The Role of Pharmacists in Optimizing Molecular Testing with Evolving Biomarkers and Treatment for Non-Small Cell Lung Cancer


1 Department of Pharmaceutical Sciences, Faculty of Science and Engineering, Dibrugarh University, Dibrugarh-786004, Assam, India.
2 Department of Pharmacy, Girijananda Chowdhury Institute of Pharmaceutical Sciences-781017, Guwahati, Assam, India.
3 Department of Pharmacy, Himalayan Pharmacy Institute, Majhitar, East Sikkim-737136, Sikkim, India.
4 Life Sciences Division, Institute of Advanced Study in Science and Technology, Guwahati-781035, Assam, India.
5 Karnataka College of Pharmacy, Hegde Nagar, Bengaluru- 560064, Karnataka, India.

Abstract
Molecular testing and the development of targeted therapies have revolutionized the treatment of non-small cell lung cancer (NSCLC). Despite the advantages of molecular testing in patients with NSCLC and guideline recommendations, there is no specific standard testing method, resulting in variable testing practices based on institution protocol and access. Pharmacists can help to improve coordination of care around appropriate testing as results are important in determining the most appropriate targeted treatment course. The majority of patients with NSCLC are tested for PD-L1, EGFR, ALK, ROS1, and BRAF mutations. These biomarkers and their corresponding targeted therapies are more understood than the remaining biomarkers, such as KRAS, RET, MET exon 14 (METex14), and NTRK. Multiple new and emerging therapies target these latter biomarkers, and this article will focus on these lesser-known biomarkers. As the treatment of NSCLC becomes increasingly biomarker-driven and more therapies are added to the armamentarium for the management of NSCLC, pharmacists will be called upon to assist the oncology care team to optimize NSCLC treatment to improve patient outcomes.
(Keywords: Lung cancer; biomarker; oncology pharmacists; molecular testing)
1. Introduction
In the United States, lung cancer is becoming the leading cause of cancer fatalities in both men and women [1]. The low survival rate of lung cancer is mostly due to the fact that by the time patients are diagnosed, half of them are already in an advanced stage of the disease. The US Preventive Services Task Force drafted revised screening recommendations in 2020 in an attempt to diagnose more patients at an earlier stage of lung cancer when disease cure is a possibility; however, more effective and tolerable therapies for the advanced disease remain an urgent need [2].

Patients with lung cancer may present with cough, hemoptysis, dyspnoea, weight loss, or chest pain, or a tumor may be suspected based on screening computed tomography scan or incidentally discovered on imaging performed for another reason [3]. The diagnostic approach should be individualized based on tumor size and location, presence of mediastinal or distant disease, patient comorbidities, and local expertise. Some patients will undergo initial surgical excision and others a biopsy. Immunohistochemical staining is used to make a diagnosis of non-small cell lung cancer (NSCLC) and determine if the tumor is an adenocarcinoma, squamous cell, adenosquamous carcinoma, large cell carcinoma, carcinoid type, or a less common subtype [3]. Adenocarcinoma is the most common subtype and numerous genetic variants have been identified that drive therapy selection [4]. Tissue should be preserved for biomarker testing for patients with NSCLC. Approximately 40% to 45% of adenocarcinoma NSCLC tumors have mutations with targeted therapies currently available and an additional 25% of tumors express KRAS mutations. However, these numbers do not include NSCLC mutations of unknown clinical significance or mutations that are still unknown and could yield future directions for treatment. Table 1 summarizes the various genes and proteins that are being targeted to treat non-small cell lung cancer [5].

Table 1. Genes and proteins targeted in the treatment of non-small cell lung cancer

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Gene/ Protein</th>
<th>Frequency</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>Epidermal growth factor receptor</td>
<td>17-32%</td>
<td>Both a gene and its receptor tyrosine kinase. also known as ERBB1</td>
</tr>
<tr>
<td>KRAS</td>
<td>Kirsten rat sarcoma viral oncogene homolog</td>
<td>20-30%</td>
<td>A gene that encodes the K-Ras protein as part of the RAS/MAPK pathway.</td>
</tr>
<tr>
<td>ALK</td>
<td>Anaplastic lymphoma kinase</td>
<td>3-13%</td>
<td>Both a gene and its receptor tyrosine kinase.</td>
</tr>
<tr>
<td><strong>MET</strong></td>
<td>Mesenchymal-epithelial transition factor</td>
<td>2-5%</td>
<td>Both a gene and its receptor tyrosine kinase. also known as c-Met.</td>
</tr>
<tr>
<td>---------</td>
<td>---------------------------------------</td>
<td>------</td>
<td>------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>RET</strong></td>
<td>Rearranged during transfection</td>
<td>1.2-2%</td>
<td>Both a gene and its receptor tyrosine kinase. it technically is an abbreviation for &quot;rearranged during transfection&quot;.</td>
</tr>
<tr>
<td><strong>BRAF</strong></td>
<td>v-Raf murine sarcoma viral oncogene homolog B</td>
<td>1-3%</td>
<td>A gene that encodes the B-Raf protein, with V600E the most effectively targeted oncogenic mutation.</td>
</tr>
<tr>
<td><strong>ROS7</strong></td>
<td>Cross oncogene 1</td>
<td>1-2%</td>
<td>Both a gene and its receptor tyrosine kinase</td>
</tr>
<tr>
<td><strong>NTRK</strong></td>
<td>Neurotrophic tyrosine receptor kinase</td>
<td>0.2%</td>
<td><strong>NTRK7, NTRK2, NTRK3</strong> genes encode tropomyosin receptor kinases (TRKA, TRKB, TRKC).</td>
</tr>
<tr>
<td><strong>HER2</strong></td>
<td>Human epidermal growth factor</td>
<td>2-9%</td>
<td>Both a gene and its receptor tyrosine kinase. also known as ERBB2</td>
</tr>
<tr>
<td><strong>NRG7</strong></td>
<td>Neuregulin 1</td>
<td>0.2%</td>
<td>Both a gene and a cell adhesion molecule that interacts with the ERBB receptor tyrosine kinases</td>
</tr>
<tr>
<td><strong>MEK</strong></td>
<td>Mitogen-activated protein kinase</td>
<td>1%</td>
<td>Proteins (MEK1 and MEK2) that are part of the MAPK pathway.</td>
</tr>
</tbody>
</table>

More than 20 therapies targeting 8 different biomarkers are currently recommended by the National Comprehensive Cancer Network (NCCN) guidelines panel for the management of metastatic NSCLC. The incorporation of targeted and immunotherapies in the management of metastatic NSCLC is credited for an improvement in the 5-year survival of patients from 25%
to up to 50% in patients who are eligible for targeted therapies, with variation reflecting the tumor biomarker present [6].

2. Biomarker Testing

A biomarker is considered *predictive* if there is an association between the biomarker, a specific therapy, and patient outcome [7]. A prognostic biomarker reflects an association between patient survival and the biomarker that is independent of treatment received because the biomarker reflects innate tumor behavior. Currently, \textit{KRAS} is considered a prognostic biomarker, whereas sensitizing \textit{EGFR} mutations, the \textit{ALK} fusion oncogene, \textit{ROS1} gene fusions, \textit{NTRK} gene fusions, \textit{RET} rearrangements, \textit{MET} ex14 skipping mutations, \textit{BRAF} V600E point mutations, and programmed cell death protein ligand 1 (PD-L1) expression are predictive biomarkers [8].

2.1 Biomarker Testing Strategies

Biomarker testing recommendations in NSCLC are rapidly evolving. The College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) updated their 2013 guidelines for molecular testing used to guide targeted therapy of NSCLC in 2018 [9]. This guideline was endorsed with a few modifications by the American Society of Clinical Oncology (ASCO) later that year [10]. The current version of the NCCN guidelines endorses testing for a broader array of biomarkers that reflects current research. The NCCN guidelines panel recommends a minimum of the following biomarkers be tested for all patients with metastatic, nonsquamous NSCLC: \textit{EGFR} mutations, \textit{BRAF} mutations, \textit{ALK} fusions, \textit{ROS1} fusions, \textit{NTRK} gene fusions, \textit{RET} rearrangements, \textit{MET} ex14 skipping mutations, and PD-L1 expression [11]. These somatic (spontaneously originating) mutations are generally considered mutually exclusive, with just 1% to 3% of NSCLC tumors harboring concurrent mutations. Patient factors such as smoking status, ethnicity, and histology are associated with specific genetic variants; however, these features should not be used to select patients for testing [12]. Targeted therapies directed at all biomarkers included in broad molecular profiling are not currently approved by the FDA; however, testing is still recommended because patients may be directed to clinical trials based on the molecular profile [13].

Several methods may be employed to determine biomarker expression. The NCCN guidelines panel recommends that testing be done at an accredited laboratory that meets Clinical Laboratory Improvement Amendment standards for accreditation [14]. Biomarker testing methods include next-generation sequencing (NGS), multiplex polymerase chain reaction (PCR), immunohistochemistry (IHC), and fluorescence in situ hybridization (FISH). The NCCN guidelines panel does not endorse any specific commercially available biomarker assay. Table 2 outlines the most common biomarker testing assays [15].
<table>
<thead>
<tr>
<th>Molecular Methods</th>
<th>Variant Types</th>
<th>Sensitivity (%)</th>
<th>Turnaround time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sizing assays</td>
<td>+/-</td>
<td></td>
<td>3 to 4 days</td>
</tr>
<tr>
<td>PCR and Sanger sequencing</td>
<td>✓</td>
<td>✓</td>
<td>20-50</td>
</tr>
<tr>
<td>PCR and pyrosequencing</td>
<td>✓</td>
<td>+/-</td>
<td>20-50</td>
</tr>
<tr>
<td>PCR and mass spectrometry</td>
<td>✓</td>
<td>+/-</td>
<td>1-10</td>
</tr>
<tr>
<td>PCR and single-base</td>
<td>✓</td>
<td></td>
<td>1-10</td>
</tr>
<tr>
<td>qPCR and digital PCR</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Allele-specific PCR</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FISH</td>
<td>✓</td>
<td>+/-</td>
<td>✓</td>
</tr>
<tr>
<td>NGS: targeted amplicon capture</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>NGS: targeted hybridization capture</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>NGS: whole-exome</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>NGS: whole genome</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

PCR: polymerase chain reaction; qPCR: quantitative PCR; FISH: fluorescent in situ hybridization.
2.1.1 Next-Generation Sequencing (NGS)
Massively parallel or NGS is a broad molecular profiling technique that detects panels of mutations and gene fusions as well as copy number variations [16]. It is important to note that NGS represents a type of testing platform and individual NGS assays will detect different genes and abnormalities depending on the design of the NGS assay. NGS is the preferred testing method when it is available to the patient and adequate tissue is obtainable [17]. Testing with ribonucleic acid (RNA)-based NGS should be considered in patients with NSCLC that do have identifiable mutations on deoxyribonucleic acid (DNA)-based NGS, especially in never smokers, as RNA-based NGS will also detect fusion events [18]. In clinical practice, targeted NGS panels are preferred over whole-exome or whole-genome testing because they provide higher coverage of genomic regions of interest in an adequate time frame [19, 20].

2.1.2 Real-time PCR (RT-PCR)
Another type of mutation screening assay that detects multiple biomarkers simultaneously is RT-PCR [21]. In general, RT-PCR does not detect gene fusions (e.g. ROS1 and ALK mutations are gene fusion events). The Mass ARRAY and SNapshot Multiplex System are examples of RT-PCR assays [22]. While RT-PCR can detect more than 50 point mutations, it detects fewer biomarkers than NGS panels[23].

2.1.3 Sanger Sequencing
Sanger sequencing refers to DNA sequencing by capillary electrophoresis. Although this testing was previously the gold standard, the ability to sequence only 1 gene at a time now limits its use. If a sample has fewer than 25% to 30% tumor cells, tumor enrichment methodologies should be used with Sanger sequencing[24].

2.1.4 Immunohistochemistry (IHC)
The expression of the gene as assessed by IHC may be used as a surrogate for fusion testing in some scenarios[25]. The CAP/IASLC/AMP guidelines indicate the performance of IHC is suboptimal for EGFR mutations; however, the use of ALK IHC is equivalent to FISH for routine biomarker assessment. IHC is also used to determine PD-L1 expression[26].

2.1.5 Fluorescent in situ Hybridization (FISH)
Targeted gene amplification, copy number, and/or rearrangement is often assessed by FISH. Despite the availability of targeted therapies directed at specific biomarkers and broad endorsement of biomarker testing in multiple guidelines, there is variable uptake for biomarker testing in clinical practice [26]. Rates of biomarker testing have improved in recent years for EGFR, ALK, and ROS1 with reports of testing before therapy initiation in 88% to 100% of patients. Barriers to testing may include inadequate sample size and the need for re-biopsy to obtain adequate tissue; lack of payer coverage of testing; and performance of tests as single-gene tests rather than a broad panel assay [27]. In 2018, the Centres for Medicare & Medicaid Services (CMS) approved a national coverage decision for NGS testing in patients with recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer who had not been previously tested using the same NGS test and decided to seek further cancer treatment [28]. The NCCN guidelines panel recommends that an adequate volume of tissue be obtained for both diagnosis and molecular testing and a strategy of rapid on-site evaluation during biopsy may be used to ensure specimens are adequate for molecular testing [11]. Another strategy to improve the rate of testing is the use of reflex testing rather than waiting
for a physician’s order. Ensuring biomarker testing has analytical validity, discerns an appropriate magnitude of difference for an endpoint of value, and is backed by a high level of evidence will facilitate adoption by both payers and clinicians alike [29].

The FDA maintains a website of tests cleared or approved by the Centre for Devices and Radiological Health to analyze variations in the sequence, structure, or expression of DNA and RNA to diagnose a disease or medical conditions, infection with an identifiable pathogen, or determine genetic carrier status [30]. Currently, the Oncomine Dx Target Test is the only NGS biomarker assay approved by the FDA for use in patients with NSCLC to detect single-nucleotide variants and deletions in multiple genes from DNA (e.g. ALK, BRAF, EGFR, ERBB2, KRAS, MET, and RET) and fusions in ROS1 from RNA [31].

3. Personalized Pharmacotherapy
The management of NSCLC has changed significantly in the past few years with the presence or absence of biomarkers now guiding the treatment approach. The platinum-based doublet therapy that was standard of care for decades is now reserved for patients without driver mutations who are not candidates for immunotherapy [3, 32, 33]. The majority of patients with NSCLC are tested for PD-L1, EGFR, ALK, ROS1, and BRAF mutations [15, 34]. Patients with advanced, nonsquamous NSCLC who lack driver mutations and are candidates for immunotherapy should have PD-L1 testing completed. Patients with high PD-L1 expression (>50% tumor proportion score [TPS]), nonsquamous histology, and performance status of 0 to 1 are candidates for single-agent atezolizumab or pembrolizumab [3, 33]. Similar patients with rapidly progressive disease may be offered platinum doublet therapy with immunotherapy. Patients with negative (TPS 0%) and low positive PD-L1 expression (TPS 1%-49%), nonsquamous histology, and performance status of 0 to 1, who are eligible for chemoimmunotherapy should be offered a regimen such as carboplatin, pemetrexed, and pembrolizumab or another NCCN-recommended regimen, as determined by patient-specific factors [35]. Patients with advanced NSCLC with driver mutations should be offered therapy based on those mutations, as survival rates with targeted treatments for these patients are superior to that of chemotherapy/chemoimmunotherapy. Given many clinicians are familiar with therapies targeting EGFR, ALK, ROS1, and BRAF, the remainder of this article will focus on biomarkers with recently approved therapies and those currently under review by the FDA for NSCLC [36].

Figure 1: NSCLC treatment based on biomarkers
3.1 METex14 Skipping Mutations

The MET gene encodes for the hepatocyte growth factor receptor (HGFR). MET activation promotes cell survival, proliferation, motility, invasion, and epithelial-mesenchymal transition [12]. There are 3 primary types of MET mutations: (a) amplification resulting in high expression of the receptor; (b) tyrosine kinase domain mutations resulting in constitutive activation of the receptor; (c) splicing mutations resulting in skipping of exon 14 and loss of Y1003, a binding site required for the ubiquitin-mediated degradation of the protein [37]. While oncogenesis can be driven by each of these mechanisms, the type of MET mutation a patient possesses determines which therapies can be used. For example, capmatinib, tepotinib, and savolitinib are indicated for use against METex14 skipping mutations [38]. METex14 skipping mutations occur in 3% to 4% of patients with NSCLC and are associated with a poor prognosis. METex14 mutations are more frequently observed in patients older than 70 years, those who smoke, and those with a sarcomatoid histology [39]. NGS-based assays interrogating MET as part of a wider gene panel are preferred for detecting MET mutations [40].

Capmatinib received FDA approval in adult patients with metastatic NSCLC and a METex14 skipping mutation, based on a prospective, open-label, multiple-cohort, phase 2 study of 364 patients with advanced NSCLC with a METex14 skipping mutation or MET amplification [41, 42]. The overall response rate (ORR) in patients with advanced NSCLC with a METex14 skipping mutation treated with capmatinib was 41%; the median progression-free survival (PFS) was 5.4 months in previously treated patients and 12.4 months in treatment-naïve patients [42]. In patients with MET amplification, response rates ranged from 7% to 12% in patients who had tumor tissue with a gene copy number of less than 4 versus 6 to 9, respectively. Gene copy number refers to the number of repeated genome sequences (ie, the higher the copy number, the more copies of MET are present to inhibit). The MET gene amplification cohorts were closed for futility at the interim analysis. The most common adverse effects (AEs) included edema (51%), nausea (45%), vomiting (28%), increased creatinine (24%), dyspnea (23%), and fatigue (22%). The FoundationOne CDx assay is the approved companion diagnostic test for capmatinib [43].

Crizotinib is a multikinase inhibitor with activity against ALK and ROS1 mutations, as well as MET mutations. While it is not FDA approved for patients with NSCLC with a METex14 skipping mutation, it is recommended by the NCCN guidelines panel for use in this setting. In a prospective cohort of 65 patients with METex14-altered NSCLC, 32% of patients had an objective response to crizotinib; the median PFS was 7.3 months. The most common AEs included edema (51%), vision disorder (45%), nausea (41%), diarrhea (39%), and vomiting (29%). Notably, none of the patients in this study had high levels of MET amplification as based on gene copy number [44].

Tepotinib, an inhibitor that targets METex14 skipping mutations, was approved in February 2021 [45]. Paik et al. presented results of 99 patients with metastatic NSCLC with a METex14 skipping mutation with at least 9 months of follow-up in the VISION study, a phase 2 cohort study of tepotinib [46]. The investigators reported an objective response rate of 46% and median PFS of 8.5 months in patients with a liquid-biopsy or combined liquid-tissue biopsy and 11 months in the tissue biopsy group. A response rate of 55% was observed in 11 patients with brain metastases. Similar to other MET inhibitors, common AEs included
edema (63%), nausea (26%), diarrhea (22%), and increased creatinine (18%) [47].

Savolitinib is another kinase inhibitor that targets the METex14 skipping mutation and is under clinical investigation. It has been studied in combination with osimertinib in 18 patients in the phase 1b TATTON study. The objective response rate was 44% for the combination therapy, with nausea (67%), rash (56%), and vomiting (50%) as the most frequently reported AEs [48].

3.2 Neurotrophic Receptor Tyrosine Kinase (NTRK) Gene Fusion
The NTRK genes (NTRK1, NTRK2, NTRK3) encode for the synthesis of the tropomyosin receptor kinase (TRK) proteins TRKA, TRKB, and TRKC, which help to regulate pain, proprioception, appetite, and memory [49]. NTRK fusions are present in approximately 0.2% of solid tumors and function as driver oncogenesis. NTRK fusions do not display a predisposition for a subtype of NSCLC, gender, or smoking status. NTRK fusions may be identified by NGS, RT-PCR, or FISH [50].

Two NTRK inhibitors, larotrectinib, and entrectinib, are approved by the FDA for use in patients with solid tumors expressing NTRK gene fusions [51, 52]. Larotrectinib was evaluated in a phase 1 study in 55 adult and pediatric patients with a variety of solid tumors with an NTRK fusion, including 4 patients with lung cancer. An ORR of 80% was observed, with 16% of patients demonstrating a complete response. With a median follow-up of 9.9 months, the median PFS has not been reached; after 1 year of follow-up, 55% of patients remained progression-free on larotrectinib. Frequently reported treatment-related AEs of larotrectinib include increased liver enzymes (38%), dizziness (25%), nausea (16%), fatigue (16%), and constipation (16%) [53].

Entrectinib is approved by the FDA in both patients with a tumor expressing NTRK gene fusion and adult patients with metastatic NSCLC whose tumors are ROSI-positive [54]. Approval in patients with NTRK tumors was based on a combined analysis of 3 ongoing phase 1 or 2 clinical trials of 54 adult patients with advanced or metastatic NTRK gene fusion-positive tumors. Ten patients with NSCLC were included in the study. With a median follow-up of 12.9 months, 57% of patients had an objective response to entrectinib, including 4 patients with a complete response; the median PFS was 11.2 months. In the overall safety population (n = 355), the most frequently reported grade 3 to 4 AEs were anemia (11%), increased weight (7%), dyspnea (6%), and fatigue (4%) [55].

On-target AEs of NTRK inhibitors is related to the role of the TRK pathway in appetite, balance, and pain perception. In a review of 96 patients treated with a TRK inhibitor, Liu et al. described the incidence, presentation, and management of these AEs. Weight gain greater than 5% of body weight was observed in 53% of patients and approximately 10% of all patients have been prescribed a medication to mitigate weight gain. Dizziness, described as positional light-headedness, imbalance, or vertigo, was reported in 41% of patients. The most effective strategy to manage dizziness was dose reduction; pharmacotherapy with meclizine led to symptom improvement in about half of patients. Patients with orthostatic hypotension benefited from midodrine and/or fludrocortisone. Paresthesias were reported in 18% of patients, most often involving a perioral distribution and/or “sunburn” sensation; symptoms generally improved after the first month of therapy. Lastly, withdrawal pain, described as full-body ache, muscle pain, and/or allodynia was observed in approximately one-third of patients. Withdrawal pain was reported with both temporary and permanent discontinuation.
Pain persisted between 10 and 26 days in patients permanently discontinuing therapy. Approximately half of the patients were given opioid or non-opioid therapy to manage withdrawal pain; however, it was helpful in just 23% of patients. Gradual tapering of NTRK inhibitors over 4 weeks may be beneficial in patients who experience withdrawal pain. Other less common neurologic AEs include cognitive impairment, mood disorders, sleep disturbance, and dysarthria [56].

3.3 Rearranged During Transfection (RET) Fusion

The RET proto-oncogene encodes for the development of a receptor tyrosine kinase that facilitates normal embryonic development [57]. In healthy tissue, RET plays a key role in renal and nervous system development [39]. Variants leading to RET fusion are observed in 1.2% to 2% of patients with adenocarcinoma NSCLC. RET fusions result in constitutively active, ligand-independent tyrosine kinase signaling and oncogenesis. RET fusion is observed more frequently in patients who have never smoked compared with those who have. RET fusions may be identified by NGS, RT-PCR or FISH [12].

Selercatinib and pralsetinib are recommended as first-line therapy in patients who test positive for RET rearrangement in metastatic NSCLC [14]. Both are preferred over cabozantinib and vandetanib, which are less selective, multikinase inhibitors. Selercatinib was evaluated in a phase 1/2 trial in 105 patients with RET fusion-positive NSCLC who had previously received platinum-based chemotherapy and 39 previously untreated patients; the ORR was 64% and median PFS was 16.5 months in previously treated patients [58]. With a medium follow-up of 9.2 months, the median PFS was not evaluable in previously untreated patients receiving selercatinib where an ORR of 85% was observed. Selercatinib does penetrate the central nervous system and 91% of 11 patients with measurable lesions had an objective intracranial response with a median duration of response of 10.1 months. Selercatinib received accelerated approval in May 2020 for adult patients with metastatic, RET fusion-positive NSCLC. The most frequent treatment-related AEs reported with selercatinib include xerostomia (36%), diarrhea (25%), hypertension (17%), and increased liver enzymes (22%). Selercatinib is associated with QTc prolongation, creating a need for close evaluation of concomitant medications [59].

Pralsetinib was approved by the FDA in September 2020 for adult patients with metastatic RET fusion-positive NSCLC as detected by an FDA-approved test [60]. Currently, the only approved test is the Oncomine Dx Target Test [61]. Pralsetinib was evaluated in a phase 1/2, nonrandomized, open-label, single-arm, multicohort, multicenter clinical trial in 80 patients with RET fusion-positive NSCLC who had previously received platinum-based chemotherapy and 26 previously untreated patients [62]. An abstract presented at the ASCO Annual Meeting in 2020 reported an ORR of 61% in previously treated patients and 73% in treatment-naïve patients receiving pralsetinib for advanced NSCLC. The most common AEs reported with pralsetinib included constipation (35%), hypertension (28%), fatigue (35%), musculoskeletal pain (32%), diarrhea (24%), cough (23%), edema (20%), and pyrexia (20%) [60].

3.4 Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS)

KRAS is the most frequently mutated oncogene in human cancers and is present in approximately 20% to 30% of NSCLC adenocarcinoma tumors [12, 63]. KRAS encodes for a guanosine triphosphatase that cycles between an active and inactive state to regulate cell
signal transduction. Somatic KRAS mutations result in constitutive activation of guanine nucleotide-binding proteins, which activates downstream signaling and leads to uncontrolled cell proliferation and survival [64]. Historically, the presence of a KRAS mutation is associated with poor outcomes. KRAS mutations are associated with resistance to currently available targeted and platinum-based therapies; however, some subgroups of patients with KRAS mutations may benefit from anti-PD-L1 immunotherapies [63]. KRAS mutations are more frequently observed in patients who smoke, males, Whites, and those of African ancestry compared with females and patients of Asian ancestry. KRAS mutations can be detected by RT-PCR and NGS; they are typically mutually exclusive with other driver mutations [12].

Currently, there are no KRAS inhibitors approved by the FDA for any malignancy. Sotorasib, a small-molecule tyrosine kinase inhibitor (TKI) that selectively binds to the KRAS, recently received breakthrough therapy designation from the FDA and a new drug application has been submitted through the FDA’s Real-Time Oncology Review pilot program [65, 66]. A phase 1, multicenter, open-label trial of sotorasib enrolled 59 patients with NSCLC harboring the KRAS p.G12C mutation, a KRAS mutation observed in approximately 13% of NSCLCs [63]. All patients with NSCLC had received prior platinum-based chemotherapy and 90% had received anti-PD-1 or anti–PD-L1 therapy. After a median follow-up of 11.7 months, one-third of patients with NSCLC treated with sotorasib had a confirmed response and 88% of patients had disease control. The median PFS for all patients with NSCLC was 6.3 months. Patients with KRAS p.G12C, KRAS wildtype, and other KRAS mutations have similar clinical features, treatment, and survival; however, the potential of an actionable mutation for the KRAS p.G12C mutation may improve outcomes in this subgroup [67]. Phase 2 results from the CodeBreaK 100 clinical study, evaluating sotorasib in 126 patients with KRAS G12C-mutant advanced NSCLC, were presented at the IASLC 2020 World Conference on Lung Cancer in January 2021. Sotorasib showed an objective response rate (ORR) and disease control rate (DCR) of 37.1% and 80.6%, respectively, with a median duration of response of 10 months [65].

Gastrointestinal toxicities including diarrhea, nausea, vomiting, and abdominal pain, often associated with TKI therapy, were observed in approximately one-third of patients in the sotorasib phase 1 study. Other common AEs in patients receiving sotorasib include fatigue (23%) and elevations of aminotransferase levels (12%-13% of patients) [63].

4. Emerging Biomarkers

MET amplification is both a primary driver mutation and a pathway identified in resistance to EGFR TKIs [39]. De novo MET amplification occurs in 2% to 4% of patients with newly diagnosed, metastatic NSCLC and is associated with poor outcomes. Currently, the definition of high-level MET amplification is unclear because different investigators define it differently [68]. In a phase 1 study of 40 patients categorized as low, medium, or high MET amplification, crizotinib was associated with a 40% response rate in patients with high levels of MET amplification [69]. Similarly, a phase 1 study of 55 patients with MET-dysregulated NSCLC reported an ORR of 47% in the group of patients with the highest gene copy number of MET [70]. Capmatinib and crizotinib are endorsed by the NCCN guidelines panel for use in patients with NSCLC with high-level MET amplification [14].
The **ERBB2** (HER2) biomarker is well established in breast cancer; however, the role in NSCLC is still being evaluated. **ERBB2** exon 20 mutation occurs in 2% to 9% of NSCLC adenocarcinoma tumors. Current literature suggests more benefit with the combination of monoclonal antibodies targeting **ERBB2** and chemotherapy or **ERBB2** antibody-drug conjugates than with **ERBB2**-targeted TKIs [39]. In a phase 2 basket trial, 18 patients with advanced NSCLC with **ERBB2** mutations received ado-trastuzumab emtansine [71]. The investigators observed an ORR of 44% with ado-trastuzumab emtansine and a median PFS of 5 months; toxicities included myelosuppression, infusion reactions, and elevated liver enzymes. A phase 2 trial of 42 patients with NSCLC with **ERBB2** overexpression or an **ERBB2**-activating mutation reported an ORR of 62% in patients receiving fam-trastuzumab deruxtecan with an estimated PFS of 14 months. Myelosuppression was a frequent AE in patients receiving fam-trastuzumab deruxtecan and 12% of patients presented with drug-related interstitial lung disease [72]. Ado-trastuzumab emtansine and fam-trastuzumab deruxtecan are recommended by the NCCN Guidelines for patients with **ERBB2** (HER2) mutations [73].

5. The Role of the Pharmacist

Like many other cancers, knowledge of the pathobiology of NSCLC is shifting treatment away from traditional cytotoxic chemotherapy to a more targeted approach [74]. With that, more patients are being managed at home and are being evaluated less frequently in the clinic. In general, transitioning more patients to targeted therapies is a positive change; however, it has revealed new gaps in the current cancer care delivery model for educating and monitoring patients. Oral targeted therapy management is complex given the fragmentation of care, the cost of therapy, tolerability and safety of medications, issues related to patient access, patient education, patient self-care management, and the monitoring and follow-up in the oncology patient population [75]. Also, patients and caregivers must be educated on the safe handling and disposal of oral oncolytic [76].

As the treatment of NSCLC becomes increasingly biomarker-driven, pharmacists must have a thorough understanding of the clinical impact that genetic mutations have on NSCLC treatment and the various methods available for testing each of these actionable markers. Before dispensing medication or when encountering patients with NSCLC in the hospital or clinic setting, pharmacists should review mutation testing results to ensure the prescribed therapy is appropriate for that patient. Given that the cost of novel therapies typically exceeds $150,000 per year, many patients will need support in the process of obtaining oral targeted therapies [77]. Pharmacists should be aware of the Patient Assistance & Reimbursement Guide; a resource developed by the Association of Community Cancer Centers. The guide is updated annually as a resource to help patients alleviate the financial burden of their medications [78]. Table 3 outlines pharmacotherapy used in NSCLC [79, 80].

### Table 3. Pharmacology of targeted therapy in NSCLC

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Drug Generic (Brand)</th>
<th>Mechanism of Action</th>
<th>Dose and Administration</th>
<th>Notable Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RET</strong></td>
<td>Cabozantinib (Cabometyx)</td>
<td>AXL, FLT-3, KIT, MER,</td>
<td>60 mg once daily</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Indications</td>
<td>Dosage</td>
<td>Side Effects</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------------------------------</td>
<td>------------------------------------------------</td>
<td>--------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Pralsetinib</strong></td>
<td>MET, RET, ROS1, VEGFR-1-3 inhibitor</td>
<td>400 mg once daily on an empty stomach</td>
<td>• Hepatotoxicity</td>
<td></td>
</tr>
<tr>
<td>(Gavreto)</td>
<td></td>
<td></td>
<td>• Hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Tepmetko)</td>
<td></td>
<td>• Interstitial lung disease</td>
<td></td>
</tr>
<tr>
<td><strong>Selencatinib</strong></td>
<td>RET inhibitor</td>
<td>400 mg or 160 mg twice daily with or without food</td>
<td>• QTc prolongation</td>
<td></td>
</tr>
<tr>
<td>(Retevmo)</td>
<td></td>
<td></td>
<td>• Hepatotoxicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EGFR, VEGFR, RET, SRC inhibitor</td>
<td>300 mg once daily with or without food</td>
<td>• Hypertension</td>
<td></td>
</tr>
<tr>
<td><strong>Vandetanib</strong></td>
<td></td>
<td></td>
<td>• Interstitial lung disease</td>
<td></td>
</tr>
<tr>
<td>(Caprelsa)</td>
<td></td>
<td></td>
<td>• QTc prolongation</td>
<td></td>
</tr>
<tr>
<td><strong>Capmatinib</strong></td>
<td>MET inhibitor</td>
<td>400 mg twice daily with or without food</td>
<td>• Hepatotoxicity</td>
<td></td>
</tr>
<tr>
<td>(Tabrecta)</td>
<td></td>
<td></td>
<td>• Interstitial lung disease</td>
<td></td>
</tr>
<tr>
<td><strong>NTRK</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Entrectinib</strong></td>
<td>ALK, ROS1, MET inhibitor</td>
<td>600 mg once daily with or without food</td>
<td>• Edema</td>
<td></td>
</tr>
<tr>
<td>(Rozlytrek)</td>
<td></td>
<td></td>
<td>• Hepatotoxicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Neurotoxicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• QTc prolongation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Visual disturbances</td>
<td></td>
</tr>
</tbody>
</table>

**METex14**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indications</th>
<th>Dosage</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crizotinib</strong></td>
<td>ALK, ROS1, MET inhibitor</td>
<td>250 mg twice daily with or without food</td>
<td>• Bradycardia</td>
</tr>
<tr>
<td>(Xalkori)</td>
<td></td>
<td></td>
<td>• Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Interstitial lung disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• QTc prolongation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Visual disturbances</td>
</tr>
<tr>
<td><strong>Tepotinib</strong></td>
<td>MET inhibitor</td>
<td>450 mg once daily with food</td>
<td>• Hepatotoxicity</td>
</tr>
<tr>
<td>(Tepmetko)</td>
<td></td>
<td></td>
<td>• Interstitial lung disease</td>
</tr>
</tbody>
</table>

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The Quality Oncology Practice Initiative (QOPI) program standards for certification require documentation of the patients’ ability to adhere to chemotherapy administered outside of the health care setting and to assess chemotherapy adherence at defined meaningful intervals [81]. Patient counseling and symptom management are services that a pharmacist can provide that fulfill multiple QOPI measures and may be eligible for reimbursement via the CMS Merit-Based Incentive Payment System [82]. Retrospective analyses of pharmacist-led, collaborative patient education and AE management in patients with NSCLC in community-based oncology settings have demonstrated AEs of a TKI could be successfully managed by the pharmacist and were associated with low rates of discontinuing therapy because of AEs [83, 84]. Patients were contacted regularly by phone and encouraged to use prescribed medications or over-the-counter products to manage symptoms. Pharmacists contacted the provider if they felt a patient needed additional evaluation or medication. An excellent resource for counseling patients about oral chemotherapy is the Oral Chemotherapy Education Medication Sheets, which are updated frequently [85].

In general, TKIs are hepatically metabolized and subject to drug-drug interactions (DDIs) mediated by cytochrome P450 3A4. DDIs have been reported in 23% to 78% of patients receiving cancer therapy, with potential outcomes including both therapeutic failure and increased toxicity [86, 87]. Pharmacists must ensure they obtain comprehensive and accurate information from patients on the use of other medications and natural products to ensure patient safety and optimal drug therapy [88].

6. Conclusion
Pharmacists across the health care spectrum are involved in the transition of cancer therapy to personalized medicine with therapies specifically targeted to the oncogenic pathway of the tumor. Ensuring the right patient receives the right targeted therapy, at the right dose, at the right time, and via the right method of administration is essential to optimizing outcomes for patients with NSCLC with driver mutations. Managing DDIs and AEs, mitigating financial toxicity, facilitating access to medications, and improvements in medication adherence are key roles pharmacists serve in the management of patients with NSCLC. On-going research into novel biomarkers and effective targeted therapies is expected to further improve outcomes for patients with NSCLC.

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