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Hormonal suppression in premenopausal patients with estrogen receptor-positive breast cancer: a randomized trial comparing monthly *versus* trimonthly GnRH analogs

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ABSTRACT

Background: Currently the standard of care for premenopausal women with estrogen receptor-positive breast cancer is the combined use of a gonadotropin-releasing hormone (GnRH) analog with either tamoxifen or an aromatase inhibitor in patients at high risk for relapse or when it is deemed necessary to optimize ovarian function suppression. Monthly GnRH analogs have been used for years but, recently, longer-acting formulations have been gaining approval. Yet, there is still a gap of evidence regarding the use of longer-acting formulations; only a few studies exist that examine their efficacy in breast cancer and compare them to the monthly formulations. It is the investigators' hypothesis that trimonthly injections, which are more convenient for the patient and ensure better compliance, are better suited for use in breast cancer patients and may induce equally effective estrogen suppression as the monthly injections. *Aim:* A comparison of trimonthly *versus* monthly GnRH analogs in eliciting ovarian function suppression in premenopausal patients with estrogen receptor-positive breast cancer. *Methodology:* This is a prospective randomized open-label trial involving 25 premenopausal patients that were randomized to receive either a monthly or a trimonthly GnRH analog. Estrogen (E2) levels, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels were measured on day 0 and on week 12. Patients, also, completed a questionnaire regarding exhibiting amenorrhea and other side-effects of the analogs. *Results:* All patients (N=25; 100%) from both groups achieved ovarian function suppression according to the criteria set by the researchers, which are E2 levels <30 pg/mL and amenorrhea. Both groups exhibited a statistically significant decrease (almost by 50%) in E2 levels by week 12 (monthly group: E2 levels' decrease equal to -18.5 pg/mL, p=0.00293; trimonthly group: E2 levels' decrease equal to -13.9 pg/mL, p=0.0002441). On the contrary, FSH and LH levels did not show a statistically significant difference in either group. Moreover, when the two groups were compared, there was no statistically significant difference in the variation of all hormone levels between day 0 and week 12. All patients developed amenorrhea. There were no statistically significant differences in the number of side-effects between the two groups, even though the trimonthly group had fewer (in absolute number) side-effects than the monthly. *Conclusion:* This study demonstrates that the trimonthly formulations of GnRH analogs are equally effective in eliciting ovarian function suppression and present a similar percentage of side-effects as the monthly formulations, with the added benefit that patients need not undergo monthly injections.

KEYWORDS

breast cancer, GnRH analogs, premenopausal status, ovarian suppression, trimonthly injection

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1. INTRODUCTION

Breast cancer has become the most commonly diagnosed cancer, accounting for 1 in 8 cancer diagnoses. In 2020, 2.3 million cases were diagnosed globally and 685,000 women died of it [1]. According to Eurostat, breast cancer incidence in Europe is estimated to be 144/100,000, with Northern and Western European countries exhibiting the highest rates. Greece is estimated to have an incidence of 122.3/100,000 [2]. Similarly, according to the American Cancer Society, breast cancer incidence in the United States is 128.1/100,000 [3]. Various predisposing factors have been identified; the most important are older age, hormonal status, nulliparity, hormone replacement therapy, family history of breast cancer, atypical ductal and lobular hyperplasia, exposure to ionizing radiation, alcohol consumption, smoking, and obesity [4]. Of all breast cancer cases, only 10% or even less are hereditary and are most often associated with mutations in the BRCA1 and BRCA2 genes, as well as the TP3 and PTEN genes [5]. For staging, which is the most important prognostic factor, the TNM classification has been adapted [6]; it is comprised of the assessment of the primary tumor size (T), the condition of the axillary lymph nodes (N), and the presence of a distant metastasis (M). Features such as the expression of steroid receptors (estrogen, progesterone), the human epidermal growth factor receptor 2 (HER-2), and the cellular proliferation index Ki67 are also taken into account, especially when planning treatment [7,8]. Treatment must be individualized and may involve surgery, radiotherapy, chemotherapy, hormonal and monoclonal antibody therapy or, most commonly, a combination thereof.

Currently the standard of care for premenopausal women with estrogen receptor-positive breast cancer is the combined use of a gonadotropin-releasing hormone (GnRH) analog and either tamoxifen or an aromatase inhibitor in patients at high risk for relapse or when it is deemed necessary to optimize the ovarian function suppression (OFS) [9,10]. For many years, it has been the monthly formulations of GnRH analogs (such as goserelin, triptorelin, and leuprorelin) that were approved for use in hormone-dependent breast cancer. More recently, longer-acting formulations, such as 12-week (trimonthly) and 24-week formulations, have been gaining approval for use in breast cancer in Europe, Asia, and the United States [11]. However, there is still a gap of evidence regarding the use of longer-acting formulations, and only a few studies exist that compare the use of monthly *versus* longer-acting depot injectable forms of GnRH analogs in breast cancer [12-18]. It is the investigators' hypothesis that trimonthly injections, which are more convenient for the patient and ensure better compliance, are better suited for use in breast cancer patients and may induce equally effective estrogen suppression as the monthly injections. Therefore, this study aims to compare the use of monthly GnRH analogs *versus* trimonthly analogs in order to add to the existing knowledge of their use that would ultimately serve to improve the care offered to patients.

2. METHODOLOGY

2.1. Type of study

This is a prospective randomized open-label trial involving 25 patients that have been treated by physicians from the Breast Center of REA Hospital in Athens and the University Hospital of Alexandroupolis, in Greece. It constitutes a "non-inferiority" study comparing monthly and trimonthly GnRH analogs administered to premenopausal patients with estrogen receptor-positive breast cancer. The enrolment in the study and the monitoring of patients were completed in a period of two years (December 15th, 2021 to December 15th, 2023) instead of the original plan of six months, and the number of participants was significantly lower than the goal originally set in the proposed protocol (N=100) due to difficulties in recruitment. As a result of the afore-mentioned deviations from the initial plan, the investigators consider this study to be a "preliminary" study that provides indicative information that may be corroborated by the results of a future larger study.

2.2. Participants and enrolment criteria

Participants were premenopausal females, aged 25-50 years old, with newly diagnosed estrogen-receptor-positive breast cancer, either stage I or II. Premenopausal status was determined by the following criteria: menstruation within the last 12 months or estrogen (estradiol; E2) levels equal or higher than 30 pg/mL. The estrogen level limit that was applied to determine premenopausal status is based on the normal range values employed by the laboratory of REA Hospital. Patients who had undergone prior bilateral oophorectomy or radiotherapy to the ovaries were excluded from the study. Characteristics of the patients such as age, weight, parity, smoking, type of concurrent endocrine therapy (tamoxifen or letrozole or exemestane), type (if any) of offered chemotherapy, HER-2 status, and tumor characteristics were recorded in detail.

2.3. Study design

The participants were randomized on a 1:1 basis into two arms; the group receiving a monthly GnRH analog (triptorelin, 3.75 mg) and the group receiving a trimonthly GnRH analog (triptorelin, 11.25 mg or leuprorelin, 11.25 mg). Each participant was monitored for the duration of 12 weeks. E2, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels were measured on day 0 (before the administration of a GnRH analog for the first time) and at the end of week 12 (before the next injection). By selecting week 12 as the post-injection day of blood check-up, the investigators wished to ascertain that the "flare-up effect" (the transient initial increase in gonadotropin and estrogen levels after the GnRH analog administration) would not confound the results. Upon recruitment, the physicians completed a detailed form of the patients' medical history. At the end of the 12th week, the patients completed a questionnaire regarding the experiencing of menopausal symptoms and known GnRH-analog side-effects: amenorrhea, hot flushes, sweats, insomnia, vaginal dryness, weight increase, breast tenderness, decrease in breast size, decreased libido, headaches, arthralgia, myalgia, constipation, palpitations, nausea, pain at the injection site.

The hypothesis tested is the "non-inferiority" of the trimonthly GnRH analog use in breast cancer *versus* the monthly administration. The primary endpoint of the study was the effectiveness in inducing OFS, which was determined by achieving both amenorrhea and E2 levels lower than 30 pg/mL (a limit based on the reference values for menopause employed by the REA laboratory). Investigators compared the trimonthly *versus* the monthly formulation with regards to the E2 levels' suppression achieved as well as with regards to the difference in the decrease of E2 levels observed on the 12th week. Secondary endpoints were the FSH and LH levels' suppression and the difference between the two groups as well as the comparison of the percentage of patients who experienced each side-effect between the two groups.

2.4. Ethical considerations

All formulations of the GnRH analogs under investigation are currently endorsed by the European Society of Medical Oncology (ESMO) guidelines for concomitant use with tamoxifen or an aromatase-inhibitor in patients with hormone-dependent breast cancer under the condition of regular monitoring of E2 levels. Thus, there is no breach of ethics related to this study.

Patients participated voluntarily, after having been thoroughly informed thereof, and signed a consent form at the time of enrolment. Subjects were clearly informed that choosing against participation would not affect the care received and that they could opt-out of this study at any time they wished. Confidentiality was maintained by all members of the investigation team throughout the study. The protocol of the study, the consent form, the medical history form, and the symptoms' questionnaire were submitted for review and approval at the appropriate institutional department (Ethics Committee, REA Hospital Athens; protocol number: 60; date of approval: October 13th, 2021).

2.5. Statistical analysis

In this study, every statistical analysis was performed by utilizing the R Studio Software (2022.02.3; edition 492). The R Studio is an integrated development environment which works with the R programming language and is used to clean data, calculate descriptive statistics, test hypotheses, and create graphic illustrations of the results.

For the comparisons of E2, FSH, and LH levels between day 0 and week 12, statistical analysis was performed by applying the paired-samples Wilcoxon test (Wilcoxon signed-rank test) (from the R library exactRankTests edition 0.8-35) as the values of E2, FSH, and LH did not follow the normal distribution. In order to compare the difference from day 0 to week 12 in the values of E2, FSH, and LH between the monthly and trimonthly formulations, the following were performed: first, the difference of E2, FSH, and LH levels from day 0 to week 12 was calculated for each participant and, then, the

Wilcoxon signed-rank test was applied. For the comparison of the percentage of patients experiencing each side-effect between the two groups, the Fisher exact test was used (found on the website https://www.socscistatistics.com/tests/fisher/default2.aspx). Statistical significance was determined by using the limit *p*-value of <0.05 for all comparisons.

3. RESULTS

A total of 25 patients participated in this study, 12 of whom were randomized to receive a monthly formulation of GnRH analog (triptorelin at 3.75 mg) and 13 of whom received a trimonthly formulation (o which 9 patients received triptorelin at 11.25 mg and 4 patients received leuprorelin at 11.25 mg).

Table 1. Descriptive statistics of the participants in this study.

Variable	Formulation		Number of patients
Number of patients	Monthly	12	
	Trimonthly	13	Triptorelin = 9
			Leuprorelin = 4
Age in years (standard deviation)	Monthly	46 (5.91)	
	Trimonthly	48.31 (5.56)	
Weight in kg (standard deviation)	Monthly	64.08 (5.53)	
	Trimonthly	65.23 (6.70)	
Smoking	Monthly	Yes	3
		No	9
	Trimonthly	Yes	6
		No	6
Parity (as in number of births)	Monthly	Never	3
		One time	5
		Two times	4
	Trimonthly	Never	3
		One time	3
		Two times	6
		Three times	1
Hormone therapy	Monthly	Tamoxifen	8
		Letrozole	3
		Exemestane	1
	Trimonthly	Tamoxifen	5
		Letrozole	7
		Exemestane	1
Chemotherapy	Monthly	Yes	8
		No	4
	Trimonthly	Yes	10
		No	3
Stage of cancer	Monthly	Stage I	1
		Stage II	11

	Trimonthly	Stage I	11
		Stage II	2
Human epidermal growth factor receptor 2 (HER2)	Monthly	Negative	8
		Positive	4
	Trimonthly	Negative	9
		Positive	4
Ovarian function suppression	Monthly	Yes	12
		No	0
	Trimonthly	Yes	13
		No	0

Table 2. Estrogen (E2), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels on day 0 and week 12 for both monthly and trimonthly formulations of gonadotropin-releasing hormone analogs. The calculated paired-samples Wilcoxon test *p*-value is used in order to evaluate the difference in the mean value of E2, FSH, and LH levels between day 0 and week 12 for each group.

Hormones	**Formulation**	**Mean value at 12 weeks (standard deviation)**	**Mean value on day 0 (standard deviation)**	***p*-value**
E2 (pg/mL)	Monthly	18.1 (6.4)	36.6 (22.5)	0.00293
	Trimonthly	15.2 (7.4)	29.2 (19.6)	0.0002441
FSH (mIU/mL)	Monthly	10.9 (15.4)	4.0 (4.1)	0.4766
	Trimonthly	14.4 (23.4)	5.3 (5.2)	1
LH (mIU/mL)	Monthly	3.2 (3.2)	6.2 (11.5)	0.3296
	Trimonthly	2.2 (2.6)	5.8 (10.2)	0.6714

Descriptive data regarding the participants are presented in Table 1. The mean age of the patients from the monthly group was 46 years and from the trimonthly 48 years. The mean weight of the monthly group was 64 kg and of the trimonthly group 65 kg. Most patients from the monthly group suffered from stage II breast cancer (N=11; 91.6%), whereas most patients from the trimonthly group had been diagnosed with stage I breast cancer (N=11; 84.6%). In both groups, the majority of patients (66.6% from the monthly and 76.9% from the trimonthly) received adjuvant chemotherapy. In both groups, the majority of patients (66.6% from the monthly and 69.2% from the trimonthly) were HER-2 negative. Patient demographics and baseline characteristics were well balanced between the two groups.

The results from the data analysis demonstrate that all patients (N=25; 100%) from both groups achieved OFS according to the criteria set by the researchers, which are E2 levels <30 pg/mL. Table 2 depicts the variation in E2, FSH, and LH levels that was noted between day 0 and week 12 for each group. There is a statistically significant difference in the E2 levels between day 0 and week 12 in both groups. In particular, it is noted that both groups exhibited a statistically significant decrease (almost by 50%) in their E2 levels by week 12 (monthly group: p=0.00293; trimonthly group: p=0.0002441). On the contrary, the FSH and the LH levels did not show a statistically significant difference in either group. Moreover, as shown in Table 3, when the two groups are compared, there is no statistically significant difference in the variation of their E2, FSH, and LH levels between day 0 and week 12.

It is worth noting that the majority of patients from the trimonthly group received triptorelin at 11.25 mg (N=9; 69.2%). When only the triptorelin (at 11.25 mg) subgroup was compared against the triptorelin (at 3.75 mg) group (N=12), the results did not differ from the afore-mentioned results that concern all patients (N=13) from the trimonthly group; all patients on triptorelin at 11.25 mg achieved OFS, and there was no significant difference in the E2, FSH, and LH levels' decrease in the monthly triptorelin *versus* the trimonthly triptorelin group (p>0.05).

At the end of the 12th week, all participants completed a questionnaire with regards to the side- effects experienced due to the GnRH analog use. All patients developed amenorrhea. None exhibited spotting. Table 4 presents the number of patients who exhibited each side-effect in each group. There was no statistically significant difference in the number of side-effects reported between the two groups that are being compared, even though the trimonthly group had fewer in absolute number side-effects than the monthly. Moreover, there was no statistical difference regarding side-effects when the trimonthly triptorelin subgroup was compared to the monthly triptorelin group.

Table 3. The mean value of the difference of estrogen (E2), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels from day 0 to week 12 is depicted, as well as the standard deviation, for each group. The calculated Wilcoxon test *p*-value is used in order to evaluate whether there is statistical significance in the noted differences of hormone levels from day 0 to week 12, when comparing the monthly gonadotropin-releasing hormone analog group *versus* the trimonthly group.

Hormones	**Mean value of difference from day 0 to week 12 – monthly formulation (standard deviation)**	**Mean value of difference from day 0 to week 12 – trimonthly formulation (standard deviation)**	***p*-value**
E2 (pg/mL)	-18.5 (19.7)	-13.9 (19.3)	0.7786
FSH (mIU/mL)	-6.9 (13.7)	-9.1 (20.6)	0.6973
LH (mIU/mL)	-2.9 (10.0)	-3.5 (9.8)	0.7378

Table 4. Number of patients in the monthly and trimonthly formulation groups exhibiting side-effects related to the use of gonadotropin-releasing hormone analogs. The *p*-value depicted is the Fisher exact test *p*-value that facilitates the comparison of the two formulations with regards to the number of patients with each side-effect.

Side-effects	**Number of patients** (N)		***p*-value**
	Monthly formulation (N=12)	**Trimonthly formulation** (N=13)	
Amenorrhea	12	13	0.4283
Hot flushes	5	4	0.6882
Sweats	5	4	0.6882
Insomnia	3	1	0.3217
Vaginal dryness	5	4	0.6882
Breast tenderness	0	3	0.22
Decrease in breast size	1	0	0.48
Weight increase	4	2	0.3783
Decreased libido	5	2	0.2016
Headache	3	2	0.6447
Arthralgia	5	1	0.073
Myalgia	5	3	0.411
Constipation	2	1	0.593
Palpitations	1	1	1
Nausea	0	1	1
Pain at injection site	0	0	1

4. DISCUSSION

A quarter of all breast cancer cases involve women younger than 50-years-old and 5% of them involve patients younger than 35-years-old [4]. In fact, since 2016, a rise in the incidence of breast cancer in the ages 20-49 has been observed, rendering the delineation of evidence-based directives to be

followed by healthcare providers imperative [19]. According to the guidelines of the ESMO [10] and of the American Society of Clinical Oncology (ASCO) [9], young premenopausal women with hormone-dependent breast cancer who are at an increased risk for a recurrence should receive a GnRH analog for OFS, in addition to either tamoxifen or an aromatase inhibitor. These guidelines are based mostly on studies such as the SOFT/TEXT and the SOFT-EST trials [20-22], where the monthly depot injection form was used. For this reason only, it is recommended that the monthly formulation be preferably prescribed, especially to women younger than 35 years and to patients who are on aromatase inhibitors [10]. According to the same guidelines, trimonthly and six-monthly formulations may be administered if the patient wishes to receive them, under the condition that the E2 levels are monitored regularly. In fact, some European countries, such as Italy, are already endorsing or approving the use of trimonthly forms of GnRH analogues such as triptorelin. Expert opinions, as expressed in the guidelines, are recognizing the need to be able to administer the trimonthly formulation when the patient wishes to avoid monthly injections [10]. It has, therefore, been rendered necessary that more studies be conducted in order to evaluate whether the trimonthly formulation is equally effective and safe as the monthly formulation.

A comprehensive search of the PubMed, Cochrane, and Scopus online databases was performed; to our knowledge, only seven studies comparing the monthly and the trimonthly GnRH analogs in hormone-dependent breast cancer have been published until September 2024 [12-18] (Table 5). Thus, our study would constitute the eighth such investigation. Its results are in accordance with six out of the seven previous studies, which concluded that trimonthly formulations can lead to an equally adequate OFS as the monthly. It should be noted, however, that out of the six aforementioned studies, only three were prospective, whereas the rest were retrospective. They all had, though, a large sample of patients and a long time-frame of monitoring, all of which aid in extracting reliable results. Boccardo *et al.* [13] were the first (in 1999) to compare the monthly *versus* the trimonthly formulations of leuprorelin, and discovered no difference in the OFS or the side-effects induced. Masuda *et al*. [17] compared the monthly and trimonthly depot forms of goserelin and proved that the trimonthly was non-inferior in terms of OFS, safety, and tolerability. According to Aydiner *et al.* [12], the effects of monthly goserelin and trimonthly leuprorelin on E2 and FSH levels do not differ significantly; in that study, however, patients had already undergone chemotherapy and had been receiving a GnRH analog for six months by the time the comparison was made. Noguchi *et al.* [18], on the other hand, randomized HER-2-positive premenopausal patients with advanced breast cancer in order to compare the monthly and trimonthly formulations of goserelin; once more, there was no statistical difference in the effect on the E2 levels and in the progression-free survival between the two groups. Kendzierski *et al*. [16] provided a retrospective review that is, also, in accordance with the previous authors. Finally, the most recent retrospective study by Chen *et al.* [14] (in 2024) compared the percentages of ovarian escape (that is failure to achieve OFS), defined by E2 levels higher than 30 pg/mL among three different groups of patients receiving concurrently an aromatase inhibitor: the monthly goserelin group, the monthly leuprorelin group, and the trimonthly leuprorelin group. No statistical difference with regards to ovarian escape was found among the three groups. The only study that detected a difference in OFS between monthly and trimonthly formulations was the retrospective study by Blotta *et al.* [15]; in their study, it was observed that the trimonthly depot form was superior in eliciting OFS (as seen by the decrease in E2 levels). In fact, it should be highlighted that the participants were all under an aromatase inhibitor and, thus, it was of utmost importance that premenopausal patients achieve a menopausal status.

In our study, all patients (100%) exhibited E2 levels lower than 30 pg/mL and amenorrhea, which is not in accordance with the results of previous studies. In fact, according to the relevant literature [20,23-27], a percentage of up to 25% of patients does not achieve sufficient OFS with GnRH analogs. This phenomenon (which is called “ovarian escape”) has been associated, among other factors, with an increased body mass index and an age younger than 35 years. We believe that the difference between our study and the published literature is due to the high mean age of patients in both our groups; most of them were older than 45-years-old, which means that their pretreatment levels were already on the lower side of the premenopausal range (yet, still high enough to necessitate the use of a GnRH analog for OFS). Moreover, it should be highlighted that E2 monitoring guidelines are not available, and no optimal degree of OFS has been established. The E2 levels that are used to define OFS differ greatly among different studies. For instance, the SOFT-EST trial [20] used the strict limit of E2 being <2.72 pg/mL, while other studies have employed the limits of <10, <20, <30, and <40 pg/mL. A stricter E2 limit may result in a higher percentage of detected

ovarian escape. Yet, there are studies that confirm the observed ovarian escape percentage of 25%, despite employing a less strict limit of E2 at <20 pg/mL in their analysis [20,23-27].

Our study presents certain limitations that need to be addressed. First of all, the patient sample (N=25) is small. A larger cohort might have demonstrated a statistical difference in, for instance, the side-effects, the absolute number of which was lower in the trimonthly group. Moreover, the mean age of patients was above 45 years, when the E2 levels are at the lower end of the spectrum for premenopausal women. Ideally, the study should have included a greater number of younger women (at ages <45, <40, and <35 years) so that a stratification by age could have been implemented. It is the authors' suggestion (and intention) that, in the future, a similar study with a larger patient sample be conducted. We believe that a larger trial would confirm the results of this small study and encourage the use of trimonthly depot injections so as to ensure both the safety and comfort of patients.

Table 5. Previous studies comparing the efficacy of different formulations of gonadotropin-releasing hormone analogs in eliciting ovarian function suppression (OFS).

Study	**Study type**	**Total sample size**	**Compared analogs**	**Hormone therapy**	**Estrogen limit for OFS** (in pg/mL)	**Result (as to OFS)**
Boccardo *et al.* (1999) [13]	Prospective randomized	50	Monthly *versus* trimonthly leuprorelin	Not indicated	<20	No difference between formulations
Masuda *et al.* (2011) [17]	Prospective randomized	170	Monthly *versus* trimonthly goserelin	Tamoxifen	<30	No difference between formulations
Aydiner *et al.* (2013) [12]	Prospective randomized	79	Monthly goserelin *versus* trimonthly leuprorelin	Tamoxifen	<30	No difference between formulations
Noguchi *et al.* (2016) [18]	Prospective randomized	222	Monthly *versus* trimonthly goserelin	Tamoxifen	<30	No difference between formulations
Kendzierski *et al.* (2018) [16]	Retrospective	201	Monthly *versus* trimonthly leuprorelin	Aromatase inhibitor	<40	No difference between formulations
Blotta *et al.* (2023) [15]	Retrospective	88	Monthly *versus* trimonthly goserelin	Aromatase inhibitor	<2.72	Trimonthly goserelin superior
Chen *et al.* (2024) [14]	Retrospective	264	Monthly goserelin *versus* monthly leuprorelin *versus* trimonthly leuprorelin	Aromatase inhibitor	<30	No difference between formulations

5. CONCLUSION

In conclusion, this study demonstrates that the trimonthly formulations of GnRH analogs are equally effective in eliciting OFS (as seen from the laboratory results) and present a similar percentage of side-effects as the monthly formulations, with the added benefit that patients need not undergo monthly injections. These results fortify current knowledge regarding the use of trimonthly formulations in premenopausal patients with estrogen receptor-positive breast cancer, which may improve the range of therapeutic options offered to them.

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CONFLICT OF INTEREST STATEMENT
The authors declare no conflicts of interest.

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