**Regence**

**Medical Policy Manual**

**Topic:** Molecular Analysis for Targeted Therapy of Non-Small Cell Lung Cancer (NSCLC)  
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**IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

**DESCRIPTION**

**Targeted Therapy for Non-small Cell Lung Cancer (NSCLC)**

Treatment options for NSCLC depend on disease stage and include various combinations of surgery, radiation therapy, chemotherapy, and best supportive care. In up to 85% of cases, the cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication. In addition, up to 40% of patients with NSCLC present with metastatic disease.\(^1\) Treatment of advanced NSCLC has generally been with platinum-based chemotherapy, with a median survival of 8 to 11 months and a 1-year survival of 30% to 45%.\(^2,3\) More recently, the identification of specific, targetable oncogenic “driver” mutations in a subset of NSCLCs has resulted in a reclassification of lung tumors to include molecular subtypes, which are predominantly of adenocarcinoma histology.

**Epidermal Growth Factor Receptor (EGFR)**

EGFR is a receptor tyrosine kinase (TK) frequently overexpressed and activated in NSCLC. Laboratory and animal experiments have shown that therapeutic interdiction of the \(EGFR\) pathway could be used to halt tumor growth in solid tumors that express \(EGFR\).\(^4\) These observations led to the development of two main classes of anti- \(EGFR\) agents for use in various types of cancer: small molecule TKIs and monoclonal antibodies (MAbs) that block \(EGFR\)-ligand interaction.\(^5\) The prevalence of \(EGFR\) mutations in NSCLC varies by population, with the highest prevalence in non-smoking, Asian women,
with adenocarcinoma, in whom EGFR mutations have been reported to be up to 30-50%. The reported prevalence in the Caucasian population is approximately 10%.[6]

Mutations in two regions of the **EGFR** gene (exons 18-24)—small deletions in exon 19 and a point mutation in exon 21 (L858R)—appear to predict tumor response to first and second generation tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib and afatinib.[7,8] In addition, a single point mutation in exon 20 (T790M) appears to predict tumor response to third generation TKIs such as osimertinib. These can be detected by direct sequencing or polymerase chain reaction (PCR) technologies.

Testing is intended for use in patients with advanced NSCLC. Patients with either small deletions in exon 19 or a point mutation in exon 21 (L858R) of the tyrosine kinase domain of the EGFR gene are considered good candidates for treatment with first and second generation TKIs. Patients with the point mutation in exon 20 (T790M), which is indicative of acquired resistance to first and second generation TKIs, are considered good candidates for third generation TKIs. Patients found to be wild type are unlikely to respond to TKIs, so other treatment options should be considered.

**KRAS**

**KRAS** is a G-protein involved in the **EGFR**-related signal transmission. The **KRAS** gene, which encodes RAS proteins, can harbor oncogenic mutations that result in a constitutively activated protein, independent of signaling from the EGF receptor, possibly rendering a tumor resistant to therapies that target the EFG receptor. Mutations in the **KRAS** gene, mainly codons 12 and 13, have been reported in 20-30% of NSCLC, and occur most often in adenocarcinomas in heavy smokers.

**RET**

**RET** (rearranged during transfection) is a proto-oncogene that encodes a receptor TK growth factor. Translocations that result in fusion genes with several partners have been reported.[9] **RET** fusions occur in 0.6-2% of NSCLCs and in 1.2-2% of adenocarcinomas.

**MET**

MET amplification is one of the critical events for acquired resistance in EGFR-mutated adenocarcinomas refractory to EGFR-TKIs.[9]

**BRAF**

**BRAF** proteins are serine/threonine kinases that are downstream of RAS in the RAS-RAF-ERK-MAPK pathway. In this pathway, the **BRAF** gene is the most frequently mutated in NSCLC, in approximately 1-3% of adenocarcinomas. Unlike melanoma, about 50% of the mutations in NSCLC are non-V600E mutations.[9] Most **BRAF** mutations occur more frequently in smokers.

**HER2**

Human epidermal growth factor receptor 2 (**HER2**) is a member of the HER (**EGFR**) family of TK receptors, and has no specific ligand.[9] When activated, it forms dimers with other **EGFR** family members. **HER2** is expressed in approximately 25% of NSCLC. **HER2** mutations are detected mainly in exon 20 in 1-2% of NSCLC, predominantly in adenocarcinomas in nonsmoking women.
Regulatory Status

The FDA Centers for Devices and Radiological Health (CDRH), for Biologics Evaluation and Research (CBER), and for Drug Evaluation and Research (CDER) developed a draft guidance on in vitro companion diagnostic devices, which was released on July 14, 2011,[8] to address the “emergence of new technologies that can distinguish subsets of populations that respond differently to treatment.” As stated, the FDA encourages the development of treatments that depend on the use of companion diagnostic devices “when an appropriate scientific rationale supports such an approach.” In such cases, the FDA intends to review the safety and effectiveness of the companion diagnostic test as used with the therapeutic treatment that depends on its use. The rationale for co-review and approval is the desire to avoid exposing patients to preventable treatment risk.

There are two U.S. Food and Drug Administration (FDA)-approved companion diagnostic tests for EGFR mutation testing for NSCLC, intended to be used with select FDA approved EGFR tyrosine kinase inhibitors (TKIs):

- The cobas® EGFR Mutation Test v2 is a companion diagnostic test for the detection of exon 19 deletions and exon 20 and 21 (T790M and L858R, respectively) substitution mutations in the EGFR gene in NSCLC tumor tissue. The FDA states:

  The test is intended to be used as an aid in selecting patients with NSCLC for whose tumors have defined EGFR mutations and for whom safety and efficacy of a drug have been established as follows:

  • Tarceva® (erlotinib) - Exon 19 deletions and L858R
  • Tagrisso® (osimertinib) - T790M

This test (v2) was approved 11/13/2015 as a result of an expansion of the original cobas® EGFR Mutation Test to cover testing for the T790M point mutation for use of osimertinib.

- The therascreen® EGFR Rotor Gene Q polymerase chain reaction (PCR) Kit is an automated molecular assay designed to detect the presence of EGFR exon 19 deletions and the exon 21 (L858R) substitution mutation in NSCLC tumor tissue. The test is intended to be used to select patients with NSCLC for whom GILOTRIF® (afatinib) or IRESSA® (gefitinib) is indicated.

MEDICAL POLICY CRITERIA

Note: This policy does not address genetic analyses/tests for the ALK, PD-L1 or ROS1 genes, which may be considered medically necessary.

I. Analysis of mutations within the EGFR gene—small deletions in exon 19, and point mutations in exon 20 (T790M) and exon 21 (L858R)—may be considered medically necessary to select patients with advanced or metastatic (stage III or IV) non-squamous cell-type non-small cell lung cancer (NSCLC) for treatment with FDA approved EGFR tyrosine kinases inhibitors as indicated. (See Policy Guidelines)

II. The following analyses/tests are considered investigational:
A. Analysis of mutations within the \textit{EGFR} gene for patients with NSCLC of squamous cell-type of any stage, or nonsquamous cell type of stage I or II

B. Analysis for other mutations within exons 18-24 of the \textit{EGFR} gene, or for other applications related to NSCLC

C. Analysis of mutations of the \textit{KRAS} gene as a technique to predict treatment nonresponse to \textit{EGFR} tyrosine kinase inhibitors and for the use of the anti-\textit{EGFR} monoclonal antibody cetuximab in NSCLC

D. Analysis of mutations in genes including, but not limited to, \textit{RET, MET, BRAF, and HER2} for targeted therapy in patients with NSCLC

\textbf{POLICY GUIDELINES}

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or mutations being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing?
6. Medical records related to this genetic test
   \begin{itemize}
   \item History and physical exam
   \item Conventional testing and outcomes
   \item Conservative treatment provided, if any
   \end{itemize}

The FDA approved cobas® EGFR Mutation Test v2 is only intended to be used to aid in identifying patients with NSCLC whose tumors have defined \textit{EGFR} mutations and for whom safety and efficacy of a drug have been established. Please see the Regulatory Status section, above, for a list of FDA indications for use. For further information on the approved indications for this test please visit the FDA website for approved companion diagnostic devices.

\textbf{SCIENTIFIC EVIDENCE\textsuperscript{[10]}}

The focus of the following review is on evidence related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

The clinical utility of testing for small deletions in exon 19 and a point mutation in exon 21 (L858R) in the \textit{EGFR} gene to guide TKI treatment in patients with advanced NSCLC has been unequivocally demonstrated. Therefore, this review will focus on literature that has been published on the investigational indications described in this policy.
**EGFR**

Publications demonstrate that the underlying molecular mechanism underpinning dramatic responses in favorably prognostic groups of patients with advanced NSCLC appear to be the presence of activating somatic mutations in the TK domain of the *EGFR* gene, notably small deletions in exon 19 and a point mutation in exon 21 (L858R). These activating somatic mutations are also referred to as “sensitizing” mutations because their presence strongly predicts sensitivity to TKIs. Three orally administered *EGFR*-selective small molecules (quinazolinamine derivatives) have been approved by the FDA for use in treating NSCLC patients with sensitizing mutations: erlotinib (Tarceva®, Genentech BioOncology), afatinib (GILOTRIF™, Boehringer Ingelheim Pharmaceuticals, Inc), and gefitinib (Iressa®, AstraZeneca).

There is sufficient evidence for the clinical utility of testing for small deletions in exon 19 and a point mutation in exon 21 (L858R) in the *EGFR* gene to guide TKI treatment in patients with advanced NSCLC. This evidence is published as numerous systematic reviews on monotherapies in general, clinical trials and nonrandomized studies that have been published over the past decade for the use of genetic testing to inform treatment with erlotinib, afatinib, and gefitinib.

Almost all patients who initially respond to an *EGFR* TKI subsequently develop disease progression often due to acquired resistance. Publications demonstrate that the underlying molecular mechanism underpinning TKI acquired resistance is the generation of the somatic point mutation in exon 20 (T790M). This mutation is also referred to as a “resistance” or secondary mutation, but can be overcome by a new class of TKIs (third generation). One orally administered *EGFR*-selective small molecule has been approved by the FDA for use in treating NSCLC patients with resistance mutations: osimertinib (Tagrisso®, AstraZeneca).

The clinical utility of testing for the resistance mutation T790M in the *EGFR* gene to guide treatment with third generation TKIs, such as osimertinib and rociletinib has been demonstrated in large clinical trials, and preclinical studies.

**Clinical Practice Guidelines**

**National Comprehensive Cancer Network (NCCN)**

The NCCN guidelines (v3.2017) on NSCLC make the following recommendations:

- In patients with metastatic large cell, adenocarcinoma and NSCLC histological subtypes: NCCN recommends (category 1), *EGFR* mutation testing to determine the course of therapy.
- If an *EGFR* mutation is discovered prior to first-line chemotherapy, NCCN recommends (category 1) either erlotinib, afatinib or gefitinib.
- If an *EGFR* mutation is discovered during first-line chemotherapy, NCCN recommends (category 2a) that the patient complete the planned chemotherapy or interrupt, followed by either erlotinib, afatinib or gefitinib.
- Once progression occurs after first line therapy, NCCN recommends testing for the T790M mutation to determine the course of therapy (category 2A).
- In patients with squamous cell carcinoma (SCC), the low incidence of *EGFR* mutations (2.7%) does not justify routine testing of all tumor specimens. However, “it is reasonable to test for *EGFR* mutations or *ALK* rearrangements in squamous cell histology if patients are never smokers, small
biopsy specimens were used for testing, or mixed histology was reported.” This recommendation was based on a case series of 13 patients with squamous or pseudosquamous histology.[66,67] However, seven patients were subsequently determined to have adenocarcinoma histology. The six remaining patients were nonsmokers with an exon 19 deletion or L858R substitution mutation in EGFR.

**College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology (CAP/IASLC/AMP)**[68]

The 2014 guidelines issued jointly by the CAP/IASLC/AMP recommend:

- **EGFR mutation and ALK rearrangement testing in patients with lung adenocarcinoma regardless of clinical characteristics (eg, smoking history);**
- **In the setting of fully excised lung cancer specimens, EGFR and ALK testing is not recommended in lung cancers when an adenocarcinoma component is lacking (such as pure squamous cell lacking any immunohistochemical evidence of adenocarcinomatous differentiation); and**
- **In the setting of more limited lung cancer specimens (eg, biopsies, cytology) where an adenocarcinoma component cannot be completely excluded, EGFR and ALK testing may be performed in cases showing squamous cell histology. Clinical criteria (eg, young age, lack of smoking history) may be useful to select a subset of these samples for testing.**

**American Society of Clinical Oncology (ASCO)**[69]

In 2015, the American Society of Clinical Oncology (ASCO) endorsed the 2014 CAP/IASLC/AMP joint guidelines on molecular testing to select patients with lung cancer to determine treatment. ASCO recommendations state that testing for EGFR should be prioritized over other molecular markers in lung adenocarcinoma.

**American College of Chest Physicians (ACCP)**[70]

- **ACCP updated its evidence-based clinical practice guidelines on the treatment of stage IV NSCLC in 2013. Based on their review of the literature, guideline authors reported improved response rates, progression-free survival (PFS), and toxicity profiles with first-line erlotinib or gefitinib compared with first-line platinum-based therapy in patients with EGFR mutations, especially exon 19 deletion and L858R. ACCP recommended, “testing patients with NSCLC for EGFR mutations at the time of diagnosis whenever feasible, and treating with first-line EGFR TKIs if mutation-positive.”**

**KRAS**

**KRAS and EGFR Tyrosine Kinase Inhibitors (TKIs)**

**Systematic Reviews**

In 2016, Pan et al. published a meta-analysis of 41 studies (total \(N=13,103\) patients) of prognostic and predictive values of the KRAS mutation in NSCLC.[71] **KRAS** mutation was significantly associated with poorer OS (HR=1.6; 95% CI, 1.4 to 1.8) and DFS (HR=1.57; 95% CI, 1.2 to 2.1) in early-stage resected NSCLC, and with inferior outcomes of EGFR-TKIs treatment (RR=0.21; 95% CI, 0.1 to 0.4) in advanced NSCLC. **KRAS** mutation was still significantly associated with poorer OS (HR=1.4; 95% CI,
1.2 to 1.6) and PFS (HR=1.4; 95 % CI, 1.1 to 1.6) of EGFR TKIs when patients with EGFR mutations were excluded. The reviewers concluded that KRAS mutations are weak, but valid predictors of poor prognosis and TKI treatment outcomes in NSCLC. Limitations of this review include the inclusion of unpublished (incomplete) clinical trials and lack of complete genetic information in a number of included studies.

Ying et al. conducted a meta-analysis including twelve prospective intervention trials comprised of 1,859 unselected advanced NSCLC patients. The presence of a KRAS mutation was associated with shorter overall survival (OS) and progression-free survival (PFS) [hazard ratio (HR) 2.09, 95 % confidence interval (CI) 1.56-2.80; HR 1.82, 95 % CI 1.50-2.20] in patients. Four retrospective studies on the role of KRAS status in EGFR wild-type advanced NSCLC were included in the analysis and concluded that the presence of a KRAS mutation was not associated with any of the outcomes in EGFR wild-type patients treated with EGFR-TKIs. The authors concluded that KRAS mutations could be used as a potential negative predictor of clinical benefit from EGFR-TKIs, but that KRAS testing is of limited value to identify patients for EGFR-TKIs when EGFR status is considered.

Qi et al. performed a meta-analysis including eight randomized controlled trials (N=2,417) with significant methodological limitations. The authors reported this the results of this analysis demonstrated a survival benefit of combining targeted therapy for advanced NSCLC; however, progression-free survival for patients with EGFR-mutation or wild type KRAS favored monotherapy erlotinib. Subgroup analysis based on phases of trials showed a tendency to improve PFS and OS in combining targeted therapy. Moreover, it should be noted that not all of the trials analyzed, including 2 phase III trials, demonstrated OS benefits from combining therapies. There were several limitations in this meta-analysis such as the lack of individual patient data; an individual patient data-based meta-analysis produces a more reliable estimation than one based on abstracted data. Possible survival benefits could not be determined in studies when patient clinical variables (staging, age, histologic types and general physical conditions) were unknown. In addition, different treatment duration and different combining of targeted therapies were both potential factors that increased heterogeneity amongst trials. Phase II and Phase III trials were combined in this study and thus presented an additional study limitation. Finally, publication bias was possible because papers with null results tend not to be published.

Mao et al. evaluated the association between KRAS mutations and resistance to TKIs with NSCLC, using a meta-analysis including 22 studies that included 1,470 NSCLC patients, of whom 16% had KRAS mutations (N=231). This study suggests that KRAS mutations may represent negative predictive biomarkers for tumor response in NSCLC patients treated with EGFR-TKIs. However, due to a mutually exclusive relationship between KRAS and EGFR mutation and no difference in survival between KRAS mutant/EGFR wild-type and KRAS wild-type/EGFR wild-type NSCLC, the clinical usefulness of KRAS mutation as a selection marker for EGFR -TKIs sensitivity in NSCLC is limited.

In a 2008 systematic review and meta-analysis, Linardou et al. assessed whether KRAS mutations represent a candidate predictive biomarker for anti-EGFR-targeted therapeutic strategies in NSCLC. Authors stated “substantial” evidence was found in the literature that determined KRAS mutations were appropriate markers for the identification of a subgroup of patients (20% of patients with NSCLC) with a limited probability of responding to EGFR-targeted treatments. In the meta-analysis, the presence of KRAS mutations was significantly associated with an absence of response to TKIs; however, the pooled sensitivity was low (0.21 [95% CI 0.16-0.28]). In summary, the findings of this study suggested that somatic mutations leading to gain-of-function and constitutive signaling of the KRAS pathway(s) represent a strong candidate predictive biomarker for non-responsiveness to TKI-based strategies. Authors advocated for a large cooperative prospective study that would address the prognostic and
predictive value of KRAS in predicting the efficacy of EGFR-targeted agents in lung cancer due to the limitations of this study. These limitations included the unavailability of individual patient data, inadequate reporting of survival data, heterogeneity of response endpoints, intrinsic differences in the treatment regimens, patient selection criteria, and retrospective analysis of studies.

**Randomized Controlled Trials**

Data on the role of KRAS mutations in NSCLC and response to erlotinib are available from a small number of Phase II and Phase III trials and retrospective single-arm studies. The majority of identified studies had significant methodological limitations including small sample size, variance in study populations (older individuals ≥70 and females), and inconsistent staging information. Representative studies are described below:

Papadimitrakopoulou et al. reported results of the BATTLE-2 phase II study in 2016. The BATTLE-2 study evaluated effects of targeted therapies focusing on KRAS-mutated cancers. Two hundred patients with advanced NSCLC tumors who did not have EGFR mutations or ALK gene fusions whose cancer was refractory to more than one prior therapy were assigned to one of four arms using adaptive randomization: erlotinib (n=22), erlotinib plus MEK inhibitor, MK-2206 (n=42), MK-2206 plus and AKT inhibitor AZD6244 (n=75), or sorafenib, a multi-target TKI (n=61), stratified by KRAS status. Only 186 evaluable patients were included in analyses. The 8-week disease control rate was 20%, 25%, 62%, and 44% for the four treatment groups, respectively, in the KRAS mutation positive patients. For KRAS wild-type patients, disease control rate was 36%, 57%, 49%, and 47%, respectively. Median PFS did not differ by KRAS status.

Rulli et al. reported results from biomarker analyses in the TAILOR trial. TAILOR enrolled patients from 52 Italian hospitals and genotyped patients for KRAS and EGFR mutation status. Wild-type EGFR patients (n=218) received first-line platinum-based chemotherapy and then were randomly allocated at progression to erlotinib or docetaxel. KRAS mutations were present in 23% of randomized patients. The presence of a KRAS mutation was not associated with PFS (HR=1.01; 95% CI, 0.71 to 1.41; p=0.98) or OS (HR=1.24; 95% CI, 0.87 to 1.77; p=0.23). The treatment effect did not differ by KRAS status (test for interaction: OS p=0.97; PFS p=0.42). The authors concluded that in this trial, KRAS was neither prognostic nor predictive of benefit for either docetaxel or erlotinib.

In 2013, Fiala et al. reported on a retrospective analysis of patients with squamous cell NSCLC who underwent EGFR, KRAS, and PIK3CA (phosphatidylinositol-3-kinase catalytic subunit-alpha) mutation testing. Of 215 patients tested, 16 (7.4%) had mutated KRAS. Of 174 tested patients who were treated with an EGFR TKI (erlotinib or gefitinib), median PFS in 14 KRAS-mutated patients was 1.3 months versus 2.0 months in KRAS wild-type patients (n=160 [92%]); the difference was not statistically significant (Kaplan-Meier [KM] log-rank test, p=0.120). Median OS in this treated group was 5.7 months in KRAS-mutated patients versus 8.2 months in KRAS wild-type patients, a statistically significant difference (KM log-rank test; p=0.039). The authors concluded that there was no role identified for EGFR, KRAS, PIK3CA mutations in the prediction of EGFR-TKIs efficacy in patients with advanced-stage squamous cell NSCLC.

Guan et al. reported on 1,935 consecutive patients with NSCLC who were treated at a single institution. Patients with mutated KRAS were randomly matched on tumor, node, metastasis (TNM) stage, time of first visit within 1 year, and histology, to both EGFR mutation-positive and KRAS/EGFR wild-type patients. Seventy patients (4%) received EGFR TKI therapy. In this group, median progression free-survival (PFS) was 11.8and 2.0 months in patients with EGFR and KRAS mutations,
respectively, and 1.9 months in wild-type patients; in comparison to wild-type patients, PFS was statistically longer in patients with \textit{EGFR} mutations (p<0.001) but not different in patients with \textit{KRAS} mutations (p=0.48). The authors observed that “the presence of an \textit{EGFR} mutation, but not a \textit{KRAS} mutation, was predictive of responsiveness to \textit{EGFR} TKI treatment.”

Pao and others provided analysis on 60 drug-sensitive adenocarcinomas; 9 out of 38 (24%) had \textit{KRAS} mutations, while none of the drug-sensitive tumors had mutations.\cite{76} These data suggest that tumors with the \textit{KRAS} mutation are associated with a lack of response to these kinase inhibitors. These findings suggested that patients whose lung adenocarcinomas have \textit{KRAS} mutations will not experience significant tumor regression with either gefitinib or erlotinib. Whether \textit{KRAS} mutational status can be used to predict responses to erlotinib in patients is still under investigation. Data presented here suggested that clinical decisions regarding the use of these agents in patients with lung adenocarcinomas might be improved in the future by pre-treatment mutational profiling of \textit{KRAS}. These findings warrant validation in large prospective trials using standardized mutation detection techniques.

\textit{KRAS} is frequently activated in NSCLC, and the relationship of \textit{KRAS} mutations to outcome after \textit{EGFR} inhibitor treatment has not been described. Eberhard and others detected \textit{KRAS} mutations in 21% of tumors from their patient population and determined an association of the mutation with significantly decreased time to progression and survival in erlotinib plus chemotherapy-treated patients.\cite{32} However, authors stated that further studies are needed to confirm the findings of their retrospective subset analysis.

In an additional study, the effect of \textit{KRAS} mutation on the response to erlotinib treatment was analyzed in 206 tumors; 15% of patients had \textit{KRAS} mutations.\cite{35} Erlotinib response rates were 10% for wild-type and 5% for mutant \textit{KRAS}. Significant survival benefit from erlotinib therapy was observed for patients with wild-type \textit{KRAS} but not for patients with mutant \textit{KRAS}. In multivariate analysis, \textit{KRAS} was not a prognostic for poorer survival or predictive of differential survival benefit from erlotinib.

Authors sequenced tumor samples from patients with stage IIIB/IV NSCLC.\cite{31} None of 17 patients with a \textit{KRAS} mutation had a tumor response. Authors suggest prospective, placebo-controlled studies are needed to determine the predictive value of the putative biomarkers.

A recent single prospective study with study limitations is described below:\cite{78}

In a study of 246 NSCLC patients, the presence of \textit{KRAS} mutations in plasma was suggested to be a marker of poor prognosis and thought to hold predictive value.\cite{83} Patients with a detectable plasma-\textit{KRAS} mutation had a significantly shorter overall survival and progression-free survival compared to patients without the \textit{KRAS} mutation. The response rate to chemotherapy was significantly lower in the group of patients with a mutation compared to patients without the mutation. Further validation of an independent cohort is needed.

\textit{Conclusions}

It remains unclear whether assessment of \textit{KRAS} mutation status will be clinically useful with regard to anti-\textit{EGFR} therapy in the treatment of NSCLC. Data on the role of \textit{KRAS} mutations in NSCLC and response to erlotinib are available from 2 Phase III trials that conducted non-concurrent subgroup analyses of the efficacy of TKIs in patients with wild-type (non-mutated) versus mutated \textit{KRAS} lung tumors, Phase II trials, retrospective single-arm studies, three meta-analyses, one systematic review, and two prospective study. Although studies have shown that a \textit{KRAS} mutation in patients with NSCLC
confers a high level of resistance to TKIs, data are insufficient to make a determination about an association between \textit{KRAS} mutation status and survival in these patients.

\textbf{KRAS and Anti-EGFR Monoclonal Antibodies}

Two Phase III trials, BMS-099 and FLEX, investigated platinum-based chemotherapy with and without cetuximab in the first-line setting for advanced NSCLC.\cite{84,85} Subsequently, an investigation of \textit{KRAS} mutational status and cetuximab treatment was performed from both trials.\cite{86,87} Outcomes observed (overall survival and/or progression free survival) in the cetuximab-containing and chemotherapy alone arms were similar between patients with mutant and wild-type \textit{KRAS}. However, these findings should be interpreted with caution given the small subgroup sample size and retrospective nature of the analysis.

\textit{Conclusions}

While a lack of response to the \textit{EGFR} monoclonal antibodies has been established in metastatic colorectal cancer, and use of these drugs is largely restricted to patients with wild-type \textit{KRAS}, the expectation that \textit{KRAS} mutation status would also be an important predictive marker for cetuximab use in NSCLC has not been shown. In two randomized trials with non-concurrent subgroup analyses of \textit{KRAS} mutation status and the use of cetuximab with chemotherapy, \textit{KRAS} mutations did not appear to identify patients who would not benefit from anti-\textit{EGFR} antibodies, as the outcomes observed with cetuximab were regardless of \textit{KRAS} mutational status.

\textit{Clinical Practice Guidelines}

\textit{National Comprehensive Cancer Network (NCCN)}\cite{64}

The NCCN guidelines (v3.2017) for treatment of NSCLC state that “\textit{KRAS} mutations are associated with intrinsic TKI resistance, and \textit{KRAS} gene sequencing could be useful for the selection of patients as candidates for TKI therapy. \textit{KRAS} testing may identify patients who may not benefit from further molecular diagnostic testing.” The guidelines also state that the “presence of \textit{KRAS} mutations is prognostic of poor survival for patients with NSCLC when compared to absence of \textit{KRAS} mutations, independent of therapy. \textit{KRAS} mutations are also predictive of lack of benefit from platinum/vinorelbine chemotherapy or \textit{EGFR} TKI therapy.” However, no specific recommendation for \textit{KRAS} testing is made in the NCCN guidelines.

\textit{College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology (CAP/IASLC/AMP)}\cite{68,88}

The 2014 guidelines issued jointly by the CAP/IASLC/AMP do not recommend testing for KRAS mutations “as a sole determinant of EGFR-targeted therapy; however, testing for KRAS may be performed initially to exclude KRAS-mutated tumors from EGFR and ALK testing as part of a stepwise algorithm designed to maximize testing efficiency.” In 2013 the CAP/IASLC/AMP panel also stated that, “The significance of KRAS mutational analysis may become increasingly important with the further development of new therapies targeting downstream RAS pathways, such as PI3K/AKT/mTOR and RAS/RAF/MEK, but at this time, the absence of a KRAS mutation does not add clinically useful information to the EGFR mutation result and should not be used as a determinant of EGFR TKI therapy.”\cite{88}

\textit{Other Oncogenic Mutations}
Other potentially targetable oncogenic mutations have been characterized in lung adenocarcinomas including in the genes\textit{ RET}, \textit{MET}, \textit{BRAF}, and \textit{HER2}. The data on the use of targeted therapies in NSCLC with a mutation in one of these genes is preliminary in that much of the demonstrated sensitivity of tumor to the various drugs has been in vitro or in animal studies, and published data on patient tumor response and survival outcomes are extremely limited, consisting of case reports and small case series.

The following studies are representative of the available published evidence for these investigational genes.

\textit{RET}

In a phase 2 prospective trial for patients with \textit{RET} fusion-positive tumors, preliminary data on 3 patients treated with cabozantinib showed a partial response in 2 patients, and 1 with stable disease approaching 8 months.\cite{89}

\textit{MET}

In 2016, Ye et al. conducted a meta-analysis to determine the efficacy and risk profile of c-met inhibitors in NSCLC, including nine studies (N= 1611 patients in target drug groups and 1605 patients in control groups).\cite{90} Patients in target drugs group had longer PFS (HR 0.80, 95% CI 0.66-0.99, \(p=0.04\)) but not OS than those in control group, especially in Asian (HR 0.57, 95% CI 0.42-0.76, \(p<0.001\)), Non-squamous (HR 0.79, 95% CI 0.64-0.97, \(p=0.03\)), Phase III (HR 0.66, 95% CI 0.50-0.86, \(p=0.002\)), previous treated (HR 0.77, 95% CI 0.63-0.95, \(p=0.01\)) and small molecular compounds subgroups (HR 0.62, 95% CI 0.50-0.78, \(p<0.001\)). In addition, target drugs did not affect the objective response rate (ORR) but improved disease control rate (DCR) (RR 1.22, 95% CI 1.02-1.46, \(p=0.03\)) of NSCLC patients.

Recently, Dimou et al. performed a meta-analysis to assess the effect of high \textit{MET} gene copy number on the overall survival of patients with advanced NSCLC.\cite{91} Nine retrospective studies were included that reported data regarding the prognostic impact of \textit{MET} gene copy number on the survival of patients with NSCLC who had received surgery. All of the included studies had populations of patients with mixed adenocarcinoma histology results. The authors reported that \textit{MET} gene copy number predicted poorer overall survival when all studies were combined in a random effects model (HR=1.78, 95% CI 1.22-2.60). When only the studies that had at least 50% of adenocarcinoma patients in their populations were included, the effect was significant (five studies, HR 1.55, 95% CI 1.23-1.94). This was not true when we included only the studies with no more than 50% of the patients having adenocarcinoma histology (four studies HR 2.18, 95% CI 0.97-4.90). The authors concluded that higher \textit{MET} gene copy number in the primary tumor at the time of diagnosis predicts worse outcome in patients with NSCLC; however, this may be specific to the subset of the patients with adenocarcinoma histology.

A phase II trial of \textit{MET}-positive NSCLC, in which patients were treated with an anti-\textit{MET} antibody plus erlotinib, showed improved PFS and OS.\cite{92}

\textit{BRAF}

A case series reported by Hyman et al. assessed the response to vemurafenib in patients with \textit{BRAF} V600 mutation–positive nonmelanoma cancers, including a NSCLC cohort (n=20).\cite{93} The primary end
point was the response rate; secondary end points included progression-free and overall survival, all of which were collected eight weeks after the start of therapy. In the NSCLC cohort the response rate was 42% (eight out of twenty patients) (95% confidence interval [CI], 20 to 67) and median progression-free survival was 7.3 months (95% CI, 3.5 to 10.8). Ten patients (50%) also had significant reduction in tumor diameter.

In addition, rare case reports have documented a response to vemurafenib in patients with NSCLC and a BRAF mutation.[94-96]

**HER2**

Mok et al. reported on the biomarker subgroup analyses from the FASTACT-2 study in 2016.[97] FASTACT-2 is a multicenter, randomized, placebo-controlled, double-blind, phase III study of intercalated first-line erlotinib or placebo with gemcitabine and platinum, followed by maintenance therapy with erlotinib or placebo, for Asian patients with stage IIIB or IV NSCLC. In addition to analyzing for EGFR, HER2 and HER3 biomarkers were analyzed by immunohistochemistry. Only EGFR mutations (p<0.001) were predictive of outcomes; HER2 and HER3 biomarkers were not significant in a treatment-by-biomarker interaction test.

Shen et al. retrospectively reviewed 111 patients from a Uygur population who received gefitinib 250 mg once daily and were evaluated for HER2 expression.[98] HER2 overexpression was detected in 24 patients. The ORR in patients with and without HER2 overexpression was 29% and 14%, respectively (p=0.12). Median PFS and OS in patients with and without HER2 overexpression did not differ statistically significantly (PFS, 4.7 months vs 3.9 months, p=0.09; OS, 21 months vs 19 months, p=0.09).

Mazières et al. reported on a retrospective review of a consecutive series of patients with NSCLC who were tested for a HER2 mutation, and the authors assessed clinicopathologic characteristics and patient outcomes according to mutation status.[99] A HER2 mutation was identified in 65 of 3800 (1.7%) patients, and was mutually exclusive of other driver mutations (EGFR, ALK, BRAF), with the exception of 1 case in which both a HER2 and KRAS mutation were identified. The patient population in which a HER2 mutation was found had a median age of 60 years (range, 31-86), 69% were women, and 52% were never-smokers. All of the tumors were adenocarcinomas, and 50% were stage IV (n=33). The patients with stage IV disease received conventional chemotherapy, and of these, 16 patients also received HER2-targeted therapy as additional lines of therapy (for a total of 22 individual anti-HER2 treatments that were evaluable). Four patients had progressive disease, 7 had disease stabilization, and 11 with partial response. PFS for patients with HER2 therapies was 5.1 months.

**Conclusion**

The data on the use of targeted therapies in NSCLC with a mutation in RET, MET, BRAF, or HER2 is preliminary and limited to a few case reports, retrospective analyses, and case series. Further studies are needed to determine whether testing for genetic alternation in these genes may be useful for targeted therapy in patients with NSCLC.

**Clinical Practice Guidelines**

*National Comprehensive Cancer Network (NCCN)*[64]
NCCN (v3.2016) does not give specific recommendations for testing for genetic alterations in the genes RET, MET, BRAF, or HER2 in NSCLC, however, they state that the following emerging targeted agents are now recommended for patients with genetic alterations: BRAF V600E: vemurafenib, dabrafenib, or dabrafenib + trametinib (category 2A), MET: crizotinib (category 2A), HER2: trastuzumab or afatinib (category 2B), RET: cabozantinib or vandetanib (category 2A).

Summary

**EGFR**

Several RCTs, nonconcurrent prospective studies, and single-arm enrichment studies demonstrate that the detection of somatic mutations within the EGFR gene; small deletions in exon 19, and point mutations in exon 20 (T790M) and exon 21 (L858R); identifies patients with advanced non-squamous cell-type non-small cell lung cancer (NSCLC) who are likely to benefit from use of tyrosine kinase inhibitors (TKIs), and therefore represent ideal candidates for treatment with these drugs. These observations have been made in a population composed primarily of tumors with adenocarcinoma histology. Patients who are found to have wild-type tumors are unlikely to respond to TKIs, and they should be considered candidates for alternative therapies. Therefore, EGFR mutational analysis may be considered medically necessary to predict treatment response to erlotinib and afatinib in patients with advanced non-squamous cell-type NSCLC.

There is limited evidence to indicate whether mutations within exons 18-24 of the epidermal growth factor receptor (EGFR) gene are seen in patients with squamous cell-type non-small cell lung cancer (NSCLC); therefore, EGFR mutational analysis is considered investigational in these patients.

**KRAS**

KRAS mutations may be an indicator of poor prognosis in non-small cell lung cancer (NSCLC) and may predict a lack of response to tyrosine kinase inhibitors (TKIs). However, there is insufficient data to assess any association between KRAS mutation status and survival in these patients, and the impact of testing for KRAS mutations on clinical management or to predict treatment benefit is unknown. Studies have not shown that KRAS mutations identify a population that may benefit from the use of anti-EGFR monoclonal antibodies. In two randomized trials with post hoc analyses of KRAS mutation status and use of anti-EGFR monoclonal antibody cetuximab with chemotherapy, KRAS mutations did not identify patients who would benefit from anti-EGFR antibodies, as outcomes with cetuximab were similar regardless of KRAS mutation status. Therefore, analysis of mutations of the KRAS gene is considered investigational as a technique to predict treatment non-response to EGFR TKIs and anti-EGFR monoclonal antibody therapy (e.g., cetuximab) in non-small cell lung cancer.

Other Oncogenic Mutations

Mutations and other genetic alterations in the genes RET, MET, BRAF, and HER2 have been characterized as potentially targetable in lung adenocarcinomas. Current evidence is limited to preliminary data from a few case reports, retrospective analyses, and case series with patient numbers too small to draw conclusions. Further studies are needed, particularly for tumor sensitivity to various drugs and for survival outcomes, to determine whether mutations in these genes can be used in targeted therapy. Therefore testing for genetic alternations in the genes RET, MET, BRAF, and HER2 for targeted therapy in patients with non-small cell lung cancer is considered investigational.
REFERENCES


analysis of patients from German centers in the TRUST study. *J Thorac Oncol*. 2008 Dec;3(12):1446-53. PMID: 19057271


66. Wong, DW, Leung, EL, So, KK, et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer. 2009 Apr 15;115(8):1723-33. PMID: 19170230


**CROSS REFERENCES**

**KRAS, NRAS, and BRAF Mutation Analysis in Colorectal Cancer**, Genetic Testing, Policy No. 13

**Genetic and Molecular Diagnostic Testing**, Genetic Testing, Policy No. 20

**BRAF Gene Mutation Testing To Select Melanoma Patients for BRAF Inhibitor Targeted Therapy**, Genetic Testing, Policy No. 41

**Evaluating the Utility of Genetic Panels**, Genetic Testing, Policy No. 64

OmedaRx Medication Policy Manual: [https://www.omedarx.com/medicationpolicies](https://www.omedarx.com/medicationpolicies); NOTE: Do a find (Ctrl+F) and enter drug name in the find bar to locate the appropriate policy.

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