Submitted by:
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NCCN Guidelines Panel: Non-Small Cell Lung Cancer

On behalf of Boehringer Ingelheim Pharmaceuticals Inc., I respectfully request the NCCN Non-Small Cell Lung Cancer Guidelines Panel to review the enclosed data for inclusion of afatinib (Gilotrif™) for:

a) first line treatment of metastatic epidermal growth factor receptor (EGFR) mutation positive NSCLC,
b) second line treatment of EGFR TKI naïve metastatic EGFR mutation positive NSCLC following chemotherapy, and
c) treatment of metastatic EGFR mutation positive NSCLC that has progressed following prior treatment with a reversible EGFR TKI and chemotherapy.

Specific Changes: Add afatinib (Gilotrif™) for:

- first line treatment of metastatic EGFR mutation positive NSCLC;
- second line treatment of EGFR TKI naïve metastatic EGFR mutation positive NSCLC following chemotherapy,
- treatment of metastatic EGFR mutation positive NSCLC that has progressed following prior treatment with a reversible EGFR TKI and chemotherapy.

FDA Clearance: On July 12, 2013 the FDA cleared the use of afatinib for the first line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. This approval includes the following limitation of use: Safety and efficacy of Gilotril have not been established in patients whose tumors have other EGFR mutations.

Rationale: In the proposed first line setting, in the randomized, controlled LUX-Lung 3 study afatinib demonstrated significant and meaningful improvements in PFS as well as response rate and lung cancer symptoms as compared to cisplatin/pemetrexed. In the proposed second line setting, in the LUX-Lung 2 study afatinib was found to be active in the treatment of EGFR TKI naïve patients with EGFR mutations irrespective of previous chemotherapy exposure. In patients with EGFR mutation positive NSCLC that has progressed following prior treatment with a reversible EGFR TKI and chemotherapy, in the randomized, placebo controlled LUX-Lung 1 study, afatinib demonstrated improvement in progression-free survival which was coupled with improvements in lung-cancer-related symptoms, as compared with placebo. In the LUX-Lung 4 study, which was carried out in a similar population of Japanese patients, afatinib resulted in response rates and a median PFS very similar to that observed in LUX-Lung 1.

The following articles are submitted in support of these proposed changes. 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. Sequist L et al. Phase III Study of Afatinib or Cisplatin Plus Pemetrexed in Patients With Metastatic Lung Adenocarcinoma With EGFR Mutations. J Clin Oncol. 31 (Published Ahead of Print on July 1, 2013 as 10.1200/JCO.2012.44.2806). This paper presents the safety and efficacy findings of LUX-Lung 3 a randomized controlled comparison of afatinib with cisplatin/pemetrexed in patients with metastatic EGFR mutation positive NSCLC.
2. Yang J et al. Symptom Control and Quality of Life in LUX-Lung 3: A Phase III Study of Afatinib or Cisplatin/Pemetrexed in Patients With Advanced Lung Adenocarcinoma With EGFR Mutations. *J Clin Oncol.* 31 (Published Ahead of Print on July 1, 2013 as 10.1200/JCO.2012.46.1764). This paper presents the symptom control and quality of life findings of LUX-Lung 3 a randomized controlled comparison of afatinib with cisplatin/pemetrexed in patients with metastatic EGFR mutation positive NSCLC.


4. Miller V et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol.* 2012; May;13(5):528-38. This paper presents the safety and efficacy findings of LUX-Lung 1 a randomized placebo controlled study of afatinib in patients with advanced, metastatic non-small-cell lung cancer that had progressed following prior treatment with a reversible EGFR TKI and chemotherapy.

5. Hirsh V et al. Symptom and Quality of Life Benefit of Afatinib in Advanced Non–Small-Cell Lung Cancer Patients Previously Treated with Erlotinib or Gefitinib Results of a Randomized Phase IIb/III Trial (LUX-Lung 1). *J Thorac Oncol.* 2013;8: 229–237 This paper presents the symptom control and quality of life findings of LUX-Lung 1 a randomized placebo controlled study of afatinib in patients with advanced, metastatic non-small-cell lung cancer that had progressed following prior treatment with a reversible EGFR TKI and chemotherapy.

6. Katakami N et al. LUX-Lung 4: A Phase II Trial of Afatinib in Patients With Advanced Non–Small-Cell Lung Cancer Who Progressed During Prior Treatment With Erlotinib, Gefitinib, or Both. *J Clin Oncol.* 31 (Published Ahead of Print on July 1, 2013 as 10.1200/JCO.2012.45.0981). This paper presents the safety and efficacy findings of LUX-Lung 4 a study of afatinib in Japanese patients with advanced, metastatic non-small-cell lung cancer that had progressed following prior treatment with a reversible EGFR TKI and chemotherapy.

Sincerely,

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