Letrozole plus Simvastatin versus Letrozole in Denovo Metastatic HER2/neu Negative Luminal Breast Cancer: A phase II Randomized Controlled Trial

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Abstract:

Background: Simvastatin which is a lipophilic statin shows some antitumor activity, and when used in combination with Letrozole as a example of drug repurposing in adjuvant postmenopausal females with early HR positive breast cancer showed a significant reduction in breast cancer recurrence.

Objective: We evaluated the role of simvastatin in combination with letrozole in denovo postmenopausal metastatic Her2neu negative Luminal Breast cancer as regard overall response rate (ORR), progression free survival (PFS) as a primary objectives, and overall survival (OS), and safety as a secondary objectives. especially in communities where novel drugs as CDK inhibitors are not always within reach.

Patients and Methods: This study is designed as a prospective phase II randomized controlled trial that carried out on denovo metastatic Her2neu negative luminal breast cancer patients attending medical oncology unit at Oncology Center Mansoura University (OCMU) and followed up for 2 years. Group1(investigational group):40 patients received letrozole and simvastatin at 20mg daily dose. Group 2(control group):40 patients received letrozole.

Results: There is no statistically significant difference in 2 year PFS in (p 0.709), and in OS (p 0.713), there was significant PR at investigational arm at 4th month (p 0.023), which lost with follow up along the study.

Conclusion: Although our results not achieved the original study landscape as regard PFS, but there was a marginal significance in response rate, together with the good safety and tolerability it encourages further study with a higher dosage.

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Introduction:

Female breast cancer is the second most common cause of cancer incidence worldwide in 2022 and represents a 6.9% of all cancer deaths worldwide [1]. Stage IV breast cancer is an incurable disease. Treatment classification based on 3 main molecular subtypes: hormone receptor (HR)-positive/HER2neu negative (70% of patients), HER2neu positive (15%-20%), and triple-negative (15%). Median survival for metastatic triple-negative breast cancer is about 1 year compared with about 5 years for the other 2 subgroups [2]. Single-agent tamoxifen or aromatase inhibitors show limited clinical benefit. They give the patients a PFS ranging from 5 to 16 months [3]. In addition, the commonly prescribed aromatase inhibitors; letrozole and anastrozole, both seem to increase the risk of developing hypercholesterolemia compared with tamoxifen[4]. Cholesterol-lowering medication is frequently prescribed for prevention of cardiovascular disease [5] . Statins are HMG-CoA reductase inhibitors, which block the rate-limiting step in the cholesterol biosynthesis [6]. Statins inhibit the HMG-CoA

reductase pathway in breast cancer cells, which may lower intracellular cholesterol synthesis and lead to reduced intratumoral autocrine hormone production, since cholesterol is required for the synthesis of all steroid hormones [7]. They may also indirectly influence tumor growth through reduced systemic levels of cholesterol and its metabolites; 27-hydroxy-cholesterol, which acts as an estrogen receptor ligand [8]. Lipophilic statins have been reported to have a more competent anticancer effect than hydrophilic statins and their long-term usage post-diagnosis has been associated with reduced risk of metachronous and ipsilateral recurrences among women with estrogen receptor positive breast cancer [9], [10]. Simvastatin which is a lipophilic statin when used combined with Letrozole in adjuvant postmenopausal females with early HR positive breast cancer showed a significant reduction in breast cancer recurrence over a 5 year follow up period [11].

More interestingly, It has been demonstrated that simvastatin causes G1 cell cycle arrest by lowering CDK4/6 and Cyclin D1[12]. Combining lipophilic statins and different anti cancer drugs is extensively evaluated in recent clinical trials giving their well tolerability although it is important to acknowledge their limiting side effects including myopathy that precludes its use in a subpopulation of patients [13].That is why we designed this RCT to evaluate the efficacy of addition simvastatin to letrozole in HER2neu negative luminal denovo metastatic breast cancer in communities where novel drugs as CDK inhibitors are not always within reach.

Patients and Methods:

The study was designed as a prospective phase II randomized controlled trial. The primary objectives of this trial were to assess ORR and PFS in postmenopausal female with denovo metastatic HER2neu negative luminal breast cancer with addition of simvastatin to letorozole. OS and adverse events were the secondary objectives.

Patients

Eligible patients those who were postmenopausal with Her2neu negative, luminal (A and B), denovo metastatic breast cancer, with no previous endocrinal therapy nor visceral crises and adequate bone densitometry. Premenopausal patients, and who previously received endocrinal therapy, or presented with visceral crises were excluded.

Treatment plan and randomization

Eligible 80patients were randomly assigned into two groups; Group1 (investigational group):40 patients received letrozole and simvastatin, Group 2(control group):40 patients received letrozole. Simvastatin received at dose 20mg once daily. Compliance was assessed by self reporting. Patients on both arms received calcium and vitamin D supplement. Zoledronic acid prescribed for bone metastatic disease. Study carried out on patients attending medical oncology unit at Oncology Center Mansoura University (OCMU) and followed up for 24 months from 6/2022 till 6/2024.

Study end points

Primary end points were ORR and PFS. Patients were evaluated clinically each month and radiologically by CT chest, abdomen and pelvis, and biochemically e.g. tumor markers; CA 15-3, CEA each 4 months. Bone scan done at base line and when indicated. The response assessed clinically, biochemically; tumor markers, and radiologically by using RECIST 1.1(Response Evaluation Criteria in Solid Tumors)[14].

Other laboratory investigations include; HbA1c, Lipid profile; TG, total cholesterol, LDL, VLDL, HDL, and chemistry profile; SGPT, SGOT, Serum bilirubin, serum albumin, alkaline phosphatase, serum Creatinine, serum calcium, which done at baseline and periodically for follow up.

The secondary endpoints include OS which estimated as the time from starting randomization till patient death by any cause or to the last date known to be alive, and adverse events which carried out by using 'National Cancer Institute Common Terminology Criteria' for Adverse Events, version 4.0 (CTCAE, v4)[15]

Ethical approval

This study was approved by our local institutional committee board by code number (Approval number is MD.21.12.569.R1.R1.R1.R1), and in agreement with the 1964 Helsinki declaration and its later amendments.

Sample size calculation

Outcome measure:12 months progression free survival. Assignment: equal allocation. Test: log rank, two sided. Alpha: 0.05. Beta: 0.2. Group A (control): 12 month PFS: 50%. Group B (investigational): 12 months PFS: 75%. Hazard ration: 0.42. Control arm sample size: 37 patients. Investigational arm sample size: 37 patients. Group A lost follow up: 5%. Group B lost follow up: 5%. Treatment switch: 0.0%.

Statistical analysis

Data analyzed on a personal computer running SPSS for windows (Statistical Package for Social Scientists) Release 16. P value of < 0.05 considered statistically significant. For descriptive statistics of qualitative variables, the frequency distribution procedure ran with calculation of the number of cases and percentages. For descriptive statistics of quantitative variables, the mean, and standard deviation or the median and range used as appropriate. Association between categorical variables tested by the Chi Square Test. Fishers exact test used when the assumptions of Chi square were violated. Survival analysis calculated by the Kaplan-Meier Product-Limit Estimator, comparison of the survival performed by the Log-Rank Test.

Results:

Base line characteristics

Among 80 patients enrolled in this trial, the mean age was 63 ± 5 for control group and 63.8 ± 5 for investigational group. As regard the patients co morbidities; patients with HTN represent 30% in control arm and 25% in investigational arm, and patients with DM represent 15% in control arm and 17.5% in investigational arm. Mean BMI for control group was 32 ± 5.8, and 32.3 ± 6.5 for investigational group. Patients with BMI < 25 were 7 (17.5%) in investigational arm and 5 (12.5%) in control arm Table (1). Clinicopathologic baseline characteristics between both arms were comparable and illustrated in table (2).

Lipid profile and different laboratory parameters throughout the study in the both arms

In the control arm there was significant change at 12th month in from of raised LDL (p 0.043), which lost at 24th month (p 0.477). The same for total cholesterol (p 0.007, p 0.413, respectively), while there was consistent significant increase at the VLDL level at 12th and 24th month (p <0.001, 0.013, respectively). There was no change in TG level throughout the study.

In investigational arm there was a consistent significant reduction in cholesterol and LDL, No significant change in VLDL, and that was along the study Table (3).

In spite of significant statistical changes in some laboratory parameters, it was not translated to significant adverse changes Table (4).

Primary end points.

By analyzing the follow up data in both arms, none of the patients had a complete response at any time of follow up till the end of the study. While, PR rate was 57.5% vs. 76.9% at 4th month (p 0.023), for control and investigational arms, respectively, the response was lost; 27.8% vs. 44.7% at 8th month (p 0.091), and 0% vs. 6.9% at 12th month (p 0.359). Table (5).

Interestingly, alkaline phosphates and tumor marker; CEA and CA 15-3 were significantly decreased along the study in both arms Table (6).

Median PFS was 12 month for control group, and 15 months for investigational group, and it was no statistically significant difference in 2 year PFS (p 0.709). Fig (1). Also, there was no statistically significant PFS as regard hypercholesterolemia, and high LDL, (p 0.78), (p 0.761), respectively Fig (2), (3). Univariate analysis of PFS as regard the different factors shows no statistically significant difference Table (7).

Secondary end points

There was no statistically significant difference in 2 year OS in both study arms (p 0.713). Fig (4). As regard adverse events there was statistically significant bone aches and hot flashes in investigational arm in comparison with control arm, 80% vs. 77.5% (p 0.025), 27.5% vs. 22.5% (p 0.012), respectively, with grade I/II according to CTCAE, v4. While, there was no significant difference as regard myalgia (p 0.723). In addition, there was a significant reduction in DXA scan in both arms Table (8). This is not seriously decreased in invitational arm and comparable to control arm.

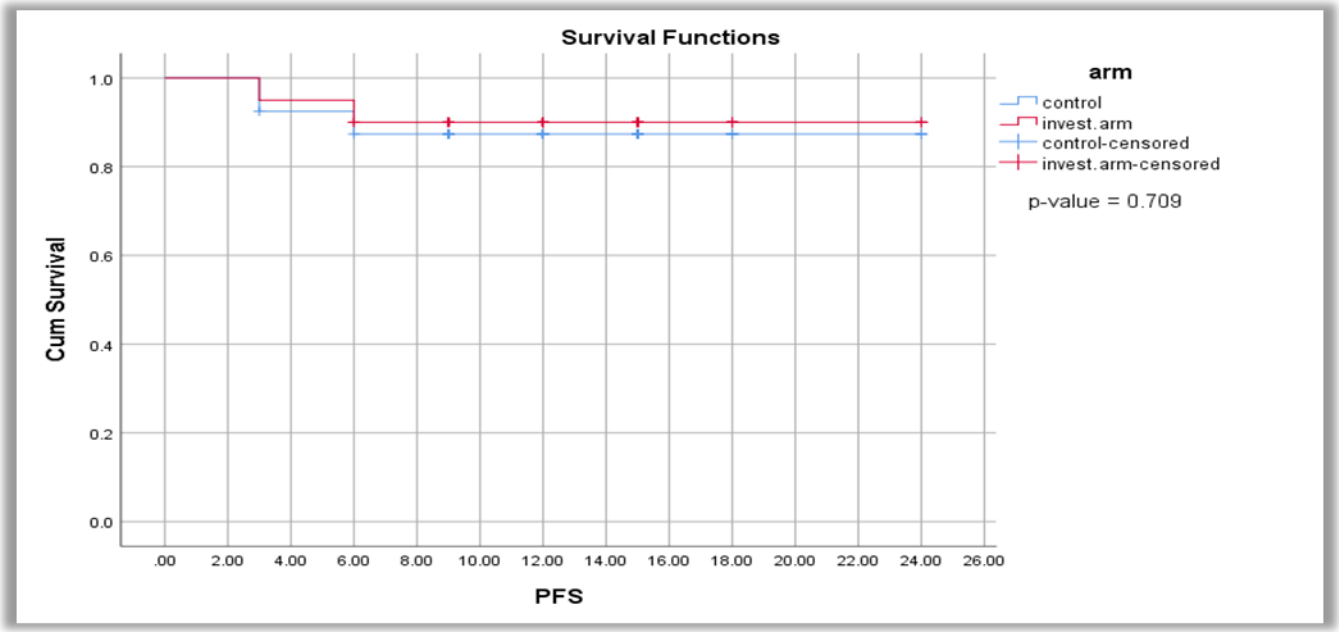

Figure 1: Kaplan Meier curve represents difference of PFS on both study arms

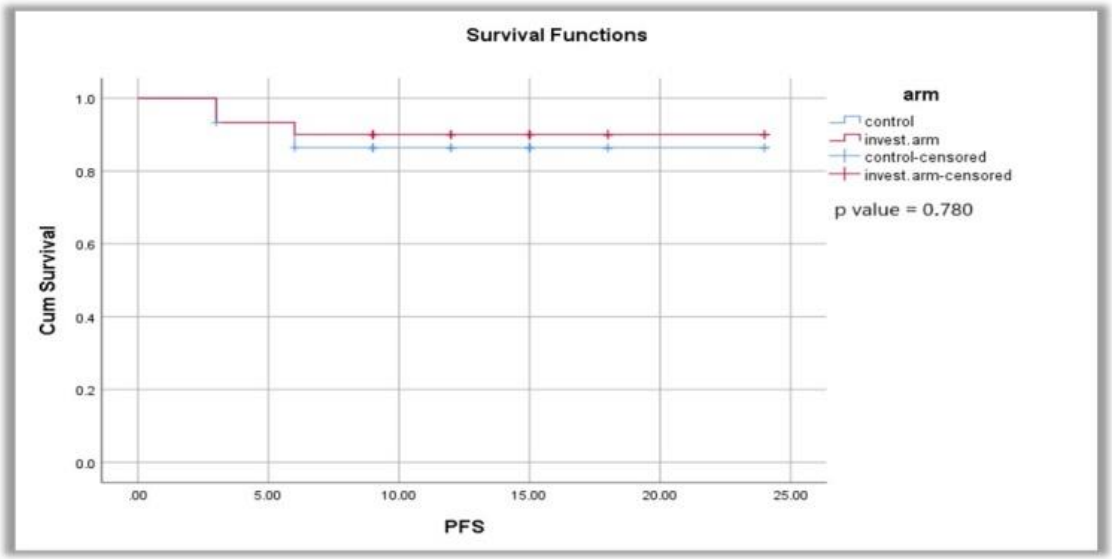

Figure 2: Kaplan Meier curve represents difference of PFS on both study arms as regard hypercholesterolemia

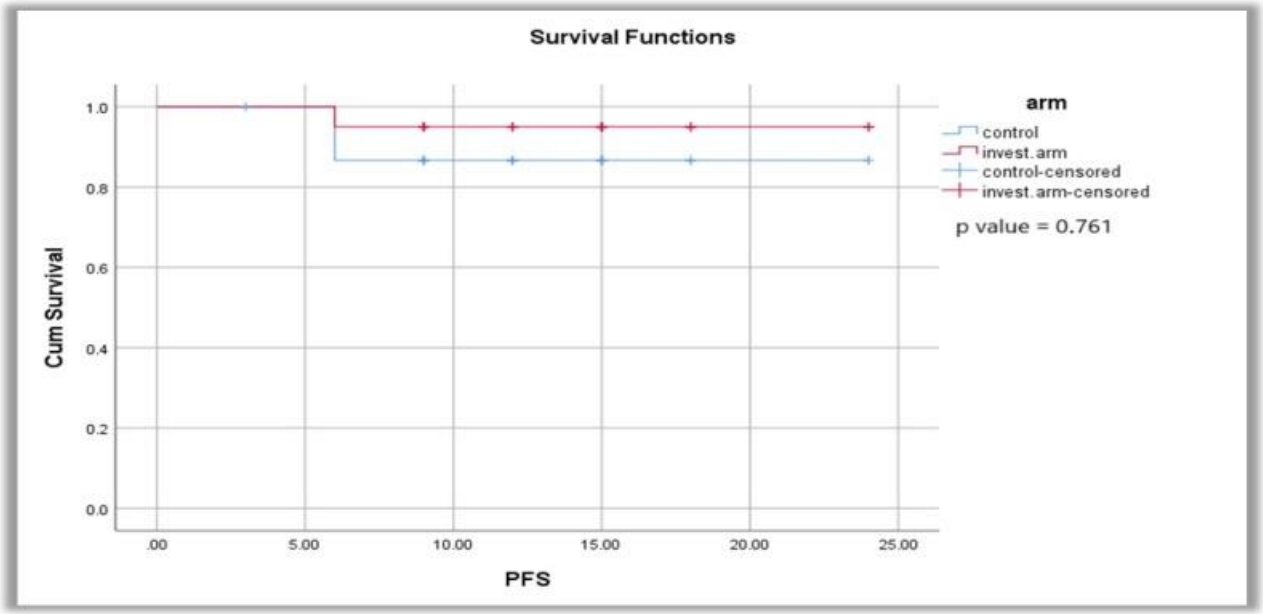

Figure 3: Kaplan Meier curve represents difference of PFS on both study arms as regard high LDL.

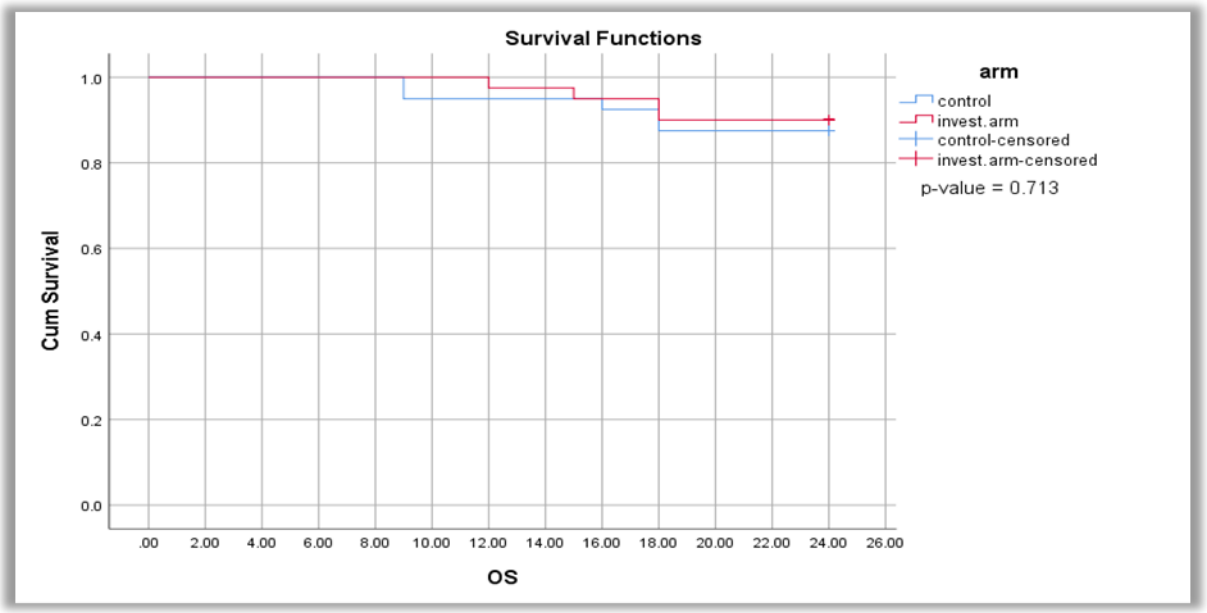

Figure 4: Kaplan Meier curve represents the OS on both study arms

Table 1: Comparison of patients' characteristics in both arms

Factor	Letrozole		Letrozole + Simvastatin	
	N: 40	%	N: 40	%
Age				
Mean	63 ± 5		63.8 ± 5	
Co-morbidity				
DM	6	15	7	17.5
HTN	12	30	10	25
BMI mean	32 ± 5.8		32.3 ± 6.5	
BMI < 25	5	12.5	7	17.5
Status at the end of the study				
Alive	35	87.5	36	90
Died	5	12.5	4	10

Table 2: Comparison of clinicopathologic baseline characteristics between both study arms

Factor	Letrozole		Letrozole + Simvastatin	
	N: 40	%	N: 40	%
Side				
Right	19	47.5	18	45
Left	18	45	17	42.5
Bilateral	3	7.5	5	12.5
T-Stage				
T2	16	40	18	45
T3	18	45	17	42.5
T4	6	15	5	12.5
N-Stage				
N0	4	10	4	10
N1	4	10	6	15
N2	19	47.5	17	42.5
N3	13	32.5	13	32.5
Pathology				
IDC	32	80	31	77.5
ILC	8	20	9	22.5
Grade				
I	12	30	12	30
II	13	32.5	15	37.5
III	15	37.5	13	32.5
LVE				
Yes	37	92.5	35	87.5
No	3	7.5	5	12.5
PNI				
Yes	37	92.5	33	82.5
No	3	7.5	7	17.5
In situ components				
Yes	7	17.5	6	15
No	33	82.5	34	85
ER				
+ve	40	100	40	100
ER positivity	6/8±2		6/8±2	
PR				
-ve	7	17.5	4	10
+ve	33	82.5	36	90
Ki67				
<15%	25	62.5	22	55
≥ 15%	15	37.5	18	45
Luminal type				
A	18	45	18	45
B	22	55	22	55
Metastatic site				
Bone	34	85	35	87.5
Liver	8	20	6	15
Lung	6	15	6	15
Visceral	12	30	9	22.5
Bone + viscera	10	25	6	15
Pleural effusion	3	7.5	2	5

Table 3: Lipid profile through the study in both arms

	Mean			
	Letrozole	p	Letrozole+ simvastatin	P
Triglyceride				
Basal	219.3 ± 46.9		258 ± 87.2	
12th month	197.1 ± 47.4	0.284	160.2 ± 38.64	<0.001
24th month	188±44.1	0.320	156.4 ± 15.4	0.251
Cholesterol				
Basal	242.5 ± 62.05		250 ± 62.6	
12th month	204.89 ± 39.6	0.007	186.7 ± 38.53	<0.001
24th month	225 ± 13.2	0.413	159.8 ± 19.65	0.004
LDL				
Basal	126.3 ± 36.69		129.2 ± 36.6	
12th month	139.07 ± 47.4	0.043	104.7 ± 30.9	<0.001
24th month	164.6 ± 10.5	0.477	89.2 ± 12.79	0.005
VLDL				
Basal	42.57 ± 18.9		48.8 ± 20.7	
12th month	75.5 ± 18.39	<0.001	48.89 ± 18.9	0.388
24th month	105.6 ± 25.89	0.013	51.8 ± 14.4	0.613
HDL				
Basal	63.12 ± 28.86		63.8 ±27.7	
12th month	82.59 ± 17.78	<0.01	78.79 ± 17.2	0.013
24th month	77.6 ± 15.14	0.327	80.6 ± 30.6	0.492

Table 4: Different laboratory parameters through the study in both arms

	Letrozole	P	Letrozole + simvastatin	P
Sr.Creatinine				
Baseline	1.19 ± 0.32		1.09 ± 0.24	
12th month	1.03 ± 0.1	0.036	1.12 ± 0.17	0.386
24th month	1.06 ± 0.15	0.121	1.1 ± 0.17	0.294
SGPT				
Baseline	38.7 ± 17.4		39 ± 16.03	
12th month	43.84 ± 14.7	0.945	38.97 ± 15.8	0.398
24th month	37.6 ± 2.5	0.707	35 ± 9.1	0.886
SGOT				
Baseline	38.7 ± 17.4		39 ± 16.03	
12th month	43.84 ± 14.7	0.361	38.97 ± 15.8	0.904
24th month	37.6 ± 2.5	0.042	35 ± 9.1	0.050
Sr.Bilirubin				
Baseline	0.92 ± 0.3		0.92 ± 0.3	
12th month	1.06 ± 0.26	0.007	0.99 ± 0.16	0.200
24th month	0.9 ± 0.15	0.462	1.2 ± 0.07	0.047
INR				
Baseline	1.17 ± 0.2		1.1 ± 0.15	
12th month	1.07 ± 0.16	0.149	1.06 ± 0.12	0.097
24th month	1.2 ± 0.1	0.966	1.1 ± 0.12	1.0
Sr.Albumin				
Baseline	4.11 ± 0.7		4 ± 0.69	
12th month	3.9 ± 0.78	0.228	4.18 ± 0.67	0.336
24th month	3.5 ± 0.45	0.170	4.22 ± 0.8	0.844
Sr.Calcium				
Baseline	9.3 ± 0.61		9.2 ± 0.78	
12th month	8.7 ± 1.05	0.046	9 ± 0.84	0.077
24th month	9.6 ± 1.21	0.693	8.7 ± 0.79	0.171

Table 5: Response rate (PR) in both arms through the study

RR (PR)	Letrozole %	Letrozole + simvastatin %	p
4th m	57.5%	76.9%	0.023
8th m	27.8%	44.7%	0.091
12th m	0%	6.9%	0.359

Table 6: Alkaline phosphates, CEA and CA 15-3 along the study

	Letrozole	P	Letrozole simvastatin	P
Alkaline phosphatase				
Baseline	210.2 ± 51.75		198.2 ± 53.5	
12th month	110.4 ± 61.4	<0.001	64.5 ± 33.7	<0.001
24th month	63.3 ± 11.5	0.003	63 ± 21.6	0.001
CEA				
Baseline	23.17 ± 16.86		22.87 ± 21.4	
12th month	8.5 ± 11.7	0.004	8.9 ± 10	0.002
24th month	1.9 ± 0.96	0.021	3.7 ± 1.25	0.009
CA 15-3				
Baseline	167.57 ± 85.03		197.9 ± 102.6	
12th month	60.6 ± 59.7	0.001	77.44 ± 65.42	<0.001
24th month	40.3 ± 19.62	0.04	26.8 ± 8.04	0.054

Table 7: Univariate analysis of PFS prognostic factors of both study arms

factors	2 year PFS %		P value
	Control	investigational	
Side			
Right	5	16.7	0.681
Left	2.5	11.8	
Bilateral	0	0	
T –stage			
T2	2.5	16.7	0.638
T3	2.5	11.8	
T4	2.5	0	
N- stage			
N0	2.5	0	0.629
N1	0	0	
N2	0	17.6	
N3	5	15.4	
Histopathological type			
IDC	2.5	16.1	0.673
ILC	5	0	
Grade			
I	2.5	25	0.687
II	0	13.3	
III	5	0	
LVE			
Yes	7.5	8.6	0.704
No	0	40	
PNI			
Yes	7.5	13.5	0.719
No	0	0	
In situ component			
Yes	0	0	0.732
No	7.5	14.7	
High ER 8/8			
ER +ve 8/8	7.5	12.5	0.705
PR			
-ve	5	0	0.788
+ve	2.5	13.9	
Ki67			
<15%	5	12.9	0.693
≥ 15%	2.5	11.1	
Luminal type			
A	2.5	11.1	0.693
B	5	12.9	
Metastatic site			
Bone	7.5	14.3	0.72
Visceral	0	0	0.994
Bone+ visceral	0	0	0.983

Table 8: DXA scan in both study arms

DXA scan	Letrozole		Letrozole + simvastatin	
	Mean	P	Mean	P
Basal	-1.9 ± 1.21	0.001	-2 ± 1.1	0.037
6-12th month	-2.4 ± 0.56		-2.1± 0.74	

Discussion:

Up till now aromatase inhibitors remain the main backbone medication in managing postmenopausal patients with denovo metastatic HER2 negative, HR positive breast cancer according to guidelines from the Egyptian Health Council. This warranted studying of drugs repurposing for cancer therapy which were established with in vivo anti tumor efficacy as statins.

This study is the first to discuss the value of adding statins; simvastatin to the standard of care aromatase inhibitor (letrozole) in patients with denovo metastatic breast cancer. However, researchers from Singapore are conducting a trial of adding simvastatin to fulvestrant, and the results are pending [16]

Investigators decided a 20mg of simvastatin at night time based on the observation that low concentrations of simvastatin can induce apoptosis of microvascular endothelial cells and reduce VEGF serum levels.[17] And drug safety at this concentration [18].

The patients' baseline and disease characteristics were well balanced across treatment arms including; age, BMI, performance status, and endocrine positivity.

The median age of patients in both arms is around 63 years, matching the definition of post-menopausal status widely accepted by NCCN panelists. Postmenopausal status for younger patients was confirmed by estradiol (E2)/ Follicle-stimulating hormone (FSH) level.

The mean BMI in both arms is similar at 32 categorized as Obesity (Class I); association of metastatic breast cancer and obesity is established by Linnea T Olsson and her colleagues [19]

By comparing different pathological baseline characteristics between both arms, it appears that both tumor sidedness, pathology, grade, ER positivity, and stage are quite similar.

Most patients presented with an advanced clinical stage at presentation (T3/T4/Node +ve) than early presentation (T1/T2/Node -ve), which is expected and follows a similar pattern in a (SEER) database by Wang and his colleagues. [20]. These weren't statistically significant independent prognostic factors on PFS in our study and Wang's work.

Both arms had quite similar histopathological type percentages approaching 80 % IDC and 20 % ILC and neither IDC histology nor ILC poses a statistically prognostic effect on PFS unlike a multicentric cohort that proved ILC inversely affects survival by Florence Dalenc and his colleagues [21] , maybe because of the limited number of our study population to discuss this matter.

Patients of both arms had nearly equal percentages of tumor grade, and unsurprisingly the majority of the patients had LVE and PNI. Both arms had the same kind of luminality and ER degree of positivity. PR or KI67 status didn't affect PFS unlike a large SEER database analysis by Shibin Cai and his colleagues [22] mostly because of disease nature – denovo metastases - of our study population.

Regarding the impact of adding simvastatin to letrozole on blood indices, there were no statistically significant differences for; Albumin, SGPT, SGOT, INR, calcium, Creatinine, and Uric acid.

There was a statistically significant difference for bilirubin at 24th month (1.2 ± 0.07, P 0.047) in investigational arm and (0.9 ± 0.15, P 0.462) in the control arm, it is still in the normal range for bilirubin levels for adults. Such observation is reported in a retrospective analysis by Pernette R.W. and her colleagues.[23]

There were statistically significant differences for ALP, CEA, and CA15-3 which showed decreasing levels for radiologically responding patients in both arms that also continue to decrease till 24th month. Such markers are Longley considered reliable for disease monitoring for patients with elevated level at baseline according to a prospective analysis by Ahmed M. Kabel [24]

The addition of simvastatin to letrozole statistically significantly lowers serum lipid profile at 12th and 24th months mainly, for cholesterol, and LDL. This denotes the drug's clinical activity at a lower dose as reported by a large pooled analysis by Kamal Awad and his colleagues [25].

On the other hand, the control arm had a statistically significant increase in serum lipid profile mainly cholesterol, LDL at 12 months, and VLDL at 12, and 24 months. A recent work by Bálint Bérczi and his colleagues confirmed the correlation between AIs and dyslipidemia [26].

Regarding clinical and radiological assessment throughout the study, there was only statistically significant improved PR at the invitational arm at 4 months (p 0.023), which lost with follow up along the study.

The 2 year PFS in both arms was not statistically significant in both arms and OS is still immature to draw a conclusion. Analyzing different variables; pathology, ER degree of positivity, PR, Ki67, luminal type, and metastatic sites as regard PFS showed no statistically significant difference.

As regard adverse events there was statistically significant bone aches and hot flashes in investigational arm in comparison with control arm, 80% vs. 77.5% (p 0.025), 27.5% vs. 22.5% (p 0.012), respectively, with grade I/II according to CTCAE, v4.

By analyzing the Likert scale for symptom severity, frequency, and distress level in both arms throughout the study, there was numerically higher symptom control in patients in the investigational arm than in the control arm, however not statistically significant. Degree of osteoporosis on DXA scan with follow up was comparable in both arms without more significant reduction in investigational arm. Combination of simvaststin and letrozole was safe and tolerable [27],[28].

Conclusion:

Repurposing drugs with established in vivo anti tumor effect is recently expanding, and aim to find drugs that improving patient's outcome with acceptable safety, and also mitigating the financial burden on

health care providers. Although our results not achieved the original study landscape as regard PFS, but there was a marginal significance in response rate, together with the good safety and tolerability it encourages further study with a higher dosage.

Competing interests

The authors declared no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution: Authors contributed equally to the study.

References:

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin 2024, 74(1):12-49.
2. Al Sukhun S, Temin S, Barrios CH, et al. Systemic treatment of patients with metastatic breast cancer: ASCO resource-stratified guideline. J CO Glob Oncol. 2024 Jan;10:e2300285.
3. Tripathy D, Blum JL, Rocque GB, et al. POLARIS: a prospective, multicenter, noninterventional study assessing palbociclib in hormone receptor-positive advanced breast cancer. Future Oncol 2020,16(31):2475-2485.
4. Ballinger TJ, Meier JB, Jansen VM. Current landscape of targeted therapies for hormone-receptor positive, HER2 negative metastatic breast cancer. Front Oncol 2018, 8:308.
5. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019,140(11):e596-e646.
6. Hirota T, Fujita Y, Ieiri I. An updated review of pharmacokinetic drug interactions and pharmacogenetics of statins. Expert Opin Drug Metab Toxicol 2020, 16(9):809-822.
7. Nelson ER. The significance of cholesterol and its metabolite, 27-hydroxycholesterol in breast cancer. Mol Cell Endocrinol 2018, 466:73-80.
8. Mcdonnell DP, Chang CY, Nelson ER. The estrogen receptor as a mediator of the pathological actions of cholesterol in breast cancer. Climacteric 2014, 17 Suppl 2:60-65.
9. Borgquist S, Giobbie-Hurder A, Ahern TP, et al. Cholesterol, cholesterol-lowering medication use, and breast cancer outcome in the BIG 1-98 study. J Clin Oncol 2017, 35(11):1179-1188.
10. Borgquist S, Broberg P, Tojjar J, et al. Statin use and breast cancer survival - a Swedish nationwide study. BMC Cancer. 2019 Jan 11;19(1):54.
11. Harborg S, Heide-Jørgensen U, Ahern TP, et al. Statin use and breast cancer recurrence in postmenopausal women treated with adjuvant aromatase inhibitors: a Danish population-based cohort study. Breast Cancer Res Treat 2020, 183(1):153.
12. Wang G, Cao R, Wang Y, et al. Simvastatin induces cell cycle arrest and inhibits proliferation of bladder cancer cells via PPARγ signalling pathway. Sci Rep 2016, 6:35783.
13. Hyder T, Marti JLG, Nasrazadani A, et al. Statins and endocrine resistance in breast cancer. Cancer Drug Resist 2021, 4(2):356-364.
14. Schwartz LH, Seymour L, Litière S, et al. RECIST 1.1 - standardisation and disease-specific adaptations: perspectives from the RECIST Working Group. Eur J Cancer 2016, 62:138-145.
15. Common Terminology Criteria for Adverse Events (CTCAE) [Internet]. Bethesda, MD: Cancer Therapy Evaluation Program; [cited 2025 Feb 6]. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.
16. Study Details:| Metformin and Simvastatin in Addition to Fulvestrant [Internet]. Bethesda, MD: U.S. National Library of Medicine; [cited 2025 Feb 6]. Available from: https://clinicaltrials.gov/study/NCT03192293?cond=Breast%20Cancer&term=Simvastatin&rank=3.
17. Giurgea AG, Margeta C, Maca T, et al. Simvastatin reduces serum level of vascular endothelial growth factor in hypercholesterolemic patients. J Cardiovasc Pharmacol 2006, 47(1):30-36.
18. Talreja O, Kerndt CC, Cassagnol M. Simvastatin. In: xPharm: The Comprehensive Pharmacology Reference. Elsevier; 2023:1-4.
19. Olsson LT, Walens A, Hamilton AM, et al. Obesity and breast cancer metastasis across genomic subtypes: a Surveillance, Epidemiology, and End Results (SEER) population-based analysis. Cancer Epidemiol Biomarkers Prev. 2022, 31(10):1944.
20. Wang R, Zhu Y, Liu X, et al. The clinicopathological features and survival outcomes of patients with different metastatic sites in stage IV breast cancer. BMC Cancer 2019,19.
21. Dalenc F, Lusque A, De La Motte Rouge T, et al. Impact of lobular versus ductal histology on overall survival in metastatic breast cancer: a French retrospective multicentre cohort study. Eur J Cancer 2022,164:70-79.
22. Cai S, Zuo W, Lu X, et al. The prognostic impact of age at diagnosis upon breast cancer of different immunohistochemical subtypes: a Surveillance, Epidemiology, and End Results (SEER) population-based analysis. Front Oncol 2020,10:1729.
23. de Sauvage Nolting PR, Kusters DM, Hutten BA, et al. Serum bilirubin levels in familial hypercholesterolemia: a new risk marker for cardiovascular disease? J Lipid Res 2011, 52(9):1755-1759.
24. Kabel AM. Tumor markers of breast cancer: new prospectives. J Oncol Sci 2017, 3(1):5-11.
25. Awad K, Serban MC, Penson P, et al. Effects of morning vs evening statin administration on lipid profile: a systematic review and meta-analysis. J Clin Lipidol 2017, 11(4):972-985.e9.
26. Bérczi B, Farkas N, Hegyi P, et al. Aromatase

inhibitors and plasma lipid changes in postmenopausal women with breast cancer: a systematic review and meta-analysis. J Clin Med 2024,13(6):1818.

27. Harborg S, Heide-Jørgensen U, Ahern TP, et al. Statin use and breast cancer recurrence in postmenopausal women treated with adjuvant aromatase inhibitors: a Danish population-based cohort study. Breast Cancer Res Treat 2020, 183(1):153.
28. Bao T, Blackford AL, Stearns V. Effect of simvastatin on the pharmacokinetics of anastrozole. Breast Cancer Res Treat 2012,131(2):709-711.