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NCCN Guidelines Panel: Non-Small-Cell Lung Cancer (NSCLC)

On behalf of Genentech, Inc., I respectfully request the NCCN NSCLC Guideline Panel to review the enclosed recent key publications for:

- **Avastin® (bevacizumab). Tarceva® (erlotinib): NSCLC**

Kato T, Seto T, Nishio M, et al. Erlotinib plus bevacizumab versus erlotinib alone as first-line treatment for advanced EGFR mutation-positive non-squamous non-small-cell lung cancer: an open-label, randomized trial. Presented at the American Society of Clinical Oncology 2014 Annual Meeting in Chicago, IL; May 30-June 3, 2014. ASCO Abstract #8005.

Kato T, Seto T, Nishio M, et al. Erlotinib plus bevacizumab (EB) versus erlotinib alone (E) as first-line treatment for advanced EGFR mutation-positive non-squamous non-small-cell lung cancer (NSCLC): an open-label randomized trial. Presented at the American Society of Clinical Oncology 2014 Annual Meeting in Chicago, IL; May 30-June 3, 2014. ASCO Oral Presentation

**Specific Changes:**

There are no specific changes being requested. We are providing data on Avastin and Tarceva in NSCLC for your review and consideration.

**FDA Clearance:** Avastin is FDA-approved for first-line treatment of non-squamous NSCLC in combination with carboplatin and paclitaxel in patients with unresectable, locally advanced, recurrent or metastatic disease. Tarceva is a kinase inhibitor indicated for first-line treatment of patients with 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; maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy; and treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Tarceva is not recommended for use in combination with platinum-based chemotherapy. Safety and efficacy of Tarceva have not been evaluated as first-line treatment in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution.

Please refer to the enclosed prescribing information for the full FDA-approved indications and safety information.

**Rationale:**

In an open-label, randomized, Phase II trial evaluating the safety and efficacy of Avastin in combination with Tarceva vs. Tarceva alone in non-squamous NSCLC, progression-free survival (PFS) was significantly prolonged with the combination of Avastin and Tarceva ( $p=0.0015$ ). There was no significant difference in overall response rate, or duration of response. There was a significant difference for disease

control rate (p=0.0177). Overall survival data is not yet mature. In a pre-specified biomarker analysis, there was a significant correlation between improved PFS and patients with the mutation sub-type EGFR exon 19 deletion (p=0.0011). There was no significant correlation between improved PFS and the EGFR exon 21-L858R substitution. There were significantly more patients with Grade  $\geq 3$  proteinuria and hypertension in the Avastin plus Tarceva arm than in the Tarceva alone arm. Additional data on the use of Avastin in combination with Tarceva in NSCLC with subset analyses on EGFR+ patients have been reported.<sup>1-7</sup> There are also two ongoing trials with Avastin in combination with Tarceva in EGFR positive NSCLC patients specifically.<sup>8-9</sup>

Please refer to the following ASCO link to view this abstract:  
[http://abstracts.asco.org/144/AbstView\\_144\\_127760.html](http://abstracts.asco.org/144/AbstView_144_127760.html)

Respectfully submitted,



#### Supplemental References

1. Herbst RS, Ansari R, Bustin F, et al. Efficacy of bevacizumab plus erlotinib versus erlotinib alone in advanced non-small cell lung cancer after failure of standard first-line chemotherapy (BeTa): a double-blind, placebo-controlled, phase 3 trial. *Lancet* 2011;377:1846-1854
2. Johnson BE, Kabbinnavar F, Fehrenbacher L, et al. Atlas: Randomized, double-blind, placebo-controlled, phase IIIb trial comparing bevacizumab therapy with or without erlotinib, after completion of chemotherapy, with bevacizumab for first-line treatment of advanced non-small cell lung cancer. *J Clin Oncol* 2013;31:3926-3934
3. Johnson B, Miller V, Amler L, et al. Biomarker evaluation in the randomized, double-blind, placebo-controlled, phase IIIb atlas trial, comparing bevacizumab (B) therapy with or without erlotinib (E), after completion of chemotherapy with b for the treatment of locally-advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC). *Eur J Cancer Suppl* 2009;7:5-6. Abstract #8LBA.
4. Zappa F, Droege C, Betticher D, et al. Bevacizumab and erlotinib (BE) first-line therapy in advanced non-squamous non-small cell lung cancer (NSCLC) (stage IIIb/IV) followed by platinum-based chemotherapy (CT) at disease progression: A multicenter phase II trial (SAKK 19/05). *Lung cancer* 2012;78:239-244
5. Thomas M, Reuss A, Fischer J, et al. INNOVATIONS - inoperable non-squamous NSCLC stage IIIB/IV: a randomized Phase II study with bevacizumab plus erlotinib or gemcitabine / cisplatin plus bevacizumab. Presented at the American Society of Clinical Oncology 2011 Annual Meeting June 3-7, 2011. ASCO Oral Presentation.
6. West H, Moon J, Hirsch FR, et al. The combination of erlotinib/bevacizumab in never-smokers with advanced lung adenocarcinoma: Southwest Oncology Group (SWOG) trial 0636. Presented at the 14th World Conference on Lung Cancer in Amsterdam Rai, The Netherlands; July 3-7, 2011. WCLC Oral Presentation.
7. Mack PC, Moon J, West HJ, et al. Molecular marker analysis of SWOG S0636, a Phase II trial of erlotinib and bevacizumab in never-smokers with advanced NSCLC. Presented at the American Society of Clinical Oncology 2012 Annual Meeting in Chicago, IL; June 1-5, 2012. ASCO Abstract #7552. <http://www.asco.org>.
8. Academic and Community Cancer Research United (ACCRU). Erlotinib With or Without Bevacizumab Treating Patients With Stage IV Non-Small Cell Lung Cancer With EGFR Mutations. Available at: <http://clinicaltrials.gov/ct2/show/NCT01532089>. Accessed June 5, 2014.
9. European Thoracic Oncology Platform. BELIEF (Bevacizumab and Erlotinib In EGFR Mut+ NSCLC). Available at <https://clinicaltrials.gov/ct2/show/NCT01562028>. Accessed June 6, 2014.