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Date of Request:	July 27, 2015
NCCN Guidelines Panel:	Lung Cancer

Dear Sir or Madam:

This letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for review of data for IRESSA[®] (gefitinib). IRESSA is a tyrosine kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

The enclosed information is intended to provide supporting data and may include information that is not found in the currently approved prescribing information for IRESSA. The information should not be construed as a recommendation for the use of this product in any manner other than as approved by the Food and Drug Administration and as described in the prescribing information (PI) for IRESSA.

The rationale for the recommended change is to provide health care professionals with information regarding the efficacy and safety of IRESSA that have been evaluated in clinical trials.

Specific Changes: Recommend inclusion of IRESSA as an acceptable targeted therapy for metastatic NSCLC whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.

FDA Status: IRESSA was approved by FDA on July 13, 2015. IRESSA is a tyrosine kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

Rationale: The FDA approval of IRESSA as a treatment for EGFR mutation-positive NSCLC were based on four clinical trials (citations below). The four clinical trials include:

- Study 1: IFUM (Douillard et al.)
- Study 2: IPASS (Mok et al.)
- Study 3: ISEL (Thatcher et al.)
- Study 4: INTEREST (Kim et al.)

Study 1 is the single-arm, open-label confirmatory clinical trial that demonstrated efficacy and safety of IRESSA. Study 2 is the exploratory, randomized, open-label clinical trial that supported the data and analysis identified in Study 1.

Study 2, 3, and 4 demonstrated safety for the use of IRESSA (pooled safety data to evaluate serious and uncommon adverse reactions). Study 3 evaluated common adverse reactions associated with use of IRESSA.

Treatment response to IRESSA has also been demonstrated in patients unable to tolerate chemotherapy, including elderly patients or those with poor performance status. Three supportive studies (citations below) that were not included in the Prescribing Information had the following results:

- The INVITE (Crino et al.) study compared IRESSA with vinorelbine in unselected chemotherapy-naïve elderly patients (aged ≥ 70 years) with advanced NSCLC and demonstrated Overall Response Rate (ORR) of 3.1%, Disease Control Rate (DCR) of 43.3%, and median PFS of 2.7 months for IRESSA. IRESSA also appeared to have better tolerability based on the observed safety profile in the patient population aged ≥ 70 years with advanced NSCLC.
- The NEJ003 (Maemondo et al.) study evaluated chemotherapy-naïve patients that were 75 years of age or older with EGFR mutation positive advanced NSCLC and demonstrated ORR of 74.2%, DCR of 90.3% and median PFS of 12.1 months.
- The NEJ001 (Inoue et al.) study evaluated first-line IRESSA monotherapy in patients with EGFR mutation positive advanced NSCLC who were unable to tolerate chemotherapy due to poor performance status. The study demonstrated ORR of 66%, DCR of 90% and median PFS of 6.5 months.

The following articles are submitted in support of this proposal. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

1. Thatcher N, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebocontrolled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005; 366:1527-37.
2. Kim ES, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet* 2008; 372: 1809–18.
3. Mok TS, et al. Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma. *N Engl J Med* 2009; 361:947-57.
4. Douillard J-Y, et al. First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: a phase-IV, open-label, single-arm study. *BJC*. 2014; 110:55–62.
5. Crinò L, Cappuzzo F, Zatloukal P, et al. Gefitinib versus vinorelbine in chemotherapy-naive elderly patients with advanced non-small-cell lung cancer (INVITE): a randomized, phase II study. *J Clin Oncol*. 2008;26(26):4253-60.
6. Maemondo M, Minegishi Y, Inoue A, et al. First-line gefitinib in patients aged 75 or older with advanced non-small cell lung cancer harboring epidermal growth factor receptor mutations NEJ003 study. *J Thorac Oncol*. 2012;7(9):1417-1422.
7. Inoue A, Kobayashi K, Usui K, et al. First-line gefitinib for patients with advanced non-small cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy. *J Clin Oncol*. 2009;27(9):1394-1400.

Sincerely,

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