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IMPORTANT CORRECTION OF DRUG INFORMATION

June 27, 2016

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Dear Healthcare Professional,

OSI Pharmaceuticals, LLC, (an affiliate of Astellas Pharma US, Inc.) and Genentech USA, Inc. would like to inform you of plans to modify the approved indication for TARCEVA (erlotinib). The US prescribing information will be revised to limit non-small cell lung cancer (NSCLC) indications to patients with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitutions. This action is being taken as a result of the IUNO study which failed to demonstrate efficacy in patients with EGFR wild-type NSCLC in the maintenance setting.

Summary:

- In a phase 3 study (IUNO) of TARCEVA in patients whose tumors did not harbor EGFR exon 19 deletion or exon 21 (L858R) substitution mutations, overall survival (OS) was not superior in patients who received maintenance TARCEVA compared with patients randomized to receive TARCEVA upon progression. Additionally, patients who received TARCEVA did not have superior progression-free survival compared with patients who received placebo.

Additional information:

In April 2010, the FDA approved TARCEVA for single agent maintenance treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has not progressed after four cycles of platinum based first-line chemotherapy.[1] This approval was based on the results from the BO18192 study (SATURN), a randomized, double-blind, placebo-controlled, phase 3 study of single-agent TARCEVA as first-line maintenance therapy in patients with locally advanced or metastatic NSCLC.[2] The FDA required that a subsequent study be conducted post-approval to determine the relative benefit of TARCEVA as first-line maintenance in patients with NSCLC whose tumor did not harbor an EGFR exon 19 deletion or exon 21 (L858R) substitution mutation.[1] OSI Pharmaceuticals, LLC designed the BO25460 study (IUNO) to answer this question.

The IUNO study was a randomized, double-blind, placebo-controlled phase 3 study of first-line maintenance TARCEVA versus TARCEVA at the time of disease progression in patients with advanced or recurrent (Stage IIIB) or metastatic (Stage IV) NSCLC whose tumors did not harbor an EGFR exon 19 deletion or exon 21 (L858R) substitution mutation and who have not progressed following four cycles of platinum-based chemotherapy.[3] Patients were randomized to receive maintenance TARCEVA or placebo.

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A total of 643 patients (321 randomized to placebo and 322 randomized to TARCEVA maintenance) were enrolled globally.[4] Following disease progression, 160 (50%) patients randomized to TARCEVA maintenance received second-line chemotherapy and 250 (78%) patients randomized to placebo received second-line TARCEVA with the exception of 2 patients who crossed over and received second-line chemotherapy. Overall survival (OS) was not superior in patients randomized to receive maintenance TARCEVA followed by chemotherapy upon progression compared to patients randomized to receive maintenance placebo followed by TARCEVA upon progression. The median OS, was 9.46 months in patients randomized to receive maintenance TARCEVA followed by chemotherapy second-line compared to 9.72 months in the patients randomized to receive maintenance placebo followed by TARCEVA second-line [Hazard Ratio (HR) 1.02 (95% Confidence Interval (CI) 0.85, 1.22), p=0.82]. The median duration of treatment in second-line was 2.6 months for TARCEVA and 2.1 months for chemotherapy (which was mainly docetaxel and to a lesser extent pemetrexed or other chemotherapies. Patients who received TARCEVA did not have superior progression-free survival (median 13 weeks) compared with patients who received placebo (median 12 weeks) [HR 0.94 (95% CI 0.80 - 1.11), p=0.48].

The safety data from the IUNO study are consistent with the TARCEVA safety profile noted in the accompanying USPI.

Astellas and Genentech are working with the FDA on revisions to the currently approved USPI as a result of these data. **This letter is not intended as a complete description of the benefits and risks related to the use of TARCEVA. Please refer to the accompanying currently approved full prescribing information which does not include the changes noted above. In addition, the IUNO study design and results can be accessed on the clinical trials.gov website (https://clinicaltrials.gov/ct2/show/results/NCT01328951).** Clinicians should use the available data and clinical judgement to guide their decision making process for the treatment of patients.

Other Information:

Medical Inquiries: Please contact Genentech Medical Communications at 1-800-821-8590.

Drug Safety/Adverse Events: In the event of any adverse health effects with this product, contact Genentech Drug Safety/Adverse Events at 1-888-835-2555.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Sincerely,

Jeffery Bloss, MD
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for OSI Pharmaceuticals, LLC, an affiliate of
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References

1. Food and Drug Administration, Center for Drug Evaluation and Research. TARCEVA NDA 021743/S-014 and S-016 supplement approval letter, April 16, 2010. Retrieved from http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/021743s014,s016ltr.pdf.

2. Cappuzzo F, Ciuleanu T, Stelmakh L et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol* 2010; 11(6):521-529. http://www.ncbi.nlm.nih.gov/pubmed/20493771.

3. Hoffmann-La Roche. TARCEVA. A randomized, double-blind, placebo-controlled phase 3 study of first-line maintenance Tarceva vs Tarceva at the time of disease progression in patients with advanced non-small cell lung cancer (NSCLC) who have not progressed following 4 cycles of platinum-based chemotherapy. https://clinicaltrials.gov/ct2/show/results/NCT01328951. Accessed 6-9-2016.

4. F. Hoffman-La Roche Ltd. TARCEVA. BO25460 (IUNO) Clinical Study Report - Research Report No. 1052824 (November 2015). Data on File.