

Phuong Khanh (PK) Morrow, MD  
Executive Medical Director  
Oncology Therapeutic Area Lead, US Medical Organization  
Amgen, Inc.  
One Amgen Center Drive, MS 38-2-B  
Thousand Oaks, CA 91320  
(805) 447-1540  
pmorrow@amgen.com

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NCCN Guidelines Panel: Breast Cancer

On behalf of Amgen, I respectfully request that the NCCN Breast Cancer Guideline Panel review the enclosed data in consideration for updates to the **NCCN Breast Cancer Guidelines and corresponding Evidence Blocks** regarding the use of Prolia® (denosumab) in postmenopausal patients with early hormone receptor-positive breast cancer receiving treatment with aromatase inhibitors and the use of XGEVA® (denosumab) in patients with solid tumors and bone metastases.

### **Specific Recommended Changes to the NCCN Breast Cancer Guidelines:**

#### **Updates-3**

- 1<sup>st</sup> Column, 6<sup>th</sup> bullet: Revised footnote "†pp": "The use of estrogen, progesterone, or selective estrogen receptor modulators to treat osteoporosis or osteopenia in women with breast cancer is discouraged. [Adjuvant denosumab 60mg administered every 6 months significantly reduced the risk of clinical fractures in postmenopausal women with breast cancer receiving an aromatase inhibitor for up to 7 years. This effect was observed in women with both normal \(T-score ≥ -1.0\) and abnormal \(T-score < -1.0\) bone mineral density at initiation of therapy.](#) The use of a bisphosphonate or denosumab is acceptable to maintain or to improve bone mineral density. Optimal duration of either therapy has not been established. [The potential benefits of dDuration of bisphosphonate therapy](#) beyond 3 y is not known. Factors to consider for duration of anti-osteoporosis therapy include bone mineral density, response to therapy, and risk factors for continued bone loss or fracture. Women treated with a bisphosphonate or denosumab should undergo a dental examination with preventive dentistry prior to the initiation of therapy, and should take supplemental calcium and vitamin D.

### **Specific Recommended Changes to the NCCN Breast Cancer Guidelines and Corresponding Evidence Blocks:**

#### **BINV-16**

- 8<sup>th</sup> Bullet: Women on an aromatase inhibitor or who experience ovarian failure secondary to treatment should have monitoring of bone health with a bone mineral density determination at baseline and periodically thereafter [discuss treatment options to maintain or to improve bone mineral density.](#)
- Footnote pp: The use of estrogen, progesterone, or selective estrogen receptor modulators to treat osteoporosis or osteopenia in women with breast cancer is discouraged. [Adjuvant denosumab 60mg administered every 6 months significantly reduced the risk of clinical fractures in postmenopausal women with breast cancer receiving an aromatase inhibitor for up to 7 years. This effect was observed in women with both normal \(T-score ≥ -1.0\) and abnormal \(T-score < -1.0\) bone mineral density at initiation of therapy.](#) The use of a bisphosphonate or denosumab is acceptable to maintain or to improve bone mineral density. Optimal duration of either therapy has not been established. [The potential benefits of dDuration of bisphosphonate therapy](#) beyond 3 y is not known.

#### **BINV-19**

- Footnote zz: Denosumab, zoledronic acid, or pamidronate (all with calcium and vitamin D supplementation) should be given (category 1) in addition to chemotherapy or endocrine therapy if bone metastasis is present, expected survival is  $\geq 3$  months, and renal function is adequate **with use of a bisphosphonate. In a single phase 3, randomized, active-controlled trial, denosumab demonstrated superiority to zoledronic acid in delaying time to first on-study SRE and time to first-and-subsequent on-study SREs in patients with breast cancer and bone metastases and did not require dose modification for renal impairment.** Patients should undergo a dental examination with preventive dentistry prior to initiation of this therapy. ~~The optimal schedule for zoledronic acid, the optimal schedule is monthly x 12, and then quarterly; for denosumab, the optimal schedule is once every 4 weeks.~~

#### **MS-44**

- 2<sup>nd</sup> column, 3<sup>rd</sup> paragraph: The panel recommends that women on an adjuvant aromatase inhibitor or who experience ovarian failure secondary to treatment should have monitoring of bone health with a bone mineral density determination at baseline and periodically thereafter **discuss treatment options to maintain or to improve bone mineral density.** The use of estrogen, progesterone, or selective ER modulators to treat osteoporosis or osteopenia in women with breast cancer is discouraged. The use of a bisphosphonate **or denosumab** is ~~generally~~ the preferred intervention to **maintain or to improve** bone mineral density.

#### **MS-45**

- 1<sup>st</sup> column, 1<sup>st</sup> paragraph: Recent data show that adjuvant denosumab significantly reduces fractures in postmenopausal women receiving adjuvant therapy aromatase inhibitors, **for up to 7 years. and improves bone mineral density.**~~442 This effect was observed in women with both normal (T-score  $\geq -1.0$ ) and abnormal (T-score  $< -1.0$ ) bone mineral density at initiation of therapy.~~<sup>412</sup> Optimal duration of bisphosphonate therapy **or denosumab** has not been established. Factors to consider for duration of anti-osteoporosis therapy include bone mineral density, response to therapy, and risk factors for continued bone loss or fracture. Women treated with a bisphosphonate **or denosumab** should undergo a dental examination with preventive dentistry prior to the initiation of therapy, and should take supplemental calcium and vitamin D.

#### **MS-47**

- 2<sup>nd</sup> column, 1<sup>st</sup> paragraph: Denosumab is a fully human monoclonal antibody directed against RANK ligand, a mediator of osteoclast function.<sup>435</sup> ~~In a A single, phase 3, randomized, active-controlled trial, in metastatic breast cancer showed equivalency and superiority of time to the occurrence of SRE with denosumab, as compared with zoledronic acid.~~ **denosumab demonstrated superiority to zoledronic acid in delaying time to first on-study SRE and time to first-and-subsequent on-study SREs in patients with metastatic breast cancer.**<sup>434</sup> No study of bisphosphonate or denosumab has demonstrated an impact on OS in patients with metastatic disease.

#### **MS-48**

- 2<sup>nd</sup> column, 3<sup>rd</sup> paragraph: Women with metastatic breast cancer to bone who are candidates for bisphosphonate therapy ~~may also~~ **should** be considered for treatment with denosumab (category 1).

#### **MS-49**

- 1<sup>st</sup> column, 1<sup>st</sup> paragraph: 0.95;  $P < .001$  for non-inferiority;  $P = .01$  for superiority) and **demonstrated superiority in** time to first and subsequent SREs (rate ratio, 0.77; 95% CI, 0.66–0.89;  $P = .001$ ). No difference in time to progression or OS was observed. Adverse event profiles were similar for the two

groups, including incidence of ONJ, with a reduced risk of renal-related and acute phase adverse events in the denosumab treatment group. In open-label denosumab studies, various degrees of renal impairment did not have a significant effect on the pharmacokinetic profile or the pharmacodynamic activity of denosumab. [Block et al., *J Clin Oncol*, 2014; Block et al., *Ann Oncol*, 2014] In three phase 3 controlled studies, the dose of denosumab was not adjusted for renal function. [Stopeck et al., *J Clin Oncol*, 2010; Fizazi et al., *Lancet*, 2011; Henry et al., *J Clin Oncol*, 2011] Based on the superiority results of the phase 3 study and the benefit-risk profile of denosumab, patients who remained on study were offered denosumab for up to 2 additional years in a prespecified open-label extension treatment phase. The cumulative median exposure to denosumab was 19.1 months with a range up to 59.8 months. [Stopeck et al., *Support Care Cancer*, 2016] Long-term risks of denosumab treatment beyond 5 years are unknown.

#### **FDA Clearance:**

Prolia® (denosumab) was approved by the FDA as treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. XGEVA® (denosumab) was approved by the FDA for the prevention of skeletal-related events in patients with bone metastases from solid tumors.

#### **Rationale for Recommended Changes:**

- Data demonstrating the superior efficacy and long-term safety of denosumab warrant inclusion in current guidelines for the management of bone health in patients with breast cancer. First, denosumab has been shown to be superior in terms of time to first on-study skeletal-related event in a randomized head-to-head clinical trial (Stopeck et al., *J Clin Oncol*, 2010). Given the clinical relevance of the superiority and long-term safety of denosumab for breast cancer patients, we therefore ask that this information be included in the guidelines, as noted above. Second, the results communicated in Gnant et al. represent a meaningful advance in our understanding of both the risks associated with long term AI therapy and strategies to mitigate those risks in the non-metastatic setting (Gnant et al., *Lancet*, 2015). This was the first large clinical trial to show definitive benefit in the reduction of fractures associated with AI-induced bone loss in subjects with both normal and abnormal baseline bone mineral density. It also demonstrated a favorable safety profile for this intervention, with no major differences in any adverse event, and in particular, no cases of either ONJ or atypical femur fractures, two of the most important risks associated with anti-resorptive therapy, in either the treatment or placebo arms. Furthermore, Stopeck et al. recently published the first long-term safety data (median/maximum exposure of 19.1/59.8 months, respectively) for breast cancer subjects receiving denosumab (Stopeck et al., *Support Care Cancer*, 2016). This represents the longest follow-up to date for subjects on denosumab and highlights the long term safety of this therapy. Finally, it's important to clarify the safety profile of denosumab in patients with renal insufficiency, as evidenced by the dosing in the pivotal registrational trials as well as later abstracts by Block et al. (Stopeck et al., *J Clin Oncol*, 2010; Fizazi et al., *Lancet*, 2011; Block et al., *J Clin Oncol*, 2014; Block et al., *Ann Oncol*, 2014).

The following documents are attached in support of this proposed change.

1. Prolia® (denosumab) prescribing information
2. XGEVA® (denosumab) prescribing information

3. Block G, Egbuna O, Zeig S, et al. The evaluation of denosumab safety in patients with chronic renal disease: An open-label study. *J Clin Oncol*. 2014;32(suppl):e20649.
4. Block G, Egbuna O, Zeig S., et al. Safety of denosumab (DMAB) in patients (PTS) with stage 4 or stage 5D chronic kidney disease (CKD). *Annals of Oncology*. 2014;25(suppl 4):iv517-iv541.
5. Stopeck A, Fizazi K, Body JJ, et al. Safety of long-term denosumab therapy: results from the open label extension phase of two phase 3 studies in patients with metastatic breast and prostate cancer. *Support Care Cancer*. 2016;24:447-455.
6. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomized, double-blind study. *Lancet*. 2011;377:813-822.
7. 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.
8. Stopeck A, Lipton A, Body JJ, et al., Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol*. 2010;28:5132-5139.
9. Gnant M, Pfeiler G, Dubsy PC, et al. Adjuvant denosumab in breast cancer (ABC SG-18): a multicenter, randomized, double-blind, placebo-controlled trial. *Lancet*. 2015;386:433-43.

Thank you for your consideration of these proposed revisions. Please contact me should you have any questions.

Sincerely,

Phuong Khanh (PK) Morrow, MD  
Executive Medical Director  
Oncology Therapeutic Area Lead, US Medical Organization

Enclosures