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Pharmaceuticals Inc.

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June 16, 2016

Date of request: June 15, 2016
NCCN Evidence Blocks: Non-Small Cell Lung Cancer

On behalf of Boehringer Ingelheim Pharmaceuticals Inc., I respectfully request the NCCN Non-Small Cell Lung Cancer Panel to review the enclosed data for consideration regarding the recently issued Evidence Blocks for non-small cell lung cancer (NSCLC).

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Specific Changes: Efficacy ratings for tyrosine kinase inhibitors (TKIs) for the first line treatment of patients with epidermal growth factor receptor (EGFR) sensitizing mutations.

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Rationale: There are currently three EGFR TKIs (afatinib, erlotinib and gefitinib) each of which carries a Category 1 NCCN recommendation in the above referenced setting. The safety and efficacy of each of these agents has been evaluated in multiple randomized studies versus a variety of chemotherapy comparators. The results of these studies have recently been reviewed (1, 2) both individually and in an individual patients data meta-analysis using trials that compared gefitinib or erlotinib vs platinum doublet chemotherapy (CT) on OS outcome. Treatment-naïve patients with common EGFR mut (Del19 or L858R), were randomized to either gefitinib (IPASS, NEJ002, WJTOG3405) or erlotinib (ENSURE, EURTAC, OPTIMAL) vs CT. Cox regression was performed to obtain hazard ratios (HR) and 95% confidence intervals (CI) for the overall population and pre-specified subgroups. Pooled treatment estimate using the inverse variance weighted method was calculated. Amongst 1231 patients, 632 received EGFR tyrosine kinase inhibitor (TKI) and 599 received CT. The median follow-up was 35.0 months, and 780 (63%) pts had died. There was no difference in OS between EGFR-TKI and CT (median 25.8 vs 26.0 months, HR = 1.01 [CI 0.88-1.17; P = 0.84]). There was no significant difference between Del19 (HR = 0.96, CI 0.79-1.16, P = 0.64) and L858R (HR = 1.06, CI 0.86-1.32; P = 0.59) subgroups (P-interaction = 0.47).

Previously untreated patients with EGFR mutation-positive stage IIIB or IV lung adenocarcinoma were likewise evaluated in LUX-Lung 3 (n=345) and LUX-Lung 6 (n=364) (3). These patients were randomly assigned in a 2:1 ratio to receive afatinib or chemotherapy (pemetrexed-cisplatin [LUX-Lung 3] or gemcitabine-cisplatin [LUX-Lung 6]),

stratified by EGFR mutation (exon 19 deletion [del19], L858R, or other) and ethnic origin (LUX-Lung 3 only). In preplanned analyses, overall survival was significantly longer for patients with del19-positive tumors in the afatinib group than in the chemotherapy group independently in each of these two trials: in LUX-Lung 3, median overall survival was 33.3 months (95% CI 26.8–41.5) in the afatinib group versus 21.1 months (16.3–30.7) in the chemotherapy group (HR 0.54, 95% CI 0.36–0.79, $p=0.0015$); in LUX-Lung 6, it was 31.4 months (95% CI 24.2–35.3) versus 18.4 months (14.6–25.6), respectively (HR 0.64, 95% CI 0.44–0.94, $p=0.023$). There were no significant differences by treatment group for patients with EGFR L858R-positive tumors in either trial.

Thus, in six randomized studies comparing gefitinib or erlotinib to platinum doublet CT both individually and in a meta-analysis there was no improvement in OS either overall or in the individual common mutations (del 19 or L858R); whereas in both LUX-Lung 3 and LUX Lung 6 overall survival was significantly longer in afatinib treated patients with the del 19 mutation (~50% of the mutation positive population) than in those receiving chemotherapy. In spite of these findings, the efficacy category in the NCCN evidence blocks (version 4.2016) rates both erlotinib and gefitinib as category 5 (Highly effective: Often provides long term survival advantage or has curative potential) while afatinib is rated as category 4 (Very effective: Sometimes provides long term survival advantage or has curative potential). The relative ratings for these agents is not supported by the evidence from these eight randomized studies.

In addition, since publication of the evidence blocks the results of a large randomized study (LUX Lung 7) directly comparing the efficacy and safety of afatinib and gefitinib has been published (4). Treatment-naïve patients with stage IIIB or IV NSCLC and a common EGFR mutation (del 19 or L858R) were randomly assigned (1:1) to receive afatinib (40 mg per day) or gefitinib (250 mg per day) until disease progression, or beyond if deemed beneficial by the investigator. Progression-free survival and time-to-treatment failure were both significantly longer with afatinib than with gefitinib. (PFS: median 11.0 months [95% CI 10.6–12.9] with afatinib vs 10.9 months [9.1–11.5] with gefitinib; hazard ratio [HR] 0.73 [95% CI 0.57–0.95], $p=0.017$) (TTF: median 13.7 months [95% CI 11.9–15.0] with afatinib vs 11.5 months [10.1–13.1] with gefitinib; HR 0.73 [95% CI 0.58–0.92], $p=0.0073$). Overall survival data are not mature. The proportion of patients who achieved an objective tumor response was also significantly higher with afatinib than with gefitinib by independent review (112 [70%] of 160 patients given afatinib vs 89 [56%] of 159 patients given gefitinib; odds ratio 1.87 [95% CI 1.18–2.99]; $p=0.0083$).

We respectfully request that the totality of this evidence be taken into account in the relative ratings of efficacy for the TKIs in the sensitizing EGFR mutation positive first line treatment setting.

References

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3. Yang, J 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
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Sincerely,



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