The role of the addition of ovarian suppression to tamoxifen in young women with hormone-sensitive breast cancer who remain premenopausal or regain menstruation after chemotherapy (ASTRA): study protocol for a randomized controlled trial and progress

Hyun-Ah Kim1, Sei Hyun Ahn2, Seok Jin Nam3, Seho Park4, Jungsil Ro5, Seock-Ah Im6, Yong Sik Jung7, Jung Han Yoon8, Min Hee Hur9, Yoon Ji Choi10, Soo-Jung Lee11, Joon Jeong12, Se-Heon Cho13, Sung Yong Kim14, Min Hyuk Lee15, Lee Su Kim16, Byung-In Moon17, Tae Hyun Kim18, Chanheun Park19, Sei Joong Kim20, Sung Hoo Jung21, Heungkyu Park22, Geum Hee Gwak23, Sun Hee Kang24, Jong Gin Kim25, Jeryong Kim26, Su Yun Choi27, Cheol-Wan Lim28, Doyil Kim29, Youngbum Yoo30, Young-Jin Song31, Yoon-Jung Kang32, Sang Seol Jung33, Hyuk Jai Shin34, Kwan Ju Lee35, Se-Hwan Han36, Eun Sook Lee37, Wonshik Han38, Hee-Jung Kim39 and Woo Chul Noh1*

Abstract

Background: Ovarian function suppression (OFS) has been shown to be effective as adjuvant endocrine therapy in premenopausal women with hormone receptor-positive breast cancer. However, it is currently unclear if addition of OFS to standard tamoxifen therapy after completion of adjuvant chemotherapy results in a survival benefit. In 2008, the Korean Breast Cancer Society Study Group initiated the ASTRRA randomized phase III trial to evaluate the efficacy of OFS in addition to standard tamoxifen treatment in hormone receptor-positive breast cancer patients who remain or regain premenopausal status after chemotherapy.

Methods: Premenopausal women with estrogen receptor-positive breast cancer treated with definitive surgery were enrolled after completion of neoadjuvant or adjuvant chemotherapy. Ovarian function was assessed at the time of enrollment and every 6 months for 2 years by follicular-stimulating hormone levels and bleeding history. If ovarian function was confirmed as premenopausal status, the patient was randomized to receive 2 years of goserelin plus 5 years of tamoxifen treatment or 5 years of tamoxifen alone. The primary end point will be the comparison of the 5-year disease-free survival rates between the OFS and tamoxifen alone groups. Patient recruitment was finished on March 2014 with the inclusion of a total of 1483 patients. The interim analysis will be performed at the time of the observation of the 187th event.

(Continued on next page)
Discussion: This study will provide evidence of the benefit of OFS plus tamoxifen compared with tamoxifen only in premenopausal patients with estrogen receptor-positive breast cancer treated with chemotherapy.

Trial registration: ClinicalTrials.gov Identifier NCT00912548. Registered May 31 2009. Korean Breast Cancer Society Study Group Register KBCSG005. Registered October 26 2009.

Keywords: Ovarian function suppression, Goserelin, Tamoxifen, Adjuvant endocrine therapy, Premenopause, Breast cancer

Background
Many prospective randomized trials have shown that adjuvant endocrine therapy, such as with tamoxifen or ovarian function suppression (OFS), provides a disease-free survival benefit for young patients with hormone receptor-positive breast cancer [1–3]. However, there is insufficient information whether adding OFS to standard tamoxifen treatment for premenopausal patients is an effective therapy in reducing disease recurrence.

Premenopausal breast cancer patients with hormone receptor-positive disease have a worse prognosis than postmenopausal breast cancer patients with hormone receptor-positive disease [4, 5]. This difference in survival may be due to tamoxifen resistance in premenopausal women [5]. Theoretically, the combination of OFS and tamoxifen therapy could overcome tamoxifen resistance in premenopausal women. However, in the absence of clinical evidence of a definitive survival benefit associated with OFS plus standard tamoxifen therapy, additional toxicities from OFS treatment complicate recommendation of this treatment regimen. Therefore, it is important to identify patients most likely to benefit from additional OFS treatment.

The results of the Suppression of Ovarian Function Trial (SOFT), a randomized, phase 3 trial conducted by The International Breast Cancer Study Group (IBCSG), showed no significant benefit from the addition of ovarian suppression to tamoxifen in overall patients [6]. However, in women who remained premenopausal and were at sufficient risk of recurrence to warrant adjuvant chemotherapy, the addition of OFS improved disease outcomes. In SOFT, ovarian function was assessed by serum E2 measurement just one time within 8 months after chemotherapy regardless of menstruation. However, it is assumed that examination at only one time point may be insufficient to evaluate ovarian function after chemotherapy. The patients who regain ovarian function later may lose the chance to benefit from the addition of ovarian suppression treatment. The patients who regain ovarian function later may lose their chance to benefit from the addition of ovarian suppression treatment. As there is no standard method to predict the resumption of ovarian function at the time of chemotherapy completion, we decided to evaluate ovarian function repeatedly for 2 years.

The Korean Breast Cancer Society Study Group has designed and initiated a randomized phase III trial comparing OFS plus tamoxifen versus tamoxifen only after chemotherapy in young women with estrogen receptor-positive breast cancer (ASTRRA); participants include those with premenopausal status or those who have regained ovarian function after the completion of neoadjuvant or adjuvant chemotherapy. The primary objective of this study is to compare the 5-year disease-free survival rates between the two groups.

Methods/design
Study design and setting
ASTRRA is a phase III open-label, prospective, randomized, multicenter investigator initiated clinical trial. The trial was designed to evaluate the combination of 2 years of goserelin plus 5 years of tamoxifen (OFS group) versus 5 years of tamoxifen alone (tamoxifen alone group) as adjuvant endocrine therapy according to ovarian function after the completion of neoadjuvant or adjuvant chemotherapy in patients with estrogen receptor-positive breast cancer. The Korean Breast Cancer Society Study Group coordinates the trial, and the Steering Committee oversees the trial. The institutional review board of Korea Cancer Center Hospital was approved the protocol version 1.3 [K-0902-004-009]. The study protocol was approved by each institutional review board of all participating centers as well. Table 1 shows the list of participating centers. All patients provided written informed consent before enrollment.

Patients
The trial enrolled premenopausal women ≤ 45 years of age with histologically confirmed estrogen receptor-positive, stage I–III, primary invasive breast cancer treated with definitive surgery and chemotherapy. Premenopausal status for inclusion criteria was defined as having a regular menstruation history at the time of diagnosis. Estrogen receptor positivity was determined as expression of estrogen receptor in at least 10% of tumor cells as determined by immunohistochemistry or 10 fmol/mg cytosol protein as determined by a dextran-coated charcoal ligand binding assay.

Receipt of neoadjuvant or adjuvant chemotherapy was required, and the standard regimens were allowed except...
CMF. Adjuvant trastuzumab therapy for patients with human epidermal growth factor receptor-2-positive disease was permitted, although it was not considered as chemotherapy. We excluded patients with other primary malignancies within the last 5 years, except for adequately treated in situ carcinoma of the cervix, basal cell carcinoma, or squamous cell carcinoma of the skin. In addition, patients with thrombocytopenia, those currently treated with anti-coagulant agents, and patients that were pregnant, lactating, or treated with investigational drugs within the previous 4 weeks before baseline assessment were excluded.

**Study design**

The first screening test to evaluate ovarian function was performed within 3 months of the final dose of chemotherapy. Premenopausal status at the first screening test was defined by serum follicular stimulating hormone (FSH) levels < 30 mIU/ml. At 6, 12, 18, and 24 months following the baseline assessment, ovarian function status is to be evaluated by menstruation status and serum FSH levels. Regaining premenopausal status is defined by FSH levels < 30mIU/ml or bleeding history within 6 months of each visit. Study visits will be every 6 months for 5 years and at least yearly thereafter, according to each institute's routine practice. If the patient does not regain satisfy the definition of being premenopausal during the 24 months after enrollment, the patient will be categorized to the permanent menopause group (group A). At each visit, newly confirmed premenopausal patients will be randomly assigned in a 1:1 ratio to the OFS group (group C or group E) or the tamoxifen alone group (group B or group D). The OFS group is treated with 3.6 mg subcutaneous injection goserelin (Zoladex® [D-Ser(But)6 Azgly10 luteinizing-hormone-releasing hormone]; AstraZeneca) every 28 days for 2 years plus oral tamoxifen at a dose of 20 mg daily for 5 years. The tamoxifen only group is treated with oral tamoxifen at a dose of 20 mg daily for 5 years. Randomization is performed by means of an internet-based system and is stratified according to lymph node status (negative versus positive) and institutes (Fig. 1). Data are collected and stored in a digital case report form.

**Primary and secondary end points**

The primary end point is to compare the 5-year disease-free survival rates between the OFS and tamoxifen alone groups, particularly among patients with premenopausal status (assessed every 6 months for 2 years) after the completion of chemotherapy. Disease-free survival is defined as the time from enrollment to the detection of invasive recurrence of breast cancer (local, regional, or distant metastasis), contralateral breast cancer, secondary malignancy, or death without breast cancer recurrence. Patients who are still alive without any event at the time of the analysis will be censored.

Secondary end points are (1) to compare overall survival rates between groups, (2) to compare 5-year
disease-free survival rates between postmenopausal patients treated with tamoxifen and premenopausal patients treated with OFS plus tamoxifen, (3) to determine the tolerability of tamoxifen with or without goserelin.

**Sample size calculation and statistics**
Planned enrollment was at least 1234 patients. Initially, the design projected that 2 years of accrual, plus 5 years of additional follow-up would be sufficient to observe the target of 374 disease-free survival events across the two treatment arms, with 85% power to detect 7% reduction in hazard with OFS plus tamoxifen versus tamoxifen alone. In 2010, because of a slower-than-expected enrollment rate, the steering committee extended the accrual period from 2 years to 4 years.

An intent-to-treatment analysis and per-protocol analysis will be performed. The disease-free survival rate will be evaluated using the Kaplan-Meier method. The log-rank test will be used to compare the treatment groups. Multivariate analyses will be performed using Cox’s proportional hazards model.

**Trial progress**
Recruitment was closed on March 2014. Between March 2009 and March 2014, 1485 patients were screened, and 1483 patients from 35 institutes in South Korea were enrolled in this study. On January 12 2015, 634 patients were randomized to the OFS group, and 655 patients were randomized to the tamoxifen only group (Table 2). Eighty patients were classified as permanent menopause status. Another 114 patients continue to exhibit a status of chemotherapy-induced amenorrhea, and the ovarian function of these patients is being evaluated every 6 months. All of the patients received chemotherapy before randomization. Node-positive disease was present in 56.3% of the patients. The first interim analysis will be performed when 50% of the planned disease-free survival events (187 events) have occurred.

**Discussion**
In South Korea, 48.7% of newly diagnosed breast cancer patients in 2011 were premenopausal and less than 50 years of age [7]. Although the total number of patients is smaller than that of western countries, the rate of premenopausal patients is higher in South Korea. The Korean Breast Cancer Society has been focused on developing optimal tailored therapy for these patients because of the relatively higher proportion of premenopausal patients in the Korean breast cancer patient population. In 2008, the Korean Breast Cancer Society Study Group initiated the ASTarra trial to answer the following questions: (1) whether disease free survival benefits could be achieved with the addition of OFS to standard 5-year tamoxifen treatment after the completion of neoadjuvant or adjuvant chemotherapy in premenopausal young women with estrogen receptor-positive disease, and (2) whether delayed OFS treatment could reduce disease recurrence in patients with recovered ovarian function who experienced chemotherapy-induced amenorrhea and who were treated with standard tamoxifen therapy.

Results from phase III trials including OFS, as well as a meta-analysis of these trials, might help to advance current knowledge of the survival advantage gained with addition of OFS to standard 5-year tamoxifen treatment after the completion of neoadjuvant or adjuvant chemotherapy in premenopausal young women with estrogen receptor-positive disease, and (2) whether delayed OFS treatment could reduce disease recurrence in patients with recovered ovarian function who experienced chemotherapy-induced amenorrhea and who were treated with standard tamoxifen therapy.
of which were treated with chemotherapy, all participants in the ASTRRA trial received neoadjuvant or adjuvant chemotherapy before enrollment. Thus, ASTRRA trial focuses more on the role of OFS after completing chemotherapy. Third, ovarian function was assessed only one time (based on estradiol levels) at the time of randomization in the SOFT trial, within 8 months after completing chemotherapy. However, resumption of ovarian function occurs in about 60% of women younger than 45 years of age within 2 years after completing chemotherapy [16, 17]. We assume that patients who recently regained ovarian function may lose the chance to benefit from the addition of OFS treatment. Therefore,

| Table 2 Demographics of randomized patients |
|-------------------------------------------|
| Demographics of randomized patients        |

|                         | Tamoxifen only group (B + D group, N = 655) | Ovarian function suppression group (C + E group, N = 634) | P-value |
|-------------------------|--------------------------------------------|----------------------------------------------------------|---------|
| Age (mean, years)       | 39.7 ± 4.1                                 | 39.6 ± 4.1                                               | 0.580   |
| Stage                   |                                            |                                                          |         |
| I                       | 178 (27.2 %)                               | 169 (26.7 %)                                             | 0.977   |
| II                      | 335 (51.1 %)                               | 332 (52.4 %)                                             |         |
| III                     | 121 (18.5 %)                               | 113 (17.8 %)                                             |         |
| Unidentified            | 21 (3.2 %)                                 | 20 (3.2 %)                                               |         |
| Lymph node status       |                                            |                                                          |         |
| Negative                | 279 (42.6 %)                               | 275 (43.4 %)                                             | 0.927   |
| Positive                | 371 (56.6 %)                               | 355 (56.0 %)                                             |         |
| Unidentified            | 5 (0.8 %)                                  | 4 (0.6 %)                                                |         |
| Histology               |                                            |                                                          |         |
| Invasive ductal carcinoma | 573 (87.5 %)                           | 560 (88.3 %)                                             | 0.917   |
| Invasive lobular carcinoma | 32 (4.9 %)                                | 26 (4.1 %)                                               |         |
| Others                  | 42 (6.4 %)                                 | 41 (6.5 %)                                               |         |
| Unidentified            | 8 (1.2 %)                                  | 7 (1.1 %)                                                |         |
| Histologic grade        |                                            |                                                          |         |
| G1                      | 95 (14.5 %)                                | 118 (18.6 %)                                             | 0.229   |
| G2                      | 359 (54.8 %)                               | 323 (50.9 %)                                             |         |
| G3                      | 160 (24.4 %)                               | 151 (23.8 %)                                             |         |
| Unidentified            | 41 (6.3 %)                                 | 42 (6.6 %)                                               |         |
| Chemotherapy regimen    |                                            |                                                          |         |
| Anthracycline + cyclophosphamide | 184 (28.1 %)                             | 185 (29.2 %)                                             | 0.782   |
| Anthracyline + cyclophosphamide followed by taxane | 324 (49.5 %) | 318 (50.2 %) |         |
| Anthracyline + taxane   | 30 (4.6 %)                                 | 29 (4.6 %)                                               |         |
| 5-Fluorouracil + anthracyline + cyclophosphamide | 74 (11.3 %)                              | 73 (11.5 %)                                              |         |
| Others                  | 21 (3.2 %)                                 | 14 (2.2 %)                                               |         |
| Unidentified            | 22 (3.4 %)                                 | 15 (2.4 %)                                               |         |
| Operation               |                                            |                                                          |         |
| Total mastectomy        | 268 (40.9 %)                               | 248 (39.1 %)                                             | 0.762   |
| Breast conserving surgery | 382 (58.3 %)                           | 382 (60.3 %)                                             |         |
| Unidentified            | 5 (0.8 %)                                  | 4 (0.6 %)                                                |         |
in the ASTRRA trial, ovarian function will be evaluated by menstruation history or FSH levels every 6 months from the time of enrollment for at least 2 years. Until now, 1286 (86.7%) patients in the ASTRRA trial are premenopausal or have regained premenopausal status after chemotherapy, and only 80 (5.4%) patients have been classified to the permanent menopausal group after 2 years of observation. Examination at only one time point may thus be insufficient to evaluate ovarian function after chemotherapy.

The proportion of patients with regained ovarian function is slightly higher in the ASTRRA trial than in other reports. This might be caused by the exclusion of patients treated with CMF regimens [16, 17]. Because most patients treated with CMF do not recover from chemotherapy-induced amenorrhea, we excluded patients who had received the CMF regimen [8, 16, 17]. In contrast to the CMF regimen, modern non-CMF chemotherapy regimens result in less permanent amenorrhea after treatment. The NSABP B-30 trial assessed menstrual status after various non-CMF chemotherapy regimens at baseline and every 6 months over 24 months. The incidence of amenorrhea 12 months after random assignment was 69.8% for sequential doxorubicin and cyclophosphamide followed by docetaxel, 57.7% for concurrent docetaxel-doxorubicin-cyclophosphamide, and 37.9% for concurrent docetaxel-doxorubicin (P < 0.001) [18]. Although CMF is an effective chemotherapy regimen for breast cancer patients, use of the CMF regimen in young patients is currently decreasing in South Korea. Thus, we believe that the removal of the CMF regimen from the trial’s acceptable chemotherapy regimen list is compatible with recent trends in the care of young women with breast cancer. Another reason for the high rate of ovarian function resumption in the ASTRRA trial would be the relatively young age of participants. The NSABP B-30 trial showed that age is significantly related to the incidence of chemotherapy-induced amenorrhea [18].

The important advantage of the ASTRRA trial study design is the repeated evaluation of ovarian function. The longitudinal evaluation of ovarian function may help to select the most appropriate patients to receive additional OFS treatment, thereby avoiding unnecessary side effects. OFS causes menopausal symptoms and bone mass loss [19, 20]; menopausal symptoms, such as vasomotor symptoms, vaginal dryness, vaginal discharge, anxiety, depression, or sleep disturbances, significantly affect quality of life [19]. Sometimes these symptoms result in low compliance or destroy the physician-patient relationship. Because there is yet no reliable biomarker to select patients most likely to benefit from OFS, continuous checking of ovarian function may facilitate this patient selection.

Currently, the ASTRRA trial has closed to accrual, with a total 1483 enrolled patients. Through the ASTRRA trial, we can determine optimal endocrine therapy based on real-time ovarian function status for each premenopausal breast cancer patient with estrogen receptor-positive disease who received neoadjuvant or adjuvant chemotherapy.

**Ethics approval and consent to participate**

The institutional review board of Korea Cancer Center Hospital was approved the protocol [K-0902-004-009]. The study protocol was approved by each institutional review board of all participating centers as well (Table 1).

**Consent for publications**

Not applicable.

**Availability of data and materials**

The dataset supporting the conclusions of this article will is not available until the final report of this trial to avoid bias on the analysis.

**Abbreviations**

CMF: cyclophosphamide, methotrexate, and fluorouracil; FSH: follicular stimulating hormone; IBCSG: International Breast Cancer Study Group; OFS: ovarian function suppression; SOFT: suppression of ovarian function trial.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

HK and WN drafted the manuscript. SA, SN, SP, JR, SI, YJ, PY, MH, YC, SL, JJ, SC, SK, ML, UK, BM, TK, CP, SK, SJ, HP, GG, SK, JK, JK, SC, CL, DK, YY, YS, YK, SJ, HS, KL, SH, EL, WH, and HK have made substantial contribution to design this study. All authors have reviewed the manuscript and given final approval to be published.

**Acknowledgements**

We thank all the patients who participated in this trial, the participating investigators and Korean Breast Cancer Study Group. The following list of name show the investigators who contributed this study by making substantial contributions to acquisition of data: Byung Ho Son1, Beom Seok Ko2, Jong-Han Yu3, Jong Won Lee4, Jeong Eon Lee5, Se Kyung Lee6, Min-Ki Seong7, Jangmoo Byeon8, Yeun-Ju Sohn9, Seung Il Kim10, Han-Sung Kang11, In Hae Park12, Seeyoun Lee13, So-Youn Jung14, Dong Young Noh15, Eun Ha Kim16, Do Young Oh17, Sae-Won Han18, Kyung-Hun Lee19, Tae-Yong Kim20, Min Ho Park21, Sung-Soo Kang22, Hae Kyung Lee23, Seung Sang Ko24, Chan-Seok Yoon25, Kyong Hwa Park26, Su-Hwan Kang27, Mi-Ri Lee28, Sun-wook Han29, Jihyoun Lee30, Youn Ok Lee31, An-bok Lee32, Young Up Choi33, Hyun Jo Youn34, Seon Kwang Kim35, Jiyoung Cho36, Ki-Tae Hwang37, Jin-Sun Lee38, Young Jin Choi39, Seol-Gi Lee40, Byung Joo Chae41, Hyun Jung Choi42, Wan Sung Kim43.

**Author details**

1Department of Surgery, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Sciences, Seoul, Republic of Korea. 2Department of Surgery, University of Ulsan, Asan Medical Center, Seoul, Republic of Korea. 3Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of medicine, Seoul, Republic of Korea. 4Department of Surgery, Yonsei University College of Medicine, Seoul, Republic of Korea. 5Center for Breast Cancer, National Cancer Center, Goyang, Republic of Korea. 6Department of Internal Medicine, Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea. 7Department of Surgery, Ajou University, School of Medicine, Suwon, Republic of Korea. 8Department of Surgery, Chonnam National University Hwasun Hospital, Gwangju, Republic of Korea. 9Department of Surgery, Cheil General Hospital and Women’s Healthcare Center, Dankook University College of Medicine, Seoul, Republic of Korea. 10Department of Internal Medicine, Korea University Anam Hospital, Seoul, Republic of Korea. 11Department of Internal Medicine, Korea University Anam Hospital, Seoul, Republic of Korea.
11Department of Surgery, Yeungnam University Hospital, Daegu, Republic of Korea. 12Department of Surgery, Gunnam Severance Hospital, Yonsei University, Seoul, Republic of Korea. 13Department of Surgery, Dong-A University Hospital, Busan, Republic of Korea. 14Department of Surgery, Soochunhyang University College of Medicine, Cheonan Hospital, Cheonan, Republic of Korea. 15Department of Surgery, Soochunhyang University College of Medicine, Seoul, Republic of Korea. 16Division of Breast & Endocrine Surgery, Hallym University Sacred Heart Hospital, College of Medicine, Hallym University, Anyang, Republic of Korea. 17Department of Surgery, Mokdong Hospital, Ewha Womans University, Seoul, Republic of Korea. 18Department of Surgery, Inje University Busan Paik Hospital, Busan, Republic of Korea. 19Department of Surgery, Sungkyunkwan University School of Medicine, Kangbuk Samsung Hospital, Seoul, Republic of Korea. 20Department of Surgery, Inha University Hospital, Inha University, Incheon, Republic of Korea. 21Department of Surgery, Chonbuk National University Medical School, Jeonju, Republic of Korea. 22Department of Breast Surgery, Gachon University Gil Hospital, Incheon, Republic of Korea. 23Department of Surgery, Inje University Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Republic of Korea. 24Department of Surgery, Keimyung University School of Medicine, Daegu, Republic of Korea. 25Departments of Surgery, Seoul National University Boramae Medical Center, Seoul, Republic of Korea. 26Department of Surgery, Chungnam National University Hospital, Daejeon, Republic of Korea. 27Department of Surgery, Kangdong Sacred heart hospital, Hallym university, Seoul, Republic of Korea. 28Department of Surgery, Soochunhyang University College of Medicine, Bucheon Hospital, Bucheon, Republic of Korea. 29Department of Surgery, Kangseo Mizmedi Hospital, Seoul, Republic of Korea. 30Department of Surgery, Konkuk University School of Medicine, Seoul, Republic of Korea. 31Department of Surgery, Chungbuk National University College of Medicine and Medical Research Institute, Cheongju, Republic of Korea. 32Department of Surgery, Eulji University Hospital, Daejeon, Republic of Korea. 33Department of Surgery, Seoul St. Mary’s Hospital, Medical College of The Catholic University of Korea, Seoul, Republic of Korea. 34Breast and thyroid care center, Department of Surgery, Myongji Hospital, Goyang, Republic of Korea. 35Department of Surgery, Daejeon St. Mary’s Hospital, The Catholic University of Korea, Daejeon, Republic of Korea. 36Department of Surgery and Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea.

Received: 24 March 2015 Accepted: 11 May 2016

Published online: 19 May 2016

References

1. Fisher B, Dignam J, Bryant J, DeCillis A, Wickerham DL, Wolmark N, et al. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. J Natl Cancer Inst. 1996;88:1529–42.

2. Early Breast Cancer Trialists’ Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival of an overview of the randomised trials. Lancet. 2005;365:1687–717.

3. Fisher B, Jeong J, Bryant J, Anderson S, Dignam J, Fisher ER, et al. Treatment of lymph-node-negative, oestrogen-receptor-positive breast cancer: long-term findings from National Surgical Adjuvant Breast and Bowel Project randomised clinical trials. Lancet. 2004;364:858–68.

4. Fowble BL, Schultz DJ, Overmoyer B, Solin LJ, Fox K, Jardines L, et al. Influence of young age on outcome in early stage breast cancer. Int J Radiat Oncol Biol Phys. 1994;30:23–33.

5. Ahn SH, Son BH, Kim SW, Kim SJ, Jeong J, Ko SS, et al. Poor outcome of adjuvant hormone receptor-positive breast cancer patients with young age: is it due to tamoxifen resistance? nationwide survival data in Korea—a report from the Korean Breast Cancer Society. J Clin Oncol. 2007;25:2360–8.

6. Francis PA, Regan MM, Fleming GF, Lang J, Cibas ES, Gnant M, et al. Adjuvant ovarian suppression in premenopausal patients with hormone-responsive breast cancer. N Engl J Med. 2015;372:436–46.

7. Kim Z, Min SY, Yoon CS, Lee HJ, Lee JS, Youn HY, et al. The basic facts of Korean breast cancer in 2011: results of a nationwide survey and breast cancer registry database. J Breast Cancer. 2014;17:99–106.

8. Jakobs H, Hausmaninger H, Cubilla A, Gnant M, Moisko M, et al. Adjuvant chemotherapy followed by goserelin compared with either modality alone: the impact on amenorrhea, hot flashes, and quality of life in premenopausal patients—the International Breast Cancer Study Group Trial. Breast Cancer Res Treat. 2007;100:251–63.

9. LHRH-agonists in Early Breast Cancer Overview Group. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. Lancet. 2007;369:1711–23.

10. Pagani O, Regan MM, Walley BA, Fleming GF, Colloni M, Läng J, Gomez HL. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med. 2014;371:107–18.

11. Jankowitz RC, McGuire WP, Davidson NE. Optimal systemic therapy for premenopausal women with hormone receptor-positive breast cancer. Breast. 2013;22 Suppl 2:S5–67.

12. Grant M, Milner-Thomson L, Stoeger H, Luschin-Ebengreuth G, Knaur M, Moisko M, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up of the ABCSG-12 randomised trial. Lancet. 2011;377:31–41.

13. Davidson NE, Doherty GM, Osborne CK, Martino S, White DR, et al. Exemestane and adjuvant tamoxifen in postmenopausal women with estrogen receptor-positive, node-negative breast cancer: results from the ATAC trial. J Natl Cancer Inst. 2005;97:1814–25.

14. Jankowitz RC, McGuire WP, Davidson NE. Optimal systemic therapy for premenopausal women with hormone receptor-positive breast cancer. Breast. 2013;22:1094–100.

15. Kim H, Shin D, Moon N, Paik N, Noh W. The incidence of chemotherapy-induced amenorrhea and recovery in young (<45-year-old) breast cancer patients. J Breast Cancer. 2009;12:206–10.

16. Petrek JA, Naughton MJ, Case LD, Paskett ED, Naftals EZ, Singletary SE, et al. Incidence, time course, and determinants of menstrual bleeding after breast cancer treatment: a prospective study. J Clin Oncol. 2006;24:1045–51.

17. Ganj PA, Land SR, Geyer JR, et al. Menstrual history and quality-of-life outcomes in women with node-positive breast cancer treated with adjuvant therapy on the NSABP B-30 trial. J Clin Oncol. 2011;29:1106–10.

18. Nystedt M, Berglund G, Bolund C, Fernander T, Rutqvist LE. Side effects of adjuvant endocrine treatment in premenopausal breast cancer patients: a prospective randomized study. J Clin Oncol. 2003;21:1836–44.

19. Ganj PA, Land SR, Geyer JR, et al. Menstrual history and quality-of-life outcomes in women with node-positive breast cancer treated with adjuvant therapy on the NSABP B-30 trial. J Clin Oncol. 2011;29:1106–10.

20. Nystedt M, Berglund G, Bolund C, Fernander T, Rutqvist LE. Side effects of adjuvant endocrine treatment in premenopausal breast cancer patients: a prospective randomized study. J Clin Oncol. 2003;21:1836–44.

21. Ganz PA, Land SR, Geyer JR, et al. Menstrual history and quality-of-life outcomes in women with node-positive breast cancer treated with adjuvant therapy on the NSABP B-30 trial. J Clin Oncol. 2011;29:1106–10.