In Reply

ANTONIS VALACHIS,^{a,b} NIKOLAOS P. POLYZOS^c

^aDepartment of Oncology, General Hospital of Eskilstuna, Eskilstuna, Sweden; ^bUniversity of Uppsala, Uppsala, Sweden; ^cCentre for Reproductive Medicine, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium

Disclosures of potential conflicts of interest may be found at the end of this article.

We have read with great interest the letters referring to our recent meta-analysis on zoledronic acid (ZA) in the adjuvant setting in breast cancer patients [1]. We are pleased that our work raises an interesting and constructive discussion.

According to our meta-analysis, breast cancer patients receiving ZA in the adjuvant setting experienced a survival benefit compared with patients with placebo or no treatment [1]. Although this finding can be attributed to the antitumoral activity of ZA, as clearly shown by preclinical data [2–5], several other mechanisms may be synergistic with or independently related to this benefit.

The role of ZA in enhancing radiosensitivity against cancer cells, as proposed by Dr. Kapoor, may be another plausible explanation for the effect observed in our study [6]. As suggested by Dr. Kapoor, several reports support the idea that ZA might radiosensitize tumor cells [7, 8]. Moreover, in a recent study, Kijima et al. proposed a molecular mechanism in renal cell carcinoma cells by which ZA sensitizes carcinoma cells to radiation by downregulating signal transducer and activator of transcription 1 [9]. Although we agree with Dr. Kapoor regarding the plausible scientific rationale for such an underlying mechanism, we were unable to examine such a hypothesis because of the lack of subgroup analysis based on the use of radiotherapy in the trials included in our meta-analysis. In this regard, future randomized trials and individual patient data meta-analysis may need to focus on this area.

A new insight on the biological mechanism behind the antitumoral activity of ZA is presented in the letter by Dr. Welton and colleagues [10]. The higher proportion of Vγ9/Vδ2 effector memory T cells in breast cancer patients treated with ZA compared with untreated patients or patients with progress, as demonstrated in the authors' original data, supports the hypothesis that ZA could serve as an immunomodulating factor and may trigger antitumoral activity through higher immune responsiveness against breast cancer cells. In this regard, we completely agree with Dr. Welton and colleagues regarding the plausibility of such a hypothesis.

Finally, the potential effect of ZA on the suppression of aromatase activity and plasma estrogen levels, as indicated in the letter by Dr. Ghobadifar [11], might be another plausible

explanation of our results. This hypothesis of the additive effect of ZA to aromatase inhibitors has recently been tested in the neoadjuvant setting by Fasching et al. [12]. In a randomized controlled trial, breast cancer patients received either letrozole or letrozole plus ZA as neoadjuvant therapy. Although this trial revealed a numerical difference of 14.7% in objective responses in favor of combination therapy, results did not reach statistical significance, possibly because of the small number of patients included [12]. This hypothesis justifies further scrutiny.

In contrast, Dr. Zheng and Dr. Zhu further discussed our thoughts regarding the role of menopause status on the efficacy of ZA in the adjuvant setting [13]. The benefit of ZA has been observed in postmenopausal women but not in premenopausal women, as we also stated in our meta-analysis. The potential enhanced effect of ZA in patients with a low-estrogen environment is supported by recent data from trials in the neoadjuvant setting. According to these studies, higher pathologic complete remission with the addition of ZA to chemotherapy is observed only in postmenopausal women [14, 15]. We were obliged, however, to avoid performing a subgroup analysis in our study according to menopausal status because of the high between-study heterogeneity in terms of menopause definition. We believe that a definite answer to this question could be provided only by an individual patient data meta-analysis that categorizes the patients as "premenopausal," "perimenopausal," or "postmenopausal" with more consistent criteria.

In summary, we would like to thank all of the authors of the above-mentioned letters for their effort to provide additional explanations of the results of our meta-analysis of the survival benefit of ZA in the adjuvant setting. Although our analysis provides evidence that ZA in the adjuvant breast cancer setting may increase survival, additional data from basic research and clinical trials in the future will help us interpret its role with more confidence.

DISCLOSURES

The authors indicated no financial relationships.

REFERENCES

1. Valachis A, Polyzos NP, Coleman RE et al. Adjuvant therapy with zoledronic acid in patients with breast cancer: A systematic review and meta-analysis. *The Oncologist* 2013;18:353–361.
2. Daubiné F, Le Gall C, Gasser J et al. Antitumor effects of clinical dosing regimens of bisphosphonates in experimental breast cancer bone metastasis. *J Natl Cancer Inst* 2007;99:322–330.
3. van der Pluijm G, Vloedgraven H, van Beek E et al. Bisphosphonates inhibit the adhesion of breast cancer cells to bone matrices in vitro. *J Clin Invest* 1996;98:698–705.
4. Senaratne SG, Pirianov G, Mansi JL et al. Bisphosphonates induce apoptosis in human breast cancer cell lines. *Br J Cancer* 2000;82:1459–1468.

Correspondence: Antonis Valachis, M.D., Ph.D., Department of Oncology, 63188 Mälarsjukhuset Eskilstuna, Sweden. Telephone: 46-735617691; Fax: 0046-16104035; E-Mail: valachis@hotmail.com, antonis.valachis@dll.se Received June 30, 2013; accepted for publication July 3, 2013. ©AlphaMed Press 1083-7159/2013/\$20.00/0 http://dx.doi.org/10.1634/theoncologist.2013-0235

5. Gallo M, De Luca A, Lamura L et al. Zoledronic acid blocks the interaction between mesenchymal stem cells and breast cancer cells: Implications for adjuvant therapy of breast cancer. *Ann Oncol* 2012; 23:597–604.
6. Kapoor S. Zoledronic acid and its accentuating effect on tumor radiosensitivity. *The Oncologist* 2013 (in press).
7. Ural AU, Avcu F, Candir M et al. In vitro synergistic cytoreductive effects of zoledronic acid and radiation on breast cancer cells. *Breast Cancer Res* 2006;8:R52.
8. Koto K, Murata H, Kimura S et al. Zoledronic acid significantly enhances radiation induced apoptosis against human fibrosarcoma cells by inhibiting radioadaptive signaling. *Int J Oncol* 2013;42:525–534.
9. Kijima T, Koga F, Fujii Y et al. Zoledronic acid sensitizes renal cell carcinoma cells to radiation by downregulating STAT1. *PLoS One* 2013;8:e64615.
10. Welton JL, Martí S, Mahdi MH et al. $\gamma\delta$ T cells predict outcome in zoledronate-treated breast cancer patients. *The Oncologist* 2013 (in press).
11. Ghobadifar MA. Role of zoledronate in aromatase activity should be considered in future studies. *The Oncologist* 2013 (in press).
12. Fasching PA, Jud SM, Hauschild M et al. Anticancer activity of letrozole plus zoledronic acid as neoadjuvant therapy for postmenopausal patients with breast cancer: FEMZONE trial results. *Cancer Res* 2012;72(suppl):PD07–02.
13. Zheng YY, Zhu JH. Response to “Adjuvant therapy with zoledronic acid in patients with breast cancer: A systematic review and meta-analysis.” *The Oncologist* 2013 (in press).
14. Charehbili A, van de Ven S, Liefers GJ et al. NEOZOTAC: Efficacy results from a phase III randomized trial with neoadjuvant chemotherapy (TAC) with or without zoledronic acid for patients with HER2-negative large resectable or stage II or III breast cancer (BC)—a Dutch Breast Cancer Trialists’ Group (BOOG) study. *J Clin Oncol* 2013;31(suppl):1028a.
15. Horiguchi J, Hasegawa Y, Miura D et al. A randomized controlled trial comparing zoledronic acid plus chemotherapy with chemotherapy alone as a neoadjuvant treatment in patients with HER2-negative primary breast cancer. *J Clin Oncol* 2013; 31(suppl):1029a.