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Medical Policy Manual

Topic: Epidermal Growth Factor Receptor (EGFR) Mutation Analysis for Patients with 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

Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase (TK) frequently overexpressed and activated in non-small cell lung cancer (NSCLC). 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 tyrosine kinase inhibitors (TKIs) such as erlotinib.

The test 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 erlotinib. Patients found to be wild type are unlikely to respond to erlotinib, so other treatment options should be considered. ®

There are 2 recently FDA-approved tests for EGFR mutation testing. The FDA-approved cobas EGFR Mutation Test is a companion diagnostic for the cancer drug Tarceva (erlotinib).[1] This diagnostic test detects epidermal growth factor receptor (EGFR) gene mutations. The *therascreen*® EGFR RGQ PCR Kit is an automated molecular assay designed to detect the presence of EGFR mutations for selecting NSCLC patients for treatment with GILOTRIF™ (afatinib).[2] If the test results indicate that EGFR exon 19 deletion or exon 21 (L858R) substitution mutation is present in NSCLC cells, then the patient may be considered for treatment with GILOTRIF™ (afatinib).

MEDICAL POLICY CRITERIA

I. Analysis of two types of somatic mutation within the EGFR gene—small deletions in exon 19 and a point mutation in exon 21 (L858R)—may be considered **medically necessary** to predict treatment response to erlotinib (Tarceva®) or afatinib (GILOTRIF™) in patients with advanced or metastatic non-squamous cell-type non-small cell lung cancer (NSCLC).

II. Analysis of two types of somatic mutation within the EGFR gene—small deletions in exon 19 and a point mutation in exon 21 (L858R)—is considered **investigational** for patients with advanced NSCLC of squamous cell-type.

III. Analysis for other mutations within exons 18-24 of the EGFR gene, or for other applications related to NSCLC, is considered **investigational.**

SCIENTIFIC EVIDENCE[3]

Treatment options for NSCLC depend on disease stage and include various combinations of surgery, radiation therapy, chemotherapy, and best supportive care. Unfortunately, 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.[4] When treated with standard platinum-based chemotherapy, patients with advanced NSCLC have a median survival of 8 to 11 months and a 1-year survival of 30% to 45%.[5,6]

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.[7] 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.[8]

Two publications demonstrated that the underlying molecular mechanism underpinning dramatic responses in these favorably prognostic groups appeared 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).[9,10] These can be detected by direct sequencing or polymerase chain reaction (PCR) technologies.

Three orally administered EGFR-selective small molecules (quinazolinamine derivatives) have been identified for use in treating NSCLC: erlotinib (Tarceva®, Genentech BioOncology), afatinib (GILOTRIF™, Boehringer Ingelheim Pharmaceuticals, Inc), and gefitinib (Iressa®, AstraZeneca). Erlotinib and afatinib are available for use in patients in the U.S. The marketing status for gefitinib is classified as "discontinued" by the FDA.[11]

Erlotinib

Technology Assessment/Meta-analysis

- A BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment on this topic was first published in November 2007.[12] The 2007 Assessment concluded that there was

insufficient evidence to permit conclusions about the clinical validity or utility of EGFR mutation testing to predict erlotinib sensitivity or to guide treatment in patients with NSCLC. This Assessment was revised with new conclusions indicating EGFR mutation testing has clinical utility in selecting or deselecting patients for treatment with erlotinib.[13]

- Petrelli et al. reported a meta-analysis of 13 randomized trials of 1,260 patients receiving tyrosine kinase inhibitors for first line, second line or maintenance therapy and compared outcomes to standard therapy.[14] Overall they noted that in patients with EGFR mutations, use of EGFR tyrosine kinase inhibitors increased the chance of obtaining an objective response almost 2-fold when compared to chemotherapy. Response rates were 70% vs. 33% in first line trials and 47% versus 28.5% in second line trials. Tyrosine kinase inhibitors reduced the hazard of progression by 70% in all trials and by 65% in first-line trials, however, overall they did not improve survival.

Randomized studies

- In a phase 3 prospective clinical trial, Zhou et al. reported the results of first line treatment of patients with EGFR-mutation positive NSCLC randomized to treatment with erlotinib (n=83) versus standard chemotherapy (gemcitabine plus carboplatin) (n=82).[15] They observed a significant increase in progression-free survival compared to treatment with chemotherapy (13.1 vs. 4.5 months; hazard ratio 0.16 ($p<0.0001$). Patients treated with erlotinib experienced fewer grade 3 and 4 toxic effects than those on chemotherapy.
- These results were duplicated in the EURTAC trial (NCT00446225), a multicenter, open-label, randomized phase 3 trial. Adult patients with EGFR-mutations (exon 19 deletion or L858R mutation in exon 21) with NSCLC were randomized.[16] Eighty-six received erlotinib and 87 received standard chemotherapy. A planned interim analysis showed that the primary endpoint had been met. At the time the study was halted (Jan 26, 2011), median PFS 9.7 (8.4-12.3) months versus 5.2 (4.5-5.8) in the erlotinib and standard chemotherapy groups respectively. Hazard ratio 0.37 (0.25-0.54); $p<0.0001$). Six percent of patients on erlotinib had treatment-related severe adverse events compared to 20% of those receiving a standard chemotherapy regimen.

Non-randomized studies

Thirteen publications have been published that provide data on EGFR mutations in tumor samples obtained from NSCLC patients in erlotinib treatment studies. Nine of these were non concurrent, prospective studies of patients treated with erlotinib and then studied for the presence or absence of mutations.[17-25] Data comparing erlotinib results in EGFR mutation-positive versus wild-type patients have been reported in 9 studies of 630 patients.[17-21,23-25]

EGFR mutations appear to provide prognostic, as well as predictive information about the behavior of tumors.

- In the study by Eberhard et al., improved outcome parameters were observed in EGFR-positive patients compared with wild-type patients for the population as a whole (standard chemotherapy and standard chemotherapy with erlotinib) in all measurement categories with objective radiologic response of 38% versus 23% ($p=0.01$), time to progression of 8 months versus 5 months ($p<0.001$), and overall survival (OS) (not reached versus 10 months [$p<0.001$]).[22]

Four studies were prospective one-arm enrichment studies of mutation-positive patients and all patients had stage IIIA/IV NSCLC:[26-29]

- Rosell et al. compared *EGFR*-positive patients with erlotinib in treatment failure and chemotherapy naïve patients,[27] and concluded that 350 patients out of 2105 had mutations. The objective radiologic response rates were 70%, progression-free survival (PFS) times were 14 months, and overall survival (OS) times were 27 months. Additional results in this study reported mutations in 16.6% of the total patients studied but noted these were found more frequently in women (69.7%), in patients who had never smoked (66.6%), and in patients with adenocarcinomas (80.9%).[27] Based on these findings, the authors recommended EGFR-mutation screening in women with lung cancer with nonsquamous cell tumors who have never smoked.
- This study by Jackman et al. combines patient data from five trials (N=223 patients) in predominantly Western populations to assess the impact of EGFR and KRAS mutations on first-line therapy with an EGFR-tyrosine kinase inhibitor (TKI) and compare clinical versus molecular predictors of sensitivity.[26] Sensitizing EGFR mutations were associated with a 67% response rate, time to progression (TTP) of 11.8 months, and OS of 23.9 months. Exon 19 deletions were associated with longer median TTP and overall survival compared with L858R mutations. Wild-type EGFR was associated with poorer outcomes (response rate, 3%; TTP, 3.2 months) irrespective of KRAS status. No difference in outcome was seen between patients harboring KRAS transition versus transversion mutations. Authors concluded that EGFR genotype was more effective than clinical characteristics at selecting appropriate patients for consideration of first-line therapy with an EGFR-TKI.
- Sun and others studied a total of 77 patients with either an exon 19 deletion (n = 58) or L858R mutation (n = 19) who were treated with gefitinib or erlotinib.[28] The overall response rate was 69%. Patients with an exon 19 deletion had a significantly longer PFS compared with patients with L858R mutation (9.5 vs. 7.7 months; P = 0.029). The L858R mutation was independently associated with a shorter PFS compared with an exon 19 deletion, even after adjusting for other clinical factors (hazard ratio 2.72; 95% CI 1.38-5.38). However, there were no significant differences in response rate (71 vs. 63%) and OS (21.4 vs. 30.7 months) between subjects with exon 19 deletions and L858R mutations, respectively. Authors concluded, in Korean NSCLC patients, EGFR exon 19 deletions are associated with longer PFS compared with EGFR L858R mutations.
- In the first prospective biomarker study by Yoshioka and others, 30 patients were enrolled, and results for erlotinib therapy for pretreated patients with EGFR- tumors were described.[29] Objective response was observed in one patient (3.3%), and the disease became stable in 18 patients (60.0%). Skin rash was the most common side effect. Grades 3-4 adverse events included pulmonary embolism, keratitis, and anemia. Two other patients developed interstitial lung disease (grades 1 and 2). Nevertheless, all these events were reversible, resulting in no treatment-related deaths. With a median follow-up time of 10.7 months, the median survival time and median progression-free survival times were 9.2 and 2.1 months, respectively.

An increased incidence of mutations is clearly seen in these special populations (women, patients with adenocarcinoma, nonsmokers, and/or Asians); however, it does appear that a substantial number of patients without these selected demographics still exhibit EGFR mutations and would benefit from erlotinib treatment.

- In a comprehensive analysis of 14 studies involving 2,880 patients, Mitsudomi et al. noted mutations were observed in 10% of men, 7% of non-Asian patients, and 7% of current or former smokers, but only 2% of patients with non-adenocarcinoma histologies.[30]
- Park et al., in a preselected set of Korean patients treated with gefitinib, reported EGFR mutations to be present in 3 out of 20 (15%) male smokers with squamous cell carcinoma of lung (SCC), a patient subgroup that based on demographics should have a low yield of EGFR mutations.[31] Two of the 3 patients identified with the mutation exhibited a response to the drug versus a response in 1 of 17 wild-type patients. The PFS in patients with EGFR was 5.8 months, compared to 2.4 months in the wild-type group (not statistically significant, p=0.07, but suggesting a trend favoring a treatment response in patients with the mutation).
- In vivo studies by Dobashi et al. have been reported, showing that in tumors in Japanese patients with both adenocarcinomas and SCCs, EGFR mutations are associated with downstream phosphorylation of EGFR and constitutive activation of the EGFR pathway.[32]

Conclusion

In a pooled analysis of studies, EGFR mutations appear to demonstrate improved patient outcomes for patients treated with erlotinib, as compared to standard chemotherapy (median PFS of 13.2 versus 5.9 months, respectively).[33] Patients with EGFR mutations appear to be ideal candidates for treatment with erlotinib, whereas wild-type patients appear to derive little detectable benefit from erlotinib. Identification of patients likely to respond or to fail to respond to erlotinib treatment leads to tailored choices of treatment likely to result in predictable and desirable outcomes.

In studies of treatment with erlotinib, objective radiologic response rates in patients with EGFR-mutation-positive tumors ranged from 0% to 83% (median 45%) compared with objective radiologic response rates in patients with wild-type tumors of between 0% and 18% (median 5.5%). In the 5 studies statistically evaluating results, patients with EGFR-mutation-positive tumors always demonstrated statistically significant increases in objective radiologic response.

Afatinib

Studies on afratinib demonstrate the preclinical efficacy in NSCLC with common EGFR-activating mutations and the T790M mutation typically associated with EGFR TKI resistance. Clinically, afatinib has been evaluated in the LUX Lung trial program, with significant activity seen in the first and later-line settings, and these studies are described below.

Randomized studies

- In this phase III study by Sequist et al., eligible patients with stage IIIB/IV lung adenocarcinoma were screened for EGFR mutations.[16] A total of 1,269 patients were screened, and 345 were randomly assigned to treatment. Median PFS was 11.1 months for afatinib and 6.9 months for chemotherapy (hazard ratio [HR], 0.58; 95% CI, 0.43 to 0.78; P = .001). Median PFS among those with exon 19 deletions and L858R EGFR mutations (n = 308) was 13.6 months for afatinib and 6.9 months for chemotherapy (HR, 0.47; 95% CI, 0.34 to 0.65; P = .001). The most common treatment-related adverse events were diarrhea, rash/acne, and stomatitis for afatinib and nausea, fatigue, and decreased appetite for chemotherapy. Authors concluded that afatinib is associated with prolongation of PFS when compared with standard doublet chemotherapy in patients with advanced lung adenocarcinoma and EGFR mutations.

- In this phase 2b/3 trial, Miller et al. enrolled patients with stage IIIB or IV adenocarcinoma and an Eastern Cooperative Oncology Group performance (ECOG) performance score of 0-2 who had received one or two previous chemotherapy regimens and had disease progression after at least 12 weeks of treatment with erlotinib or gefitinib.[34] Authors identified 697 patients, 585 of whom were randomly allocated to treatment (390 to afatinib, 195 to placebo). Median overall survival was 10·8 months (95% CI 10·0-12·0) in the afatinib group and 12·0 months (10·2-14·3) in the placebo group (hazard ratio 1·08, 95% CI 0·86-1·35; p=0·74). Median progression-free survival was longer in the afatinib group (3·3 months, 95% CI 2·79-4·40) than it was in the placebo group (1·1 months, 0·95-1·68; hazard ratio 0·38, 95% CI 0·31-0·48; p<0·0001). No complete responses to treatment were noted; 29 (7%) patients had a partial response in the afatinib group, as did one patient in the placebo group. Subsequent cancer treatment was given to 257 (68%) patients in the afatinib group and 153 (79%) patients in the placebo group. The most common adverse events in the afatinib group were diarrhea (339 [87%] of 390 patients; 66 [17%] were grade 3) and rash or acne (305 [78%] patients; 56 [14%] were grade 3). These events occurred less often in the placebo group (18 [9%] of 195 patients had diarrhoea; 31 [16%] had rash or acne), all being grade 1 or 2. Drug-related serious adverse events occurred in 39 (10%) patients in the afatinib group and one (<1%) patient in the placebo group. Authors recorded two possibly treatment-related deaths in the afatinib group. Authors concluded that findings for progression-free survival and response to treatment suggest that afatinib could be of some benefit to patients with advanced lung adenocarcinoma who have failed at least 12 weeks of previous EGFR tyrosine-kinase inhibitor treatment.

Non-randomized studies

- In a phase 2 study (LUX-Lung 2) by Yang and others, authors enrolled 129 patients from 30 centers with lung adenocarcinoma (stage IIIb with pleural effusion or stage IV) with EGFR mutations, who had no more than one previous chemotherapy regimen for advanced disease, an Eastern Cooperative Oncology Group performance status of 0-2, and no previous treatment with EGFR tyrosine-kinase inhibitors.[35] Patients were treated with afatinib, 99 with a starting dose of 50 mg and 30 with a starting dose of 40 mg. 79 (61%) of 129 patients had an objective response (two complete responses, 77 partial responses). 70 (66%) of the 106 patients with the two common activating EGFR mutations (deletion 19 or L858R) had an objective response, as did nine (39%) of 23 patients with less common mutations. Similar proportions of patients had an objective response when analyzed by starting dose (18 [60%] of 30 patients at 40 mg vs 61 [62%] of 99 patients at 50 mg). Of the two most common adverse events (diarrhea and rash or acne), grade 3 events were more common in patients receiving a 50 mg starting dose (22 [22%] of 99 patients for diarrhea and 28 [28%] of 99 patients for rash or acne) than they were in those receiving a 40 mg starting dose (two [7%] of 30 patients for both diarrhea and rash or acne); possibly treatment-related serious adverse events were also less common in patients receiving a 40 mg starting dose (two of 30 patients vs 14 of 99 patients). Authors recorded one possibly drug-related death (interstitial lung disease). Authors concluded that afatinib shows activity in the treatment of patients with advanced lung adenocarcinoma with EGFR mutations, especially in patients with deletion 19 or L858R mutations.
- In this single-arm phase II trial conducted in patients with stage IIIB to IV pulmonary adenocarcinoma who progressed after ≥ 12 weeks of prior erlotinib and/or gefitinib, patients received afatinib 50 mg per day.[36] Of 62 treated patients, 45 (72.6%) were EGFR mutation positive in their primary tumor according to local and/or central laboratory analyses. Fifty-one patients (82.3%) fulfilled the criteria of acquired resistance to erlotinib and/or gefitinib. Of 61 evaluable patients, five (8.2%; 95% CI, 2.7% to 18.1%) had a confirmed objective response rate

(partial response). Median PFS was 4.4 months (95% CI, 2.8 to 4.6 months), and median OS was 19.0 months (95% CI, 14.9 months to not achieved). Two patients had acquired T790M mutations: L858R + T790M, and deletion in exon 19 + T790M; they had stable disease for 9 months and 1 month, respectively. The most common afatinib-related adverse events (AEs) were diarrhea (100%) and rash/acne (91.9%). Treatment-related AEs leading to afatinib discontinuation were experienced by 18 patients (29%), of whom four also had progressive disease. Authors concluded that afatinib demonstrated modest but noteworthy efficacy in patients with NSCLC who had received third- or fourth-line treatment and who progressed while receiving erlotinib and/or gefitinib, including those with acquired resistance to erlotinib, gefitinib, or both.

Conclusion

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are valuable treatments for EGFR-mutated non-small cell lung cancer (NSCLC). First-generation, reversible EGFR inhibitors erlotinib and gefitinib therapies may eventually fail due to primary or acquired resistance. Irreversible inhibitors targeting ErbB family receptor tyrosine kinases, such as afatinib, have been developed to confer sustained disease control in ErbB-dependent cancers. Clinically, afatinib has been evaluated in the broad-reaching LUX Lung trial program, with significant activity seen in the first and later-line settings.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

The National Comprehensive Cancer Network (NCCN) in the V3.2012 guidelines on non-small-cell lung cancer recommends EGFR mutational analysis in patients with advanced NSCLC.[37] EGFR mutational analysis is not routinely recommended in patients with squamous cell carcinomas because of the low incidence of mutation in this histopathology type. NCCN recommends (category 1) both erlotinib and afatinib as first-line therapy for the treatment NSCLC for patients with sensitizing EGFR mutations based on category 2A evidence: 1) “Erlotinib is recommended as a first-line therapy in patients with sensitizing EGFR mutations and should not be given as first-line therapy to patients negative for these EGFR mutations or with unknown EGFR status” and 2)“Afatinib is indicated for select patients with sensitizing EGFR mutations.”

NCCN[38] has recently recommended testing not be performed in SCCs because of the low incidence identified in the Catalogue of Somatic Mutations in Cancer (COSMIC) maintained by the Sanger Institute.[39] This database of 1,873 samples of squamous cell lung cancers was noted to contain EGFR mutations in 2.7% of samples with an upper CI for the true incidence of mutations reported to be 3.6% or less.

American Society of Clinical Oncology (ASCO)

In a 2011 publication the American Society of Clinical Oncology (ASCO) issued a provisional clinical opinion on EGFR mutation testing for patients with advanced non-small-cell lung cancer considering first- line EGFR tyrosine kinase inhibitor therapy.[40] It concludes patients with NSCLC being considered for first-line therapy with an EGFR tyrosine kinase inhibitor should have their tumor tested for EGFR mutations to determine whether an EGFR tyrosine kinase inhibitor or chemotherapy is the appropriate first-line therapy.

Summary

Non-concurrent prospective studies, single-armed enrichment studies, and randomized studies demonstrate that the detection of epidermal growth factor receptor (EGFR) gene mutations identifies patients who are likely to benefit from use of erlotinib and afatinib, 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 erlotinib or afatinib, 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 currently no evidence to indicate whether this behavior is also seen in patients with squamous cell histology, for other mutations within exons 18-24 of the epidermal growth factor receptor (EGFR) gene, or for other applications related to NSCLC; therefore, EGFR mutational analysis is considered investigational for these applications.

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CROSS REFERENCES

KRAS Mutation Analysis in Non-Small Cell Lung Cancer (NSCLC), Genetic Testing, Policy No. 14

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

CODES	NUMBER	DESCRIPTION
CPT	81235	EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
HCPCS	None	