarrhea was 5 days but it can occur within 24 hours after administration. Diarrhea resolved in 48% of patients and median time to resolution was 3 days. Diarrhea may lead to dehydration or electrolyte imbalance, with or without renal impairment, and should be treated promptly. Patients should be advised to increase intake of fluid and electrolytes and take an antidiarrheal agent (e.g., loperamide) at the first sign of diarrhea or increased bowel movements. Electrolytes should be monitored and the dose of mobocertinib should be withheld, reduced, or permanently discontinued depending on severity.

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.

Hemolytic Anemia

Hemolytic anemia has been reported in patients receiving alectinib; if suspected, alectinib should be withheld while laboratory testing is being performed. If confirmed, alectinib should be permanently discontinued or may be resumed at a reduced dose after resolution.

Hemorrhagic Events

Serious and fatal cases of hemorrhagic events have occurred with pralsetinib; if a serious event occurs, discontinue pralsetinib permanently.

Fatal hemorrhagic events occurred in 0.5% (n=4) of patients treated with selpercatinib, including 1 case each of tracheostomy site hemorrhage and hemoptysis and 2 cases of cerebral hemorrhage. Grade ≥ 3 hemorrhagic events were reported in 3.1% of patients treated with selpercatinib. Permanently discontinue selpercatinib in patients with severe or life-threatening hemorrhage.

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) and aspartate aminotransferase (AST), including grade 3 or 4 elevations, occurred in brigatinib-treated patients during clinical trials. Withhold brigatinib until recovery to grade 1 or less or to baseline and resume at a lower dose. Brigatinib treatment should be

discontinued for grade 2 to 4 hepatic enzyme elevation with concurrent total bilirubin elevation > 2 times the upper limit of normal (ULN) in the absence of cholestasis or hemolysis.

Elevations of ALT ≥ 5 times the ULN occurred in 28% of patients treated in 1 clinical trial of ceritinib. Liver function tests, including ALT, 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, AST, 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

withheld or permanently discontinued based on severity of hepatotoxicity. If withheld, entrectinib should only be resumed at the same or reduced dose.

Capmatinib can cause increased ALT and AST, including grades 3 or 4 toxicity, which occurred in 6% of patients and resulted in dose discontinuation in 0.9% of patients who received capmatinib in the key clinical trial for approval. The median time to onset of grade 3 or 4 toxicity was 1.4 months (range, 0.5 to 4.1 months). Patients receiving capmatinib should have baseline testing of ALT, AST, and bilirubin, followed by repeat testing every 2 weeks during for the first 3 months, then once a month or as clinically indicated. The dose should be interrupted, then reduced or permanently discontinued based on the severity of the hepatotoxicity.

Tepotinib can cause fatal hepatotoxicity. Thirteen percent of patients treated with tepotinib experienced increased ALT and increased AST, while 4.2% experienced grade 3 or 4 increased ALT/AST. Fatal hepatic failure occurred in 1 patient (0.2%). The median time-to-onset of grade 3 or higher increased ALT/AST was 30 days. Liver function tests, including ALT, AST, and total bilirubin, should be monitored prior to start of tepotinib, every 2 weeks during the first 3 months of treatment, and then monthly or as clinically indicated. In patients who develop increased transaminases or total bilirubin, more frequent testing may be necessary. Patients with grade 4 increases in ALT/AST without increased bilirubin, ALT/AST > 3 times ULN with total bilirubin > 2 times the ULN, or grade 4 increased total bilirubin without increased ALT/AST should permanently discontinue tepotinib.

Serious hepatotoxicity has occurred in patients treated with pralsetinib (incidence, 2.1%). Investigators observed the onset of elevated AST and ALT days to years after starting therapy (AST range, 5 days to 1.5 years; ALT range, 7 days to 1.7 years). Monitor AST and ALT prior to initiating therapy, every 2 weeks during the first 3 months, monthly thereafter, and as clinically appropriate.

Severe hepatotoxicity was reported in 3% of patients who received selpercatinib. Increased AST occurred in 59% of patients, including 11% who experienced a grade 3 or 4 adverse event. Increased ALT occurred in 55% of patients, including 12% with grade 3 or 4 adverse events. The median time to onset for increased AST and ALT was 6 weeks (range, 1 day to 3.4 years) and 5.8 weeks (range, 1 day to 2.5 years), respectively. Patients receiving selpercatinib should have baseline testing of ALT and AST, repeat testing every 2 weeks during for the first 3 months, and then once a month and as clinically indicated. The dose should be interrupted, then reduced or permanently discontinued based on the severity of the hepatotoxicity.

Hepatotoxicity can occur with sotorasib and can lead to drug-induced liver injury and hepatitis. Hepatotoxicity was reported in 1.7% (all grades) and 1.4% (grade 3) of patients in clinical trials. Sotorasib increased ALT and AST in a total of 18% of patients (grade 3, 6%; grade 4, 0.6%). The median time to first onset of increase was 9 weeks (range, 0.3 to 42 weeks). Liver function tests (ALT, AST, and total bilirubin) should be monitored prior to initiation of sotorasib, every 3 weeks for the first 3 months of therapy, then once monthly or as clinically indicated, with more frequent testing in patients who develop transaminase and/or bilirubin elevations.

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% to 56% 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.

In clinical trials, hyperglycemia occurred in 9% of patients treated with lorlatinib 100 mg daily, with grade 3 or 4 hyperglycemia occurring in 3.2% of the patients. The median time to onset of hyperglycemia was 4.8 months. Fasting serum glucose should be evaluated prior to and during lorlatinib therapy. In patients who experience hyperglycemia, lorlatinib 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, lorlatinib should be permanently discontinued.

Hyperlipidemia

Increases in serum cholesterol and triglycerides can occur in patients receiving lorlatinib, with grade 3 or 4 elevations in total cholesterol occurring in 18% and grade 3 or 4 elevations in triglycerides occurring in 19% of patients who received lorlatinib 100 mg once daily. These elevations had a median time to onset of 15 days. Eighty percent of patients required initiation of lipid-lowering medications, 4% to 7% required temporary discontinuation of lorlatinib, and 1% to 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.

Hypersensitivity

Hypersensitivity reactions can occur with several agents in this class. For reactions to selpercatinib, interrupt selpercatinib and administer corticosteroids until patient's hypersensitivity is resolved (refer to dosing modifications and management in the product 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 once blood pressure control resumes to grade 1 severity. If grade 4 hypertension occurs, consider permanent discontinuation of brigatinib.

In clinical trials, hypertension was reported in 13% of patients treated with lorlatinib 100 mg once daily, with 6% of patients experiencing grade 3 or 4 hypertension and 2.3% of patients temporarily discontinuing due to hypertension. Blood pressure should be monitored after 2 weeks of starting therapy and at least monthly thereafter while on therapy. Lorlatinib should be held for hypertension and resumed at a reduced dose or discontinued dependent on severity.

Pralsetinib has been associated with hypertension (incidence, 29%) and should not be initiated in patients with uncontrolled hypertension. Blood pressure should be monitored after 1 week of starting pralsetinib, at least monthly thereafter, and as clinically indicated. Pralsetinib dosing should be interrupted, reduced, or permanently discontinued based on hypertension severity. Initiate or adjust the dose of antihypertensive therapy as needed.

Hypertension was reported in 41% of selpercatinib patients, including 20.1% with grade 3 or 4 hypertension. Hypertension led to dose interruptions and dose reductions in 6.3% and 1.3% of patients, respectively. Selpercatinib should not be started in patients with uncontrolled hypertension, and blood pressure should be optimized before initiating treatment with selpercatinib. Patients receiving selpercatinib should monitor blood pressure after 1 week, and then this should be assessed at least once a month and as clinically indicated. Initiate or adjust anti-hypertensive medication if needed. The dose of selpercatinib should be interrupted, then reduced or permanently discontinued based on the severity of the hypertension.

Hyperuricemia

Hyperuricemia was report 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.

Hypothyroidism

In clinical trials, hypothyroidism occurred in 13% of patients receiving selpercatinib; all cases were grade 1 or 2 in severity. Thyroid function should be assessed before starting selpercatinib and regularly during therapy. Thyroid hormone replacement or withholding or discontinuing selpercatinib may be required, depending on severity.

Impaired Wound Healing

Pralsetinib has the potential to impair wound healing and should be withheld at least 5 days prior to elective surgery and for at least 2 weeks following major surgery until adequate wound healing is demonstrated. The safety of restarting pralsetinib after resolution of wound healing complications is unknown.

Selpercatinib inhibits the vascular endothelial growth factor (VEGF) signaling pathway and, therefore, can cause impaired wound healing. It is recommended to interrupt selpercatinib 7 days prior to elective surgery and wait 2 weeks following major surgery and until adequate wound healing before reinitiating selpercatinib.

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. Brigatinib should be permanently discontinued upon confirmation of grade 3 or 4 ILD or recurrence of grade 1 or 2 ILD.

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 1.9% of the patients treated with lorlatinib 100 mg once daily, with 0.6% of patients experiencing grade 3 or 4 ILD/pneumonitis and 4 patients (0.8%) 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 3.7% of osimertinib clinical trial patients. Osimertinib should be permanently discontinued in any patient with confirmed ILD.

Capmatinib can cause ILD/pneumonitis. In GEOMETRY mono-1 (n=69), the pivotal clinical trial leading to capmatinib's approval, 4.5% of patients who received capmatinib experienced ILD/pneumonitis, including 1.8% with grade 3 ILD/pneumonitis and 0.3% (1 patient) with a fatal adverse event. The median time to onset of grade 3 or higher ILD/pneumonitis was 1.4 months (range, 0.2 months to 1.2 years). ILD/pneumonitis led to drug discontinuation in 2.4% of capmatinib-treated patients. Immediately interrupt capmatinib in patients with suspected ILD/pneumonitis, and permanently discontinue capmatinib if no other potential causes of ILD/pneumonitis are identified.

ILD/pneumonitis can occur with mobocertinib and can be fatal. In a safety analysis, ILD/pneumonitis occurred in 4.3% of patients including grade 3 events (0.8%) and fatal events (1.2%). Patients should be monitored for new or worsening pulmonary symptoms that are indicative of ILD/pneumonitis. Mobocertinib dose should be withheld if ILD/pneumonitis is suspected and permanently discontinued if confirmed.

Tepotinib can cause fatal ILD or pneumonitis. Patients should be monitored for new or worsening pulmonary symptoms, such as dyspnea, cough, or fever. Tepotinib should be withheld if ILD is suspected and permanently discontinued if a diagnosis of ILD is confirmed.

Severe, life-threatening, and fatal cases of ILD/pneumonitis have been reported with pralsetinib; monitor the patient's pulmonary status and withhold pralsetinib therapy if acute or worsening respiratory symptoms occur. A decision to restart at a reduced dose or permanently discontinue treatment should be based on severity of confirmed ILD.

ILD/pneumonitis can occur with sotorasib and can be fatal. Patients should be monitored for new or worsening pulmonary symptoms that are indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). In

clinical trial data, grade 3 or 4 ILD/pneumonitis at onset occurred in 0.8% of patients, and 1 case was fatal. The median time to first onset was 2 weeks (range, 2 to 18 weeks). Sotorasib was discontinued in 0.6% of patients taking sotorasib due to ILD/pneumonitis. Sotorasib should be withheld immediately in patients with suspected ILD/pneumonitis and permanently discontinued if no other potential causes of ILD/pneumonitis are identified.

Patients treated with selpercatinib have experienced severe, life-threatening, and fatal ILD/pneumonitis. In clinical studies, ILD/pneumonitis occurred in 1.8% of patients with a small proportion of patients experiencing grade 3 or 4 events (0.3%) or fatal reactions (0.3%). Pulmonary symptoms suggestive of ILD/pneumonitis should be monitored for and therapy withheld for further investigation of acute or worsening respiratory symptoms (dyspnea, cough, fever). Dosage adjustments or discontinuation of selpercatinib may be required depending on the severity of 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. A baseline ophthalmologic examination should be performed prior to initiation of crizotinib therapy for pediatric and young adult patients with ALCL or IMT, with follow-up examination within 1 month of initiating crizotinib and every 3 months thereafter. All patients should have visual symptoms evaluated monthly during treatment. Report new visual symptoms to an eye specialist. Ophthalmological evaluation should be performed in patients with new onset of severe visual loss or for other visual symptoms as appropriate. Permanently discontinue crizotinib for grade 3 or 4 ocular disorders or for any patient with new onset severe visual loss (best corrected vision < 20/200 in 1 or both eyes) unless another cause is found. 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, photophobia, photopsia, 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 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.

Life-threatening QTc prolongation, including torsades de pointes, can occur with mobocertinib and can be fatal. In a safety analysis, 1.2% of patients had a QTc interval > 500 msec and 11% had a change-from-baseline QTc interval > 60 msec; 0.4% (1 patient) had grade 4 torsades de pointes. QTc and electrolytes should be monitored at baseline and periodically during treatment. Abnormalities in sodium, potassium, calcium, and magnesium should be corrected prior to initiating therapy. Increase monitoring in patients with QTc prolongation risk factors (e.g., congenital long QT syndrome, heart disease, electrolyte abnormalities). Concomitant use of drugs that prolong QTc interval and strong or moderate CYP3A inhibitors should be avoided with mobocertinib. The mobocertinib dose should be withheld, reduced, or permanently discontinued based on QTc prolongation severity.

Concentration-dependent QT interval prolongation was reported in patients treated with selpercatinib, including 7% who experienced increases in QTcF interval > 500 ms and 20% who experienced an increase in the QTcF interval ≥ 60 ms over baseline. Selpercatinib was not studied in patients with clinically significant active cardiovascular disease or patients with recent myocardial infarction. Monitor patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or

uncontrolled heart failure. Assess QT interval, electrolytes, and thyroid stimulating hormone (TSH) level prior to start of therapy and periodically during treatment as appropriate. Hypokalemia, hypomagnesemia, and hypocalcemia should be corrected before initiating selpercatinib. QT interval should be assessed more frequently in patients on concomitant strong or moderate CYP3A inhibitors or drugs known to prolong QTc interval. If adverse events occur, the dose should be interrupted, then reduced or permanently discontinued based on 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 indicted based on symptoms.

CPK elevations were reported in patients treated with brigatinib, including grade 3 and 4 elevations. CPK levels should be monitored during brigatinib therapy. Withhold brigatinib if grade 3 or 4 elevations occur with grade 2 or higher muscle pain or weakness; 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.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) has been reported in medullary thyroid carcinoma patients receiving pralsetinib and selpercatinib during clinical trials. Patients with rapidly growing tumors, high tumor burden, renal dysfunction, or dehydration may be at risk for TLS and should be monitored closely.

DRUG INTERACTIONS[101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118]

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), capmatinib (Tabrecta), ceritinib (Zykadia), crizotinib (Xalkori), entrectinib (Rozlytrek), erlotinib (Tarceva), gefitinib (Iressa), lorlatinib (Lorbrena), mobocertinib (Exkivity), osimertinib (Tagrisso), and selpercatinib (Retevmo) can increase. Avoid concomitant administration of entrectinib, mobocertinib, and osimertinib 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 use of strong CYP3A inhibitors is unavoidable with crizotinib, the crizotinib dose should be reduced to 250 mg once daily for adults with NSCLC or IMT and to the second dose reduction based on BSA in the prescribing information for pediatric and young adults with ALCL or pediatric patients with IMT. Following discontinuation of the strong CYP3A inhibitor, resume the crizotinib dose used before starting the strong CYP3A inhibitor. 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 m^2 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. Avoid concomitant use of capmatinib with strong CYP34A inhibitors due to increased risk of capmatinib toxicity (e.g., itraconazole, clarithromycin). Monitoring for capmatinib toxicity should be increased when given concomitantly with strong CYP34A inhibitors. Use of tepotinib with dual strong CYP3A inhibitors and P-gp inhibitors should be avoided. Although the effects have not been studied clinically, metabolism and *in vitro* data suggest that concomitant use of these drugs may increase tepotinib exposure. Coadministration of pralsetinib with strong CYP3A inhibitors increases pralsetinib exposure, and thereby increases risk of adverse effects; coadministration should be avoided. Coadministration with combined P-glycoprotein (P-gp) and strong CYP3A inhibitors should also be avoided; reduce the pralsetinib dose if avoidance is not possible. Avoid concomitant use of mobocertinib or selpercatinib with strong and moderate CYP34A inhibitors due to increased risk of toxicity, including QTc interval prolongation. Reduce the dose of the mobocertinib and selpercatinib according to prescribing information if concomitant use with a strong or moderate CYP34A inhibitor is unavoidable. Increase monitoring of QT interval when mobocertinib or selpercatinib is given concomitantly with strong and moderate CYP34A inhibitors.

Co-administration of CYP3A4 Inducers

Brigatinib, capmatinib, ceritinib, crizotinib, entrectinib, erlotinib, gefitinib, lorlatinib, mobocertinib, osimertinib, selpercatinib, and tepotinib 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 should be avoided, but if unavoidable, increase the lorlatinib dose to 125 mg daily. Avoid concomitant use of capmatinib, mobocertinib or selpercatinib with strong or moderate CYP3A inducers, as pharmacologic activity may be reduced. Coadministration of pralsetinib with strong CYP3A inducers may decrease efficacy of pralsetinib and should be avoided; increase the pralsetinib dose if concomitant use is required. CYP3A inducers can reduce tepotinib efficacy by decreasing tepotinib exposure based on metabolism and *in vitro* data; concomitant use should be avoided. Coadministration of sotorasib and a strong CYP3A4 inducer (repeated doses of rifampin) can decrease sotorasib maximum concentration (Cmax) by 35% and AUC by 51%, which may reduce the efficacy of sotorasib; coadministration should be avoided. Coadministration of sotorasib with itraconazole, rifampin (single dose), or metformin had no clinically meaningful effect on the exposure of sotorasib.

Substrates of CYP3A4/CYP2C9/CYP1A2/BCRP/P-glycoprotein (P-gp)/multidrug and toxin extrusion protein 1 (MATE1) or MATE2K

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 with certain substrates for which minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, increase the CYP3A4 substrate dosage in accordance with approved product labeling. In addition, concomitant use of lorlatinib decreases the concentration of P-

gp substrates and should be avoided with certain P-gp substrates for which minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, increase the P-gp substrate dosage in accordance with approved product labeling.

Osimertinib can increase the exposure of a breast cancer resistance protein (BCRP) or P-gp substrates, monitor for adverse reactions.

Avoid concomitant use of capmatinib with CYP1A2 substrates due to an increased risk of toxicity with these substrates. Reduce the dose of the CYP1A2 substrate according to prescribing information if concomitant use is unavoidable and concentration changes lead to serious adverse reactions. Avoid concomitant use of capmatinib with a P-gp substrates or BCRP substrates due to increased exposure and risk of toxicity due to these substrates. Reduce the dose of the P-gp or BCRP substrate according to prescribing information if concomitant use is unavoidable and concentration changes lead to serious adverse reactions. Avoid concomitant use of capmatinib with a multidrug and toxin extrusion protein 1 (MATE1) or MATE2K substrate due to increased risk of toxicity due to these substrates. Reduce the dose of the MATE1 or MATE2K substrate according to the substrate's prescribing information if concomitant use is unavoidable and concentration changes lead to serious adverse reactions.

Use of mobocertinib with a CYP3A substrate may decrease plasma concentration and efficacy of the substrate. Mobocertinib should be avoided with concomitant use of hormonal contraceptives and with other CYP3A substrates where minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, the CYP3A substrate dose should be increased as appropriate.

Concomitant use of tepotinib with P-gp substrates increases the concentration of P-gp substrates. Use of tepotinib with P-gp substrates should be avoided if minimal concentration changes may lead to serious or life-threatening toxicities.

Avoid concomitant use of selpercatinib with a CYP3A or CYP2C8 substrates due to increased exposure and risk of toxicity of the substrates. Follow recommendations for CYP3A or CYP2C8 substrate according to the substrate's prescribing information if concomitant use is unavoidable and minimal concentration changes lead to serious adverse reactions.

Coadministration of sotorasib and a CYP3A4 substrate (midazolam) was shown to decrease midazolam Cmax by 48% and AUC by 53%, which may reduce the efficacy of the substrate; coadministration should be avoided. If coadministration with a CYP3A4 substrate cannot be avoided, the CYP3A4 substrate dosage should be increased according to its prescribing information. Coadministration of sotorasib with a P-gp substrate (digoxin) increased substrate Cmax by 91% and AUC by 21%, which may increase adverse reactions of the substrate; therefore, coadministration should be avoided, including with drugs where minimal concentration changes may lead to serious toxicities. If coadministration of sotorasib and P-gp substrates cannot be avoided, the P-gp substrate dosage should be decreased according to its prescribing information.

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.

Use of tepotinib with dual strong CYP3A inhibitors and P-gp inhibitors should be avoided. Although the effects have not been studied clinically, metabolism and *in vitro* data suggest that concomitant use of these drugs may increase tepotinib exposure.

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.

P-glycoprotein (P-gp) Substrates

As selpercatinib is a P-gp inhibitor, concurrent use with P-gp substrates can increase plasma levels of the substrates which can increase substrate adverse events. As a result, avoid concurrent use of selpercatinib with P-gp substrates where small changes in concentration could result in adverse events. If concurrent use cannot be avoided, consult the P-gp substrate product labeling for recommendations.

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

Histamine-2 (H_2)-receptor antagonists and proton pump inhibitors (PPIs) are associated with long-term suppression of gastric acid secretion that may result in reduced systemic exposure of dacomitinib and erlotinib. Concomitant use of PPIs with erlotinib is not recommended and erlotinib should be given 10 hours after or 2 hours before any dose of a H_2-receptor antagonist. Dacomitinib should be taken at least 6 hours before or 10 hours after an H_2-receptor antagonist.

PPIs, H_2-receptor antagonists, and antacids may reduce plasma concentrations of gefitinib. Avoid concomitant use of gefitinib with PPIs, if possible. If a PPI is required, gefitinib should be taken 12 hours after the last dose or 12 hours before the next dose of the PPI. Gefitinib should be taken 6 hours after or 6 hours before an H_2-receptor antagonist or an antacid.

Avoid concomitant use of selpercatinib with acid-reducing agents (e.g., PPI, H_2-receptor antagonist, and locally-acting antacid) as activity of selpercatinib may be reduced. Take selpercatinib with food if concomitant use with a PPI is unavoidable; modify dosing interval of selpercatinib according to labeling if concomitant use with an H_2-receptor antagonist or locally-acting antacid is unavoidable.

Use of sotorasib in combination with (PPIs), histamine-2 (H2) receptor antagonists, and locally acting antacids should be avoided due to decreased sotorasib Cmax and AUC. Sotorasib should be administered 4 hours before or 10 hours after acid-reducing agents if coadministration cannot be avoided.

Cigarette Smoking

Cigarette smoking has been shown to reduce the erlotinib 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

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

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. Ceritinib, crizotinib and entrectinib (Rozlytrek) can prolong the QT interval and should be avoided with other QT-prolongating agents.

The effect of coadministration of QTc interval-prolonging medications with osimertinib is unknown; avoid coadministration when possible or conduct periodic ECG monitoring. Monitor the QT interval more frequently when selpercatinib is used concurrently with drugs known to prolong QTc interval. The dose should be interrupted and then reduced or permanently discontinued based on the severity of the adverse events. Use of mobocertinib with drugs known to prolong the QTc interval may increase the risk of QTc interval prolongation, and concomitant use should be avoided. If concurrent use is unavoidable, frequent ECG monitoring is recommended.

Concomitant use of fluconazole may increase lorlatinib concentrations. Concomitant use should be avoided, but if use is unavoidable, then the dose of lorlatinib should be decreased to 75 mg once daily.

ADVERSE EFFECTS[119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136]

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
brigatinib (Alunbrig) versus crizotinib	53 (57)	40 (17)	13 (8.8)	30 (58)	7.4 (53)	nr	12 (23)
ceritinib (Zykadia)	86	16	nr	20	9	nr	3
crizotinib (Xalkori) versus pemetrexed or docetaxel (NSCLC)	60 (19)	9	nr	57 (37)	60 (9)	nr	5 (0)
crizotinib (Xalkori) in ALCL	92	23	46	92	65	nr	19
crizotinib (Xalkori) in IMT in pediatric patients	64	57	29	86/93	50	nr	14
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) 2nd/3rd 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
mobocertinib (Exkivity)	92	78	46	37/40	11	nr	nr
osimertinib (Tagrisso)	47	45	26	nr	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.

Adverse Effects (continued)

Drug	Diarrhea	Rash	Stomatitis	Nausea/Vomiting	Vision Problems	Conjunctivitis	Bradycardia
MET Kinase Inhibitors							
capmatinib (Tabrecta)	18	nr	nr	44	nr	nr	nr
tepotinib (Tepmetko)	26	nr	nr	27	nr	nr	nr
RET Kinase Inhibitors							
pralsetinib (Gavreto)	24	nr	nr	nr	nr	nr	nr
selpercatinib (Retevmo)	47	33	nr	31/22	nr	nr	nr
KRAS Protein Inhibitors							
sotorasib (Lumakras)	42	12	nr	26/17	nr	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 for NSCLC previously treated with crizotinib, 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. Clinically relevant adverse reactions in this patient population who received brigatinib included photosensitivity (0.9%).

In brigatinib clinical trials for advanced ALK-positive NSCLC without prior ALK-targeted therapy, serious adverse reactions occurred in 33% of patients treated with brigatinib. The most common serious adverse reactions were pneumonia (4.4%), ILD/pneumonitis (3.7%), pyrexia (2.9%), dyspnea (2.2%), pulmonary embolism (2.2%), and asthenia (2.2%). Fatal adverse reactions occurred in 2.9% of patients, including pneumonia (1.5%), cerebrovascular accident (0.7%), and multiple organ dysfunction syndrome (0.7%). Thirteen percent of brigatinib patients permanently discontinued treatment due to adverse reactions. Discontinuation was most often due to ILD/pneumonitis (3.7%) and pneumonia (2.2%). Clinically relevant adverse reactions in this patient population who received brigatinib included photosensitivity (up to 3.7%).

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, nausea, and photosensitivity. 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 with mobocertinib occurring in ≥ 2% of patients included diarrhea, dyspnea, vomiting, pyrexia, acute kidney injury, nausea, pleural effusion, and cardiac failure. Fatal adverse events occurred in 1.8% of patients, including cardiac failure (0.9%), and pneumonitis (0.9%).

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%)

In adults with NSCLC, the most common adverse reactions (≥ 20%) were vision disorders (60% to 71%), nausea (55% to 56%), diarrhea (60% to 61%), vomiting (46% to 47%), edema (31% to 49%), constipation (42% to 43%), elevated transaminases (61% to 79%), fatigue (27% to 29%), decreased appetite (27% to 30%), upper respiratory infection (26% to 32%), dizziness (18% to 22%), and neuropathy (19% to 21%). In ALCL patients, the most common adverse effects (≥ 35%) were diarrhea (92%), vomiting (92%), nausea (77%), vision disorder (65%), headache (58%), musculoskeletal pain (58%), abdominal pain (50%), stomatitis (46%), fatigue (46%), decreased appetite (42%), pyrexia (38%), cough (35%), and pruritus (35%). The most common grade 3 or 4 laboratory abnormalities (≥ 15%) in ALCL patients were neutropenia (77%), lymphopenia (38%), and thrombocytopenia (19%). In adults with IMT, the most common adverse reactions (≥ 20%) were vision disorders, nausea, and edema. In pediatric patients with IMT, the most common adverse reactions (≥ 35%) were vomiting (93%), nausea (86%), diarrhea (64%), upper respiratory tract infection (64%), cough (64%), abdominal pain (57%), rash (57%), vision disorder (50%), pyrexia (50%), musculoskeletal pain (43%), fatigue (43%), edema (36%), constipation (36%), and headache (36%).

The most common (≥ 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%). Additionally, clinically significant psychotic effects were reported in 7% of patients. The most common lab value abnormalities (≥ 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 (≥ 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 (≥ 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 common adverse reactions occurring in ≥ 20% of capmatinib patients (reported as incidence of grades 1 to 4) were peripheral edema (52%), nausea (44%), fatigue (32%), vomiting (28%), dyspnea (24%), and decreased appetite (21%). Serious adverse reactions that occurred in ≥ 2% of patients included dyspnea (7%), pneumonia (4.8%), pleural effusion (3.6%), general physical health deterioration (3%), vomiting (2.4%), and nausea (2.1%).

The most common adverse effects or all grades (incidence > 10%) reported with tepotinib in the VISION trial were edema (70%), fatigue (27%), nausea (27%), diarrhea (26%), musculoskeletal pain (24%), dyspnea (20%), abdominal pain (16%), constipation (16%), decreased appetite (16%), cough

(15%), pleural effusion (13%), vomiting (13%), and pneumonia (11%). Clinically relevant adverse effects occurring in < 10% reported with tepotinib include ILD/pneumonitis, rash, fever, dizziness, pruritis, and headache. Select laboratory abnormalities of all grades (≥ 20%) worsening from baseline in the VISION clinical trial included decreased albumin (76%), increased creatinine (55%), increased alkaline phosphatase (50%), decreased lymphocytes (48%), increased ALT (44%), increased AST (35%), decreased sodium (31%), decreased hemoglobin (27%), increased potassium (25%), increased gamma-glutamyltransferase (24%), increased amylase (23%), and decreased leukocytes (23%). Serious adverse reactions were reported in 45% of patients receiving tepotinib, with the most common reactions being pleural effusion (7%), pneumonia (5%), edema (3.9%), dyspnea (3.9%), general health deterioration (3.5%), pulmonary embolism (2%), and musculoskeletal pain (2%).

The most common adverse effects reported in clinical trials (incidence ≥ 10%) with pralsetinib included fatigue (35%), constipation (35%), musculoskeletal pain (32%), hypertension (28%), diarrhea (24%), cough (23%), edema (20%), pyrexia (20%), pneumonia (17%), and dry mouth (16%). The most common grade 3 or 4 adverse effects reported in clinical trials included hypertension (14%), pneumonia (8%), diarrhea (3.2%), fatigue (2.3%), constipation (1%), and cough (0.5%). Grade 1 to 4 laboratory value abnormalities reported in clinical trials (incidence ≥ 20%) included increased AST (69%), decreased hemoglobin (54%), decreased lymphocytes (52%), decreased neutrophils (52%), increased ALT (46%), increased creatinine (42%), increased alkaline phosphatase (40%), decreased calcium (29%), decreased sodium (27%), decreased phosphate (27%), and decreased platelets (26%). The most common grade 3 or 4 effects (incidence ≥ 5%) included decreased lymphocytes (20%), decreased neutrophils (10%), decreased phosphate (9%), and decreased hemoglobin (5%).

The most common adverse reactions reported with selpercatinib (≥ 25%) were increased AST (59%), decreased calcium (59%), increased ALT (56%), decreased albumin (56%), increased glucose (53%), decreased lymphocytes (52%), edema (49%), diarrhea (47%), increased creatinine (47%), fatigue (46%), dry mouth (43%), decreased sodium (42%), hypertension (41%), increased alkaline phosphatase (40%), decreased platelets (37%), increased total cholesterol (35%), abdominal pain (34%), rash (33%), constipation (33%), nausea (31%), decreased hemoglobin (28%), headache (28%), and decreased neutrophils (25%).

The most common adverse reactions reported in sotorasib clinical trials (≥ 20%) were diarrhea (42%), musculoskeletal pain (35%), nausea (26%), fatigue (26%), hepatotoxicity (25%), and cough (20%). The most common laboratory abnormalities reported (≥ 25%) were decreased lymphocytes (48%), decreased hemoglobin (43%), increased AST (39%), increased ALT (38%), decreased calcium (35%), increased alkaline phosphatase (33%), increased urine protein (29%), and decreased sodium (28%).

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[137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154]

Pediatrics

With the exception of crizotinib (Xalkori), entrectinib (Rozlytrek), pralsetinib (Gavreto), and selpercatinib (Retevmo), none of the products included in this review have established safety and efficacy in patients < 18 years old. The safety and efficacy of crizotinib in pediatric patients 1 year of age and older with relapsed or refractory, systemic, ALK-positive ALCL or with unresectable, recurrent,

or refractory ALK-positive IMT have been established. The safety and efficacy of crizotinib in pediatric patients less than 1 year of age with ALCL or with IMT and in any NSCLC pediatric patients have not been established. 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. The safety and efficacy of pralsetinib and selpercatinib have been established in pediatric patients ≥ 12 years of age with advanced or metastatic RET-mutant MTC who require systemic therapy or pediatric patients ≥ 12 years of age with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

Pregnancy

All of the agents included in this review are Pregnancy category D except alectinib (Alecensa), brigatinib (Alunbrig), capmatinib (Tabrecta), entrectinib (Rozlytrek), gefitinib (Iressa), lorlatinib (Lorbrena), mobocertinib (Exkivity), osimertinib (Tagrisso), pralsetinib (Gavreto), tepotinib (Tepmetko), selpercatinib (Retevmo), and sotorasib (Lumakras), 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), brigatinib (Alunbrig), capmatinib (Tabrecta), gefitinib (Iressa), erlotinib (Tarceva), topotecan (Hycamtin), crizotinib (Xalkori), lorlatinib (Lorbrena), pralsetinib (Gavreto), selpercatinib (Retevmo), sotorasib (Lumakras) or tepotinib (Tepmetko).

Clinical trials with alectinib, 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.

In clinical trials, no difference in effectiveness of mobocertinib was observed between patients ≥ 65 years of age and younger populations; however, exploratory data suggested a higher incidence of grade 3 or grade 4 adverse reactions (69% versus 47%, respectively) and serious adverse reactions (64% versus 35%, respectively) in patient ≥ 65 years of age versus younger population.

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 m^2 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 adults with NSCLC or IMT or to the second dose reduction based on BSA in pediatric and young adult ALCL patients or pediatric IMT 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). In patients with severe renal impairment (CrCl, 15 to < 30 mL/min), the daily dose of lorlatinib should be reduced by approximately 25%.

Dose adjustments of mobocertinib are not required in mild to moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2); the impact of severe renal impairment (eGFR < 30 mL/min/1.73 m^2) on mobocertinib dose has not been determined.

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.

No dose adjustment for capmatinib is required for patients with mild (CrCl, 60 to 89 mL/min) to moderate (CrCl, 30 to 59 mL/min) renal impairment. The pharmacokinetics of capmatinib in severe (CrCl < 30 mL/min) renal impairment have not been established.

Dose adjustments of tepotinib are not required in mild to moderate renal impairment (CrCl, 30 to 89 mL/min); the impact of severe renal impairment (CrCl < 30 mL/min) on tepotinib safety or effectiveness has not been determined.

Mild and moderate renal impairment (creatinine clearance [CrCl], 30 to 89 mL/min) do not affect pralsetinib exposure. Pralsetinib has not been studied in patients with severe renal impairment (CrCl < 15 mL/min).

No dose adjustment for selpercatinib is required for patients with mild to severe renal impairment (CrCl ≥ 15 mL/min to 89 mL/min). The recommended dosages of selpercatinib in ESRD have not been established.

No dose adjustment for sotorasib is required for patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥ 30 mL/min/1.73 m^2). The impact of severe renal impairment has not been determined.

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 and indication. Adults with NSCLC or IMT 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 NSCLC patients with severe impairment (any AST and total bilirubin > 3 times ULN) are recommended to take 250 mg daily. In pediatric and young adult ALCL patients or pediatric patients with IMT with moderate hepatic impairment, the first dose adjustment based on BSA as detailed in the prescribing information should be followed. In pediatric and young adult ALCL patients or pediatric IMT patients with severe hepatic impairment, the second dose adjustment based on BSA as detailed in the prescribing information should be followed.

No dose adjustment of capmatinib or dacomitinib is recommended in patients with mild, moderate, or severe hepatic impairment.

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.

Dose adjustments of mobocertinib are not required in mild (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1 to 1.5 times ULN and any AST) or moderate hepatic impairment (total bilirubin ≥ 1.5 to 3 times ULN and any AST). A dose adjustment for severe hepatic impairment (total bilirubin > 3 times ULN and any AST) has not been established.

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.

Dose adjustments for tepotinib are not required in mild to moderate hepatic impairment (Child-Pugh A or B); the impact of severe hepatic impairment (Child-Pugh Class C) on tepotinib safety or effectiveness has not been determined. Patients with grade 3 increases in ALT and/or AST without increases in bilirubin should have tepotinib withheld until ALT and/or AST returns to baseline. If levels return to baseline within 7 days, resume the same dose. If levels return to baseline thereafter, resume tepotinib at a reduced dose. Patients with grade 3 increased total bilirubin without increased ALT and/or AST should have tepotinib withheld until ALT and/or AST return to baseline. If levels return to baseline within 7 days, resume the same dose. If levels return to baseline thereafter, resume tepotinib at a reduced dose.

No dosage adjustment of pralsetinib is required in patients with mild hepatic impairment. Pralsetinib has not been studied in patients with moderate or severe impairment.

The selpercatinib dose should be reduced in patients with severe hepatic impairment (total bilirubin > 3 to 10 times ULN and any AST). No dose adjustment for selpercatinib is required for patients with mild (total bilirubin ≤ ULN and AST > ULN, or total bilirubin > 1 to 1.5 times ULN with any AST) or moderate (total bilirubin > 1.5 to 3 times ULN and any AST) hepatic impairment. Monitor for adverse reactions in patients with hepatic impairment.

Clinically important differences in the pharmacokinetics of sotorasib were not found in patients with mild hepatic impairment (AST or ALT < 2.5 times ULN or total bilirubin < 1.5 times ULN). The impact of moderate to severe hepatic impairment has not been determined. A dose adjustment is needed in cases of grade 2 reactions with symptoms or grade 3 AST or ALT elevations.

DOSAGES[155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172]

<table>
<tr><th>Drug</th><th>Dose</th><th>Administration</th><th>Available Strengths</th></tr>
<tr><td colspan="4">ALK Tyrosine Kinase Inhibitors</td></tr>
<tr><td>alectinib
(Alecensa)</td><td>600 mg twice daily</td><td>Take with food; do not open or dissolve capsules</td><td>150 mg capsules</td></tr>
<tr><td>brigatinib
(Alunbrig)</td><td>90 mg once daily for 7 days; then increase to 180 mg once daily</td><td>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</td><td>30 mg, 90 mg, 180 mg tablets
90 mg/180 mg tablet pack</td></tr>
<tr><td>ceritinib
(Zykadia)</td><td>450 mg once daily</td><td>Take once daily with food</td><td>150 mg tablets</td></tr>
<tr><td>crizotinib
(Xalkori)</td><td>NSCLC or IMT in adults: 250 mg twice daily
ALCL in pediatric patients and young adults or IMT in pediatric patients: 280 mg/m^2 BSA twice daily (rounded per table below)
<table>
<tr><th>BSA</th><th>Dose (given twice daily)</th></tr>
<tr><td>0.6 to 0.8 m^2</td><td>200 mg</td></tr>
<tr><td>0.81 to 1.16 m^2</td><td>250 mg</td></tr>
<tr><td>1.17 to 1.51 m^2</td><td>400 mg</td></tr>
<tr><td>1.52 to 1.69 m^2</td><td>450 mg</td></tr>
<tr><td>≥ 1.7 m^2</td><td>500 mg</td></tr>
</table></td><td>Take with or without food; swallow capsules whole</td><td>200 mg, 250 mg capsules</td></tr>
<tr><td>entrectinib
(Rozlytrek)</td><td>NSCLC: 600 mg once daily

NTRK gene fusion-positive solid tumors
▪ Adults: 600 mg once daily
▪ Pediatric patients ≥ 12 years old
– BSA > 1.5 m^2: 600 mg once daily
– BSA 1.11 to 1.5 m^2: 500 mg once daily
– BSA 0.91 to 1.1 m^2: 400 mg once daily</td><td>Take with or without food; swallow capsules whole</td><td>100 mg, 200 mg capsules</td></tr>
<tr><td>lorlatinib
(Lorbrena)</td><td>100 mg once daily</td><td>Take with or without food; swallow tablets whole and do not ingest if tablets are broken, cracked, or otherwise not intact</td><td>25 mg, 100 mg tablets</td></tr>
</table>

BSA = body surface area; NSCLC = non-small cell lung cancer

Consult package insert for each individual medication for additional detailed information related to dosing, including any premedication recommendations) and dose modifications.

Dosages (continued)

Drug	Dose	Administration	Available Strengths
EGFR Tyrosine Kinase Inhibitors			
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
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 nasogastric (NG) tube immediately; The container should be rinsed with 4 to 8 ounces of water and readministered	250 mg tablets
mobocertinib (Exkivity)	160 mg once daily	Take with or without food; Capsules should be swallowed whole and should not be opened, chewed, or dissolved	40 mg capsule
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
MET Kinase Inhibitors			
capmatinib (Tabrecta)	400 mg twice daily	Take with or without food Do not break, crush, or chew the tablets	150 mg, 200 mg tablets
tepotinib (Tepmetko)	450 mg once daily	Take with food Do not break, crush, or chew the tablets	225 mg tablet

BSA = body surface area; NSCLC = non-small cell lung cancer

Consult package insert for each individual medication for additional detailed information related to dosing, including any premedication recommendations) and dose modifications.

Dosages (continued)

Drug	Dose	Administration	Available Strengths
RET Kinase Inhibitors			
pralsetinib (Gavreto)	400 mg once daily	Take on empty stomach 1 hour before or 2 hours after a meal	100 mg capsule
selpercatinib (Retevmo)	< 50 kg: 120 mg twice daily ≥ 50 kg: 160 mg twice daily	Take with or without food; if taken with PPI, take with food. Swallow capsules whole, do not chew or crush	40 mg, 80 mg capsules
KRAS Protein Inhibitors			
sotorasib (Lumakras)	960 mg once daily	Take with or without food. May disperse tablets in 120 mL of non-carbonated, room-temperature water without crushing. Consume within 2 hours. Do not chew pieces of the tablet. Rinse container with additional 120 mL water and consume.	120 mg tablet
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

BSA = body surface area; NSCLC = non-small cell lung cancer

Consult package insert for each individual medication for additional detailed information related to dosing, including any premedication recommendations and dose modifications.

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-Positive ALCL

crizotinib (Xalkori) – relapsed or refractory, systemic ALK-positive ALCL

A multicenter, open label, phase 1/phase 2 study included 26 patients 1 to ≤ 21 years of age with relapsed or refractory, systemic, ALK-positive ALCL who were previously treated with ≥ 1 systemic treatment.[173] All patients received crizotinib orally twice daily at a dose of 280 mg/m^2 or 165 mg/m^2 until disease progression or unacceptable toxicity. Efficacy was measured by objective response rate (ORR) and duration of response (DOR) as assessed by an independent review committee (IRC). The median time to first response was 3.9 weeks (range, 3.5 to 9.1 weeks). ORR occurred in 88% (95% confidence interval [CI], 71 to 96) of patients, with 81% achieving complete response (CR) and 8% with partial response (PR). Of 23 patients with an objective response (OR), 57%, 39%, and 22% of patients maintained their response at 3, 6, and 12 months, respectively.

ALK-Positive IMT

crizotinib (Xalkori) – unresectable, recurrent or refractory ALK-positive IMT

A multicenter, open label, phase 1/2, single-arm study (ADVL0912; NCT00939770) was conducted in pediatric patients 1 to ≤ 21 years old with unresectable, recurrent, or refractory ALK-positive IMT.[174,175] Fourteen patients were enrolled with 12 receiving crizotinib at a dose of 280 mg/m^2 twice daily until disease progression or unacceptable toxicity; the remaining 2 patients received a lower dose. Patients enrolled were a median of 6.5 years old (range, 2 to 13 years) with the majority being female (64%) and White (71%). Most patients (86%) had received prior therapy with the most common prior therapy being surgery (57%). The ORR according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1 was found to be 86% (95% CI, 57 to 98) with 36% of patients exhibiting a complete response and 50% exhibiting a partial response. For patients who responded, 58% of patients responded for ≥ 12 months.

A multicenter, open label, single-arm study (A8081013; NCT01121588) was conducted in adults with unresectable, recurrent, or refractory ALK-positive IMT.[176] All patients (n=7) received crizotinib at a dose of 250 mg twice daily. The median age of patients enrolled was 38 years (range, 23 to 73) years with the majority being male (57%) and White (57%). Patients predominantly (86%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The primary efficacy endpoint was ORR according to RECIST version 1.1, and 5 of the 7 patients experienced a response with 1 complete response. For all 5 patients who responded, the duration of response was ≥ 6 months, and 2 patients had a duration of response of ≥ 12 months.

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.[177] All patients received 600 mg alectinib orally twice daily. The primary outcome measure was ORR based on RECIST v1.1 as assessed by an IRC. At the time of analysis (median follow-up of 4.8 months), ORR occurred in 48% (95% 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.[178] 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 DOR 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 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.[179] 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. At a data report of up to 5 years, PFS was prolonged with alectinib compared to crizotinib (HR, 0.43 [95% CI, 0.32 to 0.58]; median PFS of 34.8 months versus 10.9 months, respectively).[180] The 5-year OS rate was 62.5% (95% CI, 54.3 to 70.8) with alectinib compared to 45.5% (95% CI, 33.6 to 57.4) with crizotinib.

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

ALTA[181, 182]: 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 PR rates were 44% and 50% in Groups A and B, respectively. The investigator findings of median DOR for each

group were 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 was gastrointestinal in nature, followed by headache and cough. Grade 3 adverse effects included hypertension and CPK elevation.

brigatinib (Alunbrig) versus crizotinib (Xalkori) – ALK-positive NSCLC, ALK-targeted treatment-naïve

ALTA 1L[183, 184]: A multicenter, randomized, open-label trial compared the efficacy of brigatinib and crizotinib in 275 adults with advanced ALK-positive NSCLC who had not previously received an ALK-targeted therapy. Patients were required to have had at least 1 prior chemotherapy regimen in the locally advanced or metastatic setting and an ECOG Performance Status (PS) of 0 to 2; patients with CNS metastases were eligible for inclusion. The primary efficacy outcome was PFS, as evaluated by a blinded independent review committee (BIRC) according to RECIST v1.1. Patients were randomized 1:1 to brigatinib 180 mg once daily (with 7-day lead-in dosing) or crizotinib 250 mg orally twice daily. Overall baseline demographics included a median age of 59 years (range, 27 to 89; 32% ≥ 65 years old), 59% White, 39% Asian, 55% female, and 58% never smokers. At baseline, 93% had stage IV disease. At the data cutoff time, 46% of brigatinib-treated patients had events compared to 63% of those treated with crizotinib (HR, 0.49; 95% CI, 0.35 to 0.68; p<0.0001). The ORRs were 74% (15% CR, 59% PR) and 62% (9% CR, 53% PR) in the brigatinib- and crizotinib-treated groups, respectively (p=0.0342). The median DOR was 33.1 months (95% CI, 22 months to not estimable [NE]) in the brigatinib group and was 13.8 months (95% CI, 9.3 to 20.8) in the crizotinib group. Based on final data with a median follow-up of 40.4 months, the 3-year PFS was 43% with brigatinib and 19% with crizotinib (HR, 0.48; 95% CI, 0.35 to 0.66).[185] The median OS was not reached in either group (HR, 0.81, 95% CI: 0.53 to 1.22).

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

ASCEND-5[186]: 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. 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 ALT concentration (21%), increased 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[187]: 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 to11.1) 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[188]: A multicenter, randomized, open-label phase 1 trial examined the steady-state pharmacokinetics and safety of 3 different dosing schedules of ceritinib. 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.[189] 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[190]: 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. 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). [191] 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.[192] 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).[193] The included patients had histologically confirmed, recurrent or metastatic, ROS1-positive NSCLC, ECOG PS ≤ 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), or polymerase chain reaction (PCR) laboratory-developed tests. 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 74% (95% CI, 64 to 83) with 15% achieving a CR and 59% with PR. The

range for DOR was 2.4 to ≥ 55.2 months with 75% of patients achieving DOR ≥ 9 months, 57% achieving DOR ≥ 12 months, and 38% 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).[194] 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, DOR, and intracranial DOR. The ORR was 48% (95% CI, 42 to 55) with 4% achieving a CR and 44% having a PR. The median DOR 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).

lorlatinib (Lorbrena) versus crizotinib (Xalkori) – ALK-positive metastatic NSCLC, first-line therapy

CROWN, a global, randomized, phase 3 trial, compared the efficacy of lorlatinib with crizotinib in 296 patients with advanced ALK-positive NSCLC who had not received prior systemic therapy for metastatic disease.[195,196] The primary endpoint was PFS, as determined by a BIRC, which was improved with lorlatinib compared to crizotinib (28% versus 59% with events, respectively; HR disease progression or death, 0.28; 95% CI, 0.19 to 0.41; p<0.001). ORR occurred in 76% (95% CI, 38 to 83; 3% CR, 73% PR) with lorlatinib compared to 58% (95% CI, 49 to 66; 0 CR, 58% PR) with crizotinib. Response durations ≥ 6, 12, and 18 months in the lorlatinib versus crizotinib groups, respectively, were 89% versus 62%, 70% versus 27%, and 30% versus 11%. Intracranial response occurred in 82% (CR, 71%) of those treated with lorlatinib compared to 23% (CR, 8%) treated with crizotinib. In this subpopulation, the response duration ≥ 12 months was 79% with lorlatinib compared to 0% with crizotinib.

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.[197] 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).[198] 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).[199] 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. 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).[200,201]

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.[202] 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 patient-reported outcomes (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).[203] 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).[204]

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.[205] 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.[206] 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).[207] 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.[208] 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). DOR 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 DOR 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.[209] 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 DOR 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 to1.33, p=0.99).[210] 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.

mobocertinib - previously treated with chemotherapy

The efficacy of mobocertinib was evaluated in an international, open-label, multicohort, phase 1/2 study (NCT02716116).[211] Patients with histologically or cytologically confirmed EGFR exon 20 insertion mutation-positive metastatic or locally advanced (stage 3B or 4) NSCLC who had progressed on or after platinum-based chemotherapy received mobocertinib at a dose of 160 mg once daily until disease progression or intolerable toxicity. In the eligible patients (n=114) enrolled, the median age was 60 years (range, 27 to 84 years), 66% were female, 60% were Asian, 37% were Caucasian, and 3% were African American; 71% had never smoked; and 75% had an ECOG PS of 1. The majority of patients had metastatic disease (99%) and adenocarcinoma histology (98%); brain metastasis was present at baseline in 35% of patients. There was no limit on the number of previous systemic therapies; the median number of therapies was 2 (range, 1 to 7), and 43% had received past immunotherapy. Patients had measurable disease according to RECIST v1.1, adequate organ function, minimum life expectancy of ≥ 3 months, and normal QT interval according to ECG assessment. Patients were excluded if they received small-molecule anticancer therapy ≤ 14 days prior to the first dose of mobocertinib (except for reversible EGFR TKIs [erlotinib or gefitinib], which were allowed up to 7 days prior to the first dose of mobocertinib) or radiotherapy ≤ 14 days prior to first dose or had not recovered from radiotherapy-related toxicities. Exclusion criteria also included use of immunotherapy within 28 days of first dose or moderate to strong CYP3A inhibitors or inducers within 10 days prior to

first dose, leptomeningeal disease, interstitial lung disease or radiation pneumonitis that required steroids, drug-related pneumonitis, significant active cardiovascular disease, or uncontrolled hypertension. The primary endpoint was ORR using RECIST v1.1 as evaluated by BICR, and the secondary endpoint included duration of response by BICR. The ORR evaluated by BICR was 28% (95% CI, 20 to 37), the median DOR was 17.5 months (95% CI, 7.4 to 20.3), and 59% of patients had a DOR ≥ 6 months. The investigator-assessed ORR was 35% (95% CI, 26 to 45) and the median DOR was 11.2 months (63% with observed responses > 6 months).

osimertinib (Tagrisso) – second-line therapy

AURA3, an international, randomized, open-label, phase 3 trial involving 419 patients with metastatic NSCLC and confirmed T790M EGFR mutations, was conducted.[212, 213] 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. The ORR was 65% (95% CI, 59 to 70) in those treated with osimertinib and 29% (95% CI, 21 to 37) in those treated with traditional chemotherapy (all but 1 case in each group were due to PR). The median DOR was 11 months (95% CI, 8.6 to 12.6) in those treated with osimertinib compared to 4.2 months (95% CI, 3 to 5.9) in those treated with chemotherapy. In an OS analysis, the HR was 0.87 (95% CI, 0.67 to 1.12; p=0.277) for osimertinib compared to platinum-pemetrexed (median OS of 26.8 months [95% CI, 23.5 to 31.5] versus 22.5 months [95% CI, 20.2 to 28.9], respectively).[214] The authors attributed the lack of statistical significance as possibly being related to the high crossover rate.

osimertinib (Tagrisso) – first-line therapy

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.[215] 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 DOR 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 (HR 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.[216]

osimertinib (Tagrisso) – adjuvant therapy

ADAURA was a double-blind, placebo-controlled trial that assessed the efficacy of osimertinib, compared 1:1 with placebo following recovery from surgery and standard adjuvant chemotherapy, if used, in 682 patients with EGFR exon 19 deletions or exon 21 L858R mutation-positive NSCLC who had complete tumor resection.[217,218] The primary efficacy outcome was disease-free survival (DFS). DFS events were lower in those treated with osimertinib compared to placebo in the stage II to IIIa population (HR, 0.17; 9% CI, 0.12 to 0.23; p<0.0001) and in the stage Ib to IIIa population (HR, 0.2; 9% CI, 0.15 to 0.27; p<0.0001).

KRAS G12C-mutated NSCLC

sotorasib (Lumakras)

CODEBREAK100 (NCT03600883)[219,220]: This single-arm, open-label, multicenter, phase 2 study evaluated the safety and efficacy of sotorasib monotherapy administered orally at a dose of 960 mg once daily. Patients enrolled had locally advanced or metastatic KRAS G12C-mutated NSCLC confirmed in tumor tissue, with disease progression after receiving an immune checkpoint inhibitor and/or platinum-based chemotherapy, an ECOG PS of 0 or 1, and had ≥ 1 measurable lesion as defined by RECIST v1.1. Patients were excluded if they received > 3 previous lines of therapy, had previous treatment with a direct KRAS inhibitor, received systemic anticancer therapy within 28 days prior to initiation of sotorasib, or received therapeutic or palliative radiation therapy within 2 weeks prior to initiation of therapy. Patients were also excluded if they had active untreated brain metastases. The primary efficacy endpoint was BICR-determined ORR, complete or partial, according to RECIST v1.1 criteria. A total of 124 patients met enrollment criteria with ≥ 1 measurable lesion at baseline. Median age was 63.5 years (range, 37 to 80), 50% were female, 81% were former smokers, 11.9% were current smokers, and 4.8% never smoked. Among the patients, 92.1% received prior immune checkpoint inhibitor, 89.7% received prior platinum-based chemotherapy, and 81% received both therapies. Extra-thoracic metastasis occurred in bone (48%), brain (21%), and liver (21%). The ORR was observed in 37.1% (95% CI, 28.6 to 46.2), with a complete response rate of 3.2% and partial response rate of 33.9%. Disease control was observed in 80.6% (95% CI, 72.6 to 87.2). The median time to response was 1.4 months (range, 1.2 to 10.1), and the median DOR was 11.1 months (95% CI, 6.9 to NE). The median PFS was 6.8 months (95% CI, 5.1 to 8.2), and the median OS was 12.5 months (95% CI, 10 to NE). Treatment-related adverse events occurred in 69.8% of patients, which included grade 3 events (19.8%) and grade 4 events (0.8%). The most common adverse reactions (≥20%) reported were diarrhea, musculoskeletal pain, nausea, fatigue, hepatotoxicity, and cough.

MET-mutated NSCLC

capmatinib (Tabrecta)

GEOMETRY mono-1 was a phase 2, non-randomized, multicohort, multicenter, open-label trial in adult patients with advanced NSCLC identified to have mutation leading to MET exon 14 skipping (n=364).[221,222] Patients were required to have an ECOG performance status of 0 or 1, ALK and EGFR wild-type, and stage 3B/4 NSCLC. Patients with asymptomatic brain metastases were included. Capmatinib was dosed at 400 mg orally twice daily until disease progression or unacceptable toxicity. Efficacy was assessed in a specific subpopulation of 97 patients, including previously treated (n=69) or treatment-naïve patients (n=28) with MET-altered advanced NSCLC who lacked EGFR and ALK

mutations. The primary endpoint was defined as ORR, as assessed by BICR. Secondary endpoints that were assessed included DOR and safety. Among the patients evaluated for efficacy, 60% were female, 24% were Caucasian, 60% had never smoked, and the median age was 71 years (range, 49 to 90 years). The ECOG performance status at baseline was 0 (24%) or 1 (75%). Eighty percent of patients had adenocarcinoma and 12% had brain metastases. Of the previously treated population, 88% had received prior platinum-based chemotherapy. An analysis of the primary-endpoint in the efficacy population demonstrated an ORR of 68% (95% CI, 48 to 84) in the treatment-naïve patients and 41% (95% CI, 29 to 53) for patients with prior treatment. The median DOR was 12.6 months (95% CI, 5.5 to 25.3) and 9.7 months (95% CI, 5.5 to 13) in treatment-naïve and treatment-experienced patients, respectively.

tepotinib (Tepmetko)

The phase 2, single-arm, open-label, multicenter, multicohort VISION trial (NCT 02864992) evaluated 152 adult patients (69 treatment-naïve and 83 treatment experienced) receiving a 450 mg once-daily dose of tepotinib with advanced or metastatic NSCLC with confirmed METex14 skipping mutation.[223] Patients included also had ≥ 1 measurable lesion, as defined by RECIST v1.1 and had an ECOG performance status (PS) of 0 to 1. Notable exclusion criteria included patients having EGFR activating mutations, ALK rearrangements, neurologically unstable symptomatic brain metastases, inadequate cardiac function, and prior treatment with hepatocyte growth factor c-mesenchymal epithelial transition factor (HGF/c-MET) targeted pathway. The primary endpoint, based on patients who had ≥ 9 months of follow-up and had the presence of METex14 skipping mutation on either liquid or tissue biopsy, was ORR, including CR or PR, as defined by an IRC using RECIST v1.1. PR was defined as ≥ 30% reduction from baseline in lesion sum of longest diameter (SLD). Secondary endpoints included investigator-assessed ORR, DOR, PFS, and overall survival. A total of 99 patients received tepotinib and had at least 9 months of follow-up for efficacy assessment. The median age of patients in the study was 74 years, 45% were female, 74% were White, and 21% were Asian. Forty-six percent had a smoking history, while 22% and 77% had an ECOG score of 0 and 1, respectively. Adenocarcinoma (89%) was the most common histologic subtype, followed by squamous subtype (7%). Forty-three percent of cases had no previous courses of therapy for advanced or metastatic disease, while 33% had 1 previous course and 23% had ≥ 2 courses of therapy. Eleven percent of the cases had brain metastases identified on independent review. There were 66 patients in the liquid-biopsy group and 60 patients in the tissue-biopsy group. The primary end point of ORR assessment by IRC was 46% (95% CI, 36 to 57), with all responses achieving a PR (no CR). The response rate was 48% (95% CI, 36 to 61) in the liquid-biopsy group and 50% (95% CI, 37 to 63) in the tissue-biopsy group. The median DOR in the combined-biopsy group was 11.1 months (95% CI, 7.2 to NE), in the liquid-biopsy group 9.9 months (95% CI, 7.2 to NE), and in the tissue-biopsy group 15.7 months (95% CI, 9.7 to NE). A total of 27 patients had positive results with both liquid- and tissue-biopsy methods. MET alterations can be detected in either liquid or tissue biopsy samples. Response rate was similar in both groups, including those previously treated and treatment naïve. The investigator-assessed ORR was 56% (95% CI, 45 to 66), and there was no difference in response with previously-treated and treatment-naïve patients. Observed tumor shrinkage was seen by both IRC (89%) and assessed by investigator (88%). Responses occurred within 6 weeks after initiation of tepotinib. PFS, as assessed by IRC, had a median duration of 8.5 months (95% CI, 6.7 to 11) in the combined-biopsy group, 8.5 months (95% CI, 5.1 to 11) in the liquid-biopsy group, and 11 months (95% CI, 5.7 to 17.1) in the tissue-biopsy group. The results were similar in the investigator assessment groups. Adverse events occurred in 98% of the patients in the VISION trial (safety population n=152). Twenty-five percent of patients had grade 3 or higher adverse effects, and grade 4 adverse effects occurred in 2% of patients. The most common grade 3 adverse

event was peripheral edema (7%). Serious adverse events occurred in 15% of patients and were mainly peripheral edema, pleural effusion, or dyspnea. Thirty-three percent of patients received dose reductions due to treatment-related adverse events, and 11% discontinued therapy due to adverse reactions. There were 21 reported deaths during this study, with investigators attributing 1 death from ILD to tepotinib.

RET fusion-positive NSCLC

pralsetinib (Gavreto)

ARROW, a multicenter, non-randomized, open-label clinical trial, evaluated the efficacy of oral pralsetinib 400 mg once daily in patients with RET fusion-positive metastatic NSCLC.[224] Patients with either metastatic RET fusion-positive NSCLC who had progressed on platinum-based chemotherapy or treatment-naïve patients with metastatic NSCLC were enrolled as 2 separate cohorts. Pralsetinib was continued until disease progression or unacceptable toxicity. The primary efficacy measures were ORR and DOR, as assessed by a BICR according to RECIST v1.1. A total of 87 patients with metastatic RET fusion-positive NSCLC who were previously treated with platinum chemotherapy were enrolled. Nearly all patients in this cohort (99%) had metastatic disease, and 43% had either a history of or current CNS metastasis. ECOG PS was 0 or 1 (94%) or 2 (6%). Patients received a median of 2 prior systemic therapies (range, 1 to 6), including treatment with anti-programmed cell death 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) therapy or kinase inhibitors. ORR was 57% (95% CI, 46 to 68), with a CR of 5.7%. Median DOR was NE (95% CI, 15.2 months to NE); DOR was ≥ 6 months was reported in 80% of patients. Among 8 patients with CNS metastasis, 4 patients experienced intracranial lesion response, including 2 patients with a CNS CR; 75% of CNS responders experienced a DOR ≥ 6 months. Among the 27 patients in the treatment-naïve RET fusion-positive NSCLC cohort, all had metastatic disease. ECOG performance status was 0 to 1 in 96% of patients, and 37% had a history of or current CNS involvement. Pralsetinib led to an ORR of 70% (95% CI, 50 to 86), with CR achieved in 11% of patients. The median DOR was 9 months (95% CI, 6.3 to NE), and 58% of patients experienced a DOR ≥ 6 months.

selpercatinib (Retevmo)

LIBRETTO-001 was a phase 1/2, non-randomized, multicohort, multicenter, open-label trial in adult patients with advanced or metastatic solid tumors, including RET fusion-positive NSCLC.[225,226,227] Selpercatinib was dosed 160 mg orally twice daily until disease progression or unacceptable toxicity for all types of tumors. The primary endpoint was defined as ORR and DOR, as assessed by means of a BICR using RECIST 1.1. All patients had an ECOG score of 0, 1, or 2 and adequate hematologic, hepatic, and renal function. Patients with asymptomatic brain metastases were included. Specific RET-mutations included M918T, extracellular cysteine mutation, V804M, V804L, and others. Patients with synonymous, frameshift, or nonsense RET mutations or additional known oncogenic driver were excluded per protocol. Efficacy in the NSCLC cohort was established in 105 adult patients with RET fusion-positive NSCLC who required systemic therapy. Patients received prior platinum-based chemotherapy with a median of 3 prior systemic therapies (range, 1 to 15), including 55% with prior anti-programmed cell death 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) therapy. Among the 105 patients with prior systemic therapy, the ORR was 64% (95% CI, 54 to 73) with CR in 1.9% of patients. The median DOR was 17.5 months (95% CI, 12 to NE) and lasted ≥ 6 months among 81% of the responders. Within this population, 11 patients had CNS metastases, of which 10 were considered responders; all responders achieved DOR ≥ 6 months. In 39 patients who were naïve to systemic

therapy, ORR was 85% (95% CI, 70 to 94); no CR was reported. The DOR was NE months (95% CI, 12 to NE) and the response lasted ≥ 6 months in 58% of the responders.

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.[228,229] 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).

Thyroid Cancer

pralsetinib (Gavreto)

ARROW, a multicenter, non-randomized, open-label, multi-cohort clinical trial, evaluated the efficacy of oral pralsetinib 400 mg once daily in patients with RET mutant MTC and RET fusion-positive thyroid cancer.[230] Patients with MTC had either progressed following cabozantinib or vandetanib or were treatment-naïve. In those with MTC previously treated with cabozantinib or vandetanib (n=55), the ORR was 60% (95% CI, 46 to 73; CR, 1.8%; PR, 58%) with a median DOR of not reached (range, 15.1 months to NE), of which 79% had a DOR ≥ 6 months. In cabozantinib- or vandetanib-naïve patients with MTC (n=29), the ORR was 66% (95% CI, 46 to 82; CR, 10%; PR, 55%; median DOR, NE), of which 84% had a DOR ≥ 6 months. In the 9 patients with RET fusion-positive thyroid cancer the ORR was 89% (95% CI, 52 to 100; all PR; median DOR, NE), all of which had a DOR ≥ 6 months.

selpercatinib (Retevmo)

LIBRETTO-001 was a phase 1/2, non-randomized, multicohort, multicenter, open-label trial in adult patients with advanced or metastatic solid tumors, including RET-fusion thyroid cancer and RET-mutant MTC.[231,232] Selpercatinib was dosed 160 mg orally twice daily until disease progression or unacceptable toxicity for all types of tumors. The primary endpoint was defined as ORR and DOR, as assessed by means of a BICR using RECIST 1.1. Patients with asymptomatic brain metastases were included. Select specific RET-mutations included M918T, extracellular cysteine mutation, V804M, and V804L. Patients with synonymous, frameshift, or nonsense RET mutations or additional known oncogenic driver were excluded per protocol. The RET Fusion-positive thyroid cancer cohort included 27 adult and pediatric patients ≥ 12 years of age with metastatic RET fusion-positive thyroid cancer. Primary histologies included papillary thyroid cancer (78%), poorly differentiated thyroid cancer (11%), anaplastic thyroid cancer (7%), and Hürthle cell thyroid cancer (4%). Patients were radioactive iodine (RAI)-refractory (if RAI was appropriate) and either received another prior systemic treatment (sorafenib, lenvatinib, or both) (n=19) or had not received any additional therapy (n=8). Among the 19 patients with prior systemic therapy, the ORR was 79% (95% CI, 54 to 94), including a CR of 5.3%. The DOR was 18.4 months (95% CI, 7.6 to NE) and lasted ≥ 6 months among 87% of the responders. In the 8 patients who only received prior RAI, the ORR was 100% (95% CI, 63 to 100). The DOR was NE and lasted ≥ 6 months among 75% of the responders. Efficacy in the MTC cohort included patients ≥ 12 years of age with advanced or metastatic RET mutant-positive disease. The MTC cohort included 55 patients who received prior cabozantinib or vandetanib with a median of 2 prior systemic therapies

(range, 1 to 8). The ORR was 69% (95% CI, 55 to 81), with a CR of 9%. The median DOR was NE (95% CI, 19.1 months to NE) and response lasted ≥ 6 months among 76% of responders. In 88 patients who were cabozantinib- and vandetanib-treatment naïve, the ORR was 73% (95% CI, 62 to 82), including CR of 11%. The DOR was 22 months (95% CI, NE to NE) and lasted ≥ 6 months among 61% of responders.

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/m^2/day, days 1 to 5, every 21 days) plus best supportive care (BSC) or BSC alone.[233] 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.[234] 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).[235] 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 ≥ 2 years 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 59% (95% CI, 45 to 72) with 13% achieving a CR and 46% with PR. The range for DOR was 2.8 to ≥ 47.8 months, with 72% of patients achieving DOR ≥ 6 months, 66% achieving DOR ≥ 9 months, and 56% 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.

selpercatinib (Retevmo) – RET fusion-positive solid tumors

A multicenter, open-label, phase 1/2, ongoing cohort study (LIBRETTO-001, NCT03157128) was conducted to evaluate the efficacy of selpercatinib for patients with locally advanced or metastatic RET fusion-positive solid tumors.[236, 237] Patients enrolled (n=41) had a RET fusion-positive tumors other than NSCLC and thyroid cancer and had experienced disease progression on/following past systemic therapy or did not have a satisfactory alternative option. Patients enrolled were a median of 50 years old (range, 21 to 85 years) with the majority being female (54%) and White (68%). Most patients had an ECOG performance status score of 0 to 1, and the most common cancers were pancreatic adenocarcinoma (27%; n=11), colorectal (24%; n=10), and salivary (10%; n=4). All patients received a starting dose of selpercatinib of 160 mg twice daily. The ORR was 43.9% (95% CI, 28.5 to 60.3) with the majority of patients who responded demonstrating a partial response (39%), and 5% of patients experiencing a complete response. The median duration of response was 24.5 months, and the median PFS was 13.2 months (95% CI, 7.4 to 26.2). The 1-year PFS was 53.1% (95% CI, 34.1 to 68.8), and the 2-year PFS was 32.1% (95% CI, 14 to 51.7). For the 3 most common tumor types, the ORR was 54.5% (95% CI, 23.4 to 83.3) for pancreatic adenocarcinoma, 20% (95% CI, 2.5 to 55.6) for colorectal cancer, and 50% (95% CI, 6.8 to 93.2) for salivary cancer. The most common grade 3 or higher adverse events were hypertension (22%), increased ALT (16%), and increased AST (13%). Authors concluded selpercatinib provided a meaningful benefit in patients with RET fusion-positive solid tumors with a similar safety profile observed with other indications.

META-ANALYSES

A meta-analysis was conducted to examine the effect of EGFR TKIs on PFS and OS in patients with NSCLC.[238] 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.[239] 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.

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.[240] 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.

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.[241] 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%). Another meta-analysis of the EGFR TKIs (40 trials; n=13,352) found that greater toxicity was generally found with dacomitinib and afatinib.[242]

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.[243] 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).

A meta-analysis included phase 2 and 3 clinical trials to compare the efficacy and safety of first-line medications for ALK-rearranged NSCLC.[244] A search of PubMed, Embase, Cochrane Library, and ClinicalTrials.gov databases through September 2021 identified a total of 9 randomized controlled trials with 2,484 patients with stage 3 or 4 or recurrent NSCLC with ALK-rearrangement. The analysis used Bayesian ranking profiles. The highest PFS was demonstrated with lorlatinib (63.7%), followed by alectinib 300 mg (17.6%), and alectinib 600 mg (7.2%). Although, most of the studies reported immature OS data, there was no significant difference among the ALK-TKIs or between the ALK-TKIs and chemotherapy for OS. The highest probability for better OS was reported with alectinib 600 mg

(35.9%), followed by lorlatinib (30.6%), and ensartinib (11.8%). There was also no significant difference in ORR between the ALK-TKIs. The ALK-TKIs demonstrated significantly better ORR compared to chemotherapy. The highest probability for better ORR was reported with alectinib 300 mg (37%), followed by lorlatinib (21%), and alectinib 600 mg (13%). The highest incidence of grade ≥ 3 adverse events was reported with ceritinib (60%), followed by lorlatinib (18%). Ensartinib is not FDA-approved at this time.

SUMMARY

Lung cancer continues to be the number 1 cause of cancer death in the US with 130,180 deaths predicted to occur in 2022. 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, each of these mutations occur in ≤ 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 sensitizing mutations in the epidermal growth factor receptor (EGFR), B-Raf proto-oncogene (BRAF) V600E point mutations, mesenchymal epithelial transition (MET) exon 14 skipping, and Kirsten Rat Sarcoma (KRAS) point mutations, along with anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), rearranged during transfection (RET) gene rearrangements, and neurotrophic tyrosine receptor kinase (NTRK) gene fusions. 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 NSCLC and may be considered in some patients with squamous NSCLC.

Based on consensus guidelines, patients with advanced or metastatic NSCLC should generally receive a targeted agent in the first-line setting where possible. 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. For patients with EGFR exon 20 insertion positive metastatic disease with disease progression, NCCN recommends mobocertinib (Exkivity) as an option for subsequent therapy. American Society of Clinical Oncology (ASCO) guidelines, updated in 2021, recommend osimertinib in the first-line setting for patients with T790M, L858R, or exon 19 deletion mutations (evidence quality: high; strength of recommendation: strong). Likewise, if the tumor is found to be ALK-positive upon initial testing, alectinib (Alecensa), brigatinib (Alunbrig), lorlatinib (Lorbrena) ceritinib (Zykadia), or crizotinib (Xalkori) are recommended as a first-line agents by the NCCN guidelines (all category 1 with alectinib, brigatinib, and lorlatinib being listed as preferred). The ASCO guidelines recommend alectinib or brigatinib in the first-line setting of ALK driver mutations (evidence quality: high; strength of recommendation: strong). For patients found to be ROS1 positive, crizotinib, entrectinib (Rozlytrek), or ceritinib are options, with crizotinib or entrectinib being listed as NCCN preferred options. This mirrors the ASCO guidelines, which recommend crizotinib or entrectinib in the first-line setting (type: informal consensus; evidence quality: low; strength of recommendation: moderate). Patients with BRAF V600E mutations may be treated first-line with dabrafenib (Tafinlar) plus trametinib (Mekinist) according to both the NCCN guidelines (category 2A) and the ASCO guidelines (type: informal consensus; evidence quality: low; strength of recommendation: moderate).

When an NTRK gene fusion is identified, NCCN and ASCO guidelines list larotrectinib (Vitrakvi) or entrectinib as preferred first-line options. For patients with advanced NSCLC and a MET exon 14 skipping mutation, NCCN guidelines list capmatinib (Tabrecta), tepotinib (Tepmetko), or crizotinib as 2A options but designate capmatinib or tepotinib as preferred, which concurs with the ASCO guideline recommendation of capmatinib or tepotinib in the first-line setting (type: informal consensus; evidence quality: low; strength of recommendation: moderate). NCCN preferred agents for first-line use in patients with RET rearrangements include selpercatinib (Retevmo) or pralsetinib (Gavreto). ASCO guidelines include selpercatinib (type: informal consensus; evidence quality: low; strength of recommendation: weak) while stating that pralsetinib may be offered; however, this is a provisional recommendation because confirmatory data were pending at the time of publication (type: informal consensus; evidence quality: low; strength of recommendation: weak). For patients with KRAS G12c mutation disease, NCCN guidelines recommend sotorasib (Lumakras) for patients with progression following platinum-based chemotherapy (category 2A).

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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