more than 95% received chemotherapy, and all had premenopausal levels of reproductive hormones at study entry. Only three of the premenopausal patients (0.2%) in our study received goserelin.

In a prespecified analysis, our finding of a possible benefit of zoledronic acid in patients who had undergone menopause more than 5 years before study entry is intriguing. From an endocrine perspective, the postmenopausal patients in our study were similar to the goserelin-treated patients in the ABCSG-12 study,[8] who had low levels of reproductive hormones at study entry. The curves for rates of disease-free survival in the postmenopausal subgroup diverged rapidly (absolute difference, 3 percentage points at 1 year and 5 percentage points at 2 years) and showed a small but significant survival advantage for patients who received zoledronic acid. Furthermore, the use of zoledronic acid appeared to have divergent effects on metastasis to visceral and locoregional sites according to menopausal status. Our analysis of the interaction of the various components of invasive-disease–free survival suggests a systemic effect of zoledronic acid that operates differently according to menopausal status and that is distinct from any effect in bone (Fig. 1 in the Supplementary Appendix). The explanation for this finding is unclear, but perhaps bone provides a sanctuary for cancer cells, and after treatment with zoledronic acid, the ability of cancer cells to disseminate to other body sites is dependent on the presence of reproductive hormones.

The apparent early benefits seen in the postmenopausal subgroup suggest that the initial phase of treatment, when zoledronic acid is combined with chemotherapy, may be most important. During neoadjuvant chemotherapy with zoledronic acid, an increased tumor response in the breast[16] and a reduced number of disseminated tumor cells in the bone marrow[17] have been observed, suggesting positive interactions between zoledronic acid and chemotherapy.

Adjuvant chemotherapy would be expected to induce menopause in a high proportion of women over the age of 40 years. However, it may take many months for chemotherapy to affect reproductive hormone levels, and despite causing amenorrhea, chemotherapy may not result in complete ovarian suppression. It is unclear how the endocrine environment in bone might influence interactions between chemotherapy and zoledronic acid. However, as levels of ovarian-derived inhibin decline after menopause, the control of bone-cell function changes from primary regulation through effects of inhibins on osteoblasts to control by locally produced activin interacting with bone morphogenic proteins and noggin to drive bone turnover.[18]

In our study, zoledronic acid had no demonstrable effect on chemotherapy-associated toxic

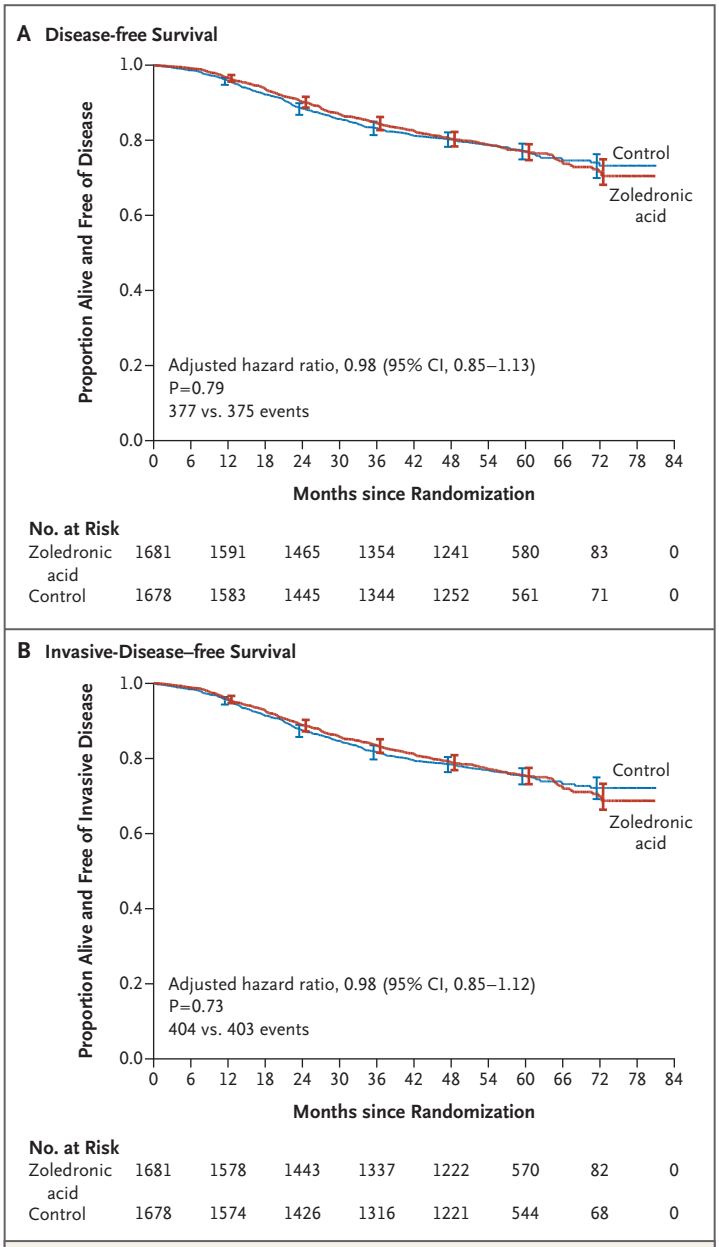

Figure 2. Disease-free Survival and Invasive-Disease–free Survival in the Intention-to-Treat Population.

Panel A shows the proportion of patients who were alive without a recurrence of disease, and Panel B shows the proportion of patients who were alive without invasive disease at 5 years and beyond. The I bars represent 95% confidence intervals.

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