Boehringer Ingelheim

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NCCN Guidelines Panel: Non-Small Cell Lung Cancer

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On behalf of Boehringer-Ingelheim Pharmaceuticals, Inc., I respectfully request the NCCN Non-Small Cell Lung Cancer Guidelines Panel to review the enclosed data regarding overall survival (OS) from two randomized trials of afatinib versus chemotherapy in first line EGFR mutation positive NSCLC as well as data regarding patients with certain specific "uncommon" EGFR mutations.

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Specific Changes: The guidelines for treatment of EGFR mutation positive NSCLC should be updated to provide additional specificity regarding individual "sensitizing" mutations and to include new higher levels of evidence (specifically an OS benefit) associated with first line treatment with afatinib in patients with the deletion 19 mutation. In addition, first line treatment with afatinib should be added for patients with G719X, L861Q and S768I mutations (NSCL-17 and MS-25).

Rationale:
Recent randomized studies of EGFR targeted tyrosine kinase inhibitors (TKIs) have demonstrated important differences among various "sensitizing" EGFR mutations in terms of both progression free (PFS) and overall survival (OS). These differences occur not only between the so-called "common" and "uncommon" mutations but also among the common mutations (i.e., deletions in exon 19 (del 19) and the L858R point mutation in exon 21). For example, two randomized studies of afatinib versus platinum doublet chemotherapy in first line EGFR mutation positive NSCLC independently showed significant and meaningful (~12 month) increases in OS for afatinib treated patients with del 19 mutations. As in studies with other TKIs patients with the L858R mutation had improvements in PFS and response rates but not in OS. Previous reports of reversible EGFR TKIs have not shown an overall survival benefit compared with chemotherapy in overall study populations or by EGFR mutation type.

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Current NCCN Guidelines characterize del 19 and L858R mutations collectively as "sensitizing" mutations. This does not facilitate appropriate differentiation and discussion of the varying levels of evidence that now exist in individual mutations which in the case of del 19 accounts for ~50% of all EGFR mutation positive patients. Updating the guidelines in a manner which takes these differences into account would bring them more in line with the emerging science in the area.

In addition, recently published data on patients with uncommon mutations demonstrate that afatinib is active in patients that harbor certain uncommon mutations while clinical benefit was lower in others. These data significantly supplement the information currently available in the guidelines. Consistent with the discussion above regarding the varying levels of evidence for individual mutations, this change would assist physicians in making informed treatment decisions for patients with these less frequent EGFR mutations.

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 Gilotrif™ have not been established in patients whose tumors have other EGFR mutations.

The following articles are submitted in support of this proposed change:

Yang, James Chih-Hsin ,et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. (Lancet Oncol. 2015 Feb;16(2):141-51).

Yang JCH, et al, Clinical Activity of Afatinib in Advanced NSCLC Harbouring Uncommon EGFR Mutations: Combined Analysis of LL 2, 3, and 6 (www.thelancet.com/oncology Published online June 5, 2015 http://dx.doi.org/10.1016/S1470-2045 (15)00026-1)

Sincerely,

Elizabeth Terlizzi

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