

Safety of tibolone in the treatment of vasomotor symptoms in breast cancer patients—Design and baseline data 'LIBERATE' trial

E. Kubista^a, P. Kenemans^b, J.M. Foidart^c, C.H. Yip^d, B. von Schoultz^e, P. Sismondi^f, R. Vassilopoulou-Sellin^g, M.W. Beckmann^h, N.J. Bundredⁱ

^a Department of Special Gynecology, Universitätsklinik für Frauenheilkunde, Wahringer Gürtel 18-20, A-1090 Wien, Austria

^b Department of Obstetrics and Gynecology, Free University, Amsterdam, De Boelelaan 1117, 1081 HV Amsterdam, Netherlands

^c Department of Obstetrics and Gynecology, University of Liège, Domaine Universitaire du Sart Tilman B35, B-4000 Liège, Belgium

^d University Malaya Medical Centre, 50603 Kuala Lumpur, Malaysia ^e Division of Obstetrics and Gynecology, Karolinska Institute/Huddinge, SE-141 86 Stockholm, Sweden

^f Unit of Gynecology Oncology, University of Turin, Via Magellano 1, 10128 Torino, Italy

^g Anderson Cancer Center, University of Texas, 1515 Holcombe Blvd, Box 435 TX77030 Houston, USA

^h University Clinic, Universitätsstrasse 21-23, 91054 Erlangen, Germany

ⁱ Department of Surgery, University of Manchester, Southmoor Road, Wytheashawe, Manchester M23 9GT, UK

Abstract

Many patients with a history of breast cancer (BC) will suffer from vasomotor symptoms, which can be induced or exacerbated by treatment with tamoxifen or aromatase inhibitors. The LIBERATE trial was designed as a randomized, double-blind, multicenter trial to demonstrate that tibolone 2.5mg/day (Livial[®]) is non-inferior to placebo regarding BC recurrence in women with vasomotor symptoms surgically treated for primary BC within the last 5 years. Secondary objectives are effects on vasomotor symptoms as well as overall survival, bone mineral density and health-related quality of life.

Mean age at randomization was 52.6 years, and the mean time since surgery was 2.1 years. The mean daily number of hot flushes and sweating episodes was 7.3 and 6.1, respectively. For the primary tumor, Stage IIA or higher was reported for > 70% of the patients. In subjects whose receptor status was known, 78.2% of the tumors were estrogen receptors positive. At randomization, tamoxifen was given to 66.2% of all patients and aromatase inhibitors to 7%. Chemotherapy was reported by 5% at randomization.

The adjuvant tamoxifen use in LIBERATE allows a comparison with the Stockholm trial (showing no risk of BC recurrence associated with hormone therapy), which was stopped prematurely subsequent to HABITS. The LIBERATE trial is the largest, ongoing, well-controlled study for treatment of vasomotor symptoms in BC patients.

Keywords: breast cancer ; tibolone (Livial[®]) ; LIBERATE ; vasomotor symptoms ; recurrence

Abbreviation: LIBERATE, livial intervention following breast cancer: efficacy, recurrence and tolerability endpoints

Introduction

Breast cancer is the most common malignancy in Western women. Treatment for early breast cancer has become highly effective, but at the price of severe side effects. A substantial proportion of patients will suffer from vasomotor symptoms, which result directly from adjuvant treatment with tamoxifen or aromatase inhibitors^{1,2} or other treatment modalities such as ovarian suppression or ablation and chemotherapy.^{3,4}

Hormone therapy (HT) containing estrogen is effective, but considered unsafe.⁵ The concern for an increased risk of breast cancer in healthy women taking postmenopausal HT⁶⁻⁸ has generally conventionally led to a contraindication for HT in women with a history of breast cancer, despite findings of observational studies that the risk of recurrence in breast cancer survivors is not increased with HT use.^{9,10} Non-hormonal therapy for severe motor symptoms is not effective.⁵

Tibolone is a synthetic steroid with a clinical profile that differs from that of both classical estrogen-based HT, as well as from that of selective estrogen receptor modulators (SERMs).^{13,14} Tibolone has shown its efficacy in reducing climacteric symptoms both in healthy menopausal women,¹⁵ as well as in women receiving tamoxifen¹⁶ or GnRH analogs¹⁷ after surgery for breast cancer. The mode of action of tibolone differs from that of conventional estrogen receptor ligands. Tibolone has been classified as a selective tissue estrogenic activity regulator (STEAR),¹⁸ a substance that has different clinical effects on different tissues due to tissue-selective metabolism and enzyme regulation. After oral administration of tibolone, three active metabolites are formed. The two estrogenic metabolites, 3 α -OH and 3 β -OH-tibolone, have been shown to have beneficial effects on vasomotor symptoms, the vagina and bone.¹⁹ The third metabolite, the delta-4-isomer, has progestogenic

properties and is locally produced within the endometrium and therefore minimizes vaginal bleeding.^{19,20} In the breast, tibolone and its metabolites reduce sulfatase²¹ and stimulate sulfotransferase activity²² thereby inhibiting the formation of active estrogenic substances (including the 3-OH metabolites of tibolone) and promoting the formation of inactive estrogens.^{23,24} Currently available clinical observations with tibolone suggest that it does not increase mammographic breast density and causes less breast tenderness than combined estrogen-progestogen therapy does.¹⁴ Tibolone in a dose of 2.5mg/day has been registered (as Livial[®]) in 90 countries for treatment of climacteric symptoms and in 45 of these countries for the prevention of osteoporosis. It has been judged to have a good overall clinical tolerability and it does not seem to increase breast density on the mammogram.¹⁴

A few pilot studies have investigated the feasibility to use tibolone as add back in breast cancer patients. In a double-blind, randomized, placebo-controlled study in 70 postmenopausal women receiving tamoxifen following surgery for early breast cancer, tibolone was more effective than placebo in reducing hot flashes. There were no recurrences in either group during the 12-month study.¹⁶ Although these findings are promising, definitive safety data can only come from a large, long-term controlled clinical trial such as the LIBERATE (livial intervention following breast cancer: efficacy, recurrence and tolerability endpoints) study. As tibolone has been increasingly prescribed preferentially in disease-free breast cancer patients who persistently seek help for their often disabling menopausal complaints,²⁵ such a trial is highly warranted.

The (LIBERATE) study was designed to investigate the safety and efficacy of 2.5mg/day oral tibolone in women with vasomotor symptoms and a history of breast cancer in the previous 5 years.

In this paper, we describe the design and rationale of the LIBERATE study, together with the baseline characteristics of the patients enrolled in the study and discuss the potential of the LIBERATE study to provide an answer to the question as to a safe way to relief symptoms in patients with a history of breast cancer.

Methods

Trial design

Study characteristics

The LIBERATE study is a randomized, placebo-controlled, double-blind, parallel-group study. The primary outcome of interest is breast cancer recurrence, defined here as loco-regional recurrence, and/or distant metastasis and/or new primary invasive tumor in the contralateral breast. The primary aim is to test the hypothesis that tibolone is non-inferior to placebo regarding breast cancer recurrence.

Adequate sample size was estimated to be at least 3000 women (> 1500 women in each arm) based on the assumption that breast cancer recurrence in the placebo group would be 15% after 3 years, assuming a yearly recurrence rate of 3% and 8% for node-negative and node-positive patients, respectively. The power was calculated to be 80.9% for a total sample size of 3100 subjects, provided that at least 1800 subjects were node positive.

Study endpoints

The primary outcome variable is breast cancer recurrence. Secondary study outcomes include vasomotor symptoms, bone mineral density (BMD), health-related quality of life (HRQL) and overall survival. All breast cancer recurrence events reported will be assessed in a blinded manner by an independent Adjudication Committee.

Eligibility criteria

Breast cancer patients with no evidence of disease were eligible for this study when they had been surgically treated within the previous 5 years for histological confirmed T1-3, N 0-2, M0 breast cancer irrespective of hormone receptor status.

Subjects had to be younger than 75 years of age, with a last menstruation 12 months or more before (when not ovariectomized, hysterectomized or on GnRH analogs). Women had to have vasomotor symptoms, either related to natural menopause or resulting from prior or current adjuvant breast cancer treatment. Prior or current use of tamoxifen hydrochloride, aromatase inhibitors, GnRH analogs or chemotherapy was allowed. Current use of estrogenic or progestagenic substances was not allowed, neither was use of raloxifene hydrochloride. Adjuvant breast cancer treatments were permitted during the trial.

In all non-hysterectomized women, the endometrium was assessed by transvaginal ultrasound scan (TVUS). Endometrial polyps in tamoxifen users and a double endometrium thickness of more than 8 mm in non-tamoxifen users led to exclusion. Non-tamoxifen users with a double endometrial thickness of more than 4 mm had to show inactive or atrophic endometrium in the biopsy.

Screening and randomization

Screening started after a subject had signed the informed consent form. Data were collected on medical, gynecological, family and breast cancer history, demographics and previous medications. Following physical (including a breast examination and a mammogram) and gynecological examination (including a cervical PAP smear), TVUS was performed in all subjects at screening.

Blood samples from non-fasting subjects were drawn for routine hematology and biochemistry; all blood samples were determined in one central laboratory. Eligible subjects were assigned to either tibolone 2.5 mg daily or placebo with a randomization ratio of 1:1.

Follow-up assessments

Follow-up visits were scheduled each half-year until a maximum of 5 years with an additional visit after the first 3 months. At each follow-up visit, a physical examination and breast examination were performed; a vasomotor symptoms form completed and vital signs, concomitant medication, vaginal bleeding episodes and adverse events are documented. Gynecological examinations (including cervical smear), mammography and blood sampling for routine laboratory safety assessments were performed annually in all patients. An endometrial biopsy was performed in subjects with vaginal bleeding that persisted beyond the first 3 months or started after the first 3 months. If biopsies were categorized as any type of hyperplasia or cancer at any time during the study, the subject was discontinued from trial medication and treated. All women who discontinued trial medication were strongly encouraged to attend subsequent visits as scheduled in the protocol. All subjects were questioned about possible adverse events at each visit.

Data analysis

The analyses of the primary outcome variable will be performed upon an average study participation of at least 3 years. The breast cancer recurrence hazard ratio of tibolone versus placebo will be estimated using survival analysis models fitted to the time to breast cancer recurrence data. Non-inferiority will be assessed by comparing the upper limit of the two-sided 95% confidence interval of the hazard ratio with the pre-specified non-inferiority margin. The analysis of the overall survival will use statistical techniques comparable to that of the primary outcome measure.

Results

The LIBERATE study protocol has been approved by the Independent Ethics Committee or the Institutional Review Board at each participating center. Written informed consent was obtained from all study participants.

Screening and randomization

Potential participants were recruited from the investigators practices, referrals from clinical staff and by other local initiatives, depending on the clinic's preference and the local regulations. The recruitment phase started on 20 June 2002 and finished on 10 December 2004. A total of 3583 women were screened, of whom 3148 were eligible. Women were randomized in 245 centers in 31 countries.

Baseline characteristics of women included

The baseline characteristics of the study population are shown in Tables 1 and 2, and in Figs. 1 and 2. **As per the database status on 5 January 2007, the mean age at randomization was 52.6 years.** The large majority of women (81.2%) was between 40 and 60 years of age, with 40.7% being younger than 50 years. Nearly 80% was Caucasian. Mean weight was 70.5 kg and mean body mass index 27.0 kg/m².

Breast cancer surgery had been breast sparing in only 42.8% of all women and mean time since surgery was 2.1 years. A pathological tumor size of > 2.0 cm (T2/3) was reported for 44.9% of the patients and a node-positive status (N1/2) for 57.8%, resulting in > 70% of Stage IIA or higher for the primary tumor. Of the patients with a known receptor status, 78.2% were estrogen receptor positive (ER+), 71.5% were progesterone receptor positive (PR+), and 61.7 were both ER+ and PR+.

The mean number of hot flashes was 7.3 per 24 h. Vasomotor symptoms were reported to interfere with normal life in 78.5% of women. Previous HT-use was reported by 745 women (23.7%).

Prior to study entry, patients underwent adjuvant radiotherapy (70.7%) and/or chemotherapy (70.2%), while adjuvant use of tamoxifen (74.6%), aromatase inhibitors (7.6%) and GnRH analogs (6.0%) also was reported. At randomization, many patients still used tamoxifen (66.2%), aromatase inhibitors (6.7%), chemotherapy (5.0%), or GnRH analogs (4.4%).

Of the total of 3148 women enrolled, 739 had had a hysterectomy. Mean double-wall endometrial thickness was 5.5 mm in tamoxifen users and 3.0 mm in other women.

Table 1 Population characteristics in the LIBERATE study at baseline

Characteristics		
Number of subjects randomized		3148
Age (years)	Mean (S.D.)	52.6 (7.3)
≤ 50 years of age	<i>n</i> (%)	1282 (40.7)
> 50 years of age	<i>n</i> (%)	1866 (59.3)
Body mass index (kg/m ²)	Mean (S.D.)	27.0 (4.9)
Weight (kg)	Mean (S.D.)	70.5 (13.9)
Height (cm)	Mean (S.D.)	161.5 (6.8)
Hot flushes per day (24 h)	Mean (S.D.)	7.3 (5.9)
Time since BC surgery (years)	Mean (S.D.)	2.1 (1.3)
Type of breast cancer surgery	<i>n</i> (%)	
Breast sparing		1346 (42.8)
Mastectomy		1802 (57.2)
E receptor status	<i>n</i> (%)	
Positive		2181 (69.3)
Negative		609 (19.3)
Unknown		358 (11.4)
P receptor status	<i>n</i> (%)	
Positive		1878 (59.7)
Negative		750 (23.8)
Unknown		520 (16.5)
Lymph node status	<i>n</i> (%)	
Positive		1822 (57.8)
Negative		1322 (42)
Unknown		4 (0.1)
Previous HT-use	<i>n</i> (%)	744 (23.7)
<i>Relevant co-medications</i>		
Chemotherapy	<i>n</i> (%)	
Previous		2209 (70.2)
At randomisation		158 (5.0)
GnRH analogs	<i>n</i> (%)	
Previous		188 (6.0)
At randomisation		137 (4.4)
Tamoxifen	<i>n</i> (%)	
Previous		2348 (74.6)
At randomisation		2083 (66.2)
Aromatase inhibitors	<i>n</i> (%)	
Previous		238 (7.6)
At randomisation		211 (6.7)

E, estrogen; P, progestogen; GnRH, gonadotropin releasing hormone.

Table 2 Relevant characteristics in non-tamoxifen users vs. tamoxifen users

	Use of adjuvants at baseline			
	No (n = 865)	Tamoxifen (n = 2072)	Aromatase inhibitors* (n = 211)	Total (n = 3148)
TVUS double wall endometrial thickness (mm) (mean (S.D.))	2.9 (1.5)	5.4 (4.7)	3.2 (1.9)	4.6 (4.1)
Hot flashes per 24 h (mean (S.D.))	6.8 (5.3)	7.4 (6.2)	7.8 (6.2)	7.3 (5.9)
(Very) severe hot flashes (%)	32.5	35.1	43.2	34.8
(Very) severe flashes/sweats interfering with normal life (%)	24.2	24.0	34.9	24.7
(Very) severe palpitations (%)	7.3	4.6	7.8	5.6
(Very) severe joint pain (%)	12.8	9.1	15.6	10.5
(Very) severe dryness of vagina (%)	13.2	8.3	17.5	10.2
(Very) severe incontinence (%)	1.9	1.5	1.5	1.6

*Fourteen subjects also received tamoxifen within 14 days of baseline.

Fig. 1. Study of population characteristics at baseline.

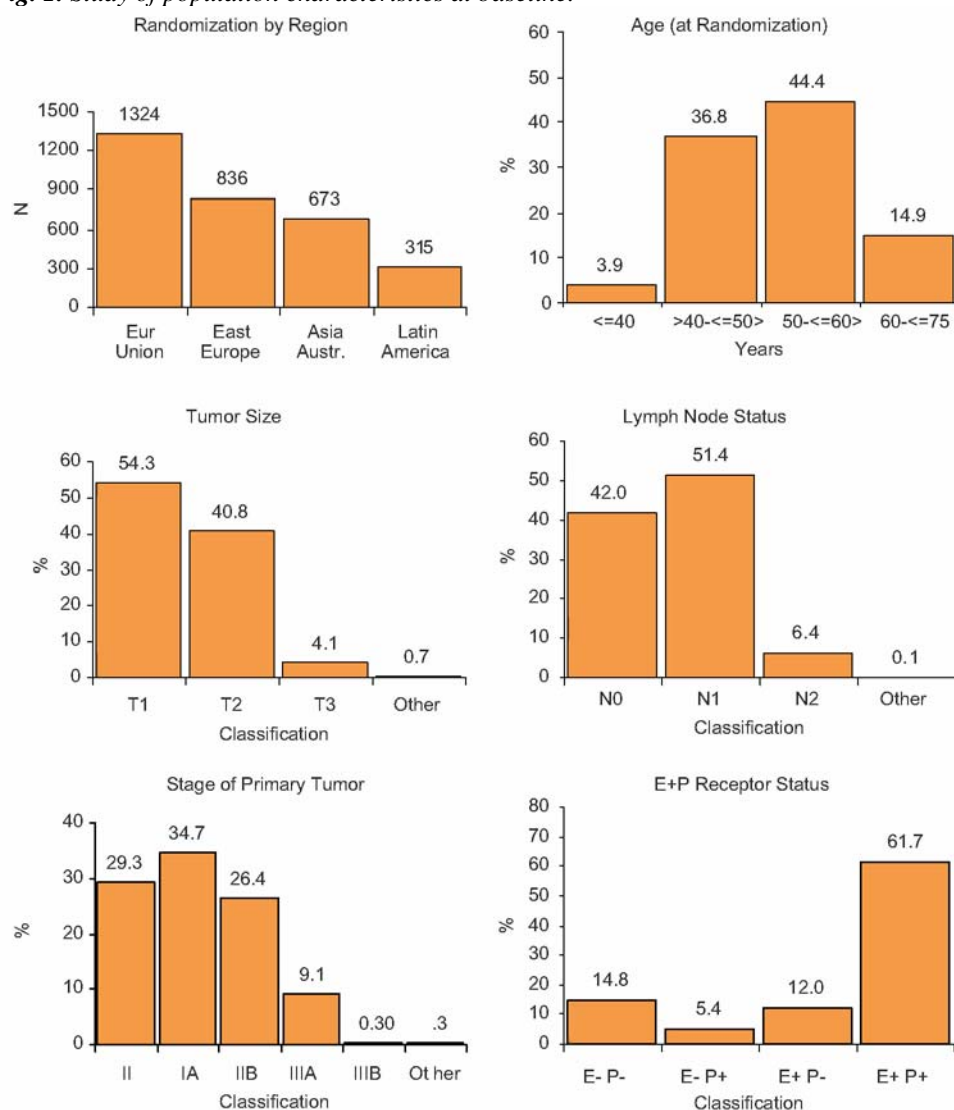
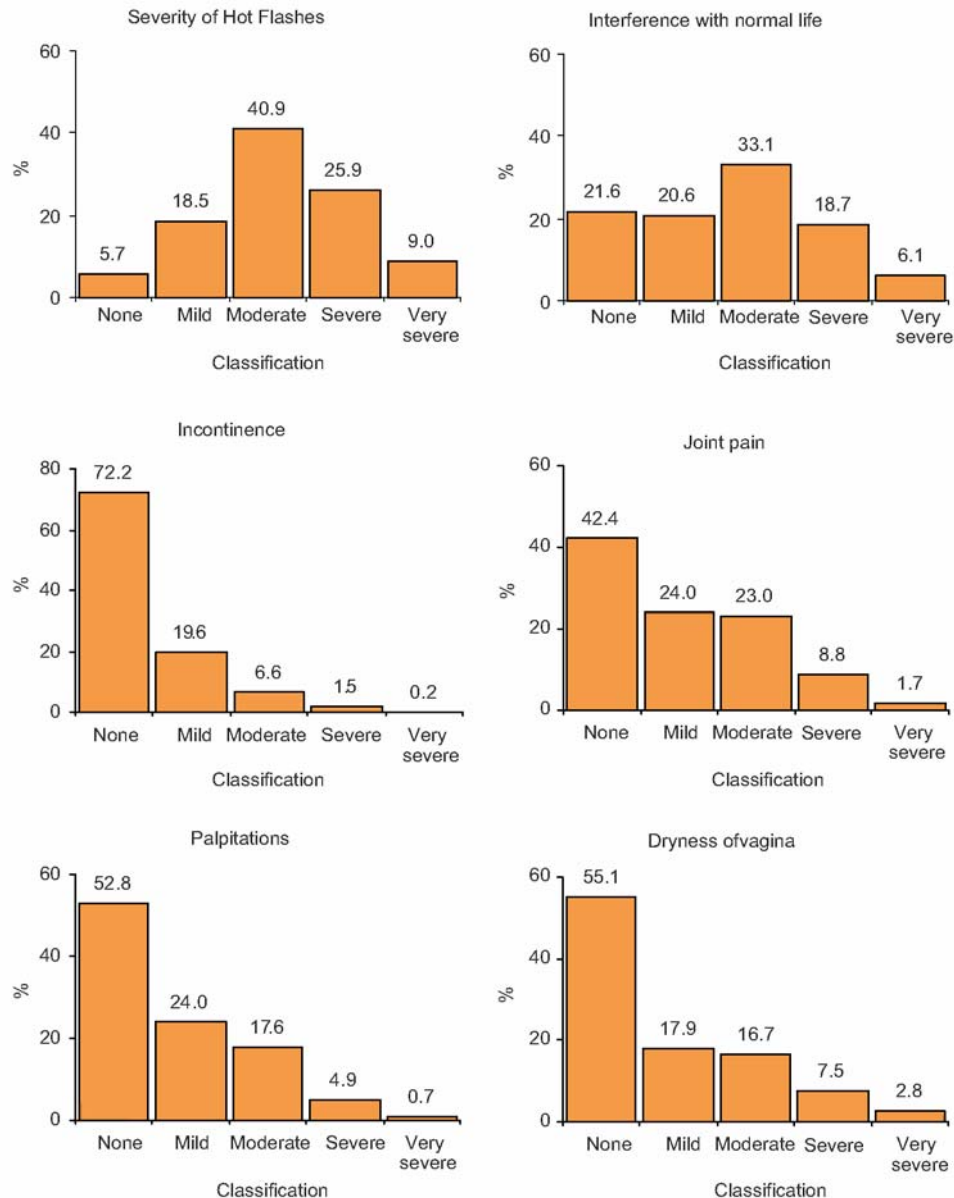


Fig. 2. Climacteric complaints at baseline.



Discussion

The LIBERATE study is currently the only ongoing randomized, double-blind controlled study seeking to provide information about the safety and efficacy of a potential treatment option for vasomotor symptoms in women with a history of breast cancer. Evidence from this large, multinational study is vital to determine whether or not tibolone is indeed equal to placebo with regard to breast cancer recurrence and hence to provide evidence-based advice for a group of breast cancer patients for whom there is a pressing need for a safe and effective treatment of vasomotor symptoms.⁵ Based on the data reported here, it can be expected that LIBERATE through its design, size and successful accrual of participants, will provide a sufficient basis for this evidence. The 3148 women were included in a relative short period of 2.5 years. Over 70% of women enrolled in the study were breast cancer Stage IIA or higher. In total 1830 women (58.1%) had a positive lymph node status in accordance with the assumptions for the power calculation and sample size estimate. The LIBERATE population is not an average early breast cancer population and many physicians would be highly reluctant to treat ER+, lymph node positive, tamoxifen using breast cancer patients with hormones. Therefore, non-inferiority to placebo demonstrated in this population would be of large clinical significance. LIBERATE showed the feasibility of such a trial. Based on a thorough review of unblinded data (of in total 6371 women years of exposure and 7260 women years of trial participation), the Data and Safety Monitoring Board in its 6th meeting statement of 6 October 2006 recommended again that the LIBERATE trial continue with no alterations to the protocol or patient information sheet.

Presence of vasomotor symptoms was required at baseline. However, there were no criteria specified with regard to the number or severity of hot flashes. Several guidelines propose criteria that need to be fulfilled in order to show the efficacy of a treatment in managing vasomotor symptoms. Therefore, in addition to the overall sample, analyses of hot flashes will also focus on subgroups of highly symptomatic subjects according to EMEA²⁶ and FDA guidelines.²⁷ In addition, the LIBERATE study may also provide valuable information on overall survival, BMD and HRQL, important issues in this disease-free patient group of which 40% is younger than 51 years of age, and with a moderate to excellent prognosis.

As menopausal symptoms can severely affect quality of life, it was decided to complement conventional efficacy evaluations with HRQL assessments in order to provide a comprehensive picture of the impact of symptoms and to assess the potential benefits of treatment. In addition to relief of vasomotor symptoms, tibolone has been reported to positively influence both mood and sexual well-being,¹⁴ and therefore possibly HRQL. Thus, also compliance to adjuvant cancer treatment could be increased and, therefore, overall survival.

It is particularly important to ensure endometrial safety in women taking tamoxifen due to an increased risk of endometrial cancer. A well-known problem of performing TVUS in tamoxifen-treated women is a high incidence of apparent endometrial thickening and an associated increase in invasive procedures, most of which are not indicated.²⁸⁻³⁰ Measurement of endometrial thickness by TVUS in tamoxifen-treated women therefore appears not to be a reliable screening tool. In the LIBERATE study, TVUS was performed in tamoxifen-treated women at screening only in order to exclude endometrial polyps. As almost all endometrial carcinomas are detected after the occurrence of vaginal bleeding, both in tamoxifen users and in non-users,²⁸⁻³⁰ an endometrial biopsy was taken to exclude endometrial cancer, when significant vaginal bleeding occurred during the trial.

Current evidence suggests that postmenopausal HT is associated with an increased risk of breast cancer, and that this risk is greater with combined HT⁸ than with estrogen alone.^{7,31} The Million Women Study also reported an increased risk of breast cancer with tibolone (relative risk, 1.45; 95% confidence interval, 1.25-1.67), although this was significantly ($p < 0.0001$) less than that with combined HT.⁷ However, it appears that the risks reported in this study may have been overestimated³²⁻³⁴ and this, combined with the relatively small numbers of women who were treated with tibolone (6%) and the potential for preferential prescribing²⁵ probably implies that the current evidence is inconclusive. Another epidemiological study conducted in the UK, using the General Practice Research Database, revealed a similar number of women with breast cancer as the Million Women Study (7192 vs. 7140 cases, respectively), but showed no increased risk with tibolone (relative risk, 1.02; 95% confidence interval, 0.78-1.33).³⁵ However, this study still awaits appropriate publication.

Because of the concerns about HT and breast cancer risk, and fears that HT might promote breast cancer recurrence, only a few studies, mostly small and observational in design, have been conducted to assess HT use in women with a history of breast cancer.^{9,10,36-38} With most observational studies on HT use in breast cancer survivors being reassuring, the need for prospective randomized clinical trials becomes evident. Marsden et al.³⁹ proved in a small pilot randomized trial, that such trials would be feasible. Unfortunately, two large open randomized trials that were designed to resolve some of the uncertainty were stopped prematurely.^{11,12} One of these, the HABITS (hormonal replacement therapy after breast cancer—is it safe?) study (only 434 women randomized), was stopped in December 2003 after a median follow-up of 2.1 years because the risk of recurrence was significantly higher amongst women receiving HT than amongst those with no menopausal therapy (relative hazard, 3.3; 95% confidence interval, 1.5-7.4).¹¹ In contrast, the Stockholm trial (378 women randomized) revealed no evidence of an increased risk of recurrence in women treated with HT compared with untreated women after a median follow-up of 4.1 years (relative hazard, 0.82; 95% confidence interval, 0.35-1.9).¹² However, due to anticipated problems with recruitment and compliance, the trial was terminated prematurely. Possible reasons proposed for these conflicting findings included differences in the clinical characteristics of the patients, less use of adjuvant tamoxifen therapy in the HABITS trial and an attempt to minimize the use of progestogen in the Stockholm trial.

At present, LIBERATE is the only randomized trial to provide an answer for breast cancer survivors with severe climacteric complaints, eagerly awaited both by patients and doctors. The successful accrual of 3148 women and the characteristics of the population at baseline as described here would allow for such an answer.

Conflict of Interest Statement

None declared.

Acknowledgments

The LIBERATE study is supported by a grant from NV Organon. C. Peters, MD (2004f) had a major input in the preparation of the trial protocol.

References

1. Howell A, Cuzick J, Baum M, et al. ATAC Trialists' Group. Results of the ATAC (arimidex, tamoxifen, alone or in combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005;365:60-2.
2. Thürlimann B, Keshaviah A, Coates AS, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med* 2005;353:2747-57.
3. Goodwin PJ, Ennis M, Pritchard KI, et al. Risk of menopause during the first year after breast cancer diagnosis. *J Clin Oncol* 1999;17:2365-70.
4. Bines J, Oleske DM, Cobleigh MA. Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. *J Clin Oncol* 1996;14:1718-29.
5. Hickey M, Saunders CM, Stuckey BGA. Management of menopausal symptoms in patients with breast cancer: an evidence-based approach. *Lancet Oncol* 2005;6:687-95.
6. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet* 1997;350:1047-59.
7. Million Women Study. Breast cancer and hormone replacement therapy in the Million Women Study. *Lancet* 2003;362:419-27.
8. Chlebowski RT, Hendrix SL, Langer RD, et al. The Writing Group for the Women's Health Initiative Investigators. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA* 2003;289:3243-53.
9. Col NF, Hirota LK, Orr RK, et al. Hormone replacement therapy after breast cancer: a systematic review and quantitative assessment of risk. *J Clin Oncol* 2001;19:2357-63.
10. O'Meara ES, Rossing MA, Dalling JR, et al. Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. *J Natl Cancer Inst* 2001;93:754-62.
11. Holmberg L, Anderson H. The HABITS steering and data monitoring committees. HABITS (hormonal replacement therapy after breast cancer-is it safe?), a randomised comparison: trial stopped. *Lancet* 2004;363:453-5.
12. von Schoultz E, Rutqvist LE. The Stockholm Breast Cancer Study Group. Menopausal hormone therapy after breast cancer: the Stockholm Randomized Trial. *J Natl Cancer Inst* 2005;97:533-5.
13. Modelska K, Cummings S. Tibolone for postmenopausal women: systematic review of randomized trials. *J Clin Endocrinol Metab* 2002;87:6-23.
14. Kenemans P, Speroff L. Tibolone: clinical recommendations and practical guidelines. A report of the International Tibolone Consensus Group. *Maturitas* 2005;51:21-8.
15. Landgren MB, Coelingh Bennink HJT, Engelen S. Dose-response analysis of effects of tibolone on climacteric symptoms. *Br J Obstet Gynaecol* 2002;109:1109-14.
16. Kroiss R, Fentiman IS, Helmond FA, et al. The effect of tibolone in postmenopausal women receiving tamoxifen after surgery for breast cancer: a randomised, double-blind, placebo-controlled trial. *Br J Obstet Gynaecol* 2005;112:228-33.
17. Pollow K, Schaffrath M, Kölbl A, et al. Phase II study of goserelin adjuvant therapy combined with exemestane with or without tibolone in premenopausal women with receptor positive, node negative mammary carcinoma: ADAGIO Study. *Geburtsh Frauenheilk* 2005;65:612-9.
18. Smith CL, O'Malley BW. Coregulator function: a key to understanding tissue specificity of selective receptor modulators. *Endocr Rev* 2004;25:45-71.
19. Kloosterboer HJ. Tibolone: a steroid with a tissue-specific mode of action. *J Steroid Biochem Mol Biol* 2001;76:231-8.
20. Tang B, Markiewicz L, Kloosterboer HJ, et al. Human endometrial 3 β -hydroxysteroid dehydrogenase/isomerase can locally reduce intrinsic estrogenic/progestogenic activity ratios of steroidal drugs. *J Steroid Biochem Mol Biol* 1993;45:345-51.
21. Gooyer de ME, Overkluft Vaupel Kleyn GT, Smits KC, et al. Tibolone: a compound with tissue specific inhibitory effects on sulfatase. *Mol Cell Endocrinol* 2001;183:55-62.
22. Chetrite GS, Kloosterboer HJ, Philippe J-C, et al. Effect of Org OD14 (Livial) and its metabolites on human estrogen sulfotransferase activity in the hormone-dependent MCF-7 and T47D, and the hormone-independent MDA-MB-231, breast cancer cell lines. *Anticancer Res* 1999;19:269-76.
23. Kloosterboer HJ. Tissue-selective effects of tibolone on the breast. *Maturitas* 2004;49:S5-S15.
24. Chetrite GS, Kloosterboer HJ, Philippe J-C, et al. Effect of Org OD14 (Livial) and its metabolites on 17 β -hydroxysteroid dehydrogenase activity in the hormone-dependent MCF-7 and T47D breast cancer cells. *Anticancer Res* 1999;19:261-7.
25. Trinh X-B, van Hal G, Weyler J, et al. The thoughts of physicians regarding the need to start hormone replacement therapy in breast cancer survivors. *Eur J Obstet Gynecol Reprod Biol* 2006;124: 207-11.
26. CPMP/EWP/021/97. Points to consider on hormone replacement therapy. *The European Agency for the evaluation of medicinal products*, 19 November 1997.
27. Guidance for Industry. *Guidance for clinical evaluation of combination estrogen/progestin-containing drug products used for HRT of post-menopausal women*. FDA; 1995.

28. Carter JR, Twiggs LB. The role of transvaginal sonography in gynecologic oncology. Studd J, editor. *Progress in obstetrics and gynaecology*, vol. 10. London: Churchill Livingstone; 1993. p. 341-57.
29. Barakat RR. Benign and hyperplastic endometrial changes associated with tamoxifen use. *Oncology* 1997;11(S 1):35-7.
30. Seoud M, Shamseddine A, Khalil A, et al. Tamoxifen and endometrial pathologies: a prospective study. *Gynecol Oncol* 1999;75:15-9.
31. Anderson GL, Limacher M, Assaf AR, et al. the Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701-12.
32. Shapiro S. The Million Women Study: potential biases do not allow uncritical acceptance of the data. *Climacteric* 2004;7:3-7.
33. Whitehead M, Farmer R. The Million Women Study: a critique. *Endocrine* 2004;24:187-94.
34. Kenemans P. Postmenopausal hormone therapy and breast cancer: what is the problem? *Maturitas* 2005;51:75-82.
35. Allen DS, de Vries C, Farmer DT. Pharmaceutical content and regimen of hormone replacement therapy and risk of breast cancer. *Pharmacoepidemiol Drug Saf* 2002;1(S 1):296-8.
36. Biglia N, Gadducci A, Ponzoni R, Roagna R, Sismondi P. Hormone replacement therapy in cancer survivors. *Maturitas* 2004;48:333-46.
37. Beckmann MW, Jap D, Djahansouzi S, Nestle-Krämling C, Kuschel B, Dall P, et al. Hormone replacement therapy after treatment of breast cancer: effects on postmenopausal symptoms, bone mineral density and recurrence rates. *Oncology* 2001;60:199-206.
38. Vassilopoulou-Sellin R, Asmar L, Hortobagyi GN, et al. Estrogen replacement therapy after localized breast cancer: effects on postmenopausal symptoms, bone mineral density and recurrence rates. *J Clin Oncol* 1999;17:1482-7.
39. Marsden J, Whitehead M, A'Hern R, et al. Are randomized trials of hormone replacement therapy in symptomatic women with breast cancer feasible? *Fertil Steril* 2000;73:292-9.