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Medical Policy Manual

Topic: KRAS Mutation Analysis in Non-Small Cell Lung Cancer (NSCLC)

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Section: Genetic Testing

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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

Epidermal growth factor receptor (EGFR), a receptor tyrosine kinase (TK), is frequently overexpressed and activated in non-small cell lung cancer (NSCLC). Anti-EGFR drugs that target EGFR include tyrosine kinase inhibitors (TKIs) (eg, erlotinib and gefitinib) and monoclonal antibodies (eg, cetuximab, panitumumab). TKIs and monoclonal antibodies interfere with EGFR signaling pathways important in cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.

KRAS is a G-protein involved in the EGFR-related signal transmission. The KRAS gene 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.

Note: Gefitinib is currently in very limited use in the U.S., hence this policy only addresses studies that assess the response to erlotinib.

MEDICAL POLICY CRITERIA

Analysis of somatic mutations of the KRAS gene is considered **investigational** as a technique to predict treatment non-response to anti-EGFR therapy with the tyrosine kinase inhibitor erlotinib and the anti-EGFR monoclonal antibody cetuximab in non-small cell lung carcinoma.

SCIENTIFIC EVIDENCE[1]

The focus of this 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.

KRAS and EGFR Tyrosine Kinase Inhibitors (TKIs)

Studies suggest that NSCLC patients with KRAS mutations may be nonresponsive to treatment with EGFR TKIs; however, the number of patients in the currently published studies who had KRAS-mutated tumors is relatively small and studies are mostly retrospective in nature.

Systematic Review

- The aim of this systematic review and meta-analysis was to assess if KRAS mutations represent a candidate predictive biomarker for anti-EGFR-targeted therapeutic strategies in NSCLC.[2] Authors state "substantial" evidence was found in the literature that determined KRAS mutations are 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 (sensitivity=0.21 [95% CI 0.16-0.28]). In summary, the findings of this study suggest 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 advocate 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. 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.

Meta-Analyses

- In the most recent meta-analysis identified, authors suggest it is the first study to demonstrate 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.[3] Though more studies are still needed to identify patients who will most likely benefit from the appropriate combining targeted therapy, 8 randomized controlled trials, including 2417 patients, with significant methodological limitations were included. Sub-group analysis based on phases of trials showed a tendency to improve progression-free survival and overall survival in combining targeted therapy. Moreover, it should be noted that not all trials analyzed, including 2 phase III trials, demonstrated overall survival benefits from combining therapies. There were several limitations in this meta-analysis including the issue that this study was not based on 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 present an additional study limitation. Finally publication bias was possible because papers with null results tend not to be published.

- Due to inconclusive results on studies that have evaluated the association between KRAS mutations and resistance to TKIs with NSCLC, authors in the second cited meta-analysis analyzed 22 studies that included 1470 NSCLC patients, of whom 16% had KRAS mutations (N=231).[4] 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.

Randomized Controlled Trials (RCTs)

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.[5-13] 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:

- Guan et al (2013) reported on 1935 consecutive patients with NSCLC who were treated at a single institution.[14] 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 2.0months in patients with *EGFR* and *KRAS* mutations, respectively, and 1.9 months in wild-type patients; in comparison with wild-type patients, PFS was statistically longer in patients with *EGFR* mutations ($p<0.001$) but not different in patients with KRAS mutations ($p=0.48$). The authors observed that "the presence of an *EGFR*mutation, but nota *KRAS*mutation, was predictive of responsiveness to EGFR TKI treatment.".
- In 2013, Fiala et al. reported on a retrospective analysis of patients with squamous cell NSCLC who underwent *EGFR*, *KRAS*, and *PIK3CA*(phosphatidylinositide-3-kinase catalytic subunit-alpha) mutation testing.[15] 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 overall survival (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 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.
- Pao and others provide analysis on 60 drug-sensitive adenocarcinomas; 9 out of 38 (24%) had KRAS mutations, while none of the drug-sensitive tumors had mutations [5]. These data suggest that tumors with the KRAS mutation are associated with a lack of response to these kinase inhibitors. These findings suggest that patients whose lung adenocarcinomas have *KRAS* mutations will not experience significant tumor regression with either getinib or erlotinib. Whether KRAS mutational status can be used to predict responses to erlotinib in patients is still under investigation. Data presented here suggest 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 KRAS. These findings warrant validation in large prospective trials using standardized mutation detection techniques.

- KRAS is frequently activated in NSCLC, and the relationship of KRAS mutations to outcome after EGFR inhibitor treatment has not been described. Eberhard and others detected 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 eroltinib plus chemotherapy-treated patients.[7] However, authors state that further studies are needed to confirm the findings of their retrospective subset analysis.
- In an additional study, the effect of KRAS on the response to erlotinib treatment was analyzed in 206 tumors; 15% of patients had KRAS mutations.[6] Erlotinib response rates were 10% for wild-type and 5% for mutant KRAS. Significant survival benefit from erlotinib therapy was observed for patients with wild-type KRAS but not for patients with mutant KRAS. In multivariate analysis, 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.[12] None of 17 patients with a 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:[13]

In a study of 246 NSCLC patients, the presence of KRAS mutations in plasma was suggested to be a marker of poor prognosis and thought to hold predictive value.[16] Patients with a detectable plasma-KRAS mutation had a significantly shorter overall survival and progression-free survival compared to patients without the 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.

Conclusions

It remains unclear whether assessment of KRAS mutation status will be clinically useful with regard to anti-EGFR therapy in the treatment of non-small-cell lung cancer (NSCLC). Data on the role of 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 KRAS lung tumors, Phase II trials, retrospective single-arm studies, 2 meta-analyses, 1 systematic review, and 1 prospective study. Although studies have shown that a 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 KRAS mutation status and survival in these patients.

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.[17,18] Subsequently, an investigation of KRAS mutational status and cetuximab treatment was performed from both trials.[19,20] 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 KRAS. However, these findings should be interpreted with caution given the small subgroup sample size and retrospective nature of the analysis. In addition, findings from the FLEX trial have not yet been published in full and are currently available only in abstract.

Conclusions

A lack of response to the EGFR monoclonal antibodies has been established in metastatic colorectal cancer, and the use of these drugs is mostly restricted to patients with wild-type KRAS. The expectation that KRAS mutation status would also be an important predictive marker for cetuximab use in NSCLC has not been shown. In 2 randomized trials with non-concurrent subgroup analyses of KRAS mutation status and the use of cetuximab with chemotherapy, KRAS mutations did not appear to identify patients who would not benefit from anti-EGFR antibodies, as the outcomes observed with cetuximab were regardless of KRAS mutational status.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

The 2014 National Comprehensive Cancer Network (NCCN) guidelines for treatment of non-small cell lung cancer (NSCLC)[21] state that KRAS mutations are associated with intrinsic TKI resistance, and KRAS gene sequencing could be useful for the selection of patients as candidates for TKI therapy, but make no specific recommendations(evidence category 2A: the recommendation is based on lower level evidence and there is uniform NCCN consensus). The guidelines state the presence of KRAS mutations areprognostic of poor survival for patients with NSCLC when compared to absence of KRAS mutations, independent of therapy. No recommendation for KRAS testing is made in the NCCN guidelines as to the use of cetuximab, a monoclonal antibody that targets EGFR, in patients with NSCLC.

College of American Pathologists (CAP) Joint Guideline

In 2013, CAP, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology published evidence-based guidelines for molecular testing to select patients with lung cancer for treatment with EGFR and alkaline phosphatase TKI therapy.[22] Based on good quality evidence (category B), *KRAS* mutation testing is not recommended as a sole determinant of EGFR TKI therapy. The guideline authors 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."

Summary

The presence of KRAS mutation has been shown to be associated with a poor prognosis in non-small cell lung cancer (NSCLC); however, improvement in patient health outcomes related to the use of KRAS mutational analysis to predict treatment benefit is uncertain. Therefore, KRAS mutation analysis to predict treatment non-response to EGFR TKI therapy (e.g., erlotinib) is considered investigational.

Although a lack of response to the EGFR monoclonal antibodies has been established in metastatic colorectal cancer, the expectation that KRAS mutation status would also be an important predictive marker for cetuximab use in NSCLC has not been shown. Therefore, KRAS mutation analysis is considered investigational as a technique to predict treatment non-response to anti-EGFR monoclonal antibody therapy (e.g., cetuximab) in non-small cell lung carcinoma.

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CROSS REFERENCES

Epidermal Growth factor Receptor (EGFR) Mutation Analysis for Patients with Non-Small Cell Lung Cancer (NSCLC), Genetic Testing, Policy No. 56

CODES	NUMBER	DESCRIPTION
CPT	81275	KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis, variants in codons 12 and 13
	88363	Examination and selection of retrieved archival (ie, previously diagnosed) tissue(s) for molecular analysis (eg, KRAS mutational analysis)
HCPCS	None	