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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

Seto T, Kato T, Nishio M, et al. Erolotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomized, multicenter, phase 2 study. Lancet. E-pub Date: [published online ahead of print] 2014. DOI # 10.1016/s1470-2045(14)70381-x.

Specific Changes:
There are no specific changes being requested. We are providing the full manuscript for recently submitted data evaluating Avastin plus 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:
Results demonstrating a significant improvement in the primary outcome measure of progression-free survival (PFS), in addition to results for tumor response related secondary outcome measures and biomarker sub-analysis have been previously submitted for this phase II trial combining Avastin and Tarceva in non-squamous NSCLC patients. Data for the secondary outcome measure of overall survival is not yet mature. The recently published full manuscript for this study is now being submitted for your review. Additional data on the use of Avastin in combination with Tarceva in NSCLC with subset analyses on EGFR+ patients have been reported.[1-7] There are also two ongoing trials with Avastin in combination with Tarceva in EGFR positive NSCLC patients specifically.[8-9]

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, Kabbinavar 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 therpay 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.