

# Efficacy and Feasibility of Long-Acting Every Three Months Goserelin for Premenopausal Breast Cancer Patients during the COVID Pandemic

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# Abstract:

**Background:** Monthly Goserelin has demonstrated safety and efficacy in treating pre-menopausal breast cancer patients. This study aims to evaluate the safety and efficacy of every 3-monthly goserelin 10.8 mg.

**Methods:** Cohort A: Patients received 10.8 mg of goserelin every 12 weeks. Cohort B: Retrospective review of patients' files who received monthly Goserelin.

**Results**: 41 patients (cohort A) and 42 patients (cohort B) were included, and the median ages were 37y and 35y respectively. Cohort A vs B: stage II (21.9% vs 21.4%), stage III (48.8% vs 52.4%) and stage IV (29.3% vs 26.2%). Luminal A (34.1% vs 30.9%), B1 (56.1% vs 57.1%) and B2 (9.8 vs 11.9%). The mean baseline E2 level in cohort A was 254.9 pg/dl. The median follow-up duration was 21 months.

The mean E2 levels in cohort A were 15.4 ng/dl, 10.8 ng/dl, and 9.6 ng/dl at weeks 12, 24, and 36 respectively. All patients developed amenorrhea. For non-metastatic patients the disease-free survival (DFS) was 86.2% for cohort A (n=29) and 87.1% for cohort B (n=31) without statistically significant difference (p=0.71). Metastatic patients' progression-free survival (PFS) was 66.7% for cohort A (n= 12) and 63.6% for cohort B (n= 11) without statistically significant difference (p=0.88). All patients are alive, and no serious adverse events were observed in both group, hot flushes (65.8 % vs 66.7%), headache (36.6 % vs 40.5%), arthralgia (26.8% vs 28.5%), and hyperhidrosis (7.3 % vs 7.1%).

**Conclusion:** 3-monthly goserelin is safe and effective with less frequent hospital visits that reduce exposure to infection, especially during the COVID pandemic.

**Keywords:** breast cancer – hormone receptor-positive – ovarian function suppression – COVID pandemic.

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# **Background:**

About two-thirds of breast cancer patients have hormone-receptor-positive tumors and are candidates for endocrine therapy. [1] For pre-menopausal patients, estradiol (E2) is the main source of estrogen and is synthesized and released from the ovaries under the effect of luteinizing hormone-releasing hormone (LHRH) and follicle-stimulating hormone (FSH).[2] Ovarian function suppression or ablation will inhibit estradiol production, thereby suppressing estrogendependent tumor growth in adjuvant or metastatic settings. This could be achieved medically using a Gonadotropin-releasing hormone (GnRH) agonist such as monthly goserelin, surgically through bilateral oophorectomy, or by radiation therapy. Data from several trials suggested that GnRH analogs have similar efficacy as these other treatment modalities. [3–6]

Meta-analysis of many trials for metastatic breast cancer patients comparing GnRH agonist alone or in combination with anti-estrogen as tamoxifen or aromatase inhibitor revealed that combination therapy leads to improved response rate (RR), progression-free survival (PFS), and overall survival (OS). [7-8]

In the adjuvant setting, goserelin combined with antiestrogen has demonstrated similar efficacy as chemotherapy for ER-positive pre-menopausal breast cancer patients, regarding disease-free survival (DFS) with a more favorable safety profile. [9-15]

Also, adding 5 years (SOFT and TEXT trials) or 2 years (ASTRRA trial) of ovarian function suppression (OFS) to 5 years of anti-estrogen for premenopausal patients with breast cancer who remain in a premenopausal state or resume ovarian function after completion of chemotherapy has significant improvement on DFS and OS. For the ASTRRA trial, the estimated 5-year DFS rate was 91.1% in the TAM + OFS group and 87.5% in the TAM-only group (hazard ratio, 0.69; 95% CI, 0.48 to 0.97; P = .033). The estimated 5-year OS rate was 99.4% in the TAM + OFS group and 97.8% in the TAM-only group (hazard ratio, 0.31; 95% CI, 0.10 to 0.94; P = .029). [16-20]

The rate and pattern of ovarian function recovery after chemotherapy-induced amenorrhea differ widely according to patient age and type of chemotherapy. Serum follicle-stimulating hormone (FSH) levels, serum estradiol (E2) levels, and menstruation history are used to assess the resumption of ovarian function. [21]

Goserelin is a gonadotropin-releasing hormone (GnRH) analog that when firstly administered transiently increases the plasma levels of luteinizing hormone (LH) and FSH. However, continuous administration of goserelin, down-regulates the pituitary gland receptors and become refractory to further stimulation, and serum levels of LH and FSH decline to below the pretreatment values after about 3 – 4 weeks. [22]

Although the safety and efficacy of monthly goserelin 3.6 mg, in premenopausal patients with ERpositive advanced breast cancer have been documented in many trials, the data on the effectiveness of the 3monthly long-acting formulation is still insufficient. [23]

The 3-monthly long-acting Goserelin 10.8 mg is already approved for the treatment of localized and metastatic prostate carcinoma based on several phase III trials which demonstrated non-inferiority between the two dose regimens. However, it is not currently approved for use in breast cancer patients either in early or advanced settings. [24]

The primary objective is to assess the pharmacodynamic effect of 10.8 mg goserelin depot regarding suppression of the serum E2 level (weeks 0, 12, 24, and 36) in premenopausal estrogen receptorpositive breast cancer patients.

The secondary endpoints are to assess the serum FSH level, cessation of menstruation, tolerability, and adverse events, DFS for non-metastatic patients, and PFS for metastatic patients. DFS was defined as the time from enrollment to the time of the first event (invasive local recurrence, regional recurrence, distant recurrence, invasive contralateral breast cancer, secondary malignancy, or death as a result of any reason). PFS was defined as the time from enrollment till progression or death from any cause.

## **Patients and Methods:**

Patients were recruited from the Clinical Oncology Department Faculty of Medicine, Alexandria University, Ayadi Almostakbal and Damanhour Oncology Centers. This study includes 2 cohorts of patients: Cohort A: Patients received 10.8 mg goserelin depot every 12 weeks in addition to a daily oral dose of tamoxifen 20 mg or aromatase inhibitor and continued the treatment till disease progression or adverse events that leads to discontinuation of treatment. Her 2neu +ve patients received Herceptin 8 mg/kg loading dose followed by 6 mg/kg maintenance dose every 3 weeks in the adjuvant setting.

Patients who received chemotherapy (adjuvant or metastatic) were evaluated for menopausal status within 3 months after the last chemotherapy cycle. Baseline blood samplings were obtained for serum E2, and FSH before starting treatment then estradiol was repeated every 12 weeks later (weeks 12, 24, and 36).

Cohort B: Retrospective review of patients' files to include a group of patients with comparable age and disease characteristics to cohort A and who received monthly Goserelin 3.6 mg depot in addition to a daily oral dose of tamoxifen 20 mg or an aromatase inhibitor.

Inclusion criteria: aged  $\geq 18$  years, ECOG performance status of 0 – 2, pre-menopausal women, perimenopausal (last menstruation  $\geq 6$  months before trial entry), histological confirmed breast cancer, estrogen receptor-positive in more than 10% of cells by immunohistochemistry (IHC), stage I – IV, previous chemotherapy in adjuvant or metastatic settings was allowed and 1st line hormonal treatment in the adjuvant or metastatic setting.

Pre-menopausal status was defined as still menstruating patients and/or serum concentrations of  $E2 \ge 30$  pg/mL within 4 weeks before treatment (for patients who had undergone a hysterectomy, only the latter criterion was required). Temporary chemotherapy-induced amenorrhea in the adjuvant setting was allowed, provided that the premenopausal status was confirmed by the estradiol level.

Exclusion criteria were as follows: carcinoma in situ, stage IV disease with visceral crisis, lifethreatening concurrent disease, pregnant or lactating women, previous bilateral ovarian irradiation or excision, or male breast cancer.

The effectiveness of treatment was measured based on serum E2 and FSH levels (weeks 0, 12, 24, and 36) for cohort A only. Cessation of menstruation, DFS (non-metastatic), or PFS (metastatic) were assessed in both groups.

FSH level was used to confirm the premenopausal state before enrollment in the study as FSH level cannot be used alone as an index to determine the effect of LHRH agonist as it is altered by the administration of tamoxifen. Cessation of menses and adverse events were assessed every 12 weeks with each visit. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (CTC).

The study was reviewed and approved by the Ethics committee, faculty of Medicine, Alexandria University by the Helsinki Declaration. All patients have consented to participate in the study.

## Statistical analysis of the data

Data were analyzed using IBM SPSS software package version 24.0. (Armonk, NY: IBM Corp)

Qualitative data were described using numbers and percentages. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, and median. The significance of the obtained results was judged at the 5% level.

The used tests were

- 1- Chi-square test (X2-test) For categorical variables, to compare between different groups.
- 2- Mann Whitney test (U-test) For abnormally distributed quantitative variables, to compare between two studied groups.
- 3- Friedman test for abnormally distributed quantitative variables, to compare between more than two periods or stages and Post Hoc Test (Dunn-Bonferroni) for pairwise comparisons.

### **Results:**

41 patients were included in cohort A during the period between February 2020 and March 2021 and 49 patients' files were retrospectively reviewed during the same period, 7 patients were excluded due to incomplete file data with a total of 42 patients included. Baseline patients' demographic and disease characteristics are shown in tables (1&2).

### *Follow-up duration:*

The median follow-up duration for both groups was 21 months (range 15 - 27m).

#### Cessation of menstruation:

In both groups, all patients had amenorrhea at week 12 and maintained it during the follow-up period.

### Serum E2 and FSH concentrations: Cohort (A)

40/41 (97.5 %) patients have serum E2 levels < 30 ng/dl, and only one patient had a serum E2 level of 40.5 ng/dl at week 24. The mean serum E2 levels were 15.4 ng/dl, 10.8 ng/dl, and 9.6 ng/dl at weeks 12, 24, and 36, respectively compared to 254.9 ng/dl at baseline level (table 3) (figure 1). Serum FSH was suppressed in all patients (100%). The mean serum FSH levels were 6.5, 5.5, and 4.5 at weeks 12, 24, and 36, respectively Compared to 25.9 at the baseline level (table 3) (figure 2).

# Disease Free Survival (DFS) and Progression Free Survival (PFS):

For cohort (A) non-metastatic patients (n= 29), four events were observed during the study: one bone and visceral recurrence (after 6 months), one local recurrence (after 12 months), and two bone metastasis (after 15&18 months). The DFS was 86.2%. Regarding metastatic patients (n=12), 4 patients had progressive disease and the PFS was 66.7%. All patients (metastatic and non-metastatic) were alive till the end of the study.

For cohort (B), 4/31 non-metastatic patients relapsed (one bone only after 18 months and three bone and visceral metastases after 12 and 15 months) with DFS of 87.1%. 4/11 metastatic patients progressed with a PFS of 63.6%. All patients (metastatic and nonmetastatic) are alive. There was no statistically significant difference regarding DFS or PFS between both cohorts (0.7138 & 0.8809 respectively) (table 4).

### Adverse events:

In both groups, no serious adverse events that necessitate treatment discontinuation were observed during the follow-up period. All of the adverse events were grade 1 or 2, with the most common being hot flushes (65.8 % versus 66.7% p = 0.9375), headache (36.6 % versus 40.5% p = 0.7157), arthralgia (26.8% versus 28.5% p= 0.8592) and hyperhidrosis (7.3% versus 7.1% p= 0.9755) with no statistically significant differences. No increase in the endometrial thickness was observed as tamoxifen-induced endometrial thickness was blocked by the addition of goserelin acetate. (Table 5).





Figure [2] Mean FSH level

Intervent         Control of the second	[-] P	Cohort (A)	Cohort (B)	$\mathbf{X}^2$													
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Age         (a)         (b)         (c)         (c) <th></th> <th>(n=41)</th> <th>(n=42)</th> <th>P value</th>		(n=41)	(n=42)	P value				
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| Solution         13(31.7%)         12(28.6%)         0.053           > 40y         16 (39%)         17(40.5%)         0.952           > 40y         12(29.3)         13(30.9%)         Range         25 - 45         28 - 45         U = 0.061           Metajaan         37         35         0.821           Menopausal state         9         9         0.122           Perimenopausal         34(82.9%)         36(85.7%)         0.122           Perimenopausal         7(17.1%)         6(14.3%)         0.7268           BMI         0029         225         33(80.5%)         34(81%)         0.957           Histopathology         10         3(7.3%)         2(4.8%)         0.624           Tumor Grade         11         11(26.8%)         10(23.8%)         0.7517           Stage (non-metastatic)         11         2(29.9%)         9(21.4%)         0.126           HI         2(29.9%)         9(21.4%)         0.126         11           11         2(29.9%)         9(21.4%)         0.126           HI         2(29.9%)         9(21.4%)         0.126           HI         2(29.9%)         11(26.2%)         0.8568           T3         10(34.5%)  | Age   | (11-11)   | (11-12)   | I vulue  |  |  |  |   |  
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| $-35^2$ 40y       16 (39%)       17(40.5%)       0.952         > 40y       12(29.3)       13(30.9%)       0.952         Range       25 - 45       28 - 45       U = 0.061         Median       37       35       0.821         Menopausal state       7       35       0.821         Permenopausal       34(82.9%)       36(85.7%)       0.122         Perimenopausal       7(17.1%)       6(14.3%)       0.057         Histopathology       0.957       0.957       0.957         Histopathology       0.957       0.957       0.957         ILC       37(73%)       24(4.8%)       0.624         Tumor Grade       0.122       0.1001       0.111         II       10(73.2%)       32(76.2%)       0.1001         III       11(26.8%)       10(23.8%)       0.7517         Stage       0.112       0.126       0.101         III       10(29.3%)       11(26.2%)       0.309         T stage (non-metastatic)       11       0.223.8%)       0.309         T 1       6(20.7%)       7(22.6%)       0.325         N 1       14(48.3%)       15(48.4%)       0.322         N 1       14(48  | < 35v   | 13(31.7%)   | 12(28.6%)   | 0.053  |  |  |  |   |  
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| Intege         Description         Constraint         Constraint           Medigan         37         35         0.821           Permenopausal state         7(17.1%)         6(14.3%)         0.7268           BMI         (25)         8(19.5%)         8(19%)         0.0029           ≥ 25         33(80.5%)         34(81%)         0.957           Histopathology         (12)         (12)         (12)         (12)           ILC         3(7.3%)         2(4.8%)         0.624           Tumor Grade         (11)         (126.3%)         (10)         (13)           II         9(1.9%)         9(21.4%)         0.126           III         (129.3%)         (126.2%)         0.398           IV         12(29.3%)         (126.2%)         0.398           IV         12(29.3%)         (126.2%)         0.309           T2         13(44.4%)         14(45.2%)         0.3568           T3         10(34.5%)         9(29%)         0.325           N1         14(48.3%)         15(48.4%)         0.325           N2         8(27.6%)         7(22.6%)         0.9551           N2         8(26.9%)         3(30.9%)         0.1981 <td>Range</td> <td>25 - 45</td> <td>28 - 45</td> <td>U = 0.061</td>  | Range   | 25 - 45   | 28 - 45   | U = 0.061  |  |  |  |   |  
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| Menopausal state       0.001         Premenopausal       34(82.9%)       36(85.7%)       0.122         Perimenopausal       7(17.1%)       6(14.3%)       0.7268         BMI            < 25  | Median  | 37  | 35  | 0.821  |  |  |  |   |  
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| INTRODUCTION       34(82.9%)       36(85.7%)       0.122         Perimenopausal       7(17.1%)       6(14.3%)       0.7268         BMI       (25)       8(19.5%)       8(19%)       0.0029         ≥ 25       33(80.5%)       34(81%)       0.957         Histopathology       (17.3%)       2(4.8%)       0.624         Tumor Grade       (11)       (10,23.8%)       0.1001         II       10(23.8%)       0.7517         Stage       (11)       (12,62%)       0.239         IV       11(26.8%)       10(23.8%)       0.7517         Stage       (11)       (21,9%)       9(21.4%)       0.126         II       9(21.9%)       9(21.4%)       0.126       0.398         IV       12(22.3%)       11(26.2%)       0.386       73         IV       12(23.3%)       14(45.2%)       0.8568       73       0.309       0.325         N1       14(48.3%)       15(48.4%)       0.9551       0.325       0.315       0.325       0.325       0.309       0.325       0.309       0.325       0.309       0.325       0.309       0.325       0.309       0.325       0.309       0.325       0.325       0.325   | Menonausal state  | 51  | 55  | 0.021  |  |  |  |   |  
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| 1 Interplatati $7(12.\%)$ $5(0.57.\%)$ $0.122$ Perimenopausal $7(17.\%)$ $6(14.3\%)$ $0.0226$ BMI $                                       <$  | $<<<<< < < < < < < < < < < < < < < < < <  < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < <<$ | $<<< < < < < < < < < < < < < < < < < <  < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < <<$ | $< < < < < < < < < < < < < < < < < <  < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < <<$ | < <td> &lt;<td> &lt;<td> &lt;<td> <math>&lt;<td> &lt;<td> <math>&lt;<td> &lt;<td> &lt;<td> &lt;<td> &lt;<td> &lt;<td> &lt;<td> <math>&lt;<td> &lt;<td> &lt;<td> &lt;<td>  &lt;<td> &lt;<td> 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| Initial parts $(111.1\%)$   | Perimenopausal  | 7(17,1%)  | 6(14.3%)  | 0.7268   |  |  |  |   |  
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| < 25       8(19.5%)       8(19%)       0.0029         ≥ 25       33(80.5%)       34(81%)       0.957         Histopathology       IDC       38(92.7%)       40(95.2%)       0.239         ILC       3(7.3%)       2(4.8%)       0.624         Tumor Grade       II       11(26.8%)       10(23.8%)       0.7517         Stage       II       9(21.9%)       9(21.4%)       0.126         III       9(21.9%)       9(21.4%)       0.126         III       20(48.8%)       22(52.4%)       0.938         IV       12(29.3%)       11(26.2%)       0.309         T stage (non-metastatic)       T       11(344.8%)       9(29%)         N stage (non-metastatic)       N       10(34.5%)       9(29%)         N stage (non-metastatic)       N       14(48.3%)       15(48.4%)       0.325         N1       14(48.3%)       15(48.4%)       0.9551       N3       2(6.9%)       3(9.7%)       T         Type of surgery       I2(29.3%)       11(26.2%)       0.9056       No       S(19.9%)       0.9157         MRM       18(43.9%)       13(30.9%)       0.1981       MRM       18(43.9%)       0.9265         No surgery   | RMI   | /(17.170)   | 0(14.370)   | 0.7208   |  |  |  |   |  
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| $\begin{array}{cccccccccccccccccccccccccccccccccccc$  | < 25  | 8(10,5%)  | 8(100%)   | 0.0020   |  |  |  |   |  
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| E 2D $33(01, 30)$ $34(176)$ $0.997$ Histopathology $UC$ $38(92, 7%)$ $40(95, 2%)$ $0.239$ LC $37(, 3%)$ $2(4, 8%)$ $0.624$ Tumor Grade $U$ $U$ $U$ $0.624$ II $30(73, 2%)$ $32(76, 2%)$ $0.1001$ III $11(26, 8%)$ $10(23, 8%)$ $0.7517$ Stage $U$ $11(26, 8%)$ $10(23, 8%)$ $0.126$ III $9(21, 9%)$ $9(21, 4%)$ $0.126$ $0.7517$ Stage (non-metastatic) $T$ $T$ $f (20, 7%)$ $8(25, 8%)$ $0.309$ T stage (non-metastatic) $T$ $T$ $6(20, 7%)$ $8(25, 8%)$ $0.309$ T stage (non-metastatic) $T$ $0.34(3, 5%)$ $9(29%)$ $0.325$ N a $2(7, 2%)$ $6(19, 3%)$ $0.325$ N 1 $14(48, 3%)$ $15(48, 4%)$ $0.9551$ N 2 $8(27, 6%)$ $7(22, 6%)$ $0.9551$ N 2 $8(27, 6%)$ $13(30, 9%)$ $0.1981$ MRM $18(43, 9%)$ </td <td>&lt; 25<br/>&gt; 25</td> <td>3(19.5%)<br/>22(80.5%)</td> <td>3(1770)<br/>24(810)</td> <td>0.0023</td>  | < 25<br>> 25  | 3(19.5%)<br>22(80.5%)   | 3(1770)<br>24(810)  | 0.0023   |  |  |  |   |  
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| IDC $38(92.7\%)$ $40(95.2\%)$ $0.239$ ILC $3(7.3\%)$ $2(4.8\%)$ $0.624$ <b>Tumor Grade</b> $11$ $11(26.8\%)$ $10(23.8\%)$ $0.7517$ Stage $11$ $11(26.8\%)$ $10(23.8\%)$ $0.7517$ Stage $11$ $9(21.4\%)$ $0.126$ III $9(21.9\%)$ $9(21.4\%)$ $0.126$ III $20(48.8\%)$ $22(52.4\%)$ $0.938$ IV $12(29.3\%)$ $11(26.2\%)$ $0.309$ T stage (non-metastatic) $T$ $T$ $6(29.\%)$ $0.8568$ T3 $10(34.5\%)$ $9(29\%)$ $0.325$ N stage (non-metastatic) $T$ $T$ $0.325$ N1 $14(48.3\%)$ $15(48.4\%)$ $0.9551$ N3 $2(6.9\%)$ $3(9.9\%)$ $0.9551$ N3 $2(6.9\%)$ $3(30.9\%)$ $0.1981$ MRM $18(43.9\%)$ $11(26.2\%)$ $0.9055$ No surgery $12(29.3\%)$ $11(26.2\%)$ $0.9243$ Luminal A $14(434.1\%)$ $13(30.9\%)$ $0.157$ </td <td><math>\geq 23</math></td> <td>33(80.5%)</td> <td>34(81%)</td> <td>0.937</td>   | $\geq 23$   | 33(80.5%)   | 34(81%)   | 0.937  |  |  |  |   |  
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| IDC $3(7.3\%)$ $44(95.2\%)$ $0.23\%$ ILC $3(7.3\%)$ $2(4.8\%)$ $0.624$ <b>Tumor Grade</b> 1 $11(26.8\%)$ $10(23.8\%)$ $0.7517$ Stage       11 $11(26.8\%)$ $0(21.4\%)$ $0.126$ II $9(21.9\%)$ $9(21.4\%)$ $0.126$ III $20(48.8\%)$ $22(52.4\%)$ $0.338$ IV $12(29.3\%)$ $11(26.2\%)$ T         T stage (non-metastatic)       T $T$ $6(20.7\%)$ $8(25.8\%)$ $0.309$ T2 $13(44.8\%)$ $14(45.2\%)$ $0.8568$ $337$ $0.8568$ T3 $10(34.5\%)$ $9(29\%)$ $0.8568$ $333$ $2(6.9\%)$ $3(9.7\%)$ Nstage (non-metastatic) $W$ $10(34.5\%)$ $13(30.9\%)$ $0.325$ N2 $8(27.6\%)$ $7(22.6\%)$ $0.9551$ N3 $2(6.9\%)$ $3(9.7\%)$ $0.92263$ N4 $14(48.3\%)$ $13(30.9\%)$ $0.1981$ MRM $18(43.9\%)$ $13(30.9\%)$ $0.9556$ No surgery $12(29.3\%)$ $1$   |   | 28(02 70/)  | 40(05.20/)  | 0.220  |  |  |  |   |  
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| ILC $3(7.5\%)$ $2(4.5\%)$ $0.024$ Tumor Grade $1$ $30(73.2\%)$ $32(76.2\%)$ $0.1001$ II $11(26.8\%)$ $10(23.8\%)$ $0.7517$ Stage $11$ $0(21.9\%)$ $9(21.4\%)$ $0.126$ II $20(48.8\%)$ $22(52.4\%)$ $0.938$ IV $12(29.3\%)$ $11(26.2\%)$ $0.309$ T stage (non-metastatic) $11$ $6(20.7\%)$ $8(25.8\%)$ $0.309$ T2 $13(44.8\%)$ $14(45.2\%)$ $0.8568$ T3 $10(34.5\%)$ $9(29\%)$ $0.325$ N stage (non-metastatic) $10(34.5\%)$ $9(29\%)$ $0.325$ N1 $14(48.3\%)$ $15(48.4\%)$ $0.325$ N1 $14(48.3\%)$ $15(48.4\%)$ $0.9551$ N2 $8(27.6\%)$ $7(22.6\%)$ $0.9551$ N3 $2(6.9\%)$ $3(9.7\%)$ $0.9243$ MRM $18(43.9\%)$ $13(30.9\%)$ $0.1981$ MRM $18(43.9\%)$ $13(30.9\%)$ $0.157$ Luminal B2 (Her2/neu +ve) $23(56.1\%)$ $24(57.1\%)$   |   | 38(92.1%)   | 40(93.2%)   | 0.239  |  |  |  |   |  
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| Initial of GradeII $30(73.2\%)$ $32(76.2\%)$ $0.1001$ III $11(26.8\%)$ $10(23.8\%)$ $0.7517$ StageII $9(21.9\%)$ $9(21.4\%)$ $0.126$ III $20(48.8\%)$ $22(52.4\%)$ $0.938$ IV $12(29.3\%)$ $11(26.2\%)$ $0.7517$ T stage (non-metastatic) $T$ $T$ $6(20.7\%)$ $8(25.8\%)$ $0.309$ T2 $13(44.8\%)$ $14(45.2\%)$ $0.8568$ $T3$ $00(34.5\%)$ $9(29\%)$ N stage (non-metastatic) $T$ $T$ $0.325$ $0.325$ N1 $14(48.3\%)$ $15(48.4\%)$ $0.325$ $0.9551$ N2 $8(27.6\%)$ $7(22.6\%)$ $0.9551$ N3 $2(6.9\%)$ $3(9.7\%)$ $T$ Type of surgery $T$ $T$ $T$ BCS $11(26.8\%)$ $13(30.9\%)$ $0.1981$ MRM $18(43.9\%)$ $18(42.9\%)$ $0.9056$ No surgery $12(29.3\%)$ $11(26.2\%)$ $M$ Molecular subtype: $T$ $T$ $T$ Luminal A $14(34.1\%)$ $13(30.9\%)$ $0.157$ Luminal B1(Her2/neu -we) $2(50\%)$ $24(57.1\%)$ $0.9243$ Luminal B2 (Her2/neu +we) $4(25\%)$ $2(11.9\%)$ Sites of metastasis: (stage IV) $T$ $T$ Bone only $6(50\%)$ $5(45.5\%)$ $0.391$ Bone only $6(50\%)$ $2(66.1,9\%)$ $0.0991$ Chemotherapy. $26(63.4\%)$ $26(61.9\%)$ $0.0991$ Chemotherapy. $26(6$   | ILC<br>Turn on Cruede   | 3(7.5%)   | 2(4.8%)   | 0.024  |  |  |  |   |  
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| II $30(73.2\%)$ $32(76.2\%)$ $0.1001$ III $11(26.8\%)$ $10(23.8\%)$ $0.7517$ Stage $11$ $9(21.9\%)$ $9(21.4\%)$ $0.126$ III $20(48.8\%)$ $22(52.4\%)$ $0.938$ IV $12(29.3\%)$ $11(26.2\%)$ T stage (non-metastatic) $11(26.2\%)$ $0.309$ T2 $13(44.8\%)$ $14(45.2\%)$ $0.8568$ T3 $10(34.5\%)$ $9(29\%)$ $0.325$ N stage (non-metastatic) $N$ $0.345\%$ $0.929\%$ N stage (non-metastatic) $N$ $0.325$ $0.325$ N1 $14(48.3\%)$ $15(48.4\%)$ $0.9551$ N2 $8(27.6\%)$ $7(22.6\%)$ $0.9551$ N3 $2(6.9\%)$ $3(9.7\%)$ $0.1981$ MRM $18(43.9\%)$ $11(26.2\%)$ $0.9056$ No surgery $12(29.3\%)$ $11(26.2\%)$ $0.9056$ No surgery $12(29.3\%)$ $11(26.2\%)$ $0.9243$ Luminal B (Her2/neu -ve) $23(56.1\%)$ $24(57.1\%)$ $0.9243$ Luminal B 1(Her2/ne   | Tumor Grade   | 20(72.2%)   | 22(76.20)   | 0 1001   |  |  |  |   |  
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| III       11(26.8%) $0.7517$ Stage       9(21.9%)       9(21.4%) $0.126$ III       20(48.8%)       22(52.4%) $0.938$ IV       12(29.3%)       11(26.2%) $0.938$ T stage (non-metastatic)       T       T1 $6(20.7\%)$ $8(25.8\%)$ $0.309$ T2       13(44.8%)       14(45.2%) $0.8568$ $0.309$ T3       10(34.5%)       9(29%) $0.8568$ N stage (non-metastatic)       W $0.929\%$ $0.325$ N1       14(48.3%)       15(48.4%) $0.3255$ N2 $8(27.6\%)$ $7(22.6\%)$ $0.9551$ N3       2(6.9%) $3(0.7\%)$ $0.9956$ MRM       18(43.9\%)       18(42.9\%) $0.9056$ No surgery       12(29.3\%)       11(26.2\%) $0.9243$ Molecular subtype:       Uminal B1(Her2/neu -ve)       23(56.1%)       24(57.1%) $0.9243$ Luminal B2 (Her2/neu -ve)       23(56.1%)       24(57.1%) $0.9243$ Luminal B2 (Her2/neu +ve)       4(9.8%)       5(11.9%) $0.8224$ Others (distant LN, effusion)       3(25%) <td< td=""><td></td><td>30(73.2%)</td><td>32(76.2%)</td><td>0.1001</td></td<>   |   | 30(73.2%)   | 32(76.2%)   | 0.1001   |  |  |  |   |  
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| StageII9(21.9%)9(21.4%)0.126III20(48.8%)22(52.4%)0.938IV12(29.3%)11(26.2%)7T stage (non-metastatic) $V$ 12(29.3%)11(26.2%)T16(20.7%)8(25.8%)0.309T213(44.8%)14(45.2%)0.8568T310(34.5%)9(29%) $V$ N stage (non-metastatic) $V$ $V$ N0 $5(17.2\%)$ $6(19.3\%)$ $0.325$ N114(48.3%)15(48.4%) $0.325$ N2 $8(27.6\%)$ $7(22.6\%)$ $0.9551$ N3 $2(6.9\%)$ $3(9.7\%)$ $V$ BCS11(26.8%)13(30.9%) $0.1981$ MRM18(43.9%)18(42.9%) $0.9056$ No surgery12(29.3%)11(26.2%)Molecular subtype: $U$ $U$ Luminal A14(34.1%)13(30.9%) $0.157$ Luminal B 1(Her2/neu -ve)23(56.1%)24(57.1%) $0.9243$ Luminal B 2 (Her2/neu +ve)4(9.8%) $5(11.9\%)$ $0.391$ Bone and Visceral3(25%)2(18.2%) $0.8224$ Others (distant LN, effusion) $3(25\%)$ 4(36.3\%) $V$ Previous systemic treatment $11(26.8\%)$ $11(26.2\%)$ Hormonal treatment $11(26.8\%)$ $11(26.2\%)$ $0.9591$ No previous treatment $11(26.8\%)$ $5(11.9\%)$ $0.9591$ No previous treatment $10(46.3\%)$ $5(11.9\%)$ $0.9591$ No previous treatment $10(46.3\%)$ $17$   |   | 11(26.8%)   | 10(23.8%)   | 0./51/   |  |  |  |   |  
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| II $9(21.9\%)$ $9(21.4\%)$ $0.126$ III $20(48.8\%)$ $22(52.4\%)$ $0.938$ IV $12(29.3\%)$ $11(26.2\%)$ T stage (non-metastatic) $11(26.2\%)$ $0.309$ T2 $13(44.8\%)$ $14(45.2\%)$ $0.8568$ T3 $10(34.5\%)$ $9(29\%)$ $0.325$ N stage (non-metastatic) $0.92\%$ $0.92\%$ N stage (non-metastatic) $0.92\%$ $0.92\%$ N0 $5(17.2\%)$ $6(19.3\%)$ $0.325$ N1 $14(48.3\%)$ $15(48.4\%)$ $0.9551$ N2 $8(27.6\%)$ $7(22.6\%)$ $0.9551$ N3 $2(6.9\%)$ $3(9.7\%)$ $0.9056$ No surgery $12(29.3\%)$ $11(26.2\%)$ $0.9056$ No surgery $12(29.3\%)$ $11(26.2\%)$ $0.9056$ No surgery $12(29.3\%)$ $11(26.2\%)$ $0.9243$ Luminal A $14(34.1\%)$ $13(30.9\%)$ $0.157$ Luminal B1(Her2/neu -ve) $23(56.1\%)$ $24(57.1\%)$ $0.9243$ Luminal B1(Her2/neu +ve) $40.8\%$ $5(11.9\%)$  | Stage   |   |   | 0.10   |  |  |  |   |  
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| III $20(48.8\%)$ $22(52.4\%)$ $0.938$ IV $12(29.3\%)$ $11(26.2\%)$ T stage (non-metastatic)       T         T1 $6(20.7\%)$ $8(25.8\%)$ $0.309$ T2 $13(44.8\%)$ $14(45.2\%)$ $0.8568$ T3 $10(34.5\%)$ $9(29\%)$ N stage (non-metastatic) $V$ $V$ N0 $5(17.2\%)$ $6(19.3\%)$ $0.325$ N1 $14(48.3\%)$ $15(48.4\%)$ $0.9551$ N2 $8(27.6\%)$ $7(22.6\%)$ $0.9551$ N3 $2(6.9\%)$ $3(9.7\%)$ $0.9551$ MRM $18(43.9\%)$ $18(42.9\%)$ $0.9056$ No surgery $12(29.3\%)$ $11(26.2\%)$ $0.9056$ No surgery $12(29.3\%)$ $11(26.2\%)$ $0.9243$ Luminal A $14(34.1\%)$ $13(30.9\%)$ $0.157$ Luminal B1(Her2/neu -ve) $23(56.1\%)$ $24(57.1\%)$ $0.9243$ Luminal B1 $14(34.1\%)$ $13(30.9\%)$ $0.157$ Luminal B1 (Her2/neu -ve) $23(56.1\%)$ $24(57.1\%)$ $0.9243$   |   | 9(21.9%)  | 9(21.4%)  | 0.126  |  |  |  |   |  
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| IV $12(29.3\%)$ $11(26.2\%)$ T stage (non-metastatic) $(620.7\%)$ $8(25.8\%)$ $0.309$ T2 $13(44.8\%)$ $14(45.2\%)$ $0.8568$ T3 $10(34.5\%)$ $9(29\%)$ N stage (non-metastatic) $V$ $V$ N0 $5(17.2\%)$ $6(19.3\%)$ $0.325$ N1 $14(48.3\%)$ $15(48.4\%)$ $0.9551$ N2 $8(27.6\%)$ $7(22.6\%)$ $0.9551$ N3 $2(6.9\%)$ $3(9.7\%)$ $V$ BCS $11(26.8\%)$ $13(30.9\%)$ $0.1981$ MRM $18(43.9\%)$ $11(26.2\%)$ $0.9056$ No surgery $12(29.3\%)$ $11(26.2\%)$ $0.9056$ Molecular subtype: $U$ $U$ $0.9056$ Luminal B1(Her2/neu -ve) $23(56.1\%)$ $24(57.1\%)$ $0.9243$ Luminal B2 (Her2/neu +ve) $4(9.8\%)$ $5(11.9\%)$ $0.391$ Bone only $6(50\%)$ $5(45.5\%)$ $0.391$ Bone and Visceral $3(25\%)$ $2(18.2\%)$ $0.8224$ Others (distant LN, effusion) $3(25\%)$  |   | 20(48.8%)   | 22(52.4%)   | 0.938  |  |  |  |   |  
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| T stage (non-metastatic) $(20.7\%)$ $8(25.8\%)$ $0.309$ T2 $13(44.8\%)$ $14(45.2\%)$ $0.8568$ T3 $10(34.5\%)$ $9(29\%)$ N stage (non-metastatic) $(19.3\%)$ $0.325$ N1 $14(48.3\%)$ $15(48.4\%)$ $0.325$ N2 $8(27.6\%)$ $7(22.6\%)$ $0.9551$ N3 $2(6.9\%)$ $3(9.7\%)$ $0.9551$ Type of surgery $BCS$ $11(26.8\%)$ $13(30.9\%)$ $0.1981$ MRM $18(43.9\%)$ $18(42.9\%)$ $0.9056$ No surgery $12(29.3\%)$ $11(26.2\%)$ $0.9056$ Molecular subtype: $U$ $U$ $U$ $0.9243$ Luminal A (Her2/neu -ve) $23(56.1\%)$ $24(57.1\%)$ $0.9243$ Luminal B (Her2/neu +ve) $4(9.8\%)$ $5(11.9\%)$ $0.8224$ Others (distant LN, effusion) $3(25\%)$ $2(18.2\%)$ $0.8224$ Others (distant LN, effusion) $3(25\%)$ $2(6(61.9\%)$ $0.0991$ Bone and Visceral $3(25\%)$ $26(61.9\%)$ $0.9251$ No previous treatment <t< td=""><td></td><td>12(29.3%)</td><td>11(26.2%)</td><td></td></t<>   |   | 12(29.3%)   | 11(26.2%)   |  |  |  |  |   |  
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| 11 $6(20.7\%)$ $8(25.8\%)$ $0.309$ T2 $13(44.8\%)$ $14(45.2\%)$ $0.8568$ T3 $10(34.5\%)$ $9(29\%)$ N stage (non-metastatic) $0(34.5\%)$ $9(29\%)$ N0 $5(17.2\%)$ $6(19.3\%)$ $0.325$ N1 $14(48.3\%)$ $15(48.4\%)$ $0.9551$ N2 $8(27.6\%)$ $7(22.6\%)$ $0.9551$ N3 $2(6.9\%)$ $3(9.7\%)$ $0.9056$ Name $8(27.6\%)$ $13(30.9\%)$ $0.1981$ MRM $18(43.9\%)$ $18(42.9\%)$ $0.9056$ No surgery $12(29.3\%)$ $11(26.2\%)$ $0.9026$ Molecular subtype: $U$ $U$ $0.9243$ Luminal B1 (Her2/neu -ve) $23(56.1\%)$ $24(57.1\%)$ $0.9243$ Luminal B2 (Her2/neu +ve) $4(9.8\%)$ $5(11.9\%)$ $0.8224$ Others (distant LN, effusion) $3(25\%)$ $2(63.3\%)$ $0.0991$ Bone only $6(50\%)$ $5(45.5\%)$ $0.3911$ Bone divisoral $3(25\%)$ $2(661.9\%)$ $0.0991$ Chemotherapy. <td>T stage (non-metastatic)</td> <td></td> <td></td> <td></td>  | T stage (non-metastatic)  |   |   |  |  |  |  |   |  
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| T2 $13(44.8\%)$ $14(45.2\%)$ $0.8568$ T3 $10(34.5\%)$ $9(29\%)$ N stage (non-metastatic) $10(34.5\%)$ $9(29\%)$ N0 $5(17.2\%)$ $6(19.3\%)$ $0.325$ N1 $14(48.3\%)$ $15(48.4\%)$ $0.325$ N2 $8(27.6\%)$ $7(22.6\%)$ $0.9551$ N3 $2(6.9\%)$ $3(9.7\%)$ $Type of surgery$ BCS $11(26.8\%)$ $13(30.9\%)$ $0.1981$ MRM $18(43.9\%)$ $18(42.9\%)$ $0.9056$ No surgery $12(29.3\%)$ $11(26.2\%)$ $0.9056$ Molecular subtype: $U$ $U$ $U$ Luminal A $14(34.1\%)$ $13(30.9\%)$ $0.157$ Luminal B1(Her2/neu -ve) $23(56.1\%)$ $24(57.1\%)$ $0.9243$ Luminal B2 (Her2/neu +ve) $4(9.8\%)$ $5(11.9\%)$ $0.8224$ Others (distant LN, effusion) $3(25\%)$ $2(18.2\%)$ $0.8224$ Others (distant LN, effusion) $3(25\%)$ $26(61.9\%)$ $0.0991$ Chemotherapy. $26(63.4\%)$ $26(61.9\%)$ $0.0991$ Chemotherapy +Herceptin. $4(9.8\%)$ $5(11.9\%)$ $0.951$ No previous treatment $11(26.8\%)$ $11(26.2\%)$ $11(26.2\%)$ Hormonal treatment $12(46.3\%)$ $17(40.5\%)$ $0.290$ Al $27(53.7\%)$ $27(59.5\%)$ $0.5998$   |   | 6(20.7%)  | 8(25.8%)  | 0.309  |  |  |  |   |  
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| T3 $10(34.5\%)$ $9(29\%)$ N stage (non-metastatic) $0.325$ N0 $5(17.2\%)$ $6(19.3\%)$ N1 $14(48.3\%)$ $15(48.4\%)$ N2 $8(27.6\%)$ $7(22.6\%)$ N3 $2(6.9\%)$ $3(9.7\%)$ Type of surgeryBCS $11(26.8\%)$ $13(30.9\%)$ MRM $18(43.9\%)$ $18(42.9\%)$ No surgery $12(29.3\%)$ $11(26.2\%)$ Molecular subtype: $U$ Luminal A $14(34.1\%)$ $13(30.9\%)$ Luminal B1(Her2/neu -ve) $23(56.1\%)$ $24(57.1\%)$ Luminal B2 (Her2/neu +ve) $4(9.8\%)$ $5(11.9\%)$ Sites of metastasis: (stage IV) $U$ Bone only $6(50\%)$ $5(45.5\%)$ Bone only $6(50\%)$ $24(63.9\%)$ Previous systemic treatment $3(25\%)$ $2(86.3\%)$ Chemotherapy. $26(63.4\%)$ $26(61.9\%)$ Others (distant LN, effusion) $3(25\%)$ $21(8.2\%)$ No previous treatment $11(26.8\%)$ $11(26.2\%)$ Hormonal treatment $11(26.8\%)$ $11(26.2\%)$ Hormonal treatment $12(263.7\%)$ $25(59.5\%)$ Al $22(53.7\%)$ $25(59.5\%)$ $0.5908$   | 12  | 13(44.8%)   | 14(45.2%)   | 0.8568   |  |  |  |   |  
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| N stage (non-metastatic) $N0$ $5(17.2\%)$ $6(19.3\%)$ $0.325$ N1 $14(48.3\%)$ $15(48.4\%)$ $0.9551$ N2 $8(27.6\%)$ $7(22.6\%)$ N3 $2(6.9\%)$ $3(9.7\%)$ Type of surgery         BCS $11(26.8\%)$ $13(30.9\%)$ $0.1981$ MRM $18(43.9\%)$ $18(42.9\%)$ $0.9056$ No surgery $12(29.3\%)$ $11(26.2\%)$ $0.9056$ Molecular subtype: $U$ $U$ $0.157$ Luminal A $14(34.1\%)$ $13(30.9\%)$ $0.157$ Luminal B1(Her2/neu -ve) $23(56.1\%)$ $24(57.1\%)$ $0.9243$ Luminal B2 (Her2/neu +ve) $4(9.8\%)$ $5(11.9\%)$ $0.9243$ Luminal B2 (Her2/neu +ve) $4(9.8\%)$ $5(45.5\%)$ $0.391$ Bone only $6(50\%)$ $5(45.5\%)$ $0.391$ Bone only $6(50\%)$ $5(45.5\%)$ $0.391$ Bone and Visceral $3(25\%)$ $4(36.3\%)$ $0.0991$ Chemotherapy $26(63.4\%)$ $26(61.9\%)$ $0.951$ No previous treatment   | Τ3  | 10(34.5%)   | 9(29%)  |  |  |  |  |   |  
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| N0 $5(17.2\%)$ $6(19.3\%)$ $0.325$ N1 $14(48.3\%)$ $15(48.4\%)$ $0.9551$ N2 $8(27.6\%)$ $7(22.6\%)$ $0.9551$ N3 $2(6.9\%)$ $3(9.7\%)$ $0.9551$ Type of surgeryBCS $11(26.8\%)$ $13(30.9\%)$ $0.1981$ MRM $18(43.9\%)$ $18(42.9\%)$ $0.9056$ No surgery $12(29.3\%)$ $11(26.2\%)$ Molecular subtype: $U$ $U$ Luminal A $14(34.1\%)$ $13(30.9\%)$ $0.157$ Luminal B1(Her2/neu -ve) $23(56.1\%)$ $24(57.1\%)$ $0.9243$ Luminal B2 (Her2/neu +ve) $4(9.8\%)$ $5(11.9\%)$ $0.8224$ Sites of metastasis: (stage IV) $U$ $U$ $0.8224$ Bone only $6(50\%)$ $5(45.5\%)$ $0.391$ Bone and Visceral $3(25\%)$ $2(18.2\%)$ $0.8224$ Others (distant LN, effusion) $3(25\%)$ $4(36.3\%)$ Previous systemic treatment $U(26.3\%)$ $5(11.9\%)$ $0.951$ No previous treatment $11(26.8\%)$ $11(26.2\%)$ Hormonal treatment $U$ $27(53.7\%)$ $25(59.5\%)$ $0.5908$   | N stage (non-metastatic)  |   |   |  |  |  |  |   |  
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| N1 $14(48.3\%)$ $15(48.4\%)$ $0.025$ N2 $8(27.6\%)$ $7(22.6\%)$ $0.9551$ N3 $2(6.9\%)$ $3(9.7\%)$ Type of surgeryBCS $11(26.8\%)$ $13(30.9\%)$ $0.1981$ MRM $18(43.9\%)$ $18(42.9\%)$ $0.9056$ No surgery $12(29.3\%)$ $11(26.2\%)$ Molecular subtype: $Uuminal A$ $14(34.1\%)$ $13(30.9\%)$ $0.157$ Luminal B1(Her2/neu -ve) $23(56.1\%)$ $24(57.1\%)$ $0.9243$ Luminal B2 (Her2/neu +ve) $4(9.8\%)$ $5(11.9\%)$ $0.8224$ Sites of metastasis: (stage IV) $V$ $V$ $0.650\%$ Bone only $6(50\%)$ $5(45.5\%)$ $0.391$ Bone and Visceral $3(25\%)$ $2(18.2\%)$ $0.8224$ Others (distant LN, effusion) $3(25\%)$ $4(36.3\%)$ $0.0991$ Chemotherapy. $26(63.4\%)$ $26(61.9\%)$ $0.0991$ No previous treatment $11(26.8\%)$ $11(26.2\%)$ $0.951$ No previous treatment $11(26.8\%)$ $0.290$ AI $22(53.7\%)$ $25(59.5\%)$ $0.590\%$   | NO  | 5(17.2%)  | 6(19.3%)  | 0 325  |  |  |  |   |  
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| N2         8(27.6%)         7(22.6%)         0.0001           N3         2(6.9%)         3(9.7%)         7           Type of surgery         2(6.9%)         3(9.7%)         0.1981           MRM         18(43.9%)         13(30.9%)         0.1981           MRM         18(43.9%)         18(42.9%)         0.9056           No surgery         12(29.3%)         11(26.2%)         0.9056           Molecular subtype:         11(26.2%)         0.157           Luminal A         14(34.1%)         13(30.9%)         0.157           Luminal B1(Her2/neu -ve)         23(56.1%)         24(57.1%)         0.9243           Luminal B2 (Her2/neu +ve)         4(9.8%)         5(11.9%)         0.9243           Luminal B2 (Her2/neu +ve)         4(9.8%)         5(11.9%)         0.8224           Others (distant LN, effusion)         3(25%)         2(18.2%)         0.8224           Others (distant LN, effusion)         3(25%)         4(36.3%)         0.0991           Chemotherapy.         26(63.4%)         26(61.9%)         0.0951           No previous systemic treatment         11(26.8%)         11(26.2%)           Hormonal treatment         11(26.3%)         0.5909           Al         22(63.7%)   | N1  | 14(48.3%)   | 15(48.4%)   | 0.9551   |  |  |  |   |  
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| N3 $2(6.9\%)$ $3(9.7\%)$ Type of surgeryBCS $11(26.8\%)$ $13(30.9\%)$ $0.1981$ MRM $18(43.9\%)$ $18(42.9\%)$ $0.9056$ No surgery $12(29.3\%)$ $11(26.2\%)$ Molecular subtype: $11(26.2\%)$ Luminal A $14(34.1\%)$ $13(30.9\%)$ $0.157$ Luminal B1(Her2/neu -ve) $23(56.1\%)$ $24(57.1\%)$ $0.9243$ Luminal B2 (Her2/neu +ve) $4(9.8\%)$ $5(11.9\%)$ $0.391$ Bone only $6(50\%)$ $5(45.5\%)$ $0.391$ Bone and Visceral $3(25\%)$ $2(18.2\%)$ $0.8224$ Others (distant LN, effusion) $3(25\%)$ $4(6.3\%)$ $0.0991$ Chemotherapy $26(63.4\%)$ $5(11.9\%)$ $0.951$ No previous treatment $11(26.8\%)$ $11(26.2\%)$ Hormonal treatment $19(46.3\%)$ $17(40.5\%)$ $0.290$ Al $22(63.7\%)$ $25(59.5\%)$ $0.5909$   | N2  | 8(27.6%)  | 7(22.6%)  | 0.9551   |  |  |  |   |  
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| Type of surgery         BCS $11(26.8\%)$ $13(30.9\%)$ $0.1981$ MRM $18(43.9\%)$ $18(42.9\%)$ $0.9056$ No surgery $12(29.3\%)$ $11(26.2\%)$ Molecular subtype: $11(26.2\%)$ $11(26.2\%)$ Luminal A $14(34.1\%)$ $13(30.9\%)$ $0.157$ Luminal B1(Her2/neu -ve) $23(56.1\%)$ $24(57.1\%)$ $0.9243$ Luminal B2 (Her2/neu +ve) $4(9.8\%)$ $5(11.9\%)$ $0.9243$ Luminal B2 (Her2/neu +ve) $4(9.8\%)$ $5(11.9\%)$ $0.9243$ Luminal B2 (Her2/neu +ve) $4(9.8\%)$ $5(11.9\%)$ $0.8224$ Others (distant LN, effusion) $3(25\%)$ $2(18.2\%)$ $0.8224$ Others (distant LN, effusion) $3(25\%)$ $4(36.3\%)$ $0.0991$ Previous systemic treatment $11(26.8\%)$ $0.0991$ $0.951$ No previous treatment $11(26.8\%)$ $11(26.2\%)$ $0.951$ Hormonal treatment $19(46.3\%)$ $17(40.5\%)$ $0.290$ AI $22(53.7\%)$ $25(59.5\%)$ $0.5809$  | N3  | 2(6.9%)   | 3(9.7%)   |  |  |  |  |   |  
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| BCS $11(26.8\%)$ $13(30.9\%)$ $0.1981$ MRM $18(43.9\%)$ $18(42.9\%)$ $0.9056$ No surgery $12(29.3\%)$ $11(26.2\%)$ Molecular subtype: $12(29.3\%)$ $11(26.2\%)$ Luminal A $14(34.1\%)$ $13(30.9\%)$ $0.157$ Luminal B1(Her2/neu -ve) $23(56.1\%)$ $24(57.1\%)$ $0.9243$ Luminal B2 (Her2/neu +ve) $4(9.8\%)$ $5(11.9\%)$ Sites of metastasis: (stage IV)Bone only $6(50\%)$ $5(45.5\%)$ $0.391$ Bone and Visceral $3(25\%)$ $2(18.2\%)$ $0.8224$ Others (distant LN, effusion) $3(25\%)$ $4(36.3\%)$ $0.0991$ Previous systemic treatment $Chemotherapy$ $26(63.4\%)$ $26(61.9\%)$ $0.0991$ No previous treatment $11(26.8\%)$ $11(26.2\%)$ $0.951$ Hormonal treatment $13(30.9\%)$ $0.290$ $0.290$ Al $22(53.7\%)$ $25(59.5\%)$ $0.5909$   | Type of surgery   |   |   |  |  |  |  |   |  
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| MRM $18(43.9\%)$ $18(42.9\%)$ $0.9056$ No surgery $12(29.3\%)$ $11(26.2\%)$ Molecular subtype: $11(26.2\%)$ Luminal A $14(34.1\%)$ $13(30.9\%)$ $0.157$ Luminal B1(Her2/neu -ve) $23(56.1\%)$ $24(57.1\%)$ $0.9243$ Luminal B2 (Her2/neu +ve) $4(9.8\%)$ $5(11.9\%)$ $0.9243$ Sites of metastasis: (stage IV) $0.5(45.5\%)$ $0.391$ $0.8224$ Bone only $6(50\%)$ $5(45.5\%)$ $0.8224$ Others (distant LN, effusion) $3(25\%)$ $4(36.3\%)$ $0.0991$ Previous systemic treatment $10(26.3\%)$ $0.0991$ Chemotherapy $26(63.4\%)$ $5(11.9\%)$ $0.951$ No previous treatment $11(26.8\%)$ $11(26.2\%)$ Hormonal treatment $10(46.3\%)$ $17(40.5\%)$ $0.290$ Al $22(53.7\%)$ $25(59.5\%)$ $0.5908$   | BCS   | 11(26.8%)   | 13(30.9%)   | 0.1981   |  |  |  |   |  
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| No surgery $12(29.3\%)$ $11(26.2\%)$ Molecular subtype: $11(30.9\%)$ $0.157$ Luminal A $14(34.1\%)$ $13(30.9\%)$ $0.157$ Luminal B1(Her2/neu -ve) $23(56.1\%)$ $24(57.1\%)$ $0.9243$ Luminal B2 (Her2/neu +ve) $4(9.8\%)$ $5(11.9\%)$ $0.9243$ Sites of metastasis: (stage IV) $0.9243$ $0.9243$ Bone only $6(50\%)$ $5(45.5\%)$ $0.391$ Bone and Visceral $3(25\%)$ $2(18.2\%)$ $0.8224$ Others (distant LN, effusion) $3(25\%)$ $4(36.3\%)$ $0.0991$ Previous systemic treatment $26(63.4\%)$ $26(61.9\%)$ $0.0991$ Chemotherapy $26(63.4\%)$ $5(11.9\%)$ $0.951$ No previous treatment $11(26.8\%)$ $11(26.2\%)$ $0.290$ Hormonal treatment $22(53.7\%)$ $25(59.5\%)$ $0.5998$   | MRM   | 18(43.9%)   | 18(42.9%)   | 0.9056   |  |  |  |   |  
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| Molecular subtype:13(30.9%)0.157Luminal A14(34.1%)13(30.9%)0.157Luminal B1(Her2/neu -ve)23(56.1%)24(57.1%)0.9243Luminal B2 (Her2/neu +ve)4(9.8%)5(11.9%)Sites of metastasis: (stage IV) $\mathbf{S}$ $\mathbf{S}$ $\mathbf{S}$ Bone only $\mathbf{G}$ $\mathbf{S}$ $\mathbf{S}$ $\mathbf{S}$ Bone and Visceral $3$ $2$ $\mathbf{S}$ $\mathbf{S}$ Others (distant LN, effusion) $3$ $2$ $\mathbf{S}$ $\mathbf{S}$ Previous systemic treatment $\mathbf{S}$ $\mathbf{S}$ $\mathbf{S}$ $\mathbf{S}$ Chemotherapy. $2$ $\mathbf{G}$ $\mathbf{S}$ $\mathbf{S}$ $\mathbf{S}$ No previous treatment $11$ $2$ $\mathbf{S}$ $\mathbf{S}$ $\mathbf{S}$ Hormonal treatment $11$ $11$ $\mathbf{S}$ $\mathbf{S}$ $\mathbf{S}$ $\mathbf{A}$ $12$ $11$ $11$ $\mathbf{S}$ <td< td=""><td>No surgery</td><td>12(29.3%)</td><td>11(26.2%)</td><td></td></td<>  | No surgery  | 12(29.3%)   | 11(26.2%)   |  |  |  |  |   |   
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| Luminal A $14(34.1\%)$ $13(30.9\%)$ $0.157$ Luminal B1(Her2/neu -ve) $23(56.1\%)$ $24(57.1\%)$ $0.9243$ Luminal B2 (Her2/neu +ve) $4(9.8\%)$ $5(11.9\%)$ $0.9243$ Sites of metastasis: (stage IV) $6(50\%)$ $5(45.5\%)$ $0.391$ Bone only $6(50\%)$ $2(18.2\%)$ $0.8224$ Others (distant LN, effusion) $3(25\%)$ $4(36.3\%)$ $0.0991$ Previous systemic treatment $Chemotherapy.$ $26(63.4\%)$ $26(61.9\%)$ $0.0991$ No previous treatment $11(26.8\%)$ $11(26.2\%)$ $0.591$ Hormonal treatment $22(53.7\%)$ $25(59.5\%)$ $0.5909$  | Molecular subtype:  |   |   |  |  |  |  |   |  
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| Luminal B1(Her2/neu -ve) $23(56.1\%)$ $24(57.1\%)$ $0.9243$ Luminal B2 (Her2/neu +ve) $4(9.8\%)$ $5(11.9\%)$ $5(11.9\%)$ Sites of metastasis: (stage IV) $6(50\%)$ $5(45.5\%)$ $0.391$ Bone only $6(50\%)$ $2(18.2\%)$ $0.8224$ Others (distant LN, effusion) $3(25\%)$ $4(36.3\%)$ $0.0991$ Previous systemic treatment $26(63.4\%)$ $26(61.9\%)$ $0.0991$ Chemotherapy + Herceptin. $4(9.8\%)$ $5(11.9\%)$ $0.951$ No previous treatment $11(26.2\%)$ $11(26.2\%)$ Hormonal treatment $22(53.7\%)$ $25(59.5\%)$ $0.5909$  | Luminal A   | 14(34.1%)   | 13(30.9%)   | 0.157  |  |  |  |   |  
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| Luminal B2 (Her2/neu +ve) $4(9.8\%)$ $5(11.9\%)$ Sites of metastasis: (stage IV) $(50\%)$ $5(45.5\%)$ $0.391$ Bone only $6(50\%)$ $5(45.5\%)$ $0.8224$ Others (distant LN, effusion) $3(25\%)$ $2(18.2\%)$ $0.8224$ Others (distant LN, effusion) $3(25\%)$ $2(663.4\%)$ $0.0991$ Previous systemic treatment $26(63.4\%)$ $26(61.9\%)$ $0.0991$ Chemotherapy $26(63.4\%)$ $5(11.9\%)$ $0.951$ No previous treatment $11(26.8\%)$ $11(26.2\%)$ $0.290$ Hormonal treatment $22(53.7\%)$ $22(59.5\%)$ $0.5908$  | Luminal B1(Her2/neu -ve)  | 23(56.1%)   | 24(57.1%)   | 0.9243   |  |  |  |   |  
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| Sites of metastasis: (stage IV)         6(50%)         5(45.5%)         0.391           Bone only         6(50%)         2(18.2%)         0.8224           Others (distant LN, effusion)         3(25%)         4(36.3%)         0.8224           Previous systemic treatment         26(63.4%)         26(61.9%)         0.0991           Chemotherapy         26(63.4%)         5(11.9%)         0.951           No previous treatment         11(26.8%)         11(26.2%)         0.951           Hormonal treatment         22(53.7%)         25(59.5%)         0.5908  | Luminal B2 (Her2/neu +ve)   | 4(9.8%)   | 5(11.9%)  |  |  |  |  |   |  
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| Bone only         6(50%)         5(45.5%)         0.391           Bone and Visceral         3(25%)         2(18.2%)         0.8224           Others (distant LN, effusion)         3(25%)         4(36.3%)         9           Previous systemic treatment         26(63.4%)         26(61.9%)         0.0991           Chemotherapy         26(63.4%)         5(11.9%)         0.951           No previous treatment         11(26.8%)         11(26.2%)         9           Hormonal treatment         22(53.7%)         25(59.5%)         0.5908   | Sites of metastasis: (stage IV)   |   |   |  |  |  |  |   |  
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| Bone and Visceral         3(25%)         2(18.2%)         0.8224           Others (distant LN, effusion)         3(25%)         4(36.3%)         9           Previous systemic treatment         26(63.4%)         26(61.9%)         0.0991           Chemotherapy         26(63.4%)         5(11.9%)         0.951           No previous treatment         11(26.8%)         11(26.2%)         0.951           Hormonal treatment         19(46.3%)         17(40.5%)         0.290           AI         22(53.7%)         25(59.5%)         0.5808  | Bone only   | 6(50%)  | 5(45.5%)  | 0.391  |  |  |  |   |  
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| Previous systemic treatment         26(63.4%)         26(61.9%)         0.0991           Chemotherapy         4(9.8%)         5(11.9%)         0.951           No previous treatment         11(26.8%)         11(26.2%)           Hormonal treatment         20(46.3%)         17(40.5%)         0.290           AI         22(53.7%)         25(59.5%)         0.5808   | Others (distant LN, effusion)   | 3(25%)  | 4(36.3%)  |  |  |  |  |   |  
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| Chemotherapy +Herceptin.       4(9.8%)       5(11.9%)       0.951         No previous treatment       11(26.8%)       11(26.2%)         Hormonal treatment       12(46.3%)       17(40.5%)       0.290         AI       22(53.7%)       25(59.5%)       0.5808  | Chemotherapy.   | 26(63.4%)   | 26(61.9%)   | 0.0991   |  |  |  |   |  
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| No previous treatment     11(26.8%)     11(26.2%)       Hormonal treatment     11(26.3%)     17(40.5%)     0.290       AI     22(53.7%)     25(59.5%)     0.5808  | Chemotherapy +Herceptin.  | 4(9.8%)   | 5(11.9%)  | 0.951  |  |  |  |   |  
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| Hormonal treatment         19(46.3%)         17(40.5%)         0.290           AI         22(53.7%)         25(59.5%)         0.5808  | No previous treatment   | 11(26.8%)   | 11(26.2%)   | 0.701  |  |  |  |   |  
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| Tamoxifen $19(46.3\%)$ $17(40.5\%)$ $0.290$ $\Delta I$ $22(53.7\%)$ $25(59.5\%)$ $0.5808$   | Hormonal treatment  | · /   | × /   |  |  |  |  |   |  
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| $\Delta I = \frac{1}{2} \frac{1}{40.3} \frac{1}{60} = \frac{1}{1} \frac{1}{40.3} \frac{1}{60} = \frac{1}{1} \frac{1}{40.3} \frac{1}{60} = \frac{1}{1} \frac{1}{40.3} \frac{1}{60} = \frac{1}{10} \frac$ | Tamoxifen   | 19(46 3%)   | 17(40.5%)   | 0.290  |  |  |  |   |   |   |  
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|   | ΔΙ  | 22(53.7%)   | 25(50,5%)   | 0.290  |  |  |  |   |  
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Table [1]: Baseline patients' characteristics.

BMI: Body mass index, IDC: infiltrating duct carcinoma, ILC: infiltrating lobular carcinoma, T: tumor, N: lymph node, BCS: breast conservative surgery, MRM: modified radical mastectomy, AI: aromatase inhibitor

	Baseline E2 concentration (pg/ml)	Baseline FSH concentration (IU/ml)
Mean	254.9	25.9
Median	137.6	18.5
Range	55 - 2182	4.5 - 43

Table [2]: Cohort (A) Baseline serum Estradiol (E2) and FSH leve
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E2: estradiol. FSH: follicle stimulating hormone.

Table	[3].	Serial	measurements	of	E2	and	FSH
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	Mean E2 (range) (pg/ml)	Mean FSH (range) (IU/ml)
Baseline	254.9 (55 - 2182)	25.9 (4.5 - 43)
12 weeks	15.4 (3 – 50)	6.5 (1.5 – 16)
24 weeks	10.8 (3 - 50)	5.5 (1.1 – 14.7)
36 weeks	9.6 (3 – 45)	4.5 (1 – 11)
Friedman-test	28.2	16.98
P value	0.001*	0.003*

E2: estradiol. FSH: follicle-stimulating hormone. Significant P value < 0.05.

Table (4). Comparison between conorts A and D regarding D15, 115, and overall survival.						
	Cohort (A) (n=41)	Cohort (B) (n=42)	X <sup>2</sup> P value			
DFS (non-metastatic)	35 (86.2%)	37 (87.1%)	0.1344			
			0.7138			
PFS (metastatic)	27 (66.7%)	27 (63.6%)	0.0224			
			0.8809			
Median OS	41 (100%)	41 (100%)	-			
DFS: disease-free survival	PFS: progression_free si	rvival OS: overall survival				

# Table (4): Comparison between cohorts A and B regarding DFS, PFS, and overall survival.

DFS: disease-free survival. PFS: progression-free survival. OS: overall survival. Significant P value < 0.05.

Table (5): 0	Comparison	between	cohort A	and B	regarding	side effects.
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	Cohort (A) (n=41)	Cohort (B) (n=42)	X <sup>2</sup> P value
Hot flushes	27 (65.8%)	28 (66.7%)	0.0006 0.9375
Headache	15 (36.6%)	17 (40.5%)	0.1326
Hyperhidrosis	3 (7.3%)	3 (7.1%)	0.0009 0.9755
Bone and joint pain	11 (26.8%)	12 (28.5%)	0.0314 0.8592

Significant P value < 0.05.

# **Discussion:**

The Long-acting goserelin 10.8 mg has been approved for patients with prostatic carcinoma as it is similarly effective as goserelin 3.6 mg in terms of suppression of serum testosterone, PSA suppression, PFS, and OS without more adverse events. On contrary, this formula has not been approved for breast cancer patients neither in the adjuvant nor in the metastatic settings. [25]

Both goserelin 10.8 and 3.6 mg are sustained-release depot formulations. For the 3.6 mg formula, it is absorbed slowly during the first 8 days, then more rapid continuous release reaches its peak level of approximately 3ng/ml at day 15 and then declines to approximately 0.5 ng/mL by the end of the treatment period. The 10.8 mg depot reaches its peak level of about 8 ng/ml within 24 hours, then decline rapidly until day 4, then concentrations stabilize in the range of about 0.3 to 1 ng/mL up to the end of the treatment period. [26]

Masuda et al, from Japan, conducted a phase II study comparing monthly versus every 3 months goserelin in pre-menopausal women with estrogen receptor-positive early breast cancer. The primary endpoint was the area under the concentration-time curve (AUC) of E2 serum concentration for the first 24 weeks of treatment. Secondary endpoints were E2 and FSH serum concentrations, cessation of menstruation, and tolerability. 170 patients were included and randomized to receive either monthly (n=84) or 3monthly goserelin (n=86). It was found that 3-monthly goserelin 10.8 mg was non-inferior to monthly goserelin 3.6 mg for the primary endpoint of serum E2 suppression with no difference in the safety profile. All the patients experienced amenorrhea by week 12, the mean AUCs for E2 were similar between treatment groups (18.32 and 18.95 pg/ml per week for goserelin 10.8 and 3.6 mg respectively). [27]

In our study, the serum E2 and FSH levels are adequately suppressed in 97.5% and 100% of patients respectively. All patients (100%) had amenorrhea without any serious adverse events or treatment discontinuation. For non-metastatic patients, the DFS was 86.2 % for cohort A compared to 87.1% for cohort B without statistically significant differences (p= 0.7138).

A phase III trial was carried out by Noguchi et al., 2016 (Japan) comparing 3-monthly versus monthly goserelin in pre-menopausal women with estrogen receptor-positive advanced breast cancer. The primary endpoint was PFS.

222 patients were randomized to goserelin 10.8 mg (n = 109) or goserelin 3.6 mg, (n = 113). PFS rate at week 24 were 61.5 % and 60.2 % for goserelin 10.8 mg and goserelin 3.6 mg, respectively; treatment difference (95 % CI) was 1.3 % (-11.4, 13.9), confirming non-inferiority of goserelin 10.8 mg compared with goserelin 3.6 mg. The overall response rates were 23.9 % (goserelin 10.8 mg) and 26.9 % (goserelin 3.6 mg); treatment difference (95 % CI) was -3.0 % (-15.5, 9.7). At week 24, mean serum E2 concentrations were

similar in the goserelin 10.8 mg and goserelin 3.6 mg groups (20.3 pg/mL and 24.8 pg/mL, respectively). [28]

In the present study, for metastatic patients, the PFS was 66.7% for cohort A compared to 63.6% for cohort B without statistically significant differences (p=0.8809).

Limitations of this study include a small number of patients, short duration of follow-up that determine the effect of the monthly versus 3-monthly dosing regimen on DFS, PFS, or OS uncertain, the inclusion of metastatic and non-metastatic patients, and the comparator arm was retrospective. However, our outcomes still reflect the similar effects of goserelin 10.8 mg and 3.6 mg on estradiol and FSH levels.

# **Conclusion:**

These findings reported here show that 3 monthly goserelin 10.8 mg is as effective as monthly goserelin 3.6 mg in achieving and maintaining ovarian suppression and obtaining similar DFS or PFS in premenopausal women with early and advanced-stage breast cancer respectively with similar toxicity profiles. In addition, it is more convenient to the patients with fewer injections, and less costly which reduces the burden on the health care system. Also, less frequent hospital visits reduce the exposure and transmission of infection, especially during the COVID pandemic.

## List of abbreviations:

COVID: coronavirus-induced disease.

- E2: estradiol.
- FSH: follicle-stimulating hormone.
- LH: luteinizing hormone.

GnRH: gonadotropin hormone-releasing hormone.

- LHRH: luteinizing hormone-releasing hormone.
- RR: response rate.

PFS: progression-free survival.

- OS: overall survival.
- DFS: disease-free survival.

OFS: ovarian function suppression.

SOFT: Suppression of Ovarian Function Trial.

TEXT: Tamoxifen and Exemestane Trial.

ASTRRA: Adding Ovarian Suppression to Tamoxifen for premenopausal breast cancer.

### **Competing interest:**

There was no financial nor non-financial competing interest.

## Author contributions:

The authors contribute to the paper as follows: S.E: study conception and design. S. E and G. K: data collection, analysis of the results, manuscript preparation, revision, and approval of the final version of the manuscript.

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