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OC-11

A phase II, randomized, open-label, pilot study to evaluate the safety and the effects on bone resorption of saracatinib (AZD0530) in patients with prostate cancer or breast cancer with metastatic bone disease

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Introduction: Metastatic bone disease is a significant cause of morbidity in cancer patients. Src kinase, a non-receptor tyrosine kinase highly expressed in osteoclasts and cancer cells, is critical for osteoclast function and attachment to bone. Saracatinib (AZD0530), an investigational, orally-active and selective Src inhibitor, potently inhibits bone resorption and may reduce the formation or progression of metastatic bone lesions. **Methods:** In this study, we provide an initial comparison of saracatinib's effects on bone turnover to zoledronic acid (ZA) by measuring biomarkers of bone resorption, bone formation and calcium homeostasis. Prostate or breast cancer patients with metastatic bone disease receiving standard of care (SOC, including hormonals but excluding chemotherapy) but bisphosphonate naive were randomized 1:1 to receive either saracatinib 175 mg once daily for 28 days or ZA 4 mg as a single iv infusion. The primary objective was to estimate the effect on bone resorption by assessment of serum β CTx. **Results:** From February 2008 to November 2009, 69 patients were randomized to saracatinib and 70 to ZA. 83% (116) had prostate cancer and 17% (23) had breast cancer. After 4 weeks of therapy, bone resorption was inhibited in both treatment arms as evidenced by changes in bone turnover markers. Serum β CTx decreased by 74% (95% CI 67–79%) from baseline in the saracatinib arm and 68% (95% CI 62–74%) in the ZA arm (Table). Saracatinib was generally well tolerated in the majority of patients. **Conclusion:** In breast and prostate cancer patients with metastatic bone disease, once daily therapy with saracatinib produced a reduction in bone resorption similar to ZA. Further trials are warranted to assess the efficacy of saracatinib to prevent skeletal complications from metastatic bone disease.

Table. Geometric least squares mean change from baseline [% (95% CI)].

Marker	Saracatinib + SOC		Zoledronic acid + SOC	
	N		N	
s β CTx	42	−74 (−79, −67)	60	−68 (−74, −62)
sbALP	42	−18 (−28, −6)	61	−9 (−19, 1)
sICTP	42	−40 (−46, −33)***	61	7 (−2, 17)
sPINP	40	−25 (−34, −14)	56	−33 (−40, −25)
sTRAP 5b	42	−37 (−42, −32)*	59	−45 (−49, −41)
uNTx/Cr	40	−51 (−60, −41)**	56	−69 (−74, −63)
u α CTx/Cr	40	−73 (−80, −62)*	56	−83 (−88, −78)

SOC, standard of care; s, serum; u, urine; β CTx, beta C-terminal cross-linking telopeptide of Type I collagen; sbALP, bone-specific alkaline phosphatase; ICTP, cross-linked C-terminal telopeptide of Type I collagen; PINP, N-terminal propeptide of Type I procollagen; TRAP 5b, tartrate-resistant acid phosphatase 5b; NTx/Cr, N-terminal cross-linking telopeptide of Type I collagen/creatinine ratio; α α CTx/Cr, alpha-alpha C-terminal cross-linking telopeptide of Type I collagen/creatinine ratio; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

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OC-12

62-Month follow-up of ABCSG-12: Adjuvant endocrine therapy, alone or in combination with zoledronic acid, in premenopausal patients with endocrine-responsive early breast cancer

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Background: ABCSG-12 examined the efficacy of tamoxifen (TAM) or anastrozole (ANA) \pm zoledronic acid (ZOL) in premenopausal patients with endocrine-responsive early breast cancer (EBC) receiving ovarian suppression with goserelin. Results at 48 months showed that ZOL significantly reduced the risk of disease-free survival (DFS) events by 36% ($P = 0.01$). Longer follow-up is now available. **Methods:** 1803 premenopausal patients with EBC were randomized to goserelin (3.6 mg q28d) and TAM (20 mg/d) or ANA (1 mg/d) \pm ZOL (4 mg q6mo). Endpoints included DFS as a primary endpoint and overall survival (OS) as a secondary endpoint, both analyzed using log-rank test and Cox models. **Results:** After 62 months' median follow-up, 186 DFS events and 66 deaths were reported. ZOL reduced the risk of DFS events overall (HR = 0.68; $P = 0.009$), in the TAM and ANA arms (HR = 0.68 [95% CI = 0.44, 1.05] for TAM, HR = 0.68 [0.45, 1.02] for ANA), and in node-negative and node-positive patients. Overall, ZOL produced a 34% trend toward reduced risk of death (HR = 0.66; $P = 0.10$) that was more pronounced in node-positive patients (HR = 0.61; $P =$ not significant). There was no DFS difference between patients who received TAM alone versus ANA alone (HR = 1.11; $P = 0.44$). However, ANA patients had worse OS (HR = 1.74; $P = 0.03$) versus TAM. Treatments were generally well tolerated, with no cases of renal failure or confirmed osteonecrosis of the jaw (ONJ). **Conclusions:** In the ABCSG-12 trial, adding ZOL (4 mg q6mo) consistently improves disease outcomes in the TAM and ANA strata, and in node-negative and node-positive patients. Although there was no DFS difference between TAM and ANA, ANA patients had inferior OS versus TAM, likely due to fewer treatment options after relapse. Based on these results and on the anticancer activity of adjuvant ZOL, adding ZOL to endocrine therapy could benefit premenopausal patients with EBC.

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