Neoadjuvant Degarelix Versus Triptorelin in Premenopausal Patients Who Receive Letrozole for Locally Advanced Endocrine-Responsive Breast Cancer: A Randomized Phase II Trial

Silvia Dellapasqua, MD[1]; Kathryn P. Gray, PhD[2]; Elisabetta Munzone, MD[1]; Daniela Rubino, MD[3]; Lorenzo Gianni, MD[4]; Harriet Johansson, PhD, MSc[1]; Giuseppe Viale, MD[1]; Karin Ribi, PhD, MPH[5]; Jürg Bernhard, PhD[5]; Roswitha Kammler[5]; Rudolf Maibach, PhD[5]; Manuela Rabaglio-Poretti, MD[5]; Barbara Ruepp, PharmD[5]; Angelo Di Leo, MD, PhD[6]; Alan S. Coates, MD[7]; Richard D. Gelber, PhD[8,9]; Meredith M. Regan, ScD[9]; Aron Goldhirsch, MD[1]; and Marco Colleoni, MD[1], for the International Breast Cancer Study Group

PURPOSE To evaluate endocrine activity in terms of ovarian function suppression (OFS) of degarelix (a gonadotropin-releasing hormone [GnRH] antagonist) versus triptorelin (a GnRH agonist) in premenopausal patients receiving letrozole as neoadjuvant endocrine therapy for breast cancer.

PATIENTS AND METHODS Premenopausal women with stage cT2 to 4b, any N, M0; estrogen receptor and progesterone receptor greater than 50%; human epidermal growth factor receptor 2–negative breast cancer were randomly assigned to triptorelin 3.75 mg administered intramuscularly on day 1 of every cycle or degarelix 240 mg administered subcutaneously (SC) on day 1 of cycle 1 then 80 mg SC on day 1 of cycles 2 through 6, both with letrozole 2.5 mg/day for six 28-day cycles. Surgery was performed 2 to 3 weeks after the last injection. Serum was collected at baseline, after 24 and 72 hours, at 7 and 14 days, and then before injections on cycles 2 through 6. The primary end point was time to optimal OFS (time from the first injection to first assessment of centrally assessed estradiol level ≤ 2.72 pg/mL [≤ 10 pmol/L] during neoadjuvant therapy). The trial had 90% power to detect a difference using a log-rank test with a two-sided α of .05. Secondary end points included response, tolerability, and patient-reported endocrine symptoms.

RESULTS Between February 2014 and January 2017, 51 patients were enrolled (n = 26 received triptorelin plus letrozole; n = 25 received degarelix plus letrozole). Time to optimal OFS was three times faster for patients assigned to degarelix and letrozole than to triptorelin and letrozole (median, 3 v 14 days; hazard ratio, 3.05; 95% CI, 1.65 to 5.65; P < .001). Furthermore, OFS was maintained during subsequent cycles for all patients assigned to receive degarelix and letrozole, whereas 15.4% of patients assigned to receive triptorelin and letrozole had suboptimal OFS after cycle 1 (six events during 127 measurements). Adverse events as a result of both degarelix plus letrozole and triptorelin plus letrozole were as expected.

CONCLUSION In premenopausal women receiving letrozole for neoadjuvant endocrine therapy, OFS was achieved more quickly and maintained more effectively with degarelix than with triptorelin.

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INTRODUCTION

Ovarian function suppression (OFS) was the first form of systemic treatment for advanced breast cancer.[1] Its use as an adjuvant therapy was associated with improved disease-free and overall survivals in patients younger than age 50 years who had breast cancer.[2] Currently, for premenopausal patients with endocrine-responsive breast cancer, OFS is considered an important aspect of treatment in the advanced disease[3] setting and in the adjuvant and neoadjuvant settings.[4]

Gonadotropin-releasing hormone (GnRH) analogs interact with the GnRH receptor and modify release of pituitary gonadotropins. Several GnRH analogs have been developed (eg, triptorelin, goserelin and leuprolide), and there are no apparent differences in their OFS capabilities.[5] Upon administration of GnRH agonists, an initial stimulating action of the hypophysis occurs (flare effect), which eventually causes a sustained decrease in gonadotropin secretion (downregulation) that can be observed after approximately 10 days. For some patients, there can be a delay of 2 to 4 months until downregulation of the gonadotropins occurs. Moreover, approximately 20% of women do not maintain complete OFS with GnRH analogs[6] and experience occasional elevations in estradiol (E2) as a result of sporadic escapes from OFS.

Degarelix (Firmagon; Ferring, Copenhagen, DK) is a GnRH antagonist that binds to and blocks GnRH receptors in the pituitary gland, which results in decreased secretion of gonadotropins. In men, this leads directly to a rapid decrease in the production of testosterone, for which suppression to castration levels is achieved within 1 to 3 days and remains sustained during treatment.[7,8] Degarelix is currently approved for the treatment of prostate cancer. Data are not available for the use of degarelix in patients with breast cancer.

In premenopausal women, suppression of ovarian function with degarelix might be faster than with GnRH analogs and optimally maintained throughout the treatment period. Neoadjuvant endocrine therapy (NET) is an excellent platform for the development of investigational drugs and the exploration of novel combinations that can be developed in other clinical settings.[9]

Limited data are available on NET in premenopausal patients. In the Neoadjuvant Anastrozole Versus Tamoxifen in Patients Receiving Goserelin for Premenopausal Breast Cancer (STAGE) trial, 204 premenopausal women were randomly assigned to receive goserelin 3.6 mg/month plus either anastrozole or tamoxifen for 24 weeks before surgery. More patients in the anastrozole group than in the tamoxifen group had a complete or partial response (70.4% v 50.5%, respectively).[10]

We therefore designed the TREND (Trial on the Endocrine activity of Neoadjuvant Degarelix) trial (International Breast Cancer Study Group [IBCSG] 41-13), an open-label, two-arm, phase II, randomized study, to compare the endocrine activity of triptorelin versus degarelix in premenopausal patients with breast cancer receiving letrozole as NET.

PATIENTS AND METHODS

Patients

Premenopausal women with histologically confirmed stage cT2 to 4b, any nodal stage, M0; estrogen (ER) and progesterone (PgR) receptor expression greater than 50%; human epidermal growth factor receptor 2 (HER2)–negative (by immunohistochemistry and/or in situ hybridization); invasive breast cancer were eligible. Premenopausal status was determined locally as 17-β-estradiol (ie, E2) levels greater than 54 pg/mL (or > 198 pmol/L) measured within 14 days before random assignment. Patients could not have had a prior GnRH analog, a selective ER modulator or aromatase inhibitor (AI) within 12 months before random assignment, or used hormonal treatment (eg, oral, injectable, implanted contraceptive or medicated intrauterine device) in the 2 months before random assignment.

Study Design

Patients were randomly assigned in a 1:1 ratio to receive six 28-day cycles of NET with one of the following: triptorelin 3.75 mg intramuscularly on day 1 of every cycle plus letrozole 2.5 mg/day orally; or degarelix 240 mg subcutaneously given as two subcutaneous injections of 120 mg on day 1 of cycle 1 followed by 80 mg on day 1 of cycles 2 through 6 plus letrozole. Letrozole was started on day 1, concurrent with triptorelin or degarelix. Trial treatments were to start within 14 days of random assignment and could be started at any time during the menstrual cycle. Definitive surgery was performed within 2 to 3 weeks after the last administration of triptorelin or degarelix. After postsurgery evaluation, no additional follow-up data were collected within the trial. Postsurgical treatments were given at the discretion of the investigator. Random assignment was stratified according to age at random assignment (≤ 39 v ≥ 40 years).

Study visits occurred before every 28-day cycle for 6 months and required a physical exam, an Eastern Cooperative Oncology Group performance status, weight, and collection of adverse events (AEs; 31 targeted AEs and other grades 3 to 4 AEs according to Common Terminology Criteria for AEs, version 4.0). Tumor evaluation by bilateral mammography and breast ultrasound and laboratory tests (hematology, chemistry, carcinoembryonic antigen [CEA], cancer antigen 15.3 [CA15.3]) were required at baseline, after three cycles, and before surgery. Data about AEs and concomitant medications were also collected 30 days after surgery. Patients completed the 19-item Functional Assessment of Cancer Therapy, endocrine subscale (FACT-ES) at baseline, on day 1 of cycles 2 and 4, and before surgery.

E2, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels were determined in a central laboratory from serum samples collected at day 1 of the first treatment cycle before the administration of the first dose (baseline), at 24 and 72 hours, 7 days and 14 days after first injection, and on day 1 of cycles 2 through 6. E2 concentrations were measured by gas chromatography tandem mass spectrometry detection after liquid-liquid extraction. Duplicate standard curves, water blanks, and four assay control pools were processed with samples to assess accuracy and precision of the assay. The lower limit of E2 level quantification was 0.625 pg/mL. Central pathology review of diagnostic biopsy and of the residual surgical specimen was mandatory for this trial, but patients were included on the basis of tumor characteristics as determined by the local pathologist.

The primary end point was time to optimal OFS, calculated as the time from the first injection of degarelix or triptorelin until the first occurrence of a centrally assessed E2 level in the range of optimal OFS (≤ 2.72 pg/mL or ≤ 10 pmol/L)[11] during the six cycles of NET. Secondary end points included best overall response according to WHO response criteria,[12] rate of node-negative disease at surgery, rate of breast-conserving surgery (BCS), preoperative endocrine prognostic index (PEPI) score, Ki-67 (protein encoded by

the *MKI67* gene) changes, and patient-reported endocrine symptoms (by FACT-ES summary score).[13]

The trial was conducted in three centers in Italy. The IBCSG coordinated the trial and is responsible for the study design, random assignment, collection and management of data, medical review, data analysis, and reporting. The trial was conducted in accordance with the provisions of the Declaration of Helsinki. The ethics committees at each center approved the study protocol, and all patients provided written informed consent. The IBCSG Data and Safety Monitoring Committee reviewed the trial twice yearly. Ferring donated the study drugs.

Statistical Considerations

Analyses were performed according to the intention-to-treat principle. Kaplan-Meier estimates of the cumulative proportions of patients who achieved optimal OFS were calculated. Cox proportional hazards regression and the log-rank test, stratified according to age, were used to estimate the hazard ratio, 95% CI, and *P* value in a comparison of the time to optimal OFS between the two treatment groups.

The statistical design assumed that the cumulative percentages of patients with optimal OFS by 2, 4, 8, 12, and 16 weeks were 30%, 60%, 75%, 90%, and 100% of patients, respectively, assigned to triptorelin plus letrozole and 60%, 95%, 100%, 100%, and 100% of patients, respectively, assigned to degarelix plus letrozole. With 23 patients per group, the study had 90% power to detect a between-group difference in time to optimal OFS using a two-sample log-rank test (two-sided α = .05). The calculations were performed using nQuery Advisor (Statistical Solutions Ltd. 8 South Bank Crosse's Green Cork, Ireland) for the log-rank test of survival in two groups (simulation with the aforementioned percentages specified). To allow for missing data, the study planned enrollment of 50 patients.

Secondary end points were summarized as the number and percentage of patients or as the median (interquartile range [IQR]) of values by treatment group and/or as between-group differences, and data were reported with CIs. Changes in Ki-67 between pretreatment biopsy and post-treatment surgery were assessed within and between groups using Wilcoxon signed-rank and rank-sum tests, respectively. The analysis of differences in patient-reported FACT-ES summary scores (range, 0 to 76; higher score indicated better function) between treatment groups used linear mixed-effects modeling as a function of postbaseline timepoint and treatment group and controlled for the stratification factors of age (dichotomized as $\leq$ 39 *v* $\geq$ 40 years) and baseline summary score with an autoregressive covariance structure. For each symptom, the proportion of patients who reported a clinically significant symptom level (responses of "quite a bit" or "very much" a problem)[14] at one or more postbaseline time points was summarized with 90% CIs. The analysis used SAS 9.4 (SAS Institute, Cary, NC), and R version 3.3.1.

RESULTS

Study Population

Between February 24, 2014, and January 10, 2017, 51 patients with ER-positive and PgR-positive (ER and PgR > 50%), HER2-negative, invasive breast cancer were randomly assigned (n = 26 assigned to triptorelin plus letrozole; n = 25 assigned to degarelix plus letrozole; Fig 1). The median age of the patients was 44 years (IQR, 42 to 49 years; Table 1). All patients had an Eastern Cooperative Oncology Group performance status of 0, 49% had clinically node-positive disease, and 90% had a ductal histology.

All patients started and completed six cycles of the assigned trial treatment, with the exception of one patient randomly assigned to degarelix plus letrozole who had surgery after three cycles because of progressive disease. Compliance regarding blood draws over time for the enrolled patients was excellent: 502 (99%) of the 507 blood draws required to assess OFS status over time were obtained.

Endocrine Activity

By the end of the first cycle (29 days), all patients reached optimal OFS. OFS was reached significantly faster among patients assigned to degarelix plus letrozole than among those assigned to triptorelin plus letrozole (median, 3 *v* 14 days, respectively; hazard ratio, 3.05); optimal OFS was achieved three times faster with degarelix plus letrozole than with triptorelin plus letrozole (95% CI, 1.65 to 5.65; *P* < .001; Fig 2). Notably, optimal OFS was maintained for all patients assigned degarelix plus letrozole during subsequent cycles, whereas 15.4% of patients assigned triptorelin plus letrozole had suboptimal OFS (E2 level > 2.72 pg/mL) after cycle 1 (0 events with 119 measurements and six events with 127 measurements, respectively; Fig 3; Appendix Table A1, online only; Appendix Fig A1, online
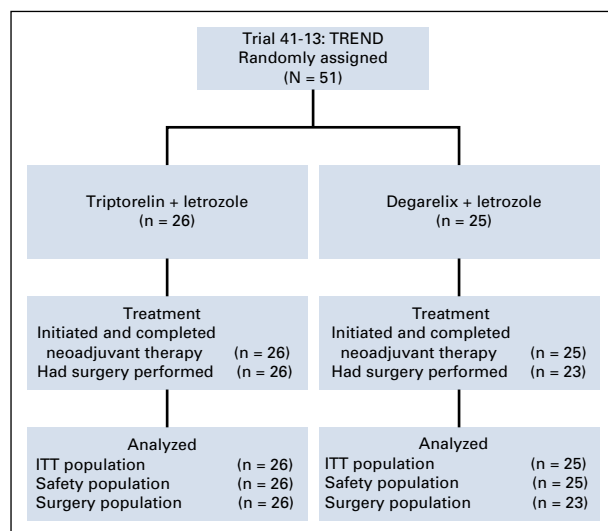
FIG 1. TREND (Trial on the Endocrine Activity of Neoadjuvant Degarelix) CONSORT diagram. ITT, intention to treat.

TABLE 1. Patient and Pretreatment Disease Characteristics According to Treatment Assignment

Characteristic	Treatment Assignment		Total (N = 51)
	Triptorelin + Letrozole (n = 26)	Degarelix + Letrozole (n = 25)	
Age, years			
Median (IQR)	44 (42-48)	45 (42-50)	44 (42-49)
Range	31.0-51.0	26.0-55.0	26.0-55.0
≤ 39	4 (15.4)	2 (8.0)	6 (11.8)
≥ 40	22 (84.6)	23 (92.0)	45 (88.2)
Body-mass index, kg/m²			
Normal (< 25)	15 (57.7)	14 (56.0)	29 (56.9)
Overweight or obese (≥ 25)	8 (30.8)	8 (32.0)	16 (31.4)
Unknown	3 (11.5)	3 (12.0)	6 (11.8)
Prior oral contraceptive use	8 (30.8)	7 (28.0)	15 (29.4)
Smoking status			
Current	2 (7.7)	5 (20.0)	7 (13.7)
Former	3 (11.5)	2 (8.0)	5 (9.8)
Never	21 (80.8)	18 (72.0)	39 (76.5)
E2, pg/mL (assessed centrally)			
Median (IQR)	86 (57-131)	98 (70-194)	94 (65-163)
Range	21.6-250.0	37.8-404.0	21.6-404.0
Histology of biopsy (assessed centrally)			
Ductal	24 (92.3)	22 (88.0)	46 (90.2)
Lobular	1 (3.8)	2 (8.0)	3 (5.9)
Other/unknown	1 (3.8)	1 (4.0)	2 (3.9)
Clinical T stage (by ultrasound)			
T2	24 (96.0)	19 (79.2)	43 (87.8)
T3	1 (4.0)	5 (20.8)	6 (12.2)
Unknown/missing	1	1	2
Clinical N stage			
N0	12 (46.2)	14 (56.0)	26 (51.0)
N1	13 (50.0)	10 (40.0)	23 (45.1)
N2-N3	1 (3.8)	1 (4.0)	2 (4.0)
ER status of biopsy			
Positive (ER > 50%)	26 (100.0)	25 (100.0)	51 (100.0)
PR status of biopsy			
Negative (PgR ≤ 50%)	1 (3.8)	0 (0.0)	1 (2.0)
HER2 status of biopsy			
Negative	26 (100.0)	25 (100.0)	51 (100.0)
Median (IQR) Ki-67 labeling index, % staining cells of biopsy*	20 (12-30)	16 (14-28)	17 (12-29)
Median (IQR) FACT-ES summary score	69 (64-75)	70 (66-73)	70 (66-74)

NOTE. Data are presented as No. (%) unless otherwise specified.

Abbreviations: E2, estradiol; ER, estrogen receptor; FACT-ES, functional assessment of cancer therapy, endocrine subscale; HER2, human epidermal growth factor receptor 2; IQR, interquartile range; Ki-67, protein encoded by the *MKI67* gene; PgR, progesterone receptor.

*Ki-67 was determined in a central laboratory.
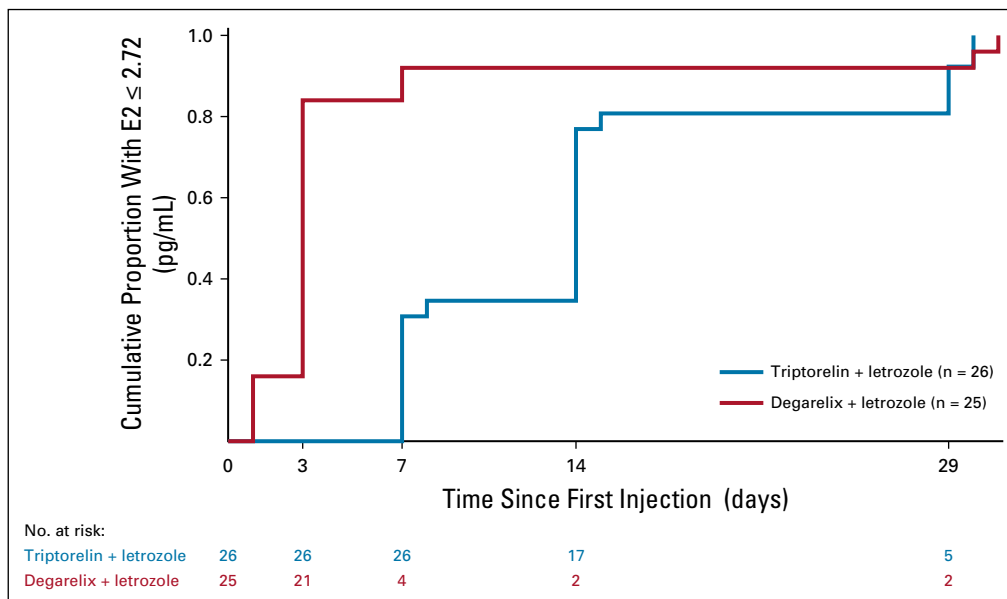
FIG 2. Kaplan-Meier estimates of the cumulative proportions of patients who achieved optimal ovarian function suppression (estradiol [E2] ≤ 2.72 pg/mL) according to treatment assignment.

only. FSH and LH over time are summarized in Figure 4 and Appendix Figures A2, A3, and A4 (online only).

Surgery and Pathology

Forty-nine patients underwent surgery after completion of NET; two patients decided to seek alternative therapies and did not receive surgery within the protocol-suggested time frame. Overall, 38.8% of patients had node-negative disease at surgery (Table 2). Node-negative disease rates were 43.5% versus 34.6% for degarelix plus letrozole versus triptorelin plus letrozole, and the estimated absolute difference was 8.9% (90% CI, −14.0% to 31.8%). Likewise, BCS rates were 52.2% versus 42.3% for degarelix plus letrozole versus triptorelin plus letrozole, and the absolute difference was 9.9% (90% CI, −13.5% to 33.3%). Thirty percent of patients (9 of 30 patients) considered candidates for mastectomy received BCS; 74% of those considered candidates for BCS at baseline (14 of 19 patients) underwent BCS, whereas the remaining 26% (five of 19 patients) underwent mastectomy.

The median PEPI score at surgery was 6 (IQR, 4 to 7); only one patient (2.0%) had a PEPI score of 0. Ki-67 expression levels were available for all patients on the diagnostic biopsy and for 47 on surgery (excision) samples. Significant reductions in Ki-67 from baseline to surgery were detected within each treatment group (Appendix Fig A5, online only). Median changes were −10.0% (90% CI, −13.5% to −5.5%; $P = .001$) for degarelix plus letrozole and −9.5% (90% CI, −15.0% to −6.0%; $P = .005$) for triptorelin plus letrozole. The changes were not different between the two treatment groups ($P = .55$).

Overall, 45.1% of patients had partial responses and 47.1% had stable disease as best overall response. Objective response rates were 44.0% versus 46.2% for degarelix plus letrozole versus triptorelin plus letrozole

(difference, −2.2%; 90% CI, −25.1% to 20.8%). For patients treated with NET, pathologic complete response is less frequent and not the appropriate surrogate of treatment benefit, so it was not a prespecified end point in the trial. We observed only one pathologic complete response in a patient treated with degarelix plus letrozole.

AEs

There were no treatment-related grade 4 AEs in either treatment group, and there were only two grade 3 AEs (hypertension and anemia) in two patients assigned to triptorelin plus letrozole (Table 3). The most common AEs with degarelix plus letrozole versus triptorelin plus letrozole were hot flashes (80.0% v 69.2%), arthralgia (32.0% v 53.8%), insomnia (24.0% v 11.5%), injection site reaction (24.0% v 0%), hypertension (12.0% v 3.8%), and nausea (16.0% v 3.8%).

Patient-Reported Endocrine Symptoms

The FACT-ES completion rates were 88% across assessment time points and were similar between treatment groups. Patients assigned to degarelix plus letrozole reported worse FACT-ES summary scores at each post-baseline time point (Appendix Fig A6, online only) compared with patients assigned to triptorelin plus letrozole. The most burdensome symptoms were hot flashes: 40.0% of patients who received degarelix plus letrozole and 30.8% of patients who received triptorelin plus letrozole reported clinically significant levels (Appendix Table A2, online only). Similar proportions in each group were indicated for night sweats. Clinically significant mood swings were noted in 32.0% of patients who received degarelix plus letrozole and in 11.5% of patients who received triptorelin plus letrozole. Feeling irritable and joint pains were reported by 24.0% (for each AE) of the degarelix-
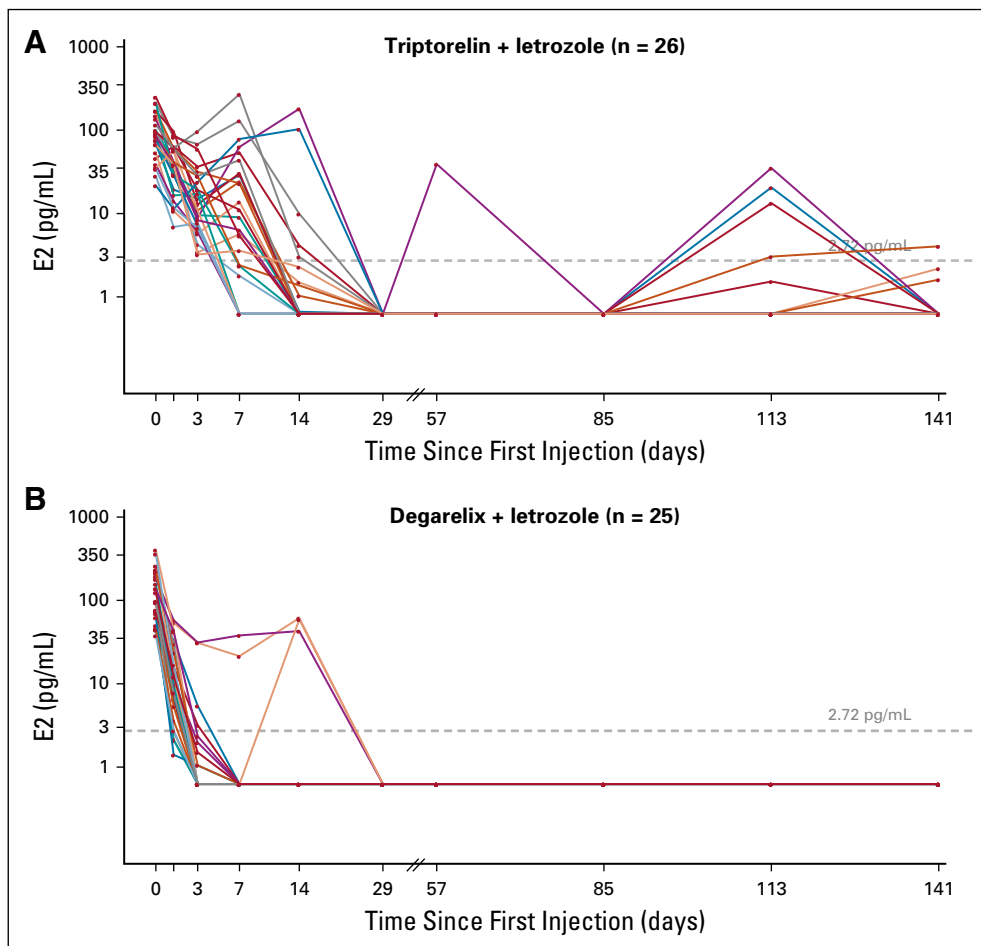
FIG 3. Estradiol (E2; pg/mL) profile over time of 51 patients according to treatment assignment. The x-axis corresponds to blood draw time (in days) before (A) triptorelin or (B) degarelix injections (0 = before cycle 1 injection; days 29, 57, 85, 113, and 141 = before cycles 2 through 6 injections, respectively). The blood draw time scale was adjusted to show the data points in cycle 1 as well as the subsequent cycles in the same figure.

plus-letrozole group and by 11.5% and 15.4%, respectively, of the triptorelin-plus-letrozole group.

DISCUSSION

The results of the TREND trial indicate that, in premenopausal patients treated with letrozole as NET for endocrine-responsive breast cancer, degarelix acted faster than triptorelin to induce optimal OFS. Moreover, degarelix ensured maintenance of optimal OFS in all patients during the subsequent (cycles 2 through 6) treatment period, whereas 15.4% of patients assigned to triptorelin plus letrozole had suboptimal OFS during NET.

These results are consistent with reports of degarelix activity in prostate cancer.[7] In two phase II dose-finding clinical trials, degarelix 240/160 mg and 240/80 mg were shown to effectively suppress testosterone levels in patients with prostate cancer without testosterone surge or inducement of clinical flare.[15,16] In another trial, both 240/160 mg and 240/80 mg doses were effective and noninferior to leuprolide 7.5 mg in suppression of testosterone.[8]

The maintenance of optimal OFS during degarelix therapy might have significant clinical value in the treatment of premenopausal patients with breast cancer not only in the

neoadjuvant setting but also in the adjuvant and metastatic settings. In the adjuvant setting, two recently published clinical trials led to a paradigm shift in the endocrine treatment of premenopausal women. The joint analysis of the SOFT (Suppression of Ovarian Function Trial) and TEXT (Tamoxifen and Exemestane Trial) trials showed that the combination of OFS plus exemestane significantly reduced recurrence compared with OFS plus tamoxifen.[17] The combination of OFS plus exemestane is currently recommended for patients at intermediate/high risk of relapse together with adjuvant chemotherapy.[4,18]

Bellet et al[19] reported that, during the first year of exemestane plus triptorelin in the SOFT trial, 17% of the patients had E2 levels greater than the threshold of 2.72 pg/mL (10 pmol/L). Baseline factors related to E2 level greater than 2.72 pg/mL were no prior chemotherapy ($P = .06$), higher BMI ($P = .05$), and lower FSH and LH (each $P < .01$).[19] Other authors reported that approximately 20% of women do not reach complete OFS with LH-releasing hormone analogs plus AIs.[6] This is consistent with our study, in which 15.4% of the patients did not maintain OFS during triptorelin treatment. In our trial, the median age was similar to that described in the SOFT and TEXT trials, but most patients were older than age 40 years and therefore less
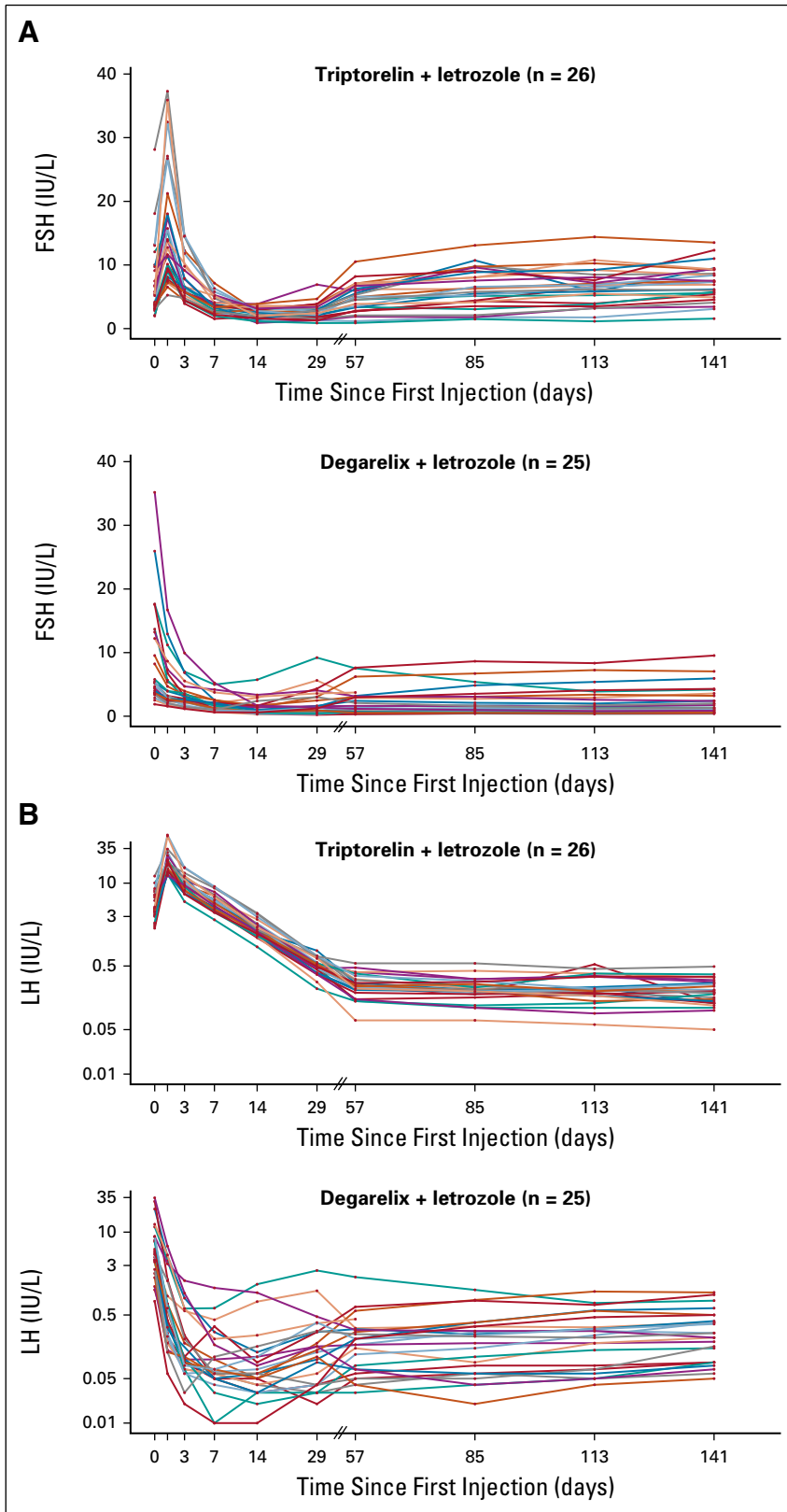
FIG 4. (A) Follicle-stimulating hormone (FSH; IU/L) and (B) luteinizing hormone (LH; IU/L) profiles over time for 51 patients according to treatment assignment. The x-axis corresponds to blood draw time (in days) before triptorelin or degarelix injections (0 = before cycle 1 injection; days 29, 57, 85, 113, and 141 = before cycles 2 through 6 injections, respectively). The blood draw time scale was adjusted to show the data points in cycle 1 as well as the subsequent cycles in the same figure.

TABLE 2. Surgical Pathology Characteristics According to Treatment Assignment

	Treatment Assignment		
Characteristic	Triptorelin + Letrozole (n = 26)	Degarelix + Letrozole (n = 23)	Total (N = 49)
Pathologic T stage			
T0	0 (0.0)	1 (4.3)	1 (2.0)
T1	8 (30.8)	5 (21.7)	13 (26.5)
T2	12 (46.2)	13 (56.5)	25 (51.0)
T3	6 (23.1)	4 (17.4)	10 (20.4)
Pathologic N stage			
N0	9 (34.6)	10 (43.5)	19 (38.8)
N1	9 (34.6)	9 (39.1)	18 (36.7)
N2	4 (15.4)	1 (4.3)	5 (10.2)
N3	4 (15.4)	3 (13.0)	7 (14.3)
Median (IQR) Ki-67 labeling index (% staining cells)*	5 (3-17)	8 (4-14)	6 (3-16)
Median (IQR) PEPI score (of 0-12 scale)	6.5 (4-7)	6 (4-7)	6 (4-7)
PEPI score of 0	0 (0.0)	1 (4.3)	1 (2.0)
pCR	0 (0.0)	1 (4.3)	1 (2.0)

NOTE. Data are presented as No. (%) of patients unless otherwise specified.

Abbreviations: IQR, interquartile range; Ki-67, protein encoded by the *MKI67* gene; pCR, pathologic complete response; PEPI, preoperative endocrine prognostic index.

*Ki-67 was determined in a central laboratory.

likely to have ovarian breakthroughs than were younger patients, who showed the greatest benefit from the association of OFS and exemestane in the SOFT and TEXT trials. One could speculate that, in a younger cohort, degarelix could have translated to an even higher percentage of maintained OFS compared with triptorelin. In the presence of incomplete OFS by GnRH analogs, treatment with AIs can stimulate the residual ovarian function and lead to an increase in plasma estrogen levels.[11] Guidelines for the use of adjuvant AIs recommend caution when E2 levels determined by highly sensitive/specific methods such as gas chromatography tandem mass spectrometry detection are more than 10 pmol/L (> 2.72 pg/mL) during treatment with AIs, because this indicates that AIs are not exerting full effectiveness.[11]

To our knowledge, this is the first report on the use of degarelix in the treatment of women with breast cancer. The toxicity profile of degarelix was as expected, and no safety signals were identified. Most commonly reported AEs were related to E2 deprivation. The maximum toxicity grade was 2, with the exception of two grade 3 AEs (hypertension and anemia) in two patients assigned to triptorelin plus letrozole. A considerable proportion of patients experienced clinically significant symptom burdens, and higher proportions occurred in patients who received degarelix plus letrozole. The open nature of this study may have affected the AE reports by patients. On the written trial information, a very common (≥ 10%) prevalence of hot flushes and injection site AEs was reported for degarelix. Although it is not

known how these issues were addressed in the discussion with the patients, it is unlikely that such an effect may explain the different profiles of the patient-reported symptoms. Patients should be made aware of lifestyle interventions and integrative therapies to minimize AEs from endocrine treatment.[20]

In this analysis, higher node-negative disease rates and higher BCS rates were observed for patients assigned to degarelix plus letrozole versus triptorelin plus letrozole. These data compare well with results from the literature. In a cohort of premenopausal patients treated with NET, the overall response rate was 50%.[21]

Potential limitations of this study are the small number of patients enrolled and the lack of postsurgery follow-up, which did not allow conclusions about the difference in disease outcomes between the treatment groups. In addition, at the time of study design, few similar data were available for breast cancer. The design assumptions of the cumulative optimal OFS rates with triptorelin at time points were based on studies from prostate cancer,[8,22] and the assumptions appeared to be different from those actually observed. Even so, the comparison depends only on rank data (log-rank test), so the study still has good power to detect a relative difference between treatment arms.

Strengths of our study are adherence to protocol requirements (all patients initiated and completed protocol NET), compliance to trial treatments (most patients received triptorelin/degarelix injections during the hospital visits), and central assessment of E2 levels. The study is

TABLE 3. Patients with Grades 1 to 4 and Grades 3 to 4 Targeted AEs and Other Grades 3 and 4 AEs Reported

	AEs by Treatment Assignment and Grade			
	Triptorelin + Letrozole (n = 26)		Degarelix + Letrozole (n = 25)	
AE by CTCAE version 4	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Hot flashes/flushes	69.2 (51.3 to 83.7)		80.0 (62.5 to 91.8)	
Arthralgia	53.8 (36.2 to 70.8)		32.0 (17.0 to 50.4)	
Insomnia	11.5 (3.2 to 27.2)		24.0 (11.0 to 42.0)	
Injection site reaction	0		24.0 (11.0 to 42.0)	
Nausea	3.8 (0.2 to 17.0)		16.0 (5.7 to 33.0)	
Hypertension	3.8 (0.2 to 17.0)	3.8 (0.2 to 17.0)	12.0 (3.4 to 28.2)	
Fatigue	11.5 (3.2 to 27.2)		4.0 (0.2 to 17.6)	
Anxiety	7.7 (1.4 to 22.3)		8.0 (1.4 to 23.1)	
Depression	3.8 (0.2 to 17.0)		8.0 (1.4 to 23.1)	
Myalgia	7.7 (1.4 to 22.3)		4.0 (0.2 to 17.6)	
Vaginal dryness	3.8 (0.2 to 17.0)		4.0 (0.2 to 17.6)	
ALT increase	3.8 (0.2 to 17.0)		0	
Other grades 3 and 4 AEs*	3.8 (0.2 to 17.0)	3.8 (0.2 to 17.0)	0	

NOTE. Data are presented as % (90% exact binomial CI). Thirty-one selected AEs, as well as other AEs of grade 3 or greater, were captured on the case report form. Only those with at least one reported event are tabulated.

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events.

*The other nontargeted grade 3 AE was anemia.

hypothesis generating and supports larger studies to assess whether maintenance of OFS with degarelix translates into a better clinical outcome and is worth a trade-off of increased rate of some AEs. Ongoing clinical trials about NET in premenopausal patients are investigating novel associations,[20] and will help identify the best candidates for such treatment as well as possible ways to optimize treatment efficacy.

In conclusion, in premenopausal women receiving letrozole for primary treatment of endocrine-responsive breast cancer, OFS was achieved more quickly and maintained more effectively with degarelix than with triptorelin throughout the NET period. These data support additional studies to assess whether degarelix improves disease control compared with the current standard of care in the treatment of premenopausal patients with breast cancer.

AFFILIATIONS

[1]IEO, European Institute of Oncology Istituto di Recovero e Cura a Carattere Scientifico (IRCCS), Milan, Italy
[2]Dana-Farber Cancer Institute and Harvard T.H. Chan School of Public Health, Boston, MA
[3]S Orsola Hospital, Bologna, Italy
[4]Ospedale Infermi di Rimini, Azienda Unita Sanitaria (AUSL) della Romagna, Italy
[5]International Breast Cancer Study Group Coordinating Center, Bern, Switzerland
[6]Hospital of Prato–AUSL Toscana Centro, Prato, Italy
[7]International Breast Cancer Study Group and University of Sydney, Sydney, Australia
[8]Frontier Science and Technology Research Foundation and Harvard Medical School, Boston, MA
[9]International Breast Cancer Study Group Statistical Center, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA

CORRESPONDING AUTHOR

Silvia Dellapasqua, MD, Division of Medical Senology, IEO, European Institute of Oncology IRCCS, Via Ripamonti 435, 20141, Milan, Italy; e-mail: silvia.dellapasqua@ieo.it.

REFERENCES

1. Beatson GT: On the treatment of inoperable cases of carcinoma of the mamma: Suggestions for a new method of treatment. Lancet 2:104-107, 1896.

2. Early Breast Cancer Trialists' Collaborative Group: Ovarian ablation in early breast cancer: Overview of the randomised trials. Lancet 348:1189-1196, 1996

3. Cardoso F, Costa A, Senkus E, et al: 3rd ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 3). Ann Oncol 28:3111, 2017

4. Curigliano G, Burstein HJ. P, Winer E, et al: De-escalating and escalating treatments for early-stage breast cancer: The St Gallen International Expert Consensus Conference on the primary therapy of early breast cancer, 2017. Ann Oncol 28:1700-1712, 2017

5. Lindner CH, Braendle W, Bettendorf G: Endocrine profiles during GnRH-agonist therapy using different application forms. Proceedings of the 13th World Congress of Gynecology and Obstetrics 1991 (abstr 1491)

6. Conte B, Poggio F, Del Mastro L: Luteininzing hormone releasing hormones analogs in combination with tamoxifen for the adjuvant treatment of premenopausal women with hormone receptor–positive breast cancer. Expert Opin Pharmacother 18:1357-1362, 2017

7. National Comprehensive Cancer Network: Clinical practice guidelines in oncology: Prostate cancer V.1.2008. https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

8. Klotz L, Boccon-Gibod L, Shore ND, et al: The efficacy and safety of degarelix: A 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. BJU Int 102:1531-1538, 2008

9. Guerrero-Zotano AL, Arteaga CL: Neoadjuvant trials in ER+ breast cancer: A tool for acceleration of drug development and discovery. Cancer Discov 7:561-574, 2017

10. Masuda N., Sagara Y, Kinoshita T, et al: Neoadjuvant anastrozole versus tamoxifen in patients receiving goserelin for premenopausal breast cancer (STAGE): A double-blind, randomised phase 3 trial. Lancet Oncol 13:345-352, 2012

11. Smith IE, Dowsett M, Yap Y, et al: Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhea: Caution and suggested guidelines. J Clin Oncol 24:2444-2447, 2006

12. WHO: WHO Handbook for Reporting Results of Cancer Treatment. Geneva, Switzerland, Offset Publication, 1979

13. Fallowfield LJ: Leaity SK, Howell A, et al: Assessment of quality of life in women undergoing hormonal therapy for breast cancer: Validation of an endocrine symptom subscale for the FACT-B. Breast Cancer Res Treat 55:189-199, 1999

14. Fallowfield LJ, Kilburn LS, Langridge C, et al: Long-term assessment of quality of life in the Intergroup Exemestane Study: 5 Years post randomisation. Br J Cancer 106:1062-1067, 2012

15. Van Poppel H, Tombal B, de la Rosette JJ, et al: Degarelix: A novel gonadotrophin-releasing hormone (GnRH) blocker—Results from a one-year, multicentre, randomised, phase 2 dosage-finding study in the treatment of prostate cancer. Eur Urol 54:805-815, 2008

16. Gittelman M, Pommerville PJ, Persson BE, et al: A 1-year, open-label, randomized phase II dose finding study of degarelix, a novel gonadotropin-releasing hormone (GnRH) receptor blocker, in the treatment of prostate cancer in North America. J Urol 180:1986-1992, 2008

17. Pagani O, Regan MM, Walley BA, et al: Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med 371:107-118, 2014

18. Burstein HJ, Lacchetti C, Anderson H, et al: Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology Clinical Practice guideline update on ovarian suppression. J Clin Oncol 34:1689-1701, 2016

19. Bellet M, Gray KP, Francis PA, et al: Twelve-month estrogen levels in premenopausal women with hormone receptor–positive breast cancer receiving adjuvant triptorelin plus exemestane or tamoxifen in the Suppression of Ovarian Function Trial (SOFT): The SOFT-EST substudy. J Clin Oncol 34:1584-1593, 2016

20. Lyman GH, Greenlee H, Bohlke K, et al: Integrative therapies during and after breast cancer treatment: ASCO endorsement of the SIO clinical practice guideline. J Clin Oncol 36 2647-2655, 2018

21. Torrisi R, Bagnardi V, Pruneri G, et al: Antitumour and biological effects of letrozole and GnRH analogue as primary therapy in premenopausal women with ER and PgR positive locally advanced operable breast cancer. Br J Cancer 97:802-808, 2007

22. Heyns CF, Simonin MP, Grosgurin P, et al: Comparative efficacy of triptorelin pamoate and leuprolide acetate in men with advanced prostate cancer. BJU Int 92:226-231, 2003

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Neoadjuvant Degarelix Versus Triptorelin in Premenopausal Patients Who Receive Letrozole for Locally Advanced Endocrine-Responsive Breast Cancer: A Randomized Phase II Trial

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Silvia Dellapasqua
Travel, Accommodations, Expenses: Ipsen

Kathryn P. Gray
Stock and Other Ownership Interests: DVAX

Elisabetta Munzone
Consulting or Advisory Role: Pierre Fabre

Lorenzo Gianni
Consulting or Advisory Role: Celgene, AstraZeneca**Travel, Accommodations, Expenses:** Roche, Genentech, Novartis, Pfizer

Giuseppe Viale
Honoraria: MSD Oncology
Consulting or Advisory Role: Dako, Roche, Genentech, AstraZeneca, Bristol-Myers Squibb, Astellas Pharma
Research Funding: Roche, Genentech, Ventana Medical Systems (Inst)
Travel, Accommodations, Expenses: Roche, Celgene

Rudolf Maibach
Honoraria: Fennec Pharma
Travel, Accommodations, Expenses: Fennec Pharma

Angelo Di Leo
Honoraria: Roche, Novartis, Pfizer, AstraZeneca, Genomic Health, Eisai, Lilly, Pierre Fabre, Bayer, Celgene, Amgen
Consulting or Advisory Role: Roche, Novartis, Pfizer, AstraZeneca, Pierre Fabre, Lilly, Bayer, Celgene, Puma Biotechnology, Daiichi Sankyo, Ipsen, Genomic Health, Genentech, Amgen, Eisai
Research Funding: Novartis, Pfizer, AstraZeneca
Travel, Accommodations, Expenses: Roche, Novartis, Pfizer, AstraZeneca, Eisai, Bayer, Celgene, Lilly, Pierre Fabre, Buma Biotechnology, Daiichi Sankyo

Richard D. Gelber
Research Funding: AstraZeneca (Inst), Novartis (Inst), Roche (Inst), Celgene (Inst), Merck (Inst), Pfizer (Inst), Ipsen (Inst), Ferring (Inst)

Meredith M. Regan
Consulting or Advisory Role: Merck, Ipsen (Inst)
Research Funding: Veridex (Inst), OncoGenex (Inst), Pfizer (Inst), Ipsen (Inst), Novartis (Inst), Merck (Inst), Ferring (Inst), Celgene (Inst), AstraZeneca (Inst), Pierre Fabre (Inst), Ipsen (Inst), Bayer (Inst), Bristol-Myers Squibb (Inst), Roche (Inst)
Travel, Accommodations, Expenses: Bristol-Myers Squibb

Marco Colleoni
Honoraria: Novartis
Consulting or Advisory Role: Pierre Fabre, Pfizer, OBI Pharma, Puma Biotechnology, Celldex, AstraZeneca

No other potential conflicts of interest were reported.

APPENDIX

TREND (Trial on the Endocrine Activity of Neoadjuvant Degarelix) Investigators and International Breast Cancer Study Group Participants

International Breast Cancer Study Group (IBCSG) Scientific Committee: M. Colleoni (Chair), A. Di Leo (Co-chair)

IBCSG Scientific Executive Committee: M. Colleoni, A. Di Leo, F. Boyle, G. Jerusalem, M. Regan, G. Viale

IBCSG Foundation Council: R. Stahel (President), S. Aebi, F. Boyle, A. Coates, M. Colleoni, A. Di Leo, R. Gelber, A. Goldhirsch, G. Jerusalem, P. Karlsson, I. Kössler, M. Regan

IBCSG Coordinating Center, Bern, Switzerland: A. Hiltbrunner (Director), Y. Chittazhathu Kurian Kuruvilla, S. Fournarakou, L. Fritzsche, A. Gasca, R. Kammler, R. Maibach, R. Pfister, M. Rabaglio, M. Weber

IBCSG Monitors: G. Achille, D. Celotto

IBCSG Statistical Center, Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA: M. Regan (Director), R. Gelber, K. Gray, H. Huang, C. Mahoney, K. Price

IBCSG Data Management Center, Frontier Science and Technology Research Foundation, Amherst, NY: L. Blacher (Director), K. Scott (Data Management Section Head), H. Shaw (Lead Trial Coordinator), M. Blackwell, R. Starkweather, A. Cesario, A. Dickinson, V. Palermo

**IBCSG Quality of Life Office**, Bern, Switzerland: J Bernhard, K Ribi

IBCSG Central Pathology Office, European Institute of Oncology, Division of Pathology, Milan, Italy: G. Viale (Director), S. Andrighetto, G. Bardeli, F. Ciocca, P. Dell'Orto, L. Russo

**Participating Centers and Principal Investigators**:

Istituto Europeo di Oncologia, Milano, Italy: M. Colleoni

Ospedale S. Orsola-Malpighi, Bologna, Italy: C. Zamagni

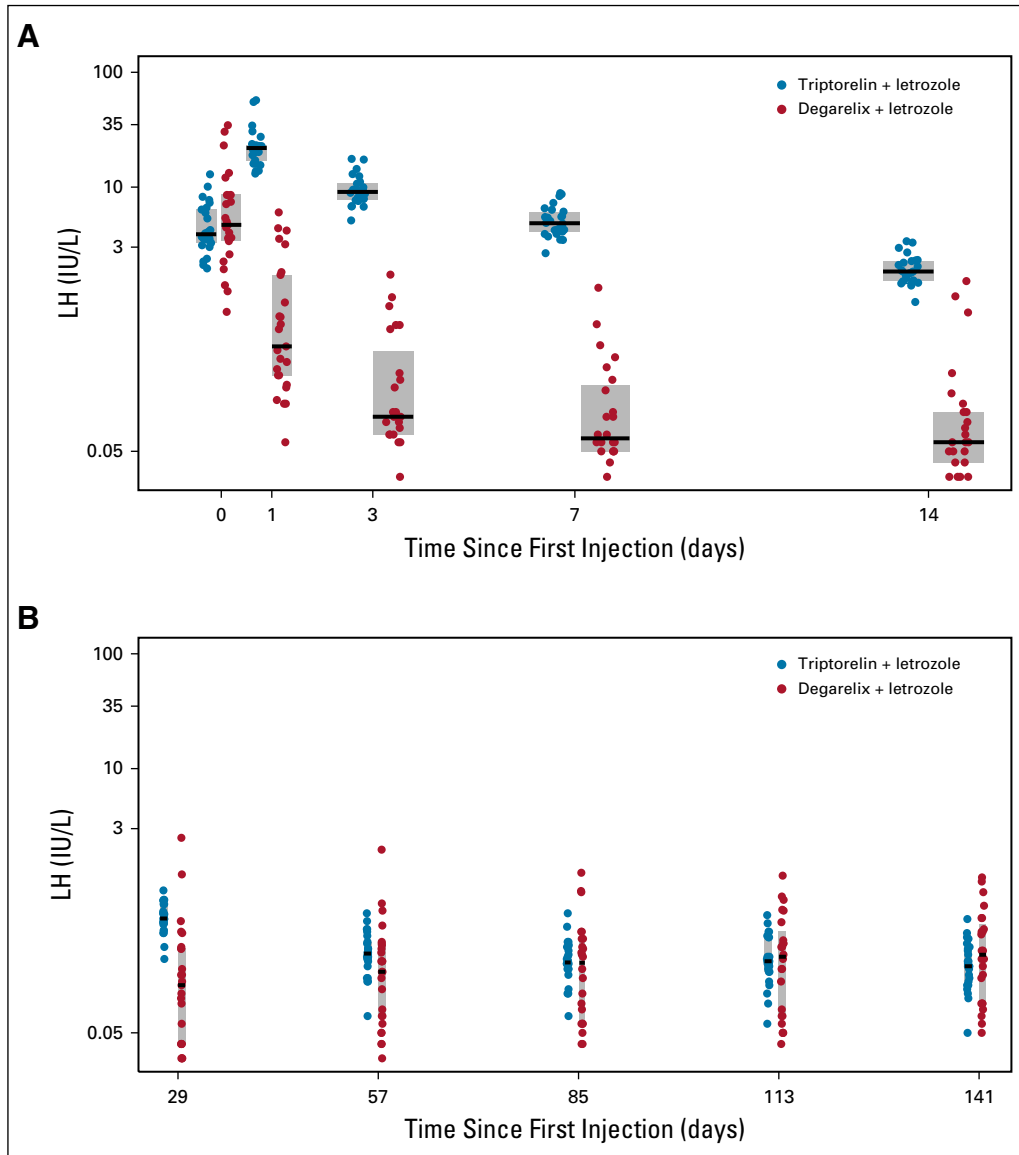Ospedale Infermi di Rimini, Rimini, Italy: L. Gianni
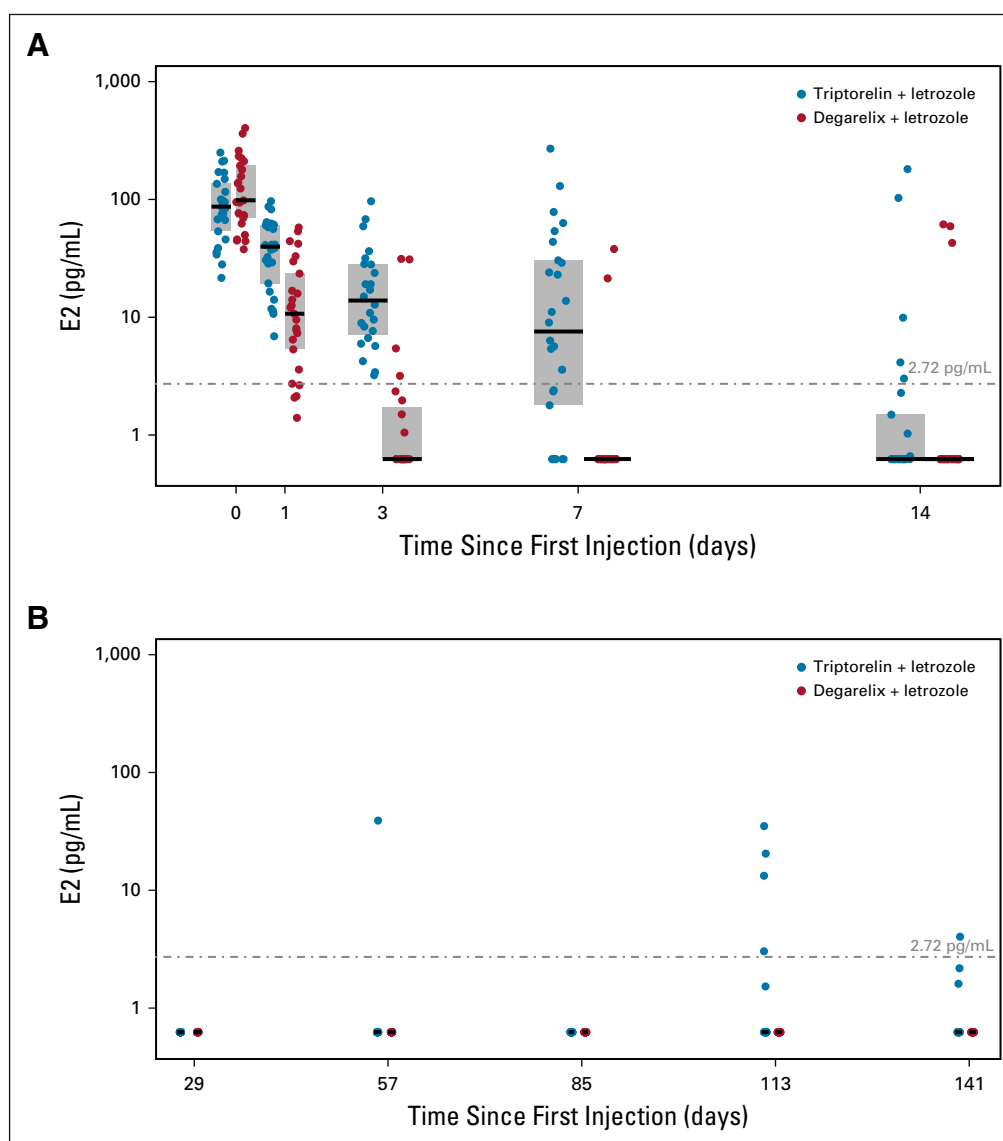
FIG A1. Distributions of estradiol (E2) levels over time according to treatment assignment. (A) Days 0 to 14 of cycle 1; (B) days 29 to 141 (before injection at cycles 2 to 6). The gray line corresponds to E2 threshold of 2.72 pg/mL.
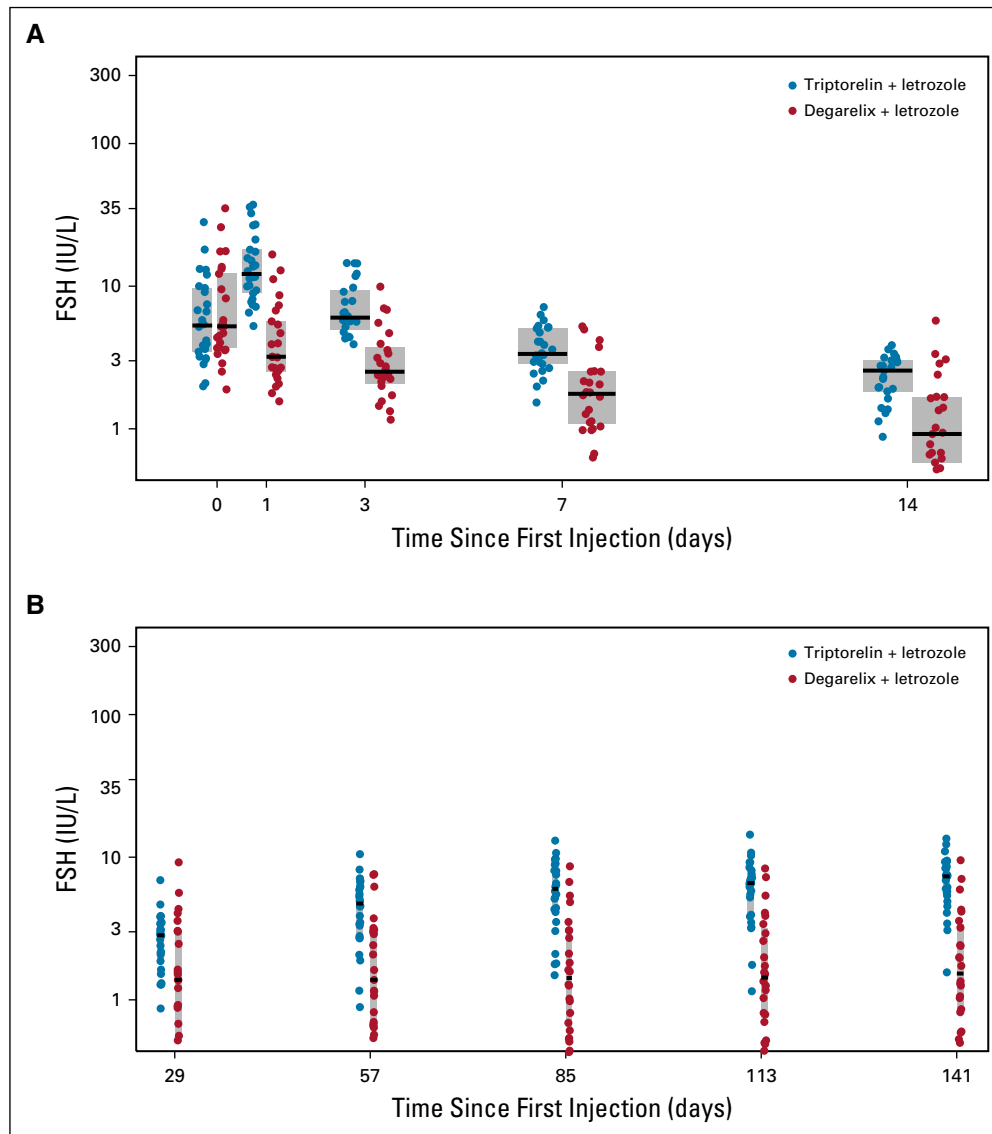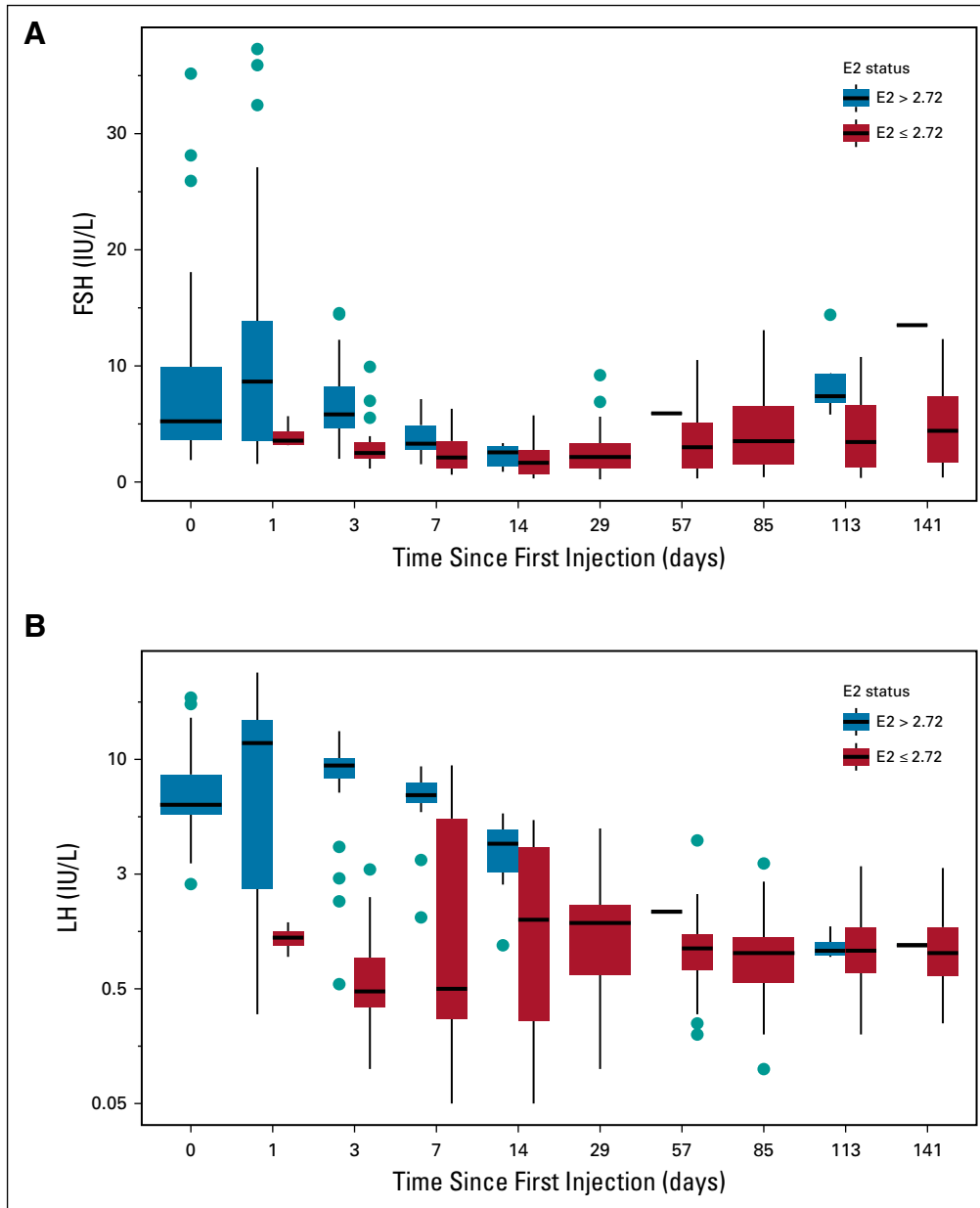
FIG A2. Distributions of follicle-stimulating hormone (FSH) levels over time according to treatment assignment. (A) Days 0 to 14 of cycle 1; (B) days 29 to 141 (before injection at cycles 2 to 6).

FIG A3. Distributions of luteinizing hormone (LH) levels over time according to treatment assignment. (A) Days 0 to 14 of cycle 1; (B) days 29 to 141 (prior to injection at cycles 2 to 6).

FIG A4. Correlation of (A) follicle-stimulating hormone (FSH) and (B) luteinizing hormone (LH) levels with estradiol (E2) status (E2 ≤ 2.72 pg/mL to reach ovarian function suppression [OFS] *v* E2 > 2.72 pg/mL for suboptimal OFS) over time.
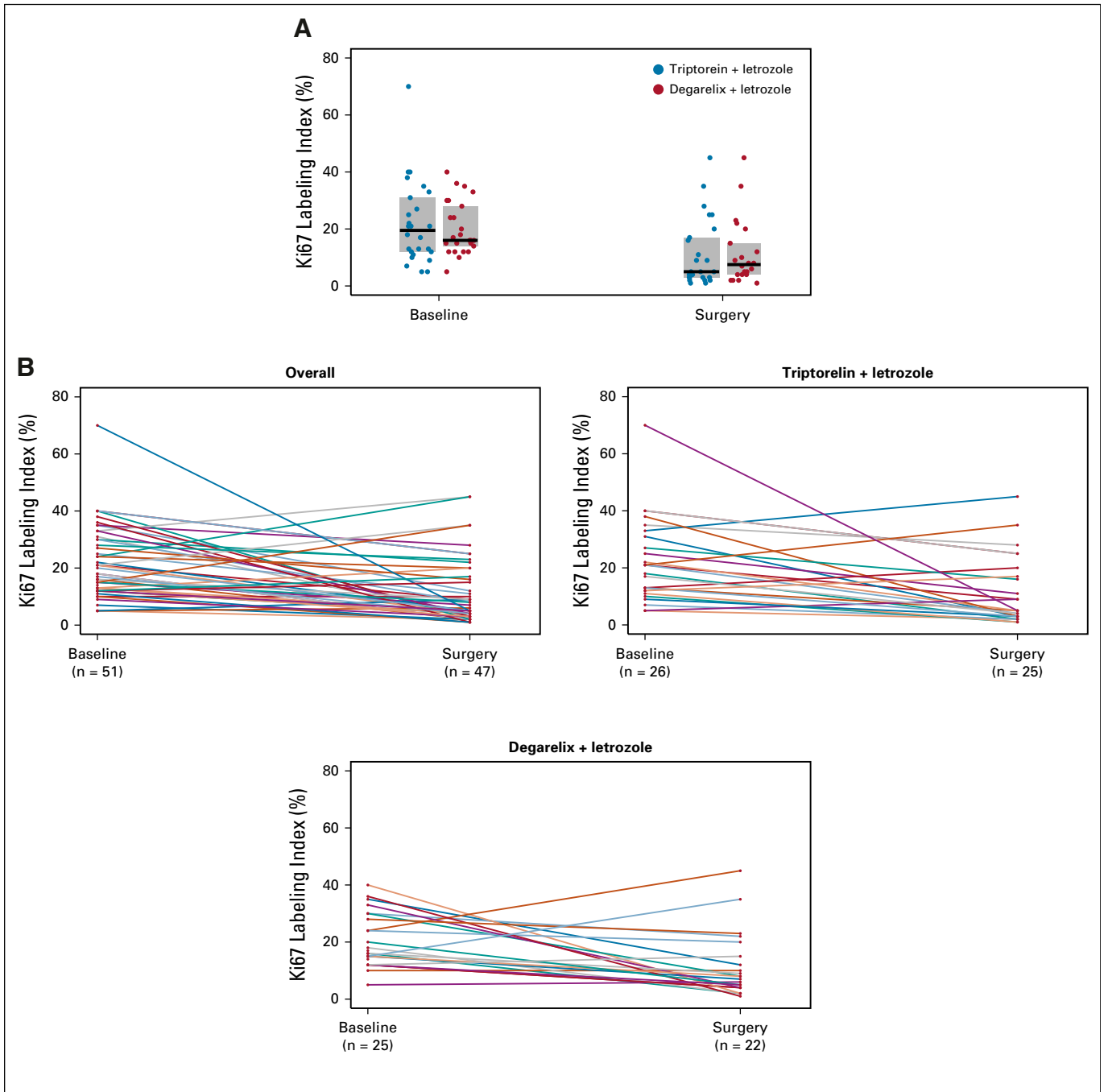
FIG A5. Ki67 (protein encoded by the MIK67 gene) labeling index (%) at baseline (pre-treatment biopsy) and at surgery (residual disease). (A) Distributions of Ki67 according to time point and treatment assignment. (B) Changes in Ki67 between time points for individual participants, overall and according to treatment assignment.
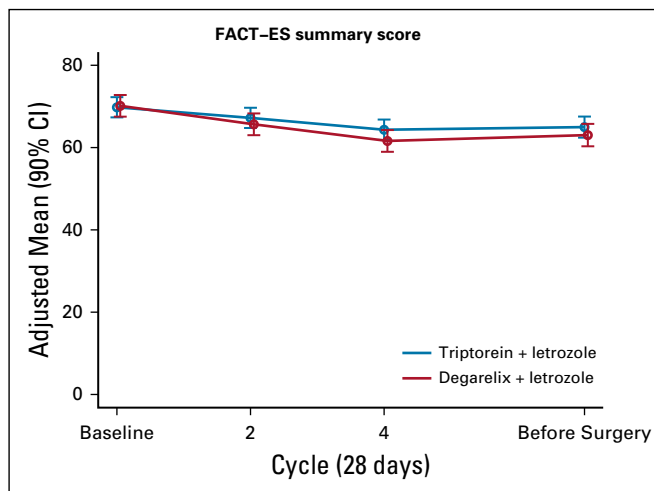
FIG A6. Functional assessment of cancer therapy, endocrine subscale (FACT-ES), summary scores (range, 0 to 76; higher score denotes better functioning) at baseline and during neoadjuvant endocrine therapy. FACT-ES was completed before the first injection and on day 1 of cycles 2 and 4 as well as before surgery. Plots are the adjusted means with 90% CIs.

TABLE A1. Percentage of Patients' E2 Levels ≤ 2.72 pg/mL During Time Points of the First Cycle According to Treatment Assignment

	Blood Draw Time (days since first injection)					
Variable	**0**	**1**	**3**	**7**	**14**	**29***
Corresponding treatment cycle	Baseline	C1 d1	C1 d3	C1 d7	C1 d14	C2 d1
Triptorelin + letrozole						
No. with E2 measurement	26	26	24	26	25	25
No. (%) with E2 ≤ 2.72 pg/mL	0 (0)	0 (0)	0 (0)	9 (35)	20 (80)	25 (100)
Degarelix + letrozole						
No. with E2 measurement	25	25	24	24	25	25
No. (%) with E2 ≤ 2.72 pg/mL	0 (0)	4 (16)	20 (83)	22 (92)	22 (88)	25 (100)

Abbreviation: E2, estradiol; C, cycle; d, day.

*Blood draw was before C2 injection.

TABLE A2. Percentage of Patients Who Experienced Clinically Significant FACT-ES Individual Item Score at Any Time During Neoadjuvant Treatment by Treatment Assignment

| FACT-ES Item | Treatment Assignment | | Difference (D + L minus T + L) |
	Triptorelin + Letrozole (n = 26)	Degarelix + Letrozole (n = 25)	
Hot flashes	30.8 (15.9 to 45.7)	40.0 (23.9 to 56.1)	9.2 (−12.7 to 31.2)
Cold sweats	7.7 (0.0 to 16.3)	12.0 (1.3 to 22.7)	4.3 (−9.4 to 18.0)
Night sweats	26.9 (12.6 to 41.2)	40.0 (23.9 to 56.1)	13.1 (−8.5 to 34.6)
Vaginal discharge	3.8 (0.0 to 10.0)	0.0 (0.0 to 0.0)	−3.8 (−10.0 to 2.4)
Vaginal irritation	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	
Vaginal bleeding	7.7 (0.0 to 16.3)	0.0 (0.0 to 0.0)	−7.7 (−16.3 to 0.9)
Vaginal dryness	3.8 (0.0 to 10.0)	8.0 (0.0 to 16.9)	4.2 (−6.7 to 15.0)
Pain or discomfort with intercourse	7.7 (0.0 to 16.3)	12.0 (1.3 to 22.7)	4.3 (−9.4 to 18.0)
Lost interest in sex	7.7 (0.0 to 16.3)	12.0 (1.3 to 22.7)	4.3 (−9.4 to 18.0)
Gained weight	3.8 (0.0 to 10.0)	0.0 (0.0 to 0.0)	−3.8 (−10.0 to 2.4)
Light-headed (dizzy)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	
Vomiting	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	
Diarrhea	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	
Headaches	7.7 (0.0 to 16.3)	12.0 (1.3 to 22.7)	4.3 (−9.4 to 18.0)
Bloated feeling	3.8 (0.0 to 10.0)	8.0 (0.0 to 16.9)	4.2 (−6.7 to 15.0)
Breast tenderness	3.8 (0.0 to 10.0)	16.0 (3.9 to 28.1)	12.2 (−1.4 to 25.7)
Mood swings	11.5 (1.2 to 21.8)	32.0 (16.7 to 47.3)	20.5 (2.0 to 38.9)
Feeling irritable	11.5 (1.2 to 21.8)	24.0 (10.0 to 38.0)	12.5 (−5.0 to 29.9)
Joint pains	15.4 (3.7 to 27.0)	24.0 (10.0 to 38.0)	8.6 (−9.6 to 26.9)

NOTE. Percentages are reported as No. (90% CI). Item scores were "quite a bit" or "very much" a problem.
Abbreviation: FACT-ES, functional assessment of cancer therapy, endocrine subscale.