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Bone mineral density and circulating biomarkers in the BIG 1-98 trial comparing adjuvant letrozole, tamoxifen and their sequences

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Abstract

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Conflicts of Interest

M. Campone: Honorarium and consultant from Novartis; B. Thürlimann stock ownership Novartis; M Debled: consultant from Novartis; A Monnier consultant from Novartis; all remaining authors have declared no conflicts of interest.

Purpose—To determine the effects of the BIG 1-98 treatments on bone mineral density. BIG 1-98 compared 5-year adjuvant hormone therapy in postmenopausal women allocated to four groups: tamoxifen (T); letrozole (L); 2-years T, 3-years L (TL); 2-years L, 3-years T (LT).

Methods—Bone mineral density T-score was measured prospectively annually by dual energy X-ray absorption in 424 patients enrolled in a sub-study after three (n=150), four (n=200), and five years (n=74) from randomization, and one year after treatment cessation. Prevalence of osteoporosis and the association of C-telopeptide, osteocalcin and bone alkaline phosphatase with T-scores were assessed.

Results—At 3 years, T had the highest and TL the lowest T-score. All arms except for LT showed a decline up to 5 years, with TL exhibiting the greatest. At 5 years, there were significant differences on lumbar T-score only between T and TL, whereas for femur T-score differences were significant for T vs. L or TL, and L vs. LT. The 5-year prevalence of spine and femur osteoporosis was highest on TL (14.5%, 7.1%) then L (4.3%, 5.1%), LT (4.2%, 1.4%) and T (4%, 0). C-telopeptide and osteocalcin were significantly associated with T-scores.

Conclusions—While adjuvant L increases bone mineral density loss compared with T, the sequence LT has an acceptable bone safety profile. C-telopeptide and osteocalcin are useful markers of bone density that may be used to monitor bone health during treatment. The sequence LT may be a valid treatment option in patients with low and intermediate risk of recurrence.

Trial registration—clinicaltrials.gov NCT00369850

Keywords

breast cancer; adjuvant drug therapy; aromatase inhibitor; bone density; bone turnover

Introduction

BIG 1-98 is the only trial comparing 5 year adjuvant hormonal therapy in over 8000 postmenopausal patients with operable, estrogen receptor (ER)-positive breast cancer in 4 arms: 5-years of tamoxifen (T), or 5 years of letrozole (L), or the sequence of two years of T followed by 3 years of L (TL); or 2 years of L followed by 3 years of T (LT). Recently updated results of this trial after a median follow-up of 8.1 years showed superiority of L over T on all efficacy endpoints, whereas sequential treatment did not improve efficacy over L alone, although LT showed the same overall survival and was the closest regimen to L alone on all remaining endpoints [1]. Ancillary biomarker studies have also indicated that L alone may be superior to all other three regimens in high risk women based on a composite measure of prognostic factors, whereas LT was equivalent to L alone in low and intermediate risk patients [2].

Since differences in efficacy between adjuvant endocrine regimens are subtle, and treatment duration up to 10 years will increasingly be used after the results of two pivotal trials [3,4], the balance between efficacy and safety/tolerability among different regimens will become a prominent aspect in the treatment decision making of endocrine adjuvant treatment. Patients who receive aromatase inhibitors (AIs) such as L have an increased risk of bone fractures [5,6] compared with those treated with T, whereas T is known to preserve bone health in postmenopausal women. In the initial report of the BIG 1-98 sequential trial after a median follow-up of 71 months bone fracture rates were more frequent in the L arm (9.8%) and TL arm (9.4%) compared with T arm (7.3%) and LT arm (7.5%), suggesting a better bone safety profile of LT over L [7]. However, the effect of the regimens on bone mineral density (BMD), the best validated surrogate marker of bone fractures, is unknown. Since the effects of these arms on BMD may provide additional clues on future bone health status and long-term fracture risk, and may influence the choice of the best endocrine regimen for an

individual patient, we prospectively compared the effects of the four regimens on serial BMD and circulating bone turnover biomarkers in a subgroup of BIG 1-98 participants from 7 countries worldwide.

Patients and Methods

The Breast International Group (BIG) 1-98 study is a randomized, phase 3, double-blind trial for postmenopausal women with hormone receptor-positive breast cancer. The BIG 1-98 bone sub-study compared the effects of the four regimens on: 1) BMD in the L2-L4 (postero-anterior, PA) region of the spine and the femur; 2) the incidence of radiological gross changes and fractures identified from spine x-rays (T4-L4); 3) the associations between serum bone markers (osteocalcin, C-telopeptide (CTX), bone alkaline phosphatase, (bone ALP)) and BMD changes. The study participants gave signed informed consent to participate in the BIG 1-98 study and the bone sub-study. The sub-study was conducted in selected participating centers based on their enrollment to the BIG 1-98 parent study and ability to carry out the required investigations. The sub-study was approved by ethics committees and review boards in accordance with governing laws.

The bone sub-study measurements were obtained at several time points during treatment. Because all of the patients had already begun the trial when the bone study started, a pre-treatment baseline measure was not available. There were three study cohorts: Cohort 1, at or before the end of year 2 from randomization; Cohort 2, after 2 years but at or before the end of year 3 from randomization; Cohort 3, after 3 years but at or before the end of year 5. Exclusion criteria included: Paget disease, parathyroid, thyroid, and pituitary disease; prior treatments for osteoporosis, including bisphosphonates within the past 6 months. Use of 800 IU vitamin D and 1000 mg calcium daily was recommended in all patients.

BMD was measured annually by dual energy x-ray absorption until one year after treatment. T4-L4 spine x-ray was performed at study entry and then again two year later only for Cohort 2 patients. Details on make and software version of DXA machine were recorded. All instruments were either HOLOGIC QDR-4500A (34% of all DXA scans) or LUNAR DPX-L (66%) with the most up-to-date software at the time of measurement, and the same machine was used in the same patient throughout the study. Radiological spine fractures were measured according to a semi quantitative scale [8] by two independent radiologists blinded to treatment allocation.

Morning fasting blood samples for biomarker determinations were centrifuged at 1850xg and serum stored at −80°C until assayed. Serum samples from the same patient obtained at different time-points were run together to reduce analytical variability. CTX and osteocalcin concentrations were measured with chemiluminescent immunometric assays designed for the “Cobas e411” automated analyzer (Roche Diagnostics, Basel, Switzerland). The detection limit was 0.01 ng/mL for CTX and 0.5 ng/mL for osteocalcin, while intra- and inter assay coefficients of variation were 1.3% and 5.3%, respectively for CTX and 2.5% and 4.5%, respectively for osteocalcin. Bone-specific alkaline phosphatase was determined by Ostase® BAP immunoenzymetric assay (Immunodiagnostic Systems Ltd, Germany). The detection limit was 0.7 ug/L and intra- and inter assay coefficients of variation were 2.9% and 6.4%, respectively.

Sample Size

The sub-study began enrollment on April 1, 2005, after patients on BIG 1-98 had been receiving protocol treatment for two or more years. The sub-study was designed to accrue 660 patients overall, 55 patients per cohort per treatment group to obtain 50 assessable patients in each cell with at least two BMD assessments one year apart, in order to detect,

with at least 80% power, a 4% difference in BMD between tamoxifen and letrozole (T+LT vs. L+TL), assuming a standard deviation in percent change of BMD of 10% and using two-sided type I error of 0.05. Since the patients in Cohort 3 were over-accrued and no more patients were available for Cohorts 1 and 2, the BIG 1-98 Steering Committee agreed to close the sub-study on January 31, 2007, with a total of 458 patients enrolled after 3, 4, and 5 years from randomization (0 patients in Cohort 1, 155 in Cohort 2 and 303 in Cohort 3). By combining patients in Cohorts 2 and 3, with approximately 70–90 patients in each of the four treatment groups, the study has 80% power to detect a difference in percent change in BMD from 0% in one group versus 4.2%–4.8% in the second group.

Statistical Analysis

The primary comparison of interest was the T-score of the L2–L4 regions of the spine and the femur neck in the four treatment arms. The T-score is the difference of the patient's BMD with that of the average healthy woman of the same sex and ethnicity. A patient with T-score below 2.5 SD is considered to have osteoporosis. Hip T-score showed similar results to femur neck T-score and is therefore not reported. Likewise, the total BMD amount and the z-score of each of the three bone areas were analyzed but not reported for brevity. It was hypothesized that patients currently on T would have a higher T-score than those who were currently taking L, whereas the effect of the sequential regimens was unknown. In order to compare the effects of T-score in the spine and femur, linear mixed effects models were created. The time from randomization into the parent study to each measurement served as the repeated factor in the model and compound symmetry was used for the error correlation within each patient. The model included the following covariates: age, BMI, prior use of postmenopausal hormone replacement therapy (HRT) at randomization, time from randomization, treatment arm and interaction between the time from randomization and treatment arm. From this multivariate model, the least squares means estimates (with all other covariates set equal to their mean values) were calculated for each treatment arm at year 3, 4, 5 and 6 (off treatment) and presented in a graph. Pairwise comparisons of each of the treatment arms were conducted.

Linear mixed effects models were also used to identify the correlation between the serum markers osteocalcin, bone alkaline phosphatase and CTX and the T score. The models included age, BMI, prior HRT at randomization, time from randomization, treatment arm and interaction between the time from randomization and treatment arm. Three separate models were fit to the data that included the log transformed serum markers individually.

In order to compare the prevalence of osteoporosis among arms, the rate of osteoporosis and their 95% exact binomial confidence intervals were calculated at year 3, 4, 5 and 6 from randomization and compared at year 5 between treatment arms using extended Fisher's exact test.

For patients randomized to receive 5 years of T but who chose to crossover to L (N=65, subsequent to the presentation of initial efficacy results favoring letrozole in 2005 [9]), all of their measurements were censored at the time they switched to letrozole. For patients who started bisphosphonates while on the present bone sub-study (N=53), all of their measurements after they started bisphosphonates were excluded.

Results

The bone sub-study was opened on April 2005 and closed accrual on 31 January 2007. A total of 458 patients were enrolled after 3, 4, and 5 years from randomization. Patients were accrued from the following countries: France, Switzerland, Italy, Australia, New Zealand, South Africa, Peru. Twenty-two patients were ineligible and 12 selectively crossed over

from T to L 30 days before sub-study registration, thus leaving a total of 424 assessable patients. Among them, 150 patients were enrolled after 3 years from randomization; 200 patients were enrolled after 4 years and 74 after 5 years from randomization. The chart of the study design and participation is shown in Figure 1. The analysis population of 424 patients is shown in the CONSORT flow diagram (Figure 2). The main patient characteristics at randomization are summarized in Table 1. All variables were evenly distributed, including age, BMI and prior HRT. Likewise, tumor size, nodal status (positive or negative), peritumoral vascular invasion (yes/no), local treatment, adjuvant/neoadjuvant chemotherapy (yes/no), local treatment therapy, smoking status, and previous history of fracture did not differ among arms (data not shown). Baseline characteristics of patients enrolled to the bone sub-study were comparable with the BIG 1-98 parent study (data not shown).

A total of 354 patients had spine T-score measurements: 122 patients had one measurement; 95 had two serial measurements; 85 had three serial measurements; and 52 had four serial measurements. A summary (median and interquartile range [IQR]) of spine and femur T-scores in the four arms during the study are shown in supplemental Table A1. The spine T-score estimates during the study in the four treatment arms from the linear mixed effects models are shown in Figure 3A. At 3 years, when BMD was first measured, T had the highest T-score relative to the other three arms, whereas TL had the lowest T-score. All arms except for LT showed a decline up to 5 years, with TL exhibiting the greatest decline. At year 5 of the treatment, there were statistically significant differences between T and TL and also when combining T and LT vs L and TL (Table 2). After one year off treatment, L and TL showed a slight recovery.

A total of 401 patients had femur T-score measurements: 150 patients had one measurement; 115 had two serial measurements; 85 had three serial measurements; and 51 had four serial measurements. The time course of femur T-score in the four treatment arms was similar to the spine, although initial levels at 3 years were on average lower than the spine T-score (Figure 3B). T had the highest T-score, whereas LT exhibited a clear trend to a recovery of bone BMD in the subsequent two years. At year 5 of the treatment, there were highly significant differences in the femur T-score when comparing T vs L, T vs TL, L vs LT and when combining T and LT vs L and TL (Table 2). After one year off treatment, little changes were noted except for a slight decrease of BMD in LT. Radiological spine was only measured in patients enrolled at 3 years from randomization. Eight patients had sub-clinical bone fractures at study entry. Among them, one patient had another bone fracture two years later. No patients developed clinical bone fractures after two years while on study.

The yearly prevalence of osteoporosis is summarized in Table 3. Overall, the rate of osteoporosis was higher in the spine (trabecular bone) relative to the femur (cortical bone). There was a moderate within-arm variability in terms of number of observations in the T arm due to the switch from T to L after the initial presentation of the BIG 1-98, which resulted in a lower number of observations in the T arm. The 5-year prevalence of spine and femur osteoporosis was lowest in the T arm followed by LT and L and highest in the TL arm (Spine P=0.08; Femur P=0.26 among arms). Specifically, spine osteoporosis was 3-fold higher in the TL arm compared with the remaining arms (approximately 14% vs 4%). The rate of femur osteoporosis was highest on TL (7.1%) followed by L (5.1%), whereas it was 1.4% and 0% in the LT and T, respectively (Table 3). In women aged over 70 years, the 5-year rate of spine osteoporosis was 0% on T, 33% on L, 22% on TL and 0% on LT (P=0.32), and 0% on T, 38% on L, 11% on TL and 10% on LT in the femur, respectively (P=0.49, data not shown).

The median and IQR of levels of serum biomarkers in the four arms during the study are shown in supplemental Table A2. The associations of serum markers of bone turnover with T-scores are summarized in Table 4. Estimates and standard errors of log(c-telopeptide), log(osteocalcin) and log(bone alkaline phosphatase) from the multivariate models are provided. CTX and osteocalcin were negatively associated with the T-score of the spine and femur neck, whereas bone alkaline phosphatase was not significantly associated with T-score levels.

Discussion

The aims of this study were to compare the T-scores and the rate of osteoporosis in a sub-group of patients on the BIG 1-98 study to provide further insight into the choice of the best adjuvant endocrine regimen for women with ER-positive breast cancer. As a 10-year endocrine treatment duration is becoming a standard of care at least in some subgroups at higher risk [3,4], treatment safety will become an increasingly important issue. Our findings confirm that adjuvant L therapy causes loss of BMD and a higher rate of osteoporosis compared with T. However, in the two sequential arms, L for 2 years followed by T for 3 years preserved BMD and led to a lower prevalence of osteoporosis compared with L alone or TL. The sequence of T followed by L was the worst in terms of bone health and had the highest rate of osteoporosis over 5 years. Finally, we found that both CTX and osteocalcin were significantly and inversely associated with BMD changes. Circulating serum CTX levels have already been shown to predict bone fracture risk and bone metastases in postmenopausal breast cancer [10,11], and may therefore be a useful marker to reduce the frequency of bone density monitoring and predict breast cancer recurrence in the bone. Additional studies addressing these issues are warranted.

Our results are consistent with a retrospective study on BMD changes involving all Swiss participants in the BIG 1-98 study, 121 of whom were also enrolled in the current study, where LT approached T changes on BMD after 5 years [12]. Whereas tamoxifen is known to counteract BMD loss and to decrease bone fracture rate in postmenopausal women [13], the sequence of T followed by L had the worse effect on BMD. Likely, the interruption of T combined with the rapid fall in estrogen levels induced by L may promote an accelerated bone turnover and loss of BMD following the TL switch [14–16]. Indeed, bone turnover biomarkers changes induced by aromatase inhibitors (AIs) occur rapidly after initiation of treatment [16–21].

Bone fracture rates vary considerably among large randomized trials, presumably reflecting different population characteristics, but the risk induced by AIs appears to be similar between the up-front schedule (ATAC [22] and BIG 1-98 trials [6]) and the switch schedule (IES [23] and ABCSG/ARNO trials [24]). The fracture rates in the ATAC, BIG 1-98 monotherapy arms and IES trials were 21.6, 22.0, and 20.1 per 1000 patients per year, respectively [24]. Notably, however, the TEAM trial investigating 5 years of exemestane alone versus 2–3 years of tamoxifen followed by exemestane reported a lower rate of fracture and osteoporosis in the sequential arm (3% versus 5% and 6% versus 10%, respectively) [26]. Exemestane has recently been associated with significantly less self-reported osteoporosis [27] and BMD loss [28] than anastrozole in a *vis a vis* comparison in the NCIC CTG MA.27 trial, although clinical and fragility fracture rates were virtually identical between arms [27]. Because of exemestane steroidal moiety, it is conceivable that the sequence T followed by exemestane has a better bone preserving effect than the sequence of T followed by L, a non-steroidal AI.

Although recent findings from BIG 1-98 have shown that the sequential treatment did not improve efficacy over L alone, LT showed the same overall survival and was the closest

regimen to L alone on all remaining endpoints [1]. Ancillary studies using a stratification by IHC subtype have also indicated that L alone may be superior to the other three regimens in high risk women based on a composite risk assessment, whereas LT was equivalent to L alone in low and intermediate risk patients [2]. Since the efficacy of L and LT regimens is very similar, treatment safety and tolerability for these two regimens may become a determining issue in the treatment decision making of a long-term endocrine adjuvant treatment. Our findings suggest that in some patient subgroups, namely, women with low and intermediate risk of recurrence, women with osteoporosis or women with bothering symptoms from AIs, the sequence LT may be a valid treatment option to retain the benefits of upfront L while minimizing its long-term bone detrimental effects. Our findings are only hypothesis generating, however, and should be tested in additional studies.

Our study has several limitations, mostly due to the lack of a baseline assessment before starting endocrine treatment, so it is not known how bone health after the initial 3 years compares with the baseline untreated state. Although randomization should have minimized any imbalance at baseline among arms, our study may have missed the impact of patients with early loss of BMD during the first 12 months of endocrine treatment, the so called “fast bone losers” [5]. Also, there was some variability in terms of number of observations at each year because patients entered the bone sub-study at different years after randomization, and there was a higher drop-out of patients on T after the initial publication showing the superiority of L over T [9]. Another limitation is the lack of assessment of bone strength by high-resolution peripheral quantitative CT, which provides a low-radiation detailed examination of bone density and structure in cortical and trabecular compartments, both important determinants of bone strength, but not evaluable by DXA [29,30]. Recent results of exemestane in a primary prevention trial showed that the loss of cortical thickness induced by two years of exemestane over placebo is underestimated by DXA compared with CT [31], so our findings may not reflect the real loss at the femur cortical bone. Finally, our findings may have limited practical importance given the likely widespread use of adjuvant bisphosphonate treatment in postmenopausal women with breast cancer after the recent evidence of a reduction in bone recurrence and breast cancer death [32].

In conclusion, we have shown that the sequence L followed by T appears to preserve BMD while retaining the efficacy of upfront L, whereas the sequence of T followed by L has the worst BMD effect. Although our study is only hypothesis generating, the sequence of letrozole followed by T may be a valid treatment option in patients with low and intermediate risk of recurrence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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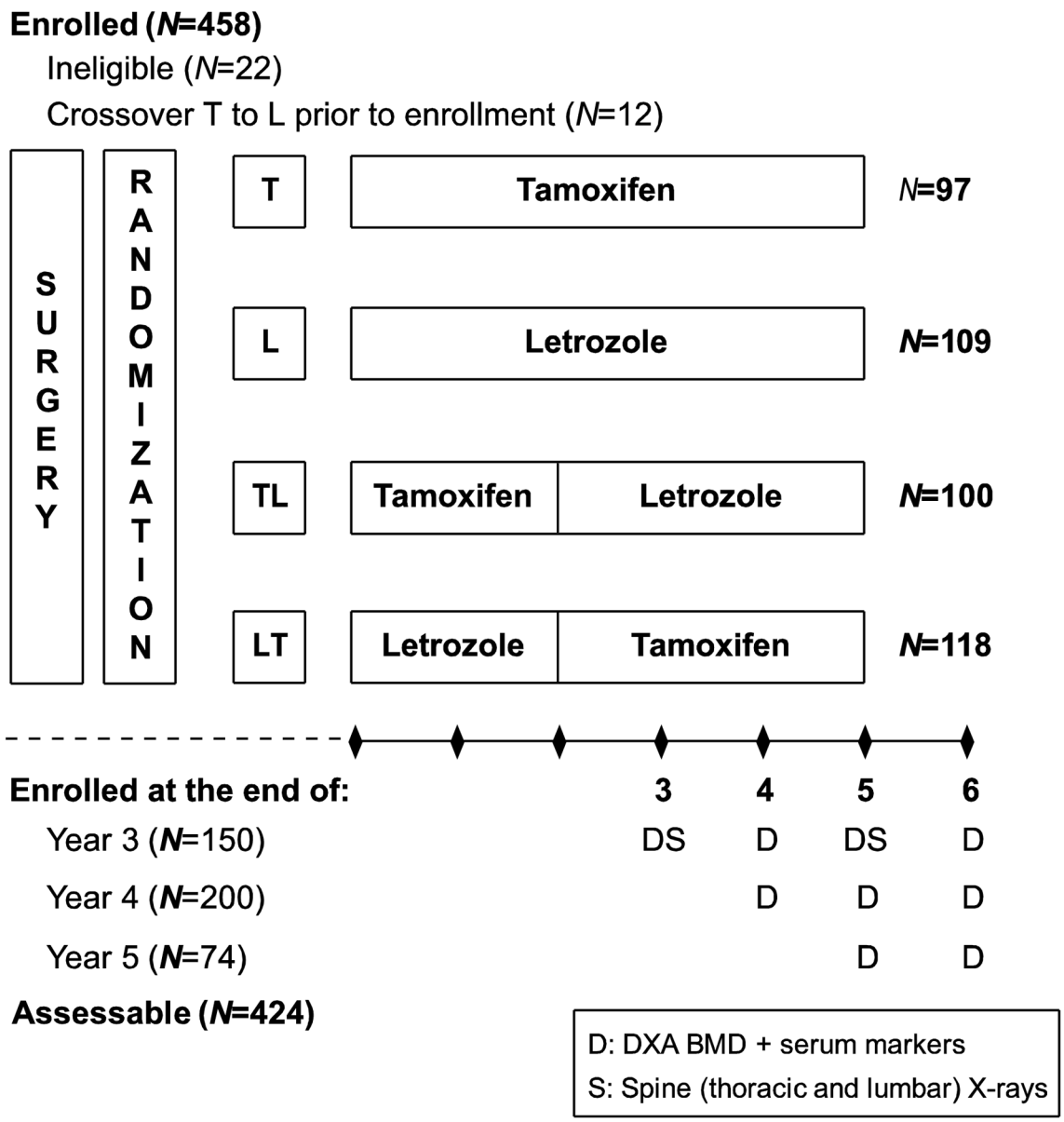

Fig 1.
Study design and participant flow diagram of the BIG 1-98 bone sub-study

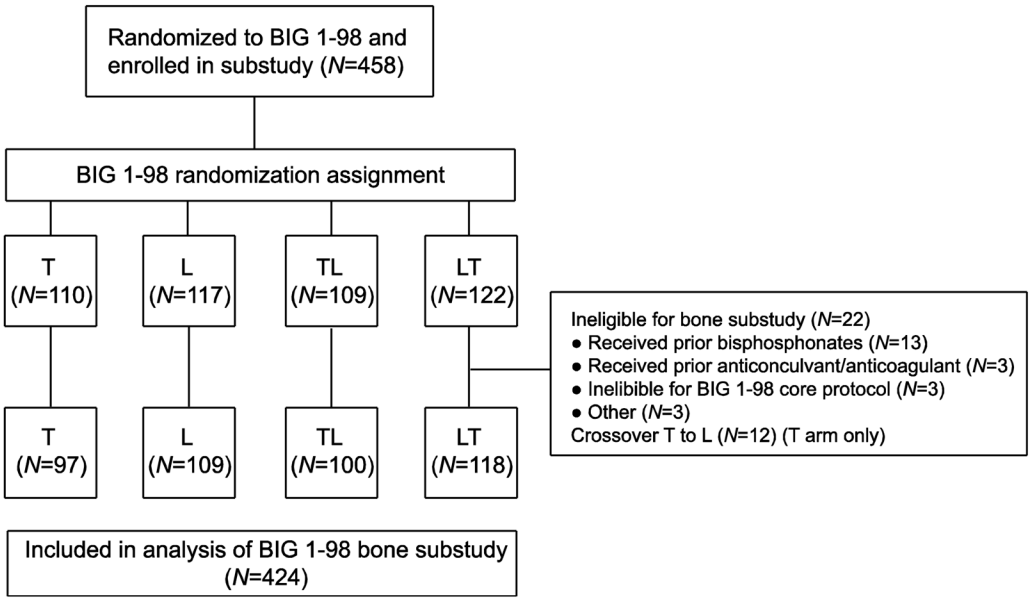

Fig 2.
CONSORT Flow Diagram

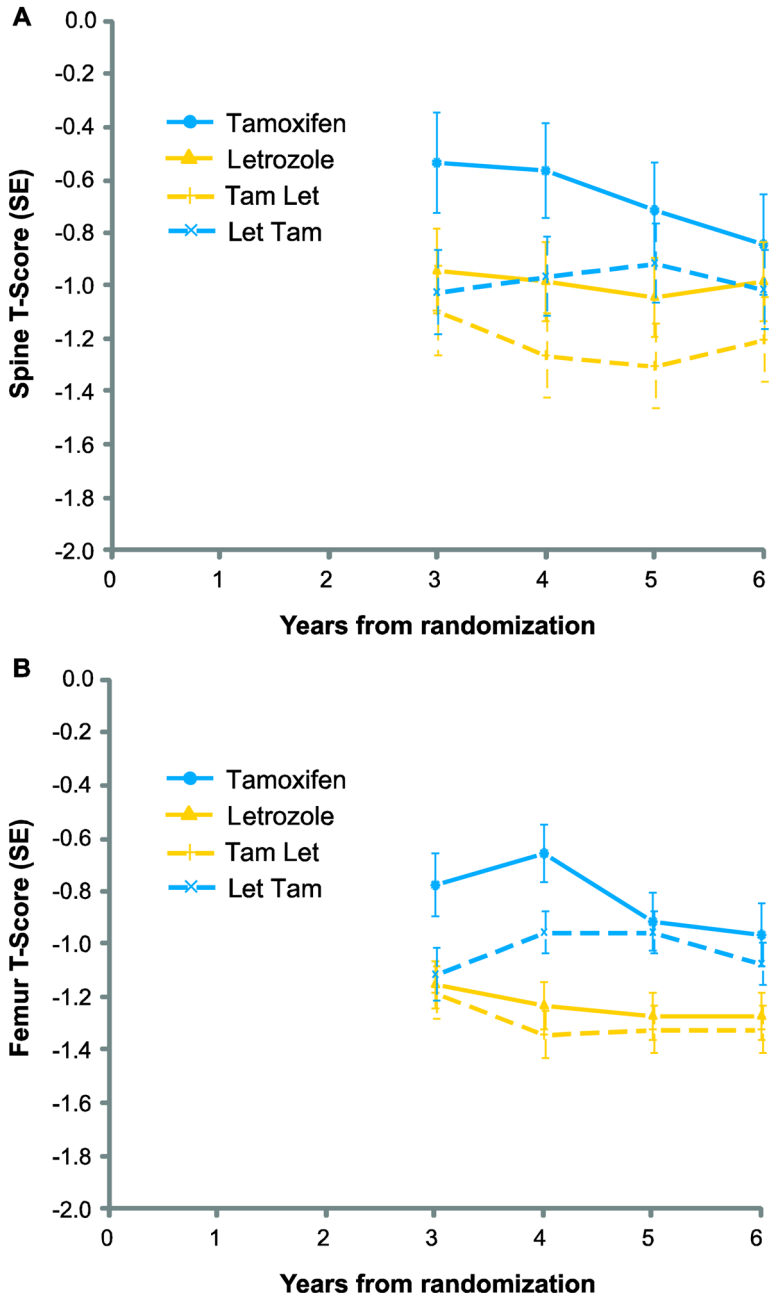

Fig 3.

Least squares means estimates ± SE for the spine T-score (A) and femur T-score (B) by treatment arm. For patients who started bisphosphonates while on the study, measurements after they started bisphosphonates were excluded

Table 1

Baseline characteristics (at time of parent study randomization) of the BIG 1-98 bone sub-study

	T (*N*=97)	**L (*N*=109)**	**TL (*N*=100)**	**LT (*N*=118)**	***P*-value**
Age–years [mean (SD)]	61.2 (7.7)	59.6 (8.2)	61.8 (8.8)	60.9 (8.4)	0.18
Age ≤ 70 [n (%)]	87 (89.7%)	96 (88.1%)	85 (85.0%)	99 (83.9%)	0.58
Age >70 [n (%)]	10 (10.3%)	13 (11.9%)	15 (15.0%)	19 (16.1%)	
BMI --kg/m^2 [mean (SD)]	26.4 (5.1)	25.0 (4.3)	25.6 (4.8)	26.3 (4.7)	0.09
Prior HRT	52.6%	44.0%	38.0%	41.5%	0.20

T, tamoxifen for 5 years; L, letrozole for 5 years; TL, tamoxifen for 2 years followed by letrozole for 3 years; LT, letrozole for 2 years followed by tamoxifen for 3 years; HRT, postmenopausal hormone replacement therapy

Table 2

Comparison of the T-score (estimates of difference and SE) of the spine and femur neck at year 5 between treatment arms based on a multivariate model adjusted for age, BMI, prior HRT, treatment arm, time from randomization, interaction between treatment arm and time from randomization.

	Spine (L2–4) at Year 5		Femur Neck at Year 5	
	Estimate (SE)	***P*-value**	**Estimate (SE)**	***P*-value**
T vs L	0.33 (0.24)	0.17	0.37 (0.14)	0.01
T vs TL	0.59 (0.25)	0.02	0.41 (0.15)	0.005
T vs LT	0.20 (0.24)	0.83	0.04 (0.14)	0.77
L vs TL	0.26 (0.22)	0.25	0.05 (0.13)	0.69
L vs LT	−0.13 (0.21)	0.62	−0.32 (0.12)	0.007
T &LT vs L &TL	0.72 (0.33)	0.03	0.74 (0.19)	<0.001

Table 3

Prevalence of osteoporosis (spine or femur T-score below −2.5 SD) by treatment arms

Year from randomization	T			L			TL			LT		
	Total*	%	95% CI	Total*	%	95% CI	Total*	%	95% CI	Total*	%	95% CI
Spine												
3	30	3.3	(0.1, 17.2)	26	15.4	(4.4, 34.9)	24	16.7	(4.7, 37.4)	20	35.0	(15.4, 59.2)
4	34	14.7	(5.0, 31.1)	66	12.1	(5.4, 22.5)	62	16.1	(8.0, 27.7)	66	12.1	(5.4, 22.5)
5	25	4.0	(0.1, 20.4)	70	4.3	(0.9, 12.0)	69	14.5	(7.2, 25.0)	72	4.2	(0.9, 11.7)
6	18	0	(0.0, 18.5)	64	1.6	(0.0, 8.4)	55	9.1	(3.0, 20.0)	64	3.1	(0.4, 10.8)
Femur												
3	32	3.1	(0.1, 16.2)	35	8.6	(1.8, 23.1)	30	10.0	(2.1, 26.5)	28	7.1	(0.9, 23.5)
4	39	0	(0.0, 9.0)	69	7.2	(2.4, 16.1)	70	8.6	(3.2, 17.7)	77	2.6	(0.3, 9.1)
5	26	0	(0.0, 13.2)	78	5.1	(1.4, 12.6)	70	7.1	(2.4, 15.9)	74	1.4	(0.0, 7.3)
6	16	0	(0.0, 20.6)	70	2.9	(0.3, 9.9)	55	7.3	(2.0, 17.6)	60	0	(0.0, 6.0)

*Total denotes the number of patients with the measurement available at that specific time.

T, tamoxifen for 5 years; L, letrozole for 5 years; TL, tamoxifen for 2 years followed by letrozole for 3 years; LT, letrozole for 2 years followed by tamoxifen for 3 years

Table 4

Association of c-telopeptide, osteocalcin and bone alkaline phosphatase with spine and femur T scores.

Association of C-telopeptide with T-scores				
	Spine (L2–4)		**Femur Neck**	
	Estimate (SE)	***P*-value**	**Estimate (SE)**	***P*-value**
Log(c-telopeptide)	−0.07 (0.03)	0.02	−0.08 (0.02)	<0.001
Age	−0.00003 (0.00003)	0.29	−0.0001 (0.00002)	<0.001
BMI	0.06 (0.02)	0.001	0.07 (0.009)	<0.001
Prior HRT	−0.28 (0.16)	0.08	0.02 (0.09)	0.83

Association of Osteocalcin with T-scores				
	Spine (L2–4)		**Femur Neck**	
	Estimate (SE)	***P*-value**	**Estimate (SE)**	***P*-value**
Log(osteocalcin)	−0.16 (0.06)	0.01	−0.17 (0.05)	<0.001
Age	−0.00003 (0.00003)	0.29	−0.0001 (0.00002)	<0.001
BMI	0.05 (0.02)	0.001	0.07 (0.009)	<0.001
Prior HRT	−0.29 (0.16)	0.07	0.01 (0.09)	0.93

Association of bone alkaline phosphatase with T-scores				
	Spine (L2–4)		**Femur Neck**	
	Estimate (SE)	***P*-value**	**Estimate (SE)**	***P*-value**
Log(bone alkaline phosphatase)	−0.08 (0.05)	0.11	−0.00002 (0.04)	1.00
Age	−0.00003 (0.00003)	0.26	−0.0001 (0.00002)	<0.001
BMI	0.06 (0.02)	0.001	0.07 (0.01)	<0.001
Prior HRT	−0.27 (0.16)	0.10	0.02 (0.09)	0.86