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NCCN Guidelines Panel: Kidney Cancer

On behalf of Amgen Inc, I respectfully request the NCCN Kidney Cancer Guideline Panel reviews the enclosed data for inclusion of XGEVA® (denosumab) for the prevention of skeletal-related events (SREs) in patients with bone metastases from kidney cancer.

Specific Changes: Recommend that denosumab be added as first line therapy for the prevention of skeletal-related events in patients with bone metastases from kidney cancer *[Footnote "J" for Best Supportive Care]*

FDA Clearance: XGEVA® (denosumab) was approved by the FDA for the prevention of skeletal-related events in patients with bone metastases from solid tumors.†

Rationale: FDA approval was based on three double-blind, double-dummy, head-to-head phase 3 studies comparing denosumab with zoledronic acid in over 5,700 patients with advanced cancer and bone metastases. One of the studies was conducted in patients with solid tumors and multiple myeloma (N = 1,776) in which denosumab demonstrated non-inferiority to zoledronic acid in delaying time to first on study SRE (hazard ratio [HR] = 0.84; 95% confidence interval [CI]: 0.71 to 0.98; *P* = 0.0007, non-inferiority test). In a subset analysis of patients with solid tumors (N = 1,597), denosumab delayed the time to the first on-study SRE (HR = 0.81; 95% CI: 0.68 to 0.96; *P* = 0.001 non-inferiority test, *P* = 0.034 superiority test) and the time to first-and-subsequent SREs (rate ratio = 0.85; 95% CI: 0.72 to 1.00; *P* = 0.048) compared with zoledronic acid.

Important Safety Information: XGEVA® (denosumab) can cause severe hypocalcemia. Osteonecrosis of the jaw (ONJ) can occur in patients receiving XGEVA®. The most common serious adverse reaction in patients receiving XGEVA® was dyspnea.

The following documents are submitted in support of this proposed change. We would like to acknowledge the contributions of the NCCN panel members who are also co-authors or co-contributors of some of these publications.

1. XGEVA® (denosumab) prescribing information. Amgen Inc.
2. Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol.* 2011;29:1125-1132.
3. Vadhan-Raj S, Henry DH, von Moos R, et al. Denosumab in the treatment of bone metastases from advanced cancer or multiple myeloma (MM): analyses from a phase 3 randomized trial. *J Clin Oncol*. 2010;28(suppl 7):Abstract 9042.
4. Vadhan-Raj S, Henry DH, von Moos R, et al. Denosumab in the treatment of bone metastases from advanced cancer or multiple myeloma (MM): analyses from a phase 3 randomized trial. Poster presented at: American Society of Clinical Oncology; June 4-8, 2010; Chicago, IL.
5. Henry D, von Moos R, Vadhan-Raj S, et al. A double-blind, randomized study of denosumab versus zoledronic acid for the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *Eur J Can Suppl*. 2009;7(3):11. Abstract 20LBA.
6. Henry D, von Moos R, Hungria V, et al. Delaying skeletal-related events in a randomized phase 3 study of denosumab versus zoledronic acid in patients with advanced cancer. Poster presented at: American Society of Clinical Oncology; June 4-8, 2010; Chicago, IL.

†XGEVA® (denosumab) is not indicated for the prevention of skeletal-related events in patients with multiple myeloma.

7. Henry DH, von Moos R, Hungria V, et al. Delaying skeletal-related events in a randomized phase III study of denosumab versus zoledronic acid in patients with advanced cancer. *J Clin Oncol*. 2010;28(suppl 7):Abstract 9133.
8. von Moos R, Patrick D, Fallowfield L, et al. Effects of denosumab versus zoledronic acid (ZA) on pain in patients (pts) with advanced cancer (excluding breast and prostate) or multiple myeloma (MM): results from a randomized phase 3 clinical trial. *J Clin Oncol*. 2010;28(suppl 7):Abstract 9043.
9. von Moos R, Patrick D, Fallowfield L, et al. Effects of denosumab versus zoledronic acid (ZA) on pain in patients (pts) with advanced cancer (excluding breast and prostate) or multiple myeloma (MM): results from a randomized phase 3 clinical trial. Poster presented at: American Society of Clinical Oncology; June 4-8, 2010; Chicago, IL.
10. Polderdijk H, Kofler C, Wang J, Sarkeshik M, Yeh H. Incidence of acute phase reactions following treatment with denosumab or zoledronic acid: results from a randomized, controlled phase 3 study in patients with advanced cancer (excluding breast and prostate) or multiple myeloma. Poster Presented at: European Oncology Nursing Society Spring Convention; April 15-17, 2010; The Hague, Netherlands.
11. Lipton A, Siena S, Rader M, et al. Comparison of denosumab versus zoledronic acid for treatment of bone metastases in advanced cancer patients: an integrated analysis of 3 pivotal trials. *Ann Oncol*. 2010;21(suppl 8):viii380. Abstract 1249P.
12. Lipton A, Siena S, Rader M, et al. Comparison of denosumab versus zoledronic acid for treatment of bone metastases in advanced cancer patients: an integrated analysis of 3 pivotal trials. Poster Presented at: 2010 Annual Meeting of the European Society for Medical Oncology; October 8-11, 2010; Milan, Italy.

Thank you for your attention to these revisions. Please contact me should you have any questions.

Sincerely,

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Executive Medical Director, Global Development

Enclosures