



## Zoledronic Acid Update

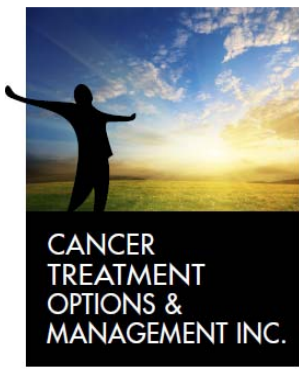
Adjuvant therapy with non-nitrogenous bisphosphonates has **not** been shown to improve progression free survival (PFS) and overall survival (OS) in estrogen positive breast cancer patients. A clinical trial meta-analysis of adjuvant clodronate therapy found no evidence of any statistically significant difference in OS, bone metastasis-free survival or non-skeletal metastasis-free survival in early or advanced breast cancer patients receiving adjuvant clodronate treatment compared with those who did not receive any active treatment (Ha & Li., 2007).

However, nitrogen-containing bisphosphonates such as zoledronic acid have been shown to produce significant improvements in PFS and OS in pre-menopausal woman undergoing estrogen suppression and post-menopausal woman treated with aromatase inhibitors (Benzaïd et al., 2011).

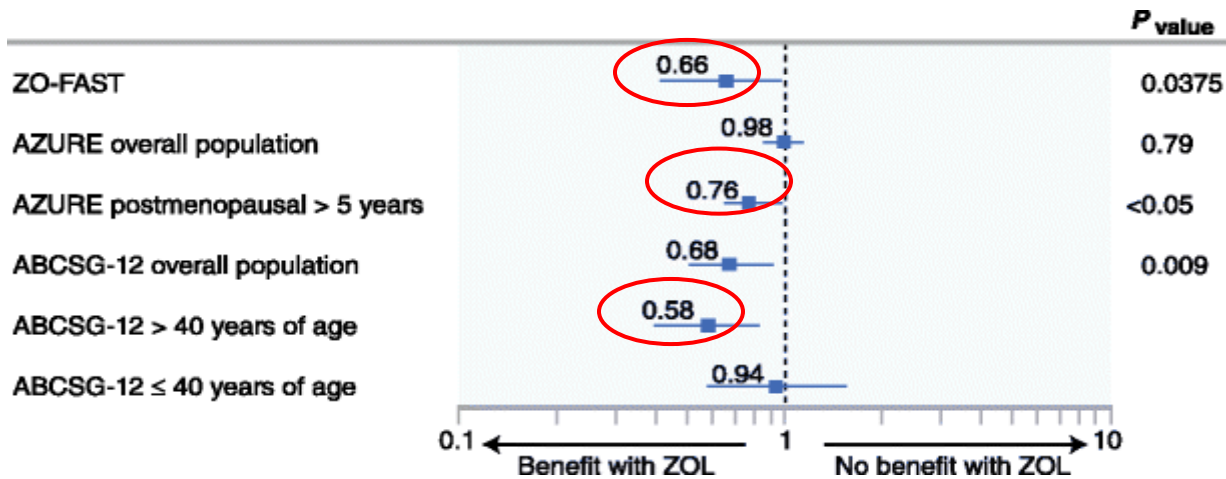
Furthermore, zoledronic acid inhibits metastasis to the bone and reduces epithelial to mesenchymal transition (EMT) by reducing the occurrence of disseminated tumour cells. Treatment with zoledronic acid has been shown to significantly reduce the ability of mesenchymal stem cells to migrate by reducing the secretion of factors such as RANTES/chemokine (C—C motif) ligand 5 (CCL5) and interleukin 6, which induce breast cancer cell migration (Normanno et al., 2011).

### Results from Clinical Trials:

The results from the recent AZURE trial have shown significant benefits with adjuvant zoledronic acid treatment. Among postmenopausal patients, the rates of invasive disease free survival (DFS) were 78.2% in the zoledronic acid group and 71.0% in the control group (adjusted hazard ratio with zoledronic acid, 0.75; 95% CI, 0.59 to 0.96; P = 0.02). In addition, among patients who had undergone menopause more than 5 years earlier, the 5-year OS rate was 84.6% in the zoledronic acid group and 78.7% in the control group (adjusted hazard ratio, 0.74; 95% CI, 0.55 to 0.98; P = 0.04). In this group, there was a 29% reduction in the risk of death (hazard ratio, 0.71; P = 0.17) (Coleman et al., 2011).



The following figure is a summary of disease free survival from the ZO-FAST, AZURE and ABCSG-12 clinical trials. See Gnant, (2011).



**FIG. 1:** Zoledronic acid (ZOL) significantly improves disease-free survival in postmenopausal women with early breast cancer (BC) (ZO-FAST and AZURE) and in premenopausal women with early BC receiving goserelin therapy (ABCSG-12), compared with no ZOL (or delayed ZOL). ABCSG-12, Austrian Breast and Colorectal Cancer Study Group trial 12; AZURE, Adjuvant Zoledronic Acid to Reduce Recurrence; ZO-FAST, Zometa-Femara Adjuvant Synergy Trial.



The following table is a summary of disease free survival from the ZO-FAST, AZURE and ABCSG-12 clinical trials (Gnant et al., 2011; Coleman et al., 2010; de Boer et al., 2010).

**TABLE 1:** Effects of zoledronic acid on disease-free survival and overall survival in 3 large phase 3 clinical trials in patients with early breast cancer. See Gnant, (2011).

	ABCSG-12		AZURE		ZO-FAST
	Total population	Subset > 40 years of age	Total population	Subset of PMW <sup>a</sup>	Total population
Patients, <i>n</i>	1803	1390	3360	1101	1065
Menopausal status	Pre + ovarian suppression	Any	Post	Post	
Median follow-up months	76	76	59	59	60
Comparator	No ZOL		No ZOL		Delayed ZOL
End point					
<b>Disease Free Survival</b>	HR, 0.73; <i>P</i> = 0.021	<b>HR, 0.66; <i>P</i> = 0.013</b>	HR, 0.98; <i>P</i> = 0.79	<b>HR, 0.76; <i>P</i> &lt; 0.05 (n = 1,041<sup>b</sup>)</b>	<b>HR, 0.66; <i>P</i> = 0.0375</b>
No. DFS events	213	144	752	263 <sup>a</sup> ; 247 <sup>b</sup>	104
No. events in bone	57	NR	240	69 <sup>a</sup>	NR
No. events outside bone	156	NR	512	194 <sup>a</sup>	NR
<b>Overall Survival</b>	HR, 0.59; <i>P</i> = 0.042	<b>HR, 0.51; <i>P</i> = 0.018</b>	HR, 0.85; <i>P</i> = 0.07	<b>HR, 0.71; <i>P</i> = 0.017 (n = 1101<sup>a</sup>)</b>	N/A

<sup>a</sup>Women who were > 5 years postmenopausal or of unknown menopausal status but > 60 years of age at baseline. <sup>b</sup>Women who were > 5 years postmenopausal only. *ABCSG-12* Austrian Breast and Colorectal Cancer Study Group trial 12, *AZURE* Adjuvant Zoledronic Acid to Reduce Recurrence, *DFS* disease-free survival, *HR* hazard ratio, *NR* not reported, *OS* overall survival, *PMW* postmenopausal women, *ZO-FAST* Zometa-Femara Adjuvant Synergy Trial, *ZOL* zoledronic acid.



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