Emerging Biomarkers in Non–Small Cell Lung Cancer

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Author's disclosures of potential conflicts of interest are found at the end of this article.

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https://doi.org/10.6004/jadpro.2017.8.5.16

Abstract

Since the identification of epidermal growth factor receptor (*EGFR*) mutations in a subset of non–small cell lung cancers and the concomitant success of front-line EGFR inhibitors in treating cancers with these mutations, interest in identifying further significant oncogenic driver mutations or biomarkers has increased. Current mutations under consideration include *BRAF*, *MET*, *RET,* and *HER2*. This article discusses the current research into these biomarkers and the significance of biomarkers for treating NSCLC.

J Adv Pract Oncol 2017;8:51–58

Since the identification of epidermal growth factor receptor (*EGFR*) mutations in a subset of non–small cell lung cancers (NSCLC) and the concomitant success of front-line EGFR inhibitors in treating these mutations, interest in identifying further significant oncogenic driver mutations or biomarkers has increased. Numerous molecular mutations or biomarkers have now been identified in NSCLC tumors. The more common and clinically relevant ones such as *EGFR*, anaplastic lymphoma kinase (*ALK*), *ROS*, and Kirsten rat sarcoma viral oncogene homolog (*KRAS*) are discussed in other sections of this supplement. Other current mutations under consideration include v-Raf murine sarcoma viral oncogene homolog B (*BRAF*), mesenchymal-epithelial transition (*MET*), rearranged during transfection (*RET*), and human epidermal growth factor receptor 2 (*HER2*; Pao & Girard, 2011; Table 1). The mutations occur in genes that control cellular proliferation, survival, maintenance, and death. Tumors rely on these genes for survival even in the absence of tumor suppressor genes—a notion called tumor or oncogene addiction (Pao & Girard, 2011). The hope is that tumors with specific mutations can be systematically identified and treated with targeted therapies or inhibitors that are also under investigation (Pao & Girard, 2011; Table 2). This article discusses some of the other current promising mutations under investigation.

BRAF MUTATIONS

BRAF is a human gene that encodes for a protein called B-Raf. Its location is intracellular, and it is part of

Table 1. Frequency of Driver Mutations in Non–Small Cell Lung Cancers

	Adenocarcinoma	Squamous cell carcinoma
EGFR	5%–15%[a]	< 5%[b]
ALK	5%–15%	< 5%
HER2	< 5%	0
BRAF	< 5%	0
KRAS	> 15%	< 5%
PIK3CA	< 5%	< 5%
AKT1	0	< 5%
MAP2K1	< 5%	0
MET	< 5%	< 5%

Note. EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase; HER2 = human epidermal growth factor receptor 2; BRAF = v-Raf murine sarcoma viral oncogene homolog B; KRAS = Kirsten rat sarcoma viral oncogene homolog; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; AKT1 = AKT serine/threonine kinase 1; MAP2K1 = mitogen-activated protein kinase kinase 1; MET = mesenchymal-epithelial transition. Adapted from Pao & Girard (2011).
[a]Mainly *EGFR* kinase domain mutations.
[b]Mainly *EGFR* VIII mutations, which result from deletion of exons 2 to 7.

the system known as the RAS-RAF-MEK-ERK kinase pathway, which is a major cancer-signaling pathway responsible for mediating growth signals that promote cell proliferation and survival (Sanchez-Torres, Viteri, Molina, & Rosell, 2013; Nguyen-Ngoc, Bouchaab, Adjei, & Peters, 2015; Figures 1 and 2). In the pathway, *BRAF* activates a protein kinase called MEK, which then activates a second protein kinase ERK. ERK is responsible for "gene expression, cytoskeletal rearrangements, and metabolism to coordinate responses to extracellular signals and regulate proliferation, differentiation, angiogenesis, senescence, and apoptosis" (Sanchez-Torres et al., 2013, p 244).

BRAF mutations are common in a wide range of cancers, most commonly malignant melanoma, papillary thyroid, and colorectal. *BRAF* mutations occur in 2% to 4% of NSCLC, mostly in adenocarcinomas, exhibit no gender or ethnic predominance, and are more common in current heavy smokers or former smokers (Marchetti et al., 2011). The most common subtype of *BRAF* mutation is the V600E, where a point mutation in exon 15 of the *BRAF* gene results in a valine to glutamate substitution at codon 600 (*BRAF* V600E; Sanchez-Torres et al., 2013). Marchetti et al. (2011) and Paik et al. (2011) found a high frequency of *BRAF* V600E mutations among females, never or light smokers, and aggressive histologies. Patients with early-stage NSCLC with the mutation had shorter disease-free and overall survival than patients with non-V600E mutations, and the V600E mutation may result in shorter progression-free survival after platinum chemotherapy (Cardarella et al., 2013; Marchetti et al., 2011).

However, *BRAF* V600E mutations do exhibit higher response rates and higher progression-free survival rates in response to BRAF inhibitor monotherapy (Nguyen-Ngoc et al., 2015). BRAF inhibitors block the mutant BRAF protein, thus interrupting the signals leading to cancer growth and reproduction (Nguyen-Ngoc et al., 2015; Figure 2). Patients with NSCLC with the *BRAF* V600E mutation have shown partial or complete responses to monotherapy with the tyrosine kinase inhibitors vemurafenib (Zelboraf) and dabrafenib (Tafinlar; Hyman et al., 2015; Planchard et al., 2016). Unfortunately, responses were not sustained, and all patients treated with BRAF inhibitors will inevitably demonstrate resistance and tumor progression (Nguyen-Ngoc et al., 2015; Sanchez-Torres et al., 2013).

The previous studies suggest that clinical-pathologic features (e.g., nonsmoking females, light or never smokers) may be one tool to identify patients who might harbor a *BRAF* mutation. Planchard et al. (2016) argue that given the efficacy of dabrafenib in *BRAF* V600E–mutated lung cancers, it is important to screen all patients for oncologic drivers. This will hopefully result in more targeted and efficacious front-line treatment, thereby avoiding many of the toxic and potentially permanent side effects of traditional platinum-based chemotherapies used for NSCLC. The authors note that a readily available molecular screen is available for *BRAF* detection in melanomas and could easily translate to NSCLC.

In non-*BRAF* V600E mutations, studies are underway with MEK inhibitors, as this subtype seems to be unresponsive to BRAF inhibitors (Nguyen-Ngoc et al., 2015). To overcome the resistance that inevitably develops with all BRAF

Table 2. Clinical Trials of Drugs Targeting Driver Mutations in Lung Cancer, by Gene and Compound

	Study phase	Selected population[a]	Clinicaltrials.gov identification number[b]
ALK			
PF-02341066	I, II, III	Yes	NCT009328451, NCT00932893
HER2			
HKI-272	I, II	No	NCT00266877
BIBW 2992	I, II, III	Yes	NCT00949650, NCT00796549
Lapatinib (Tykerb)	I, II	No	NCT00073008
Pertuzumab (Perjeta)	I, II	No	NCT00063154
Trastuzumab	II, III	Yes	NCT00003881, NCT00016367, NCT00758134
PI3K			
BEZ2235	I	No	NCT00620594
GDC-0941	I	No	NCT00975182, NCT00974584
XL147	I, II	No	NCT00692640, NCT00756847
AKT			
MK2206	I	No	NCT00848718, NCT00670488
BRAF			
Sorafenib	I, II	No	NCT00533585, NCT00300885, NCT00922584, NCT00722969, NCT00100763, NCT00801385, NCT00456716, NCT00101413, NCT00411671, NCT00600015, NCT00098540, NCT00759928
GSK2118436	I	Yes	NCT00880321
XL281	I	No	NCT00451880
MAP2K1			
CI-1040	I, II	–	NCT00033384, NCT00034827
AZD6244	I, II	No	NCT00888134
TAK-733	I	No	NCT00948467
AS703026	I	No	NCT00982865
GSK1120212	I	No	NCT00955773
PD-325901	I, II	No	NCT00174369
GDC-0973/XL518	I	No	NCT00467779
RO4987655	I	No	NCT00817518
RO5126766	I	No	NCT00773526
MET			
PF-02341066	I, II	Yes	NCT00965731
GSK1363089, formerly known as XL880	I	No	NCT00742131
XL184	I, II	Yes	NCT00596648
AMG 102	I, II	No	NCT00791154
Onartuzumab (MetMAb)	I, II	No	NCT00854308
ARQ	I, II	No	NCT00777309
SCH 900105	I, II	No	NCT01039948

Note. Not all trials are restricted to lung cancers. Adapted from Pao & Girard (2011).
[a]Denotes whether eligibility criteria include a specific molecular cluster of tumors.
[b]Database searched July 2, 2010, but updated details of all trials are available at ClinicalTrials.gov.

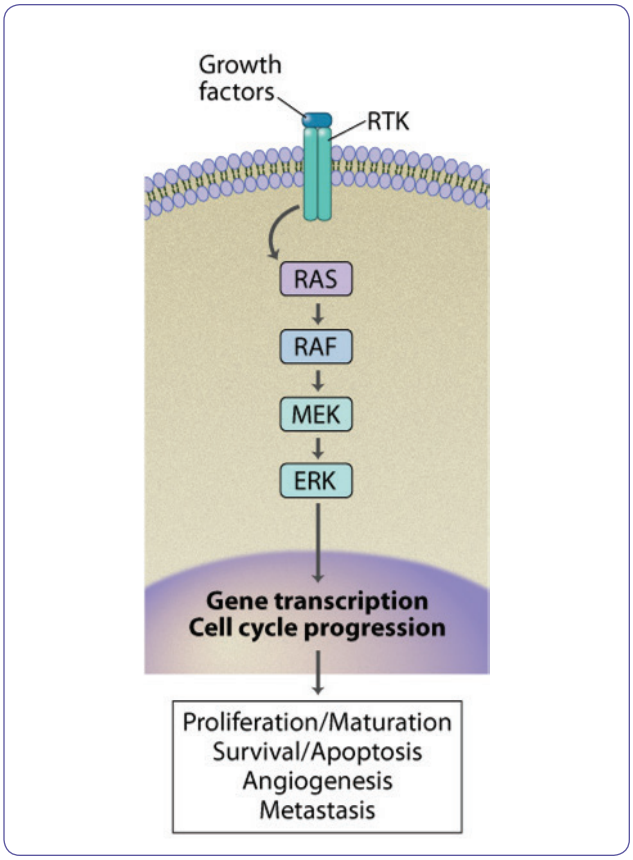

Figure 1. The RAS-RAF-MEK-ERK signaling pathway. RTK = receptor tyrosine kinase; RAS = rat sarcoma; RAF = rapidly accelerated fibrosarcoma; MEK = mitogen-activated protein kinase kinase; ERK = extracellular signal-regulated kinase. Adapted from Sanchez-Torres et al. (2013). Illustration by DNA Illustrations.

inhibitors, research is also underway to determine if combination therapies with BRAF and MEK inhibitors improve response and can better overcome resistance mechanisms. A phase II study with dabrafenib and the MEK1 inhibitor trametinib (Mekinist) showed an overall response rate of 63% in 57 patients with NSCLC (Planchard et al., 2016). Utilizing a MEK inhibitor achieves the same result as a BRAF inhibitor by shutting down the RAS-RAF-MEK-ERK MAP kinase pathway further down the signaling pathway.

MET MUTATIONS

MET is an extracellular tyrosine kinase receptor for the ligand hepatocyte growth factor (HGF; Shadeed, 2013; Figure 3). When HGF binds to MET, it activates the intracellular RAS-RAF-MEK-ERK pathway (Awad, 2016; Figure 2). MET has become an area of focus in treatment for NSCLC because up to 58% of nonsquamous NSCLCs demonstrate MET overexpression, and overexpression has been associated with worsened prognosis in early-stage NSCLC (Awad, 2016). In a study by Awad et al. (2016), some clinical-pathologic features of tumors with the *MET* exon 14 mutation included significantly older patients (median age, 72.5 years), predominantly female, a history of tobacco use, stage I presentation, and predominantly found in adenocarcinomas.

In addition to excessive amplification, another type of mutation causes impaired MET receptor degradation, and this has also been associated with oncogenesis (Frampton et al., 2015). A skipping mutation at *MET* exon 14, which occurs in about 3% of lung cancers, reduces the degradation of the MET receptor, thereby causing it to act as an oncogenic driver with continuous stimulation of the RAS-RAF-MEK-ERK pathway (Awad, 2016). Figure 4 illustrates normal MET signaling and signaling in the mutated, skipping *MET* exon 14 gene (Awad, 2016).

Studies are underway with the MET inhibitor crizotinib (Xalkori) for patients with MET amplification (Camidge et al., 2014) and with cabozantinib (Cabometyx) and capmatinib in patients with *MET* exon 14 skipping mutations (Paik et al., 2015; Frampton et al., 2015). Research has indicated that MET amplification may contribute to acquired resistance after treatment with EGFR and other tyrosine inhibitors, and research is now ongoing with combinations of MET and EGFR inhibitors in patients with concurrent *MET* and *EGFR* mutations (Nguyen-Ngoc et al., 2015; Ou et al., 2011).

RET MUTATIONS

RET is also an extracellular tyrosine kinase receptor (Shadeed, 2013, Figure 3). RET is significant in "cell proliferation, neuronal navigation, cell migration, and cell differentiation" when it binds with its family of ligands (Wang et al., 2012, p 4352). RET translocations and its common fusions with other genes have long been known to be oncogenic drivers in papillary thyroid carcinomas, and it has been shown to be a driver mutation in a subgroup of lung adenocarcinomas (Wang et al., 2012). In one study, Wang et al. (2012) examined the *RET* fusion gene in tumors of 936 patients and found

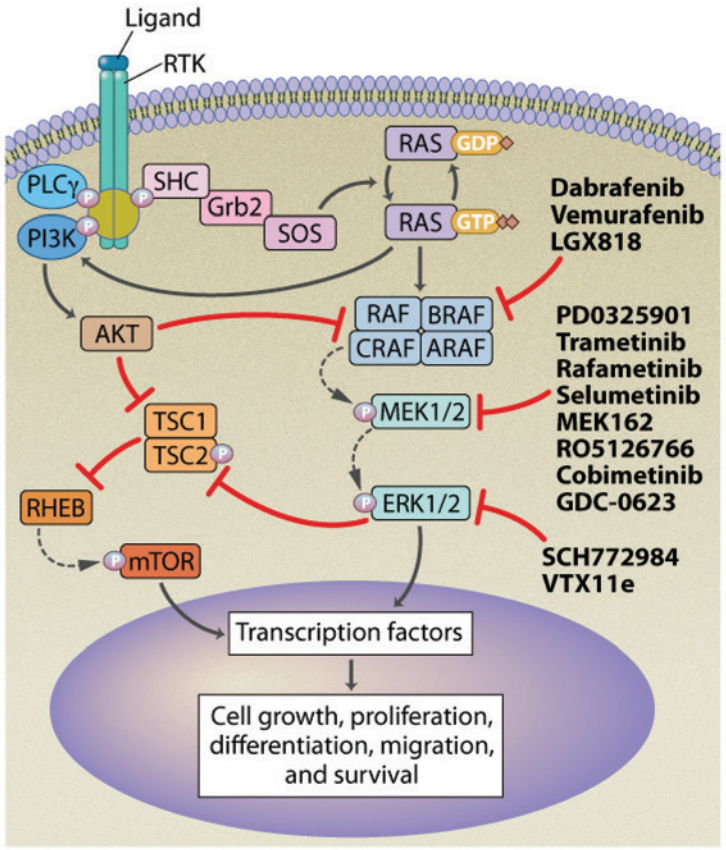

Figure 2. Illustration of RAS–RAF–MEK–ERK MAP kinase signaling pathway. Current inhibitors targeting BRAF, MEK, and ERK are depicted. RTK = receptor tyrosine kinase; PLCγ = phospholipase Cγ; SHC = Src homology 2 domain-containing-transforming protein; RAS = rat sarcoma; GDP = guanosine diphosphate; PI3K = phosphatidylinositol 3-kinase; GRB2 = growth factor receptor-bound protein 2; SOS = son of sevenless; GTP = guanosine triphosphate; AKT = Ak strain transforming; RAF = rapidly accelerated fibrosarcoma; CRAF = v-Raf murine sarcoma viral oncogene homolog C; BRAF = v-Raf murine sarcoma viral oncogene homolog B; ARAF = v-Raf murine sarcoma viral oncogene homolog A; TSC1/2 = tuberous sclerosis protein 1/2; P = phosphate; MEK1/2 = mitogen-activated protein/extracellular signal-regulated kinase kinase 1/2; RHEB = Ras homolog enriched in brain; mTOR = mechanistic target of rapamycin; ERK-1/2 = extracellular signal-regulated kinase 1/2; MAP = mitogen-activated protein. Adapted from Nguyen-Ngoc et al. (2015). Illustration by DNA Illustrations.

that fusions with three particular genes (KIF5B-RET, CCDC6-RET, and NCOA4-RET) resulted in aberrant RET activity, which drove tumor growth, indicating that suppression of the RET receptor is a potential target for treatment. The same study found 13 patients with the RET fusion accounting for 1.4% of NSCLCs and 1.7% of the adenocarcinomas, which are similar to rates in other studies. Other characteristics included "younger age, never-smokers, early lymph node metastases, poor differentiation, and a solid-predominant subtype, suggesting their idiographic mechanism of carcinogenesis (Wang et al., 2012, p 4358)."

Current inhibitors under investigation for *RET* rearrangements include cabozantinib and vandetanib (Caprelsa)—both multikinase inhibitors. In a phase II trial by Drilon et al. (2015), cabozantinib was found to produce rapid and durable responses in patients with NSCLC with *RET* rearrangements. Vandetanib has demonstrated activity in two case studies (Falchook et al., 2016; Gautschi et al., 2013). The significance of the vandetanib case studies is that prior studies did not select for the *RET* rearrangement in patients with NSCLC. Horiike et al. (2015) found that sorafenib (Nexavar), another multikinase

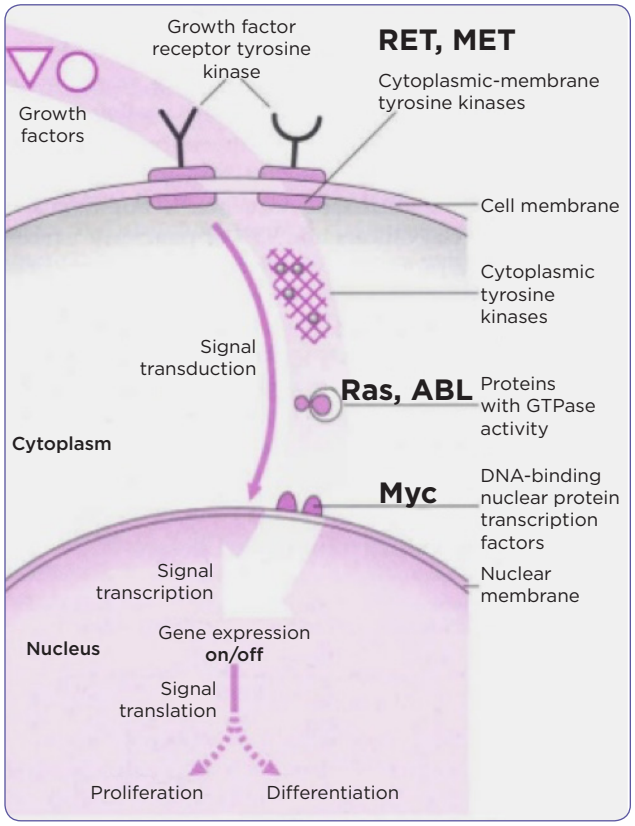

Figure 3. Receptor tyrosine kinases transduce an extracellular signal inward and bind a ligand, conformational change that results in kinase activity, leading to phosphorylation of cellular proteins. Patient mutations cause receptors to be constitutively active. *RET* mutation is associated with multiple endocrine neoplasia, and *MET* mutation is associated with hereditary papillary renal carcinoma. RET = rearranged during transfection; MET = mesenchymal-epithelial transition; Ras = rat sarcoma. Adapted from Shadeed (2013).

inhibitor used in renal cell carcinoma, exhibited some but not dramatic responses in patients with NSCLC with *RET* rearrangements. The authors concluded that current research indicates more promise with other RET inhibitors.

HER2 MUTATIONS

HER2, also known as ERBB2, is one of four in a family of tyrosine kinase receptors. The receptor is often overexpressed in many cancers, and preclinical studies have shown that overexpression or mutations play a significant role in oncogenesis (Suzawa et al., 2015). HER2 overexpression and amplification have been reported in 11% to 32% and 2% to 23% of patients with NSCLC. *HER2* mutations have been detected in 1% to 2% of NSCLC tumors (Suzawa et al., 2015). The tumors were found predominantly in women, nonsmokers, and adenocarcinomas (Arcila et al., 2012; Mazières et al., 2013). To date, *HER2* mutations are known to be mutually exclusive with *EGFR* and *KRAS* mutations (Arcila et al., 2012).

Trastuzumab (Herceptin), approved for treatment in HER2-overexpressing breast and gastric cancers, has demonstrated no benefit in patients with NSCLC HER2 amplification (Gatzemeier et al., 2004). More recent studies indicate that NSCLC with *HER2* mutations may respond to chemotherapy plus trastuzumab or to the tyrosine kinase inhibitor afatinib (Gilotrif; Zinner et al., 2004; De Greve et al., 2012). Another treatment combination being investigated is temsirolimus (Torisel), a mechanistic target of rapamycin (mTOR) inhibitor, with neratinib (Nerlynx), an irreversible tyrosine kinase inhibitor that targets all four HER receptors (Gandhi et al., 2014).

CONCLUSION

Lung cancer remains a leading cause of cancer deaths worldwide. For many years, treatment consisted of traditional chemotherapy without significant improvement in overall survival and resulted in significant toxicities for the patient. Treatment options significantly expanded with the identification of *EGFR* mutations and of *ROS* and *ALK* rearrangements in NSCLC tumors. Targeted therapies with tyrosine kinase inhibitors such as gefitinib, erlotinib, and crizotinib demonstrated significantly improved outcomes, with sustained responses and fewer toxicities in patients. As a result, research into other mutations that may be sensitive to targeted therapies has increased.

NSCLC tumors seem to exhibit a vast array of mutations. The challenges are to identify which hold the most promise for treatment and how to effectively screen for them. *BRAF*, *MET*, *RET*, and *HER2* are currently some of the most intensively researched. The studies discussed indicate that they are found with some frequency in NSCLC tumors and that current targeted inhibitors are showing efficacy when tumors are screened and selected for the specific mutation. However, most of the trials have been small. Comprehensive molecular screening technologies have become in-

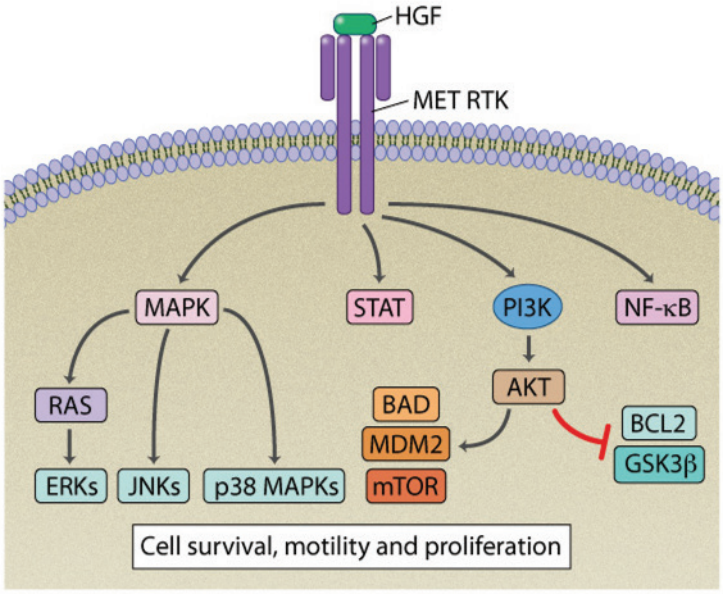

Figure 4. Normal MET signaling and signaling in the mutated skipping *MET* exon 14 gene. HGF = hepatocyte growth factor; MET = mesenchymal-epithelial transition; RTK = receptor tyrosine kinase; MAPK = mitogen-activating protein kinase; STAT = signal transducer and activator of transcription; PI3K = phosphatidylinositol 3-kinase; NF-KB = nuclear factor kappa B; RAS = rat sarcoma; ERKs = extracellular signal-regulated kinases; JNKs = c-Jun amino-terminal kinases; BAD = Bcl-2-associated death promoter; MDM2 = mouse double minute 2 homolog; mTOR = mechanistic target of rapamycin; AKT = Ak strain transforming; BCL2 = B-cell lymphoma 2; GSK3β = glycogen synthase kinase 3 beta. Adapted from Awad (2016). Illustration by DNA Illustrations.

creasingly available including blood tests for circulating tumor cells or tumor DNA (Nguyen-Ngoc et al., 2015), which should, in time, allow for rapid, but lower-cost, screening of patients with NSCLC. Screening patients with NSCLC for specific mutations at baseline, progression, and recurrence holds the promise of individualized treatment with easy-to-administer oral agents, which have demonstrated efficacy, durable responses, and fewer side effects than traditional chemotherapy.

Disclosure

The author has no potential conflicts of interest to disclose.

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