Predictive and Prognostic Biomarkers and Related Therapies in Non–Small Cell Lung Cancer

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Abstract

Non–small cell lung cancer (NSCLC) is the leading form of lung carcinoma in the United States. Systemic chemotherapy has remained the mainstay of treatment; however, advances in the identification of driver mutations have allowed the development of therapies that specifically target precise cell processes. These biomarkers have predictive value in determining the likelihood a patient will respond to a certain therapy and prognostic value in determining patient survival independent of therapy received. Common driver mutations found in NSCLC that are reviewed in this article include epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), *ROS1*, and Kirsten rat sarcoma viral oncogene (*KRAS*). This article also discusses targeted therapies available for each driver mutation including afatinib, alectinib, brigatinib, ceritinib, crizotinib, erlotinib, gefitinib, and osimertinib. Upcoming targeted therapies that are currently undergoing clinical trials are explored as well.

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Non–small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancer cases and can be divided into two major types: squamous cell carcinoma and nonsquamous cell carcinoma (Howlader et al., 2016). Nonsquamous cell carcinoma includes adenocarcinoma, large cell carcinoma, and other cell types. One of the main risk factors for lung cancer is smoking tobacco. However, adenocarcinoma occurs most frequently in patients who are nonsmokers. Additional risk factors include other comorbid conditions, personal or family history of cancer, and exposure to carcinogens such as arsenic and asbestos (Janerich et al., 1990).

Treatment options for patients with NSCLC have been rapidly evolving from conventional systemic chemotherapy with widespread cytotoxic effects toward personalized medicine with targeted therapies.

Although conventional systemic chemotherapy is still a cornerstone of lung cancer treatment, a revolution in the treatment of NSCLC has been driven by the identification of specific targets and agents geared to act on these specific processes. These findings have expanded the diagnostic workup from traditional histology to histology with additional evaluation for the presence and/or absence of driver mutations (Chan & Hughes, 2015).

Driver mutations are predictive biomarkers indicative of therapeutic efficacy, and in some instances inefficacy, of targeted drug therapy (Sequist & Neal, 2015). Rising from somatic cells, driver mutations result in the initiation or maintenance of cancerous cells, as they are found in genes responsible for encoding essential proteins for normal cell growth and mortality (Luo & Lam, 2013).

Along with serving as predictive biomarkers, driver mutations can also have prognostic value, which indicates a patient's survival independent of treatment received. For example, patients harboring the Kirsten rat sarcoma viral oncogene (*KRAS*) mutation are known to have poorer outcomes compared with patients who have the wild-type *KRAS* genotype (Slebos et al., 1991). Common driver mutations include epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), *ROS1*, and *KRAS*. These mutations are important predictive and prognostic factors in the determination of treatment for patients with NSCLC (Figure).

MOLECULAR TESTING

Molecular testing identifies changes in chromosomes, genes, or proteins of an individual patient and allows practitioners to tailor treatment to the specific patient in order to provide personalized medicine. Evidence of a driver mutation warrants targeted drug therapy, as patients are more likely to respond to these therapies; therefore, molecular testing is advised per the National Comprehensive Cancer Network (NCCN) guidelines. Testing for EGFR and ALK is now a category 1 recommendation and ROS1 testing is now a category 2A recommendation for patients with nonsquamous or not otherwise specified NSCLC (NCCN, 2017). Patients exhibiting squamous cell histology who are nonsmokers, have had a small biopsy sample, or have mixed histology reports can be considered for testing (NCCN, 2017). Results of molecular testing should be used to determine appropriate therapy for patients, as all NSCLC medications targeting driver mutations require testing by a US Food and Drug Administration (FDA)-approved test as part of their approved indication. Molecular testing has changed the paradigm for treating patients with NSCLC and has the potential to allow for discovery of new tumor markers that can be used to generate more targeted therapies.

Epidermal Growth Factor Receptor

EGFR has an extracellular domain and an intracellular tyrosine kinase domain that occupies exon 18-24. A ligand binds to EGFR, which results in autophosphorylation and activation of tyrosine kinase activity and further pathways. This signaling affects cell proliferation, apoptosis, and angiogenesis (Cheng et al., 2012). This mutation is most commonly found in adenocarcinomas, women, non-smokers, and patients of Asian descent (Arechaga-Ocampo et al., 2013). EGFR exon 19 deletions account for 44% of all *EGFR* tyrosine kinase mutations, while exon 21 mutations account for 41% (Gazdar, 2009). These mutations are known as sensitizing mutations, which lead to constituent activation of the receptor independent of ligand binding. Sensitizing mutations indicate benefit from treatment with EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy (Gazdar, 2009; Sequist et al., 2008). EGFR-TKIs used in the treatment of NSCLC include afatinib (Gilotrif), erlotinib (Tarceva), and gefitinib (Iressa).

Afatinib, erlotinib, and gefitinib have all been FDA approved for first-line treatment of patients with exon 19 deletions or exon 21 single-point substitution L858R (NCCN, 2017). Use of these targeted agents as first-line therapy improves progression-free survival (PFS) vs. conventional chemotherapy. In 2016, the first head-to-head comparison of oral EGFR-TKIs was conducted in the LUX-Lung 7 trial, which compared the use of afatinib with gefitinib (Park et al., 2016). The LUX-Lung 7 study demonstrated that PFS (11 months vs. 10.9 months, $p = .017$) and time to treatment failure were better in the afatinib vs. gefitinib group; however, it is important to note that overall survival data are not yet mature (Park et al., 2016). Expected adverse effects were seen with each agent; diarrhea and rash were

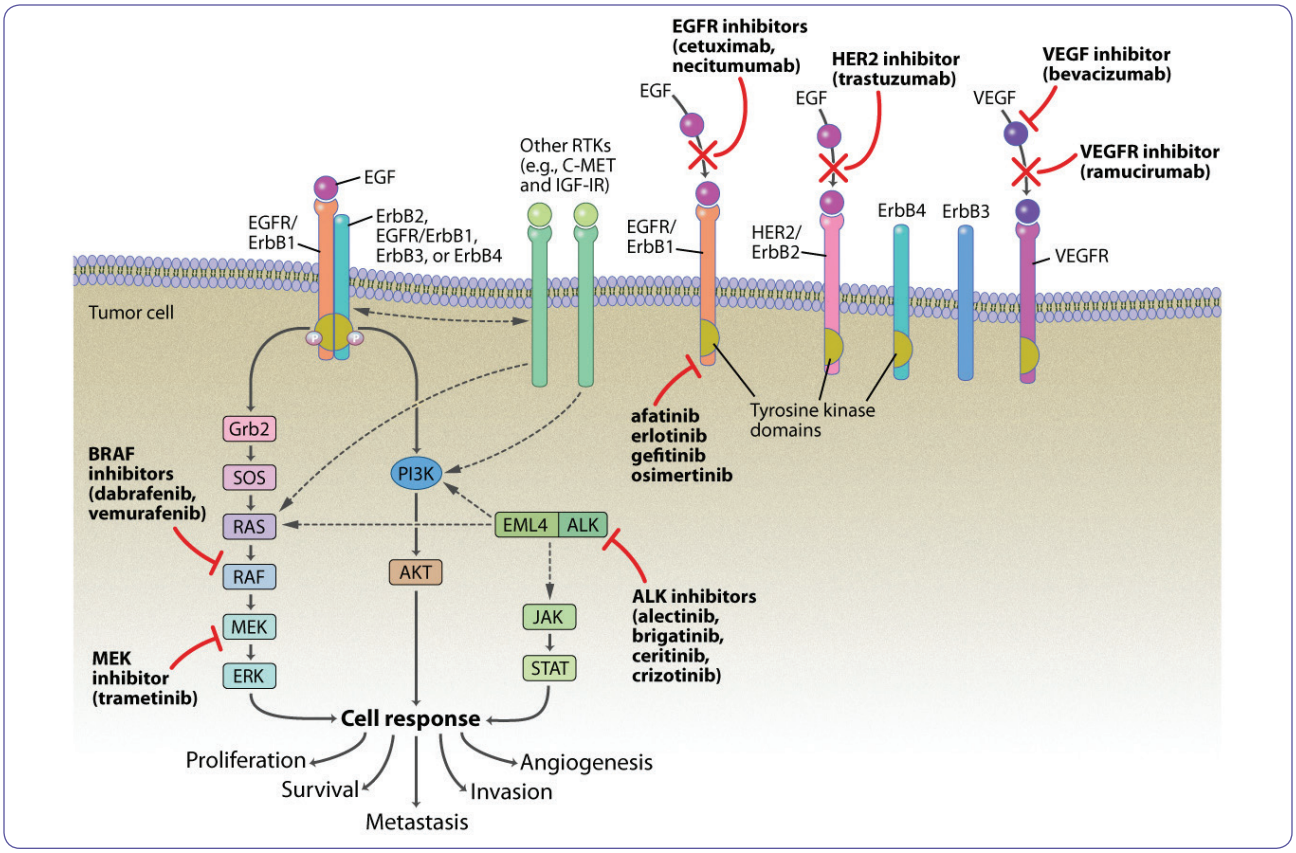

Figure. An overview of molecular pathways in non–small cell lung cancer. EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor; RTK = receptor tyrosine kinase; BRAF = v-Raf murine sarcoma viral oncogene homolog B; ALK = anaplastic lymphoma kinase; STAT = signal transducer and activator of transcription.

more frequent with afatinib, while elevated liver enzymes and interstitial lung disease were more frequent with gefitinib (Park et al., 2016). Erlotinib has never been studied in direct comparison to the other oral EGFR-TKIs. It is important to note that all agents are considered equally efficacious in current guidelines and should be used based on patient-specific parameters (NCCN, 2017; Rosell et al., 2012; Douillard et al., 2014; Sequist et al., 2013).

The use of EGFR-TKIs in sensitizing mutations can result in resistance at a median of 8 to 16 months after starting therapy (Yu et al., 2013). This resistance can be caused by a secondary mutation known as T790M, an exon 20 insertion, which can be found in 60% of patients who have been treated with EGFR-TKI therapy (NCCN, 2017). In 2015, the FDA granted osimertinib (Tagrisso) accelerated approval as second-line and subsequent therapy for patients with *EGFR* T790M mutations based on data from a phase III trial confirming a response rate of 71% and PFS of 10.1 months with osimertinib vs. 31% and 4.4 months with platinum-pemetrexed therapy (FDA, 2015; Mok et al., 2016). Another drug, rociletinib, was being studied in this patient population, but drug development has been suspended by the manufacturer after being denied accelerated approval due to a change in study results. A recent rociletinib trial update reported a response rate of 45% compared with the originally published response rate of 50% (Sequist et al., 2015; Sequist, Soria, & Camidge, 2016).

EGFR and ALK are also client proteins for heat shock protein 90 (HSP90). Tumor cells are more HSP90 dependent than normal cells for proliferation and survival because the oncoproteins are misfolded and require augmented HSP90 activity for correction (Kamal et al., 2003). The inhibition of this pathway is thought to be another potential mechanism for overcoming resistance. Inhibitors of HSP90 induce apoptosis and slow the growth of

xenografts harboring *EGFR* T790M (Johnson et al., 2015). Medications involved in this pathway are currently undergoing clinical trials. A recent phase II study did show partial responses with the treatment of an HSP90 inhibitor given in combination with erlotinib; however, duration of treatment was limited due to adverse effects, and the primary endpoint of complete plus partial response rate was not met (Johnson et al., 2015). The discovery of this pathway demonstrates the ability to uncover new markers and develop targeted agents to continue expanding personalized medicine.

Anaplastic Lymphoma Kinase

Tumors with *ALK* gene rearrangement are found in about 2% to 7% of NSCLC patients in the United States (NCCN, 2017). Continuous kinase activity results from the fusion between echinoderm microtubule-associated protein-like 4 genes and the *ALK* gene (Waxman & Fossella, 2016). The kinase activity leads to uncontrolled cell growth and proliferation (Waxman & Fossella, 2016). This mutation is more common in younger, nonsmoking patients (Arechaga-Ocampo et al., 2013).

Crizotinib (Xalkori) is FDA approved for first-line treatment for *ALK*-positive tumors due to its high response rates of 60% in clinical trials (NCCN, 2017; Solomon et al., 2014). It can also be used subsequently for patients who have received conventional chemotherapy as first-line therapy (NCCN, 2017; Shaw et al., 2013). Patients treated with crizotinib can see rapid response rates, but progression can occur within 7 to 12 months (Shaw et al., 2013).

Ceritinib (Zykadia), alectinib (Alecensa), and brigatinib (Alunbrig) are FDA approved for second-line treatment in patients who have progressed on crizotinib therapy (NCCN, 2017). Ceritinib demonstrated a response rate of 56% in these patients, with a PFS of 7 months (Shaw et al., 2013). Based on a recent phase III study, ceritinib received a category 1 recommendation to be used in the first-line setting as an alternative to crizotinib (NCCN, 2017). This study included patients with untreated NSCLC and showed a median PFS of 16.6 months with ceritinib therapy vs. 8.1 months with conventional chemotherapy (Soria et al., 2017). Alectinib showed a 50% response rate in these patients with a median duration of response of 11.2 months (Ou et al., 2016). Brigatinib showed a 54% response rate, with a median PFS of 12.9 months when dosed at 90 mg for 7 days followed by 180 mg daily (Kim, Tiseo, Ahn, & Reckamp, 2017). This newly approved medication is expected to be released for patient use during the summer of 2017. Other targeted therapies continue to be studied for the treatment of patients with *ALK* rearrangement, including lorlatinib (Solomon et al., 2016).

Table. Common Adverse Effects Associated With Targeted Therapies for Non–Small Cell Lung Cancer

Generic (Brand)	Indication(s)	Treatment line	Mechanism of action	Dosing	Common adverse effects
Afatinib (Gilotrif)	*EGFR exon 19* deletions or *exon 21 (L858R)* substitution mutations	First line	Inhibition of EGFR (ErbB1), HER2 (ErbB2), HER4 (ErbB4), tyrosine kinase activity	• 40 mg by mouth daily • Available in 20-mg, 30-mg, and 40-mg tablets • Take on empty stomach at least 1 hour before or 2 hours after meals	• Skin rash, acneiform (79%–90%) • Diarrhea (75%–96%) • Nausea (21%–25%) • Vomiting (13%–23%) • Epistaxis (17%) • Elevated liver function tests (6%–18%)
Erlotinib (Tarceva)	*EGFR exon 19* deletions or *exon 21 (L858R)* substitution mutations	First line	Inhibition of EGFR-tyrosine kinase activity	• 150 mg by mouth daily • Available in 25-mg, 100-mg, and 150-mg tablets • Take on an empty stomach at least 1 hour before or 2 hours after meals	• Skin rash (49%–85%) • Dyspnea (45%) • Cough (33%–48%) • Diarrhea (20%–62%) • Nausea (23%–33%) • Vomiting (13%–23%) • Infection (4%–24%)

Note. EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor. Information from Boehringer Ingelheim Pharmaceuticals, Inc. (2013); Kateo et al. (2015); Schwarz Pharma Manufacturing (2004); AstraZeneca Pharmaceuticals LP (2015a, 2015b); Chugai Pharmaceuticals Co., Ltd. (2015); ARIAD Pharmaceuticals, Inc. (2017); Novartis Pharmaceuticals Corporation (2014); Pfizer Inc. (2011); Sahu et al. (2013).

Table. Common Adverse Effects Associated With Targeted Therapies for Non–Small Cell Lung Cancer (cont.)

Generic (Brand)	Indication(s)	Treatment line	Mechanism of action	Dosing	Common adverse effects
Gefitinib (Iressa)	*EGFR exon 19* deletions or *exon 21 (L858R)* substitution mutations	First line	Inhibition of EGFR-tyrosine kinase activity with higher affinity for exon 19 deletion or exon 21-point mutation	• 250 mg by mouth daily • Available in 250-mg tablets • May take with or without meals	• Skin rash (52%) • Diarrhea (29%–47%) • Nausea (18%) • Vomiting (13%–14%) • Insomnia (15%) • Proteinuria (8%–35%) • Elevated transaminases (8%–40%)
Osimertinib (Tagrisso)	*EGFR* T790M mutations	Progressed on or after first-line EGFR-TKI therapy	Inhibition of EGFR tyrosine kinase activity	• 80 mg by mouth daily • Available in 40-mg and 80-mg tablets • May take with or without meals	• Pancytopenia (44%–63%) • Skin rash (41%) • Diarrhea (42%) • Nausea (17%) • Nail disease (25%)
Alectinib (Alecensa)	*ALK*-positive tumors	Progressed on or are intolerant to crizotinib	TKI of ALK and RET	• 600 mg by mouth twice daily • Available in 150-mg capsules • Take with food	• Anemia (56%) • Elevated transaminases (51%) • Constipation (34%), • Diarrhea (16%) • Hyperglycemia (36%) • Edema (30%) • Musculoskeletal pain/ myalgia (29%)
Brigatinib (Alunbrig)	*ALK*-positive tumors	Progressed on or are intolerant to crizotinib	TKI of ALK, insulin-like growth factor 1 receptor (IGF-1R), FLT-3, and ROS1	• 90 mg daily for 7 days; if tolerated, increase dose to 180 mg daily • Available in 30-mg and 90-mg tablets • May take with or without meals	• Nausea, vomiting (23%–40%) • Diarrhea (38%) • Elevated creatine phosphokinase (30%) • Headache (27%) • Hypertension (21%) • Cough, dyspnea (21%–34%)
Ceritinib (Zykadia)	*ALK*-positive tumors	First line; progressed on or are intolerant to crizotinib	TKI of ALK, insulin-like growth factor 1 receptor (IGF-1R), insulin receptor (InsR), and ROS1	• 750 mg by mouth daily • Available in 750-mg capsules • Take on an empty stomach at least 1 hour before or 2 hours after meals	• Decreased hemoglobin (84%) • Diarrhea (86%), • Constipation (29%) • Nausea (80%) • Vomiting (605) • Elevated transaminases (75–80%) • Elevated creatinine (58%) • Increased glucose (49%)
Crizotinib (Xalkori)	*ALK*-positive or *ROS1*-positive tumors	First line	TKI targeting ALK, HGFR, c-MET, ROS1, and RON	• 250 mg by mouth twice daily • Available in 200-mg and 250-mg capsules • May take with or without meals	• Vision disturbance (71%) • Elevated transaminases (61%–79%) • Diarrhea (61%) • Constipation (43%) • Nausea (56%) • Vomiting (47%) • Neutropenia (52%) • Edema (31%–49%)

Note. EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor. Information from Boehringer Ingelheim Pharmaceuticals, Inc. (2013); Kateo et al. (2015); Schwarz Pharma Manufacturing (2004); AstraZeneca Pharmaceuticals LP (2015a, 2015b); Chugai Pharmaceuticals Co., Ltd. (2015); ARIAD Pharmaceuticals, Inc. (2017); Novartis Pharmaceuticals Corporation (2014); Pfizer Inc. (2011); Sahu et al. (2013).

ROS1

ROS1 is a tyrosine kinase receptor that is very similar to ALK in that it induces upregulation of specific signaling pathways, which results in cell survival and proliferation (Waxman & Fossella, 2016). *ROS1* rearrangements are found in about 1% to 2% of patients who have NSCLC (Gainor & Shaw, 2013; Waxman & Fossella, 2016). It is more commonly seen in younger women with adenocarcinoma who have never smoked (Arechaga-Ocampo et al., 2013). There are limited treatment options for patients with this mutation.

Crizotinib is FDA approved as a first-line treatment option in patients with *ROS1* rearrangement based on studies that revealed a 70% response rate with a median duration of response of 18 months (NCCN, 2017; Kazandjian et al., 2016). There are currently no other drugs approved for patients who progress on crizotinib therapy. However, additional targeted therapies are being studied for the treatment of patients with *ROS1* rearrangement, including brigatinib, cabozantinib (Cabometyx), and lorlatinib (Katayama et al., 2015; Solomon et al., 2016; Kim et al., 2016).

KRAS

The RAS family of proteins is a central mediator of the mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription (STAT), and phosphoinositide 3-kinase (PI3K) signaling pathways, which together control cell proliferation and apoptosis (Sequist & Neal, 2015). *KRAS* mutations are the most common mutation found in patients with adenocarcinomas in North America and are often found in patients with a history of smoking (NCCN, 2017; Arechaga-Ocampo et al., 2013). *KRAS* mutations are indicative of lacking therapeutic efficacy with an EGFR-TKI, platinum, and/or vinorelbine therapy; however, chemotherapy may still be used (NCCN, 2017). There are currently no FDA-approved treatments for these select patients, but there are medications being evaluated in clinical trials. Selumetinib is currently being studied for second-line therapy in combination with docetaxel (Janne et al., 2013). There has also been promise in showing programmed cell death protein 1 expression in these patients, which would allow for the use of immunotherapies that target this pathway (Calles et al., 2015).

PHARMACOLOGIC CONSIDERATIONS

All oral targeted therapies discussed here are indicated for patients with metastatic NSCLC and should be administered until disease progression or unacceptable toxicity. Common adverse effects can be found in the Table.

CONCLUSION

Research on specific mutations and driver genes within the proto-oncogenic process has provided multiple treatment options that have altered the treatment paradigm of NSCLC. New research continues to evaluate additional generations of targeted therapies to introduce even more treatment options for patients.

Disclosure

The authors have no potential conflicts of interest to disclose.

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