Supplemental Online Content

Serrano D, Gandini S, Thomas P, et al. Efficacy of alternative dose regimens of exemestane in postmenopausal women with stage 0 to II estrogen receptor–positive breast cancer. *JAMA Oncol*. Published online March 23, 2023. doi:10.1001/jamaoncol.2023.0089

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

A bootstrap analysis (500 samples) was performed to generate 95% CIs around the Least Square Means (LSMEANS) of %changes of estradiol. The bootstrap normal confidence intervals were built around the observed value of the statistic with a bias correction to address the difference between the mean of the bootstrap statistic and the observed value. The bootstrap normal 95% confidence intervals of percentage changes of estradiol were built around the observed value of the statistic with a bias correction to address the difference between the mean of the bootstrap statistic and the observed value. Contrasts of percentage changes of estradiol of QD vs TIW and QD vs QW are presented. with low 97.5% limit.

All secondary biomarkers are presented as median values and interquartile ranges (IQR) at baseline and post treatment, with absolute and percentage change from pre- to post-treatment by arm and intention-to-treat. Differences by arm of absolute change were tested 2-sided p-values for superiority and evaluated through ANCOVA models adjusted for baseline values, BMI and age. ANOVA allows us to control for baseline imbalances of biomarkers and it generally has greater statistical power to detect a treatment effect than the other methods (Dickers and Altman Analysing controlled trials with baseline and follow up measurements, BMJ 2001).

For quality of life data, percentages of symptoms of each domain at baseline and after treatment were presented by trial arms. Data of the MenQoL questionnaire were summarized within each patient at each assessment time, by computing the mean score over distinct items of each domain. For descriptive purposes, such means were used to compute average scores of each domain according to time and treatment arm. Differences by arm of absolute change were evaluated through ANCOVA models adjusted for baseline values, BMI and age.

Normal distribution of residuals from full models were graphically checked.

Bar plots of % of patients with estradiol suppression, i. e. with estradiol below the detectable level, are presented by arms. For binary variables differences in frequencies among arms were evaluated with Chi-squares or Fisher Exact tests.

P-values for secondary endpoints are adjusted for multiple testing (Benjamini-Hochberg).

The statistical analyses were performed with SAS Version 9.4 (SAS Institute, Cary, NC, USA).

eTable 1. Participant and tumor characteristics (median, IQR) by study arm

	Exemestane 25 mg QD (n=57)	Exemestane 25 mg TIW (n=57)	Exemestane 25 mg QW (n=62)
Age at entry, yrs	66 (60 to 71)	63 (60 to 69)	65 (61 to 70)
BMI, kg/m^2	28.0 (23.9 to 32.6)	28.2 (24.1 to 31.8)	28.7 (24.1 to 33.8)
BMI category (normal, overweight, obese), %	32/35/33	28/42/30	29/34/36
Waist/Hip ratio	0.87 (0.84 to 0.92)	0.89 (0.83 to 0.94)	0.88 (0.84 to 0.91)
Smoking (never, ever, unknown)	36/20/1	36/20/1	42/20/0
Alcohol use (never, ever, unknown)	26/30/1	23/34/0	23/38/1
Histotype (invasive, in-situ; n)	54/3	48/9	58/4
ER (%)[§]	99 (95 to 99)	99 (97 to 99)	99 (95 to 99)
PgR (%)[§]	65 (10 to 95)	70 (10 to 99)	70 (8 to 95)
Ki-67 (%)[§]	13 (7 to 17)	13 (7 to 20)	12 (6 to 19)
Her2 overexpression, n[§]	1	5	1

[§] centralized evaluation

QD: once a day; TIW; three times a week, QW: once a week

eTable 2. Participant and tumor characteristics (median, IQR) by study arm and treatment adherence

	Compliant			Non-compliant		
	Exemestane 25 mg QD (n=47)	Exemestane 25 mg TIW (n=52)	Exemestane 25 mg QW (n=54)	Exemestane 25 mg QD (n=10)	Exemestane 25 mg TIW (n=5)	Exemestane 25 mg QW (n=8)
Age at entry, yrs	66 (59 to 71)	64 (60 to 70)	65 (61 to 70)	70 (61 to 79)	63 (63 to 66)	66 (61 to 70)
BMI, kg/m^2	27.7 (23.9 to 32.8)	28.2 (24.1 to 31.5)	28.7 (24.1 to 33.0)	28.1 (23.4 to 32.5)	27.8 (24.4 to 30.4)	32.3 (22.5 to 43.0)
BMI category (normal, overweight, obese), %	33/30/37	29/33/38	32/41/27	29/43/28	33/0/67	43/29/28
Waist/Hip ratio	0.87 (0.85 to 0.92)	0.88 (0.84 to 0.94)	0.88 (0.85 to 0.92)	0.8 (0.83 to 0.92)	0.89 (0.85 to 0.91)	0.88 (0.88 to 0.89)
Smoking (never, ever, unknown)	30/16/1	31/20/1	37/17/0	6/4/0	5/0/0	5/3/0
Alcohol use (never, ever, unknown)	22/24/1	23/29/0	22/31/1	0/6/4	0/5/0	0/6/2

eTable 3. Adverse Events (all grades) occurring in ≥5% of participants by study arm

Body System	CodeTerm*	QD (n=57)	TIW (n=57)	QW (n=62)
Gastrointestinal disorders	Diarrhea	5 (8.8%)	1 (1.8%)	2 (3.2%)
	Dry mouth	1 (1.8%)	3 (5.3%)	0 (0%)
	Dyspepsia	2 (3.5%)	3 (5.3%)	2 (3.2%)
	Nausea	8 (14.0%)	11 (19.3%)	1 (1.6%)
General disorders and administration site conditions	Fatigue	3 (5.3%)	7 (12.3%)	3 (4.8%)
	Irritability	1 (1.8%)	5 (8.8%)	0 (0%)
Infections and infestations	Upper respiratory tract infection	3 (5.3%)	0 (0%)	1 (1.6%)
	Urinary tract infection	1 (1.8%)	3 (5.3%)	0 (0%)
Investigations	Alanine aminotransferase increased	4 (7.0%)	1 (1.8%)	2 (3.2%)
	Aspartate aminotransferase increased	3 (5.3%)	1 (1.8%)	2 (3.2%)
	Gamma-glutamyltransferase increased	3 (5.3%)	2 (3.5%)	0 (0%)
Musculoskeletal and connective tissue disorders	Arthralgia	7 (12.3%)	2 (3.5%)	7 (11.3%)
	Muscular weakness	0 (0%)	3 (5.3%)	0 (0%)

	Pain in extremity	1 (1.8%)	2 (3.5%)	4 (6.5%)
Nervous system disorders	Dizziness	2 (3.5%)	3 (5.3%)	1 (1.6%)
	Headache	6 (10.5%)	8 (14.0%)	4 (6.5%)
Psychiatric disorders	Anxiety	3 (5.3%)	0 (0%)	3 (4.8%)
	Insomnia	3 (5.3%)	6 (10.5%)	7 (11.3%)
Reproductive system and breast disorders	Breast pain	2 (3.5%)	1 (1.8%)	4 (6.5%)
Respiratory, thoracic and mediastinal disorders	Cough	4 (7.0%)	0 (0%)	0 (0%)
Skin and subcutaneous tissue disorders	Dry skin	0 (0%)	1 (1.8%)	4 (6.5%)
	Pruritus	1 (1.8%)	5 (8.8%)	1 (1.6%)
Vascular disorders	Hot flashes	12 (21.1%)	11 (19.3%)	16 (25.8%)

No statistically significant differences were found after adjusting for multiple testing

*As classified from CTCAE version 4.0.3

QD: 25 mg once a day; TIW: 25 mg three times a week, QW: 25 mg once a week

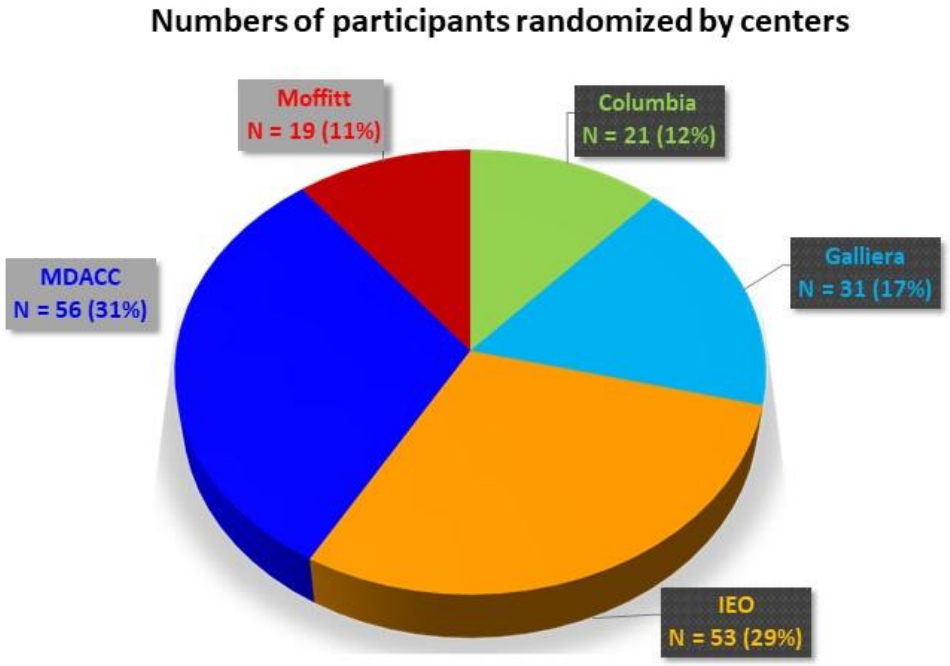
eTable 4. Quality of Life: pre-treatment, post-treatment and absolute change in MenQoL mean score (SD) by study arm

	Exe 25 mg QD (n=48)			Exe 25 mg TIW (n=54)			Exe 25 mg QW (n=57)			P QD vs TIW Adjusted*	P QD vs QW Adjusted*
Domain	Pre	Post	Absolute change	Pre	Post	Absolute change	Pre	Post	Absolute change		
Vasomotor	2.2 (1.5)	2.5 (1.7)	0.41 (1.2)	2.5 (1.9)	2.8 (1.9)	0.28 (1.4)	2.6 (1.9)	3.2 (2.1)	0.51 (1.5)	0.7349	0.7575
Psycho-social	2.5 (1.3)	2.3 (1.3)	-0.19 (0.98)	2.3 (1.2)	2.3 (1.4)	0.06 (1.2)	2.6 (1.5)	2.6 (1.6)	-0.06 (1.1)	0.4350	0.7436
Physical	2.5 (1.1)	2.2 (0.95)	-0.37 (0.77)	2.3 (0.9)	2.3 (1.2)	0.07 (0.86)	2.6 (1.4)	2.6 (1.4)	-0.09 (0.67)	0.0591	0.0524
Sexual	2.0 (1.4)	1.5 (0.99)	-0.45 (1.0)	1.9 (1.5)	1.8 (1.3)	-0.20 (1.7)	2.2 (1.8)	1.7 (1.1)	-0.52 (1.7)	0.4317	0.9000
Mean	2.3 (0.93)	2. (0.82)	-0.15 (0.58)	2.2 (1.0)	2.3 (1.0)	0.05 (0.79)	2.5 (1.1)	2.5 (1.0)	-0.06 (0.71)	0.3078	0.4574

*Adjusted for baseline, age and BMI and multiple testing; QD: once a day; TIW: three times a week, QW: once a week

MenQol item is scored from 1 to 8: 1, no symptom, 2, presence of the symptoms but not bothersome, 3-8, an increasing grade of discomfort.

eFigure 1. Number (%) of randomized participants by center



Columbia University Irving Medical Center, New York, NY, USA;

European Institute of Oncology IRCCS (IEO), Milan, Italy;

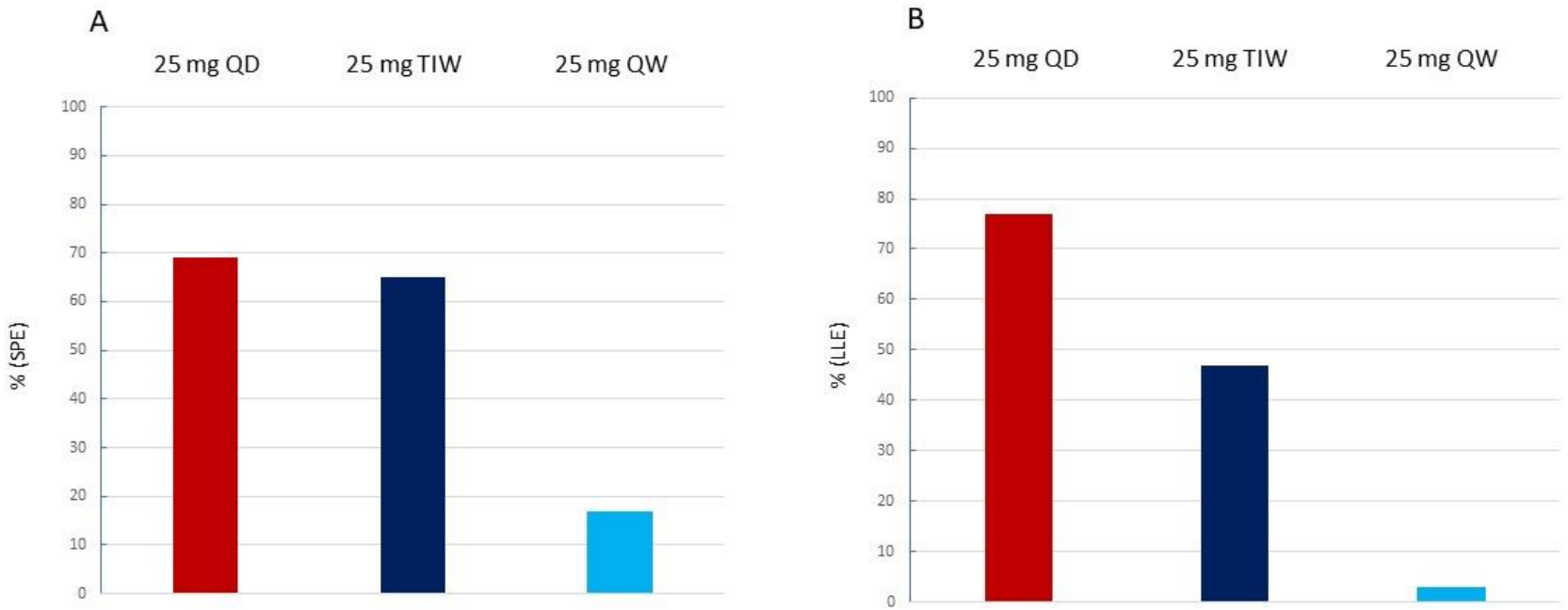
MD Anderson Cancer Center, Houston (MDACC), TX, USA;

Moffitt Cancer Center, Tampa, FL, USA;

Ospedali Galliera, Genoa, Italy;

eFigure 2. Comparison in circulating estradiol suppression by study arm

Panel A. Percentage of participants with total estradiol suppression using SPE method, by study arm (P-value for QD vs TIW= 0.7822 and for QD vs QW= 0.0040). Panel B, Percentage of participants with total estradiol suppression using LLE method, by study arm (P-value for QD vs TIW= 0.0133 and for QD vs QW= 0.0040)



eFigure 3. Median absolute change of Ki-67 by study arm in compliant participants (P-values for QD vs TIW = 0.3173 and QD vs QW=0.0480)