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Palbociclib plus endocrine therapy in Premenopausal women in HR+/Her2- Breast Cancer with Visceral Metastases versus Combined Chemotherapy

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ABSTRACT

Background: Metastatic breast cancer HR+/Her2- type with visceral metastasis in premenopausal women is one of the most aggressive breast cancer types. The objective of this study was to evaluate the comparative efficacy of first-line Palbociclib in combination with endocrine therapy versus combination chemotherapy in premenopausal women with visceral metastases from hormone receptor-positive, HER2-negative metastatic breast cancer.

Methods: In this prospective, nonrandomized study, 105 patients were enrolled: Group1: 61 patients were treated with Palbociclib+ET, either with Fulvustrant/goserelin in 38 patients (62.3%) or with AI/goserelin in 23 patients (37.7%) Group2: 44 patients were treated with combined chemotherapy (Taxol/Carboplatin, Gemzar/Carboplatin, AC or Navelbine/Xeloda). The primary endpoint of the study was progression free survival (PFS) and secondary endpoints were overall survival (OS) and overall response rate (ORR).

Results: A total of 105 patients were identified; the median age was 44 years (range 34-55 years). The median follow up was 24 months. In the ET arm, 6 patients (9.8%) received ET as 1st line, 42 patients (68.9%) as 2nd line and 13 patients (11.3%) received more than 2 prior ET. The objective response rate was significantly higher in group 1 (34.4% vs.15.9%, p =0.018).

Similarly, mPFS was higher in group 1 9.93 months compared to 6.03 months in group 2 (HR=0.64, 95% CI: 0.50–0.82, p=0.001), mOS was not reached in both groups, however 1 year OS rates were 81.82% in chemotherapy arm vs 88% in endocrine arm (HR=0.65, 95% CI: 0.48–0.88, p=0.005). Among the patients receiving palbociclib and endocrine therapy, mPFS was higher in the endocrine group regarding <40 years (17.33 vs 4.67 months P value 0.026), non-obese women (9.93 vs 6.13 months P value 0.046), PR positive tumor and multiple metastatic sites (6.7 vs 4.97 months P 0.015)

Safety: 90.16% in ET arm developed at least 1 AE vs 88.57% in chemotherapy arm, most common was neutropenia in 86.89% with ET, while in chemotherapy arm, GIT symptoms were found in 52.27% and neutropenia in 45.45%. GIII-IV toxicities were in 18.03% vs 18.18 in ET and chemotherapy respectively.

Conclusion: This is a real-world study to assess the effectiveness of Palbociclib plus endocrine therapy vs combined chemotherapy in premenopausal women with HR+/Her2- breast cancer who have visceral metastases. Palbociclib+ET was superior to combined chemotherapy in the objective response rate, median progression free survival.

Keywords: *Palbociclib, Endocrine therapy, Premenopausal, Visceral metastases, Hormone receptor-positive, HER2-negative, Chemotherapy, Metastatic breast cancer, Progression-free survival (PFS), Egypt.*

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1. INTRODUCTION

Breast cancer is the most common malignancy among women worldwide, with approximately 70% of cases classified as hormone receptor positive (HR+), HER2-negative. This subtype is generally of good prognosis. However, breast cancer in premenopausal women is known to have worse prognosis than postmenopausal. The presence of visceral metastasis is considered another factor with poor prognosis. That makes those patients with such an aggressive disease, need special

treatment consideration. Chemotherapy has been the cornerstone of the treatment because of the need of rapid response and good disease control.

In the past decade, cyclin-dependent kinase 4/6 inhibitors (CDK4/6i); Plabociclib, Ribociclib and Abemaciclib, had shown improved progression free survival (PFS) when added to endocrinal therapy (ET) compared to endocrinal monotherapy. Paloma, Monalessa and Monarch trials included premenopausal patients however, Monalessa-7 trial was the first trial designed to assess the efficacy of the addition of Ribociclib to ET in premenopausal patients with metastatic breast cancer and it showed improved PFS and ORR.

Yet, comparative efficacy between CDK4/6i-based regimens and chemotherapy in premenopausal patients presenting with visceral metastases is still not well established. The Right Choice trial is a phase II trial that discussed the efficacy of Ribociclib combined with endocrine treatment in premenopausal patients who suffer from HR+, Her2- breast cancer with visceral metastases. While ABIGAIL phase II randomized trial revealed a higher earlier overall response rate (ORR) of Abemaciclib in addition to endocrine treatment compared to paclitaxel in HR+, Her2- advanced breast cancer with aggressive criteria. Young PEARL is another trial that evaluated the efficacy of Palbociclib plus endocrine treatment in premenopausal women with HR+, Her2- metastatic breast cancer compared to Capecitabine. Our study aims to investigate the efficacy of Palbociclib with endocrine therapy as compared to combined chemotherapy in such patients.

Methods

Study Design This prospective, non-randomised study was conducted on 105 premenopausal women with HR+/HER2- negative breast cancer and radiologically confirmed visceral metastases.

Patients were divided into two treatment arms: 1) Palbociclib 125mg once daily for 3-week-on, 1-week-off plus either aromatase inhibitors AI (Letrazole 2.5mg, Anastrazole 1mg or Exmestine 25mg) once daily continuous schedule or Fulvestrant 250mg two intramuscular (IM) injection every 2 weeks for 2 doses loading then every 4 weeks. All the patients received LH/RH agonist for ovarian suppression.

2) Chemotherapy; Paclitaxel 80mg/m2 with Carboplatin AUC2 weekly, Gemcitabine 1gm day1 and 8 every 3 weeks with Carboplatin AUC2 weekly, Adriamycin 60mg/m2 with Cyclophosphamide 600mg/m2 or Vinorelbine 60mg oral day1 and 8 with Capecitabine 1000mg/m2 BID day1-14 every 3 weeks.

Participants

Premenopausal women aged 18–55 years were eligible to be recruited with pathological confirmed hormone receptor positive (ER+ or PR+) and Her2 negative breast cancer, and RECIST version 1.1 measurable visceral metastases (liver, lung, brain, etc.) All patients were Eastern Cooperative Oncology Group performance status of 0-2 and according to the 5th ESMO guidelines in 2020, they were not in visceral crisis according to the investigator judgement.

Data Collection and Analysis

Data collection included baseline characteristics such as age, comorbidities, BMI, ER/PR status, HER2 status, metastases burden, and obesity using body mass index (BMI). Primary endpoint PFS (time from the date of enrolment to the date of disease progression according to RECIST version 1.1). Secondary endpoints were overall response rate (ORR) overall survival (OS). Subgroup analyses were included by age, metastatic burden, and biomarker status. Clinical and laboratory assessments (complete blood picture CBC, liver and kidney function tests) were done every 4 weeks in the endocrine arm and every 3 weeks in the chemotherapy arm for clinical and safety evaluation. Radiological assessment (CT or PET/CT scans) were done every 3 months for disease follow up

Statistical analysis and data interpretation:

Data analysis was performed by SPSS software, version 26 (SPSS Inc., PASW statistics for windows version 26. Chicago: SPSS Inc.). Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for non-normally distributed data and mean± Standard deviation for normally distributed data after testing normality using Kolmogrov-Smirnov test. Significance of the obtained results was judged at the (0.05) level. Chi-Square, Fischer exact test, Monte Carlo tests were used to compare qualitative data between groups as appropriate Mann Whitney U and Kruskal Wallis test were used to compare between 2 studied groups and more than 2 studied groups, respectively for non-normally distributed data.

Student t test was used to compare 2 independent groups for normally distributed data.
One Way ANOVA test was used to compare more than 2 independent groups with Post Hoc Tukey test to detect pair-wise comparison

Kaplan-Meier test: Used to calculate overall survival and disease-free survival with using log rank $\chi 2$ to detect effect of

risk factors affecting survival

Ethics

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Mansoura University (IRB approval code: MD.23.05.779). Written informed consent was obtained from all participants.

Results

A total of 105 patients were enrolled, 61 women received Palbociclib plus ET and 44 women received combined chemotherapy. Demographic data and baseline characteristics were well balanced between the two arms The median age was 44 years with range between 29-55 years. 31 women were younger than 40 years (29.5%) while 74 women were older than 40 years (70.5%). In the Palbociclib arm, 20 patients (32.8%) were <40 years, while 41 patients (67.2%) were ≥40 years. In chemotherapy arm, 11 women (25%) younger than 40 years and 33 women (75%) older than 40 years.

Comorbidities were present in 22 patients (21%), with hypertension (HTN) being the most common and was found in 15 women (14.3%), 10 women had diabetes mellitus (DM) (9.5%) and 3 women had both HTN and DM (2.9%). In Palbociclib patients, 6 women (9.8%) had HTN, 5 women (8.2%) had DM, and 1 patient (1.6%) was known to have HTN and DM. In chemotherapy arm, 9 women (20.5%) were hypertensive, 5 women (11.4%) had DM and 2 of them (4.5%) had both HTN and DM.

Body mass index (BMI) was calculated. Median BMI was 29.85 in chemotherapy group and 29.68 in endocrine group. Patients were classified into 3 groups; non obese with BMI 20-25, overweight with BMI 25-30 and obese patients who had BMI over 30. 12 women were non-obese (11.4%), 53 females were overweight (50.5%) and 40 patients were obese (38.1%) 47 patients (44.8%) of the enrolled women were diagnosed by metastatic breast cancer. 58 patients (55.2%) had early breast cancer then developed metastasis. In the chemotherapy arm, 20 patients (45.5%) were diagnosed by metastatic breast cancer, and 24 patients (54.5%) had developed metastases. In the endocrine arm, 26 patients (42.6%) were diagnosed by metastatic disease while 35 patients (57.4%) developed metastases on their follow up.

Liver was the most common site of metastases in 67 patient (63.8%), followed by lung in 52 patients (49.5%). 9 patients (8.6%) had brain metastases, and 8 patients (7.6%) had peritoneal metastases. Both spleen and ovary metastases were found in 2 patients (1.9% each).

In endocrine group, 37 women (60.7%) had a single visceral metastasis while 24 women (39.3%) had multiple sites of metastases. In chemotherapy group, 20 women (45.5%) had single metastases, while 24 women (54.5%) had multiple metastatic sites.

Estrogen receptor (ER) pathological assessment was positive for all 105 patients. ER score was classified into moderate positive ER (4/8, 5/8 and 6/8) and strong positive ER (7/8 and 8/8). 14 patients (13.3%) had moderate positive ER score and 91 patients (86.7%) were strong positive ER. In chemotherapy group, 37 patients (84.1%) had strong positive ER and 7 patients (15.9%) had moderate positive ER while in endocrine arm, 54 patients (88.5%) had strong positive ER and 7 patients (11.5%) had moderate positive ER.

Progesterone receptor (PR) was evaluated our patients. 21 patients (20%) were PR negative while 84 patients (80%) were PR positive. In patients who received Palbociclib with ET, 10 of them (16.4%) were PR negative and 51 patients (83.6%) were PR positive. 14 patients (31.8%) of those who received chemotherapy were PR negative and 33 patients (68.2%) were PR positive.

Her2 score was assessed in 105 patients. 79 patients (75.24%) were Her2 score 0, 47 patients in endocrine arm and 32 patients in chemotherapy arm. 18 patients (17.14%) were Her2 1+ 8 of them received chemotherapy and 10 patients received ET. 8 patients (7.62%) were Her2 score 2 with negative SISH test, 4 patients received chemotherapy, and 4 patients received ET.

61 patients received Palbociclib, combined with aromatase inhibitors (AI) in 23 patients and with Fulvestrant in 38 patients. 44 women received chemotherapy. Paclitaxel with Carboplatin was received in 29 patients (65.9%), Gemcitabine with Carboplatin in 8 patients (18.2%), Adriamycin/Cyclophosphamide (AC) in 5 patients (11.4%) and 2 patients (4.5%) received Vinorelbine/Capecitabine.

Treatment Outcomes

The median follow-up was 24 months. In the ET arm, 6 patients (9.8%) received ET as 1st line, 42 patients (68.9%) as 2nd line and 13 patients (11.3%) received more than 2 prior ET. The objective response rate was significantly higher in group

1 (34.4% vs.15.9%, p =0.018). Similarly, the median progression-free survival was higher in group 1 9.93 months compared to 6.03 months in group 2 (HR=0.64, 95% CI: 0.50–0.82, p=0.001), mOS was not reached in both groups, however 1 year OS rates were 81.82% in chemotherapy arm vs 88% in endocrine arm (HR=0.65, 95% CI: 0.48–0.88, p=0.005).

Among the patients receiving palbociclib and endocrine therapy, mPFS was higher in the endocrine group regarding <40 years (17.33 vs 4.67 months P value 0.026), non-obese women (9.93 vs 6.13 months P value 0.046), PR positive tumor and multiple metastatic sites (6.7 vs 4.97 months P 0.015)

Safety*:* 90.16% in ET arm developed at least 1 AE vs 88.57% in chemotherapy arm, most common was neutropenia in 86.89% with ET, while in chemotherapy arm, GIT symptoms were found in 52.27% and neutropenia in 45.45%. GIII-IV toxicities were in 18.03% vs 18.18 in ET and chemotherapy respectively.

DISCUSSION

In our study, Palbociclib + ET showed improved mPFS compared to chemotherapy. That result was aligned with the mPFS in The Right Choice and Young PEARL trials

The results of our study showed a mPFS 9.93 months of Palbociclib plus ET compared to 6.03 months (HR=0.64, 95% CI: 0.50–0.82, p=0.001). In The Right Choice, mPFS was better in the Ribociclib plus ET with 21.8 months vs 12.8 months in the chemotherapy arm, P value 0.003. In Young PEARL trial, mPFS was 19.5 months in Palbociclib+ET compared to 14 months in chemotherapy, P value 0.04

In our study, secondary endpoint, ORR was better in Palbociclib+ET that chemotherapy 34.4% vs 15.9% respectively, P value 0.018. That was similar to the ORR in ABIGAIL trial with ORR 59% vs 40% in Abemaciclib+ET versus chemotherapy, P value 0.019

However, both The Right Choice and Young PEARL trials showed no ORR benefit of the ET. In the Right Choice, ORR was 66.1% in the ET vs 61.8% in chemotherapy arm. In Young PEARL, ORR was 33.3% in the ET arms vs 33.7% in chemotherapy arm

In our study, after 24 months median follow up, mOS was not reached. 12 months OS rates were 88% in Palbociclib+ET arm compared to 81.82% in chemotherapy arm. That was comparable with The Right Choice trial, as after 30 months follow up, mOS was not reached as well. 12 months OS rates were 87.9% and 92.5% in Ribocilib+ET and chemotherapy groups respectively

In Young PEARL trial, mOS was 54.8 months in the Palbociclib+ET arm compared to 57.8 months in chemotherapy arm, P value 0.77. Longer follow up is recommended to evaluate the mOS in our study Regarding the safety profile, in our study, 89.52% experienced at least one all-grade adverse event AE). 90.16% in ET arm and 88.64% in chemotherapy arm. Serious AE was found in 19.05% of our patients, mainly neutropenia. 13 patients (21.31%) had grade III-IV neutropenia in ET group versus 5 patients (11.36%) in chemotherapy group.

Compared to The Right Choice trial, 79.5% and 73.0% of patients in the Ribociclib and CT had at least one all-grade adverse event AE. The most common grade 3 or 4 AEs were neutropenia (59.8% and 36.0%) in the Ribociclib and CT arm, respectively Among the patients receiving palbociclib and endocrine therapy, mPFS was higher in the endocrine group regarding <40 years (17.33 vs 4.67 months P value 0.026), non-obese women (9.93 vs 6.13 months P value 0.046), PR positive tumor and multiple metastatic sites (6.7 vs 4.97 months P 0.015). These results are aligned with the results of The Right Choice trial. In The Right Choice trial, Ribocilib+ET showed better mPFS in all age groups, ER status >50. However, BMI, Her2 score, and number of metastatic sites were not assessed in The Right Choice trial.

LIMITATIONS:

Study limitations included the non-randomized design, that may lead to selection bias in determining who may receive chemotherapy or Palbociclib plus ET according to metastatic burden.

Relatively smaller-sized group received chemotherapy (44 patients compared to 61 patients). Further sub-analysis is necessary to determine if there was better outcome with a specific subgroup. Longer follow up is important to assess the mOS

CONCLUSION

Anti-CDK4/6 inhibitors (Palbociclib) combined with endocrine therapy compared to chemotherapy are associated with significantly PFS in premenopausal women with HR+/HER2-negative breast cancer and visceral metastases. These results support the use of Palbociclib as a preferred treatment option in this patient population. Further studies are necessary to

support these data.

CONFLICT OF INTEREST AND FUNDING

The authors declare no conflicts of interest and received no specific funding for this work.

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Table (1): Descriptive statistics of all studied cases (n=105)

	N=105	%
Age (years) **Mean ±SD** **MIN-MAX**	**43.95±6.31** **(29-55)**	
Age years **<40** **≥40**	 31 74	 29.5 70.5

Co-morbidities **NAD** **Hypertension** **DM** **HTN+DM**	 83 15 10 3	 79.0 14.3 9.5 2.9
ER **Moderate positive** **Stronge positive**	 14 91	 13.3 86.7
PR **Negative** **Positive**	 21 84	 20 80
HER2 **0** **1** **2**	 79 18 8	 75.2 17.1 7.6
BMI **non obese** **overweight** **obese**	 12 53 40	 11.4 50.5 38.1
Metastasis site		
Spleen	2	1.9
Ovary	2	1.9
Peritoneum	8	7.6
Lung and pleura	52	49.5
Brain	9	8.6
Liver	67	63.8
Single site of metastases **Multiple metastases**	57 48	54.3 45.7
First presentation **Early** **Metastasis**	 58 47	 55.2 44.8cb
Endocrine **Palbociclib/AI** **Palbociclib/Fulvestrant**	 23 38	 37.7 62.3

Chemotherapy		
Taxol/Carboplatin	29	65.9
Navelbine/Xeloda	2	4.5
Gemzar/Carboplatin	8	18.2
AC	5	11.4

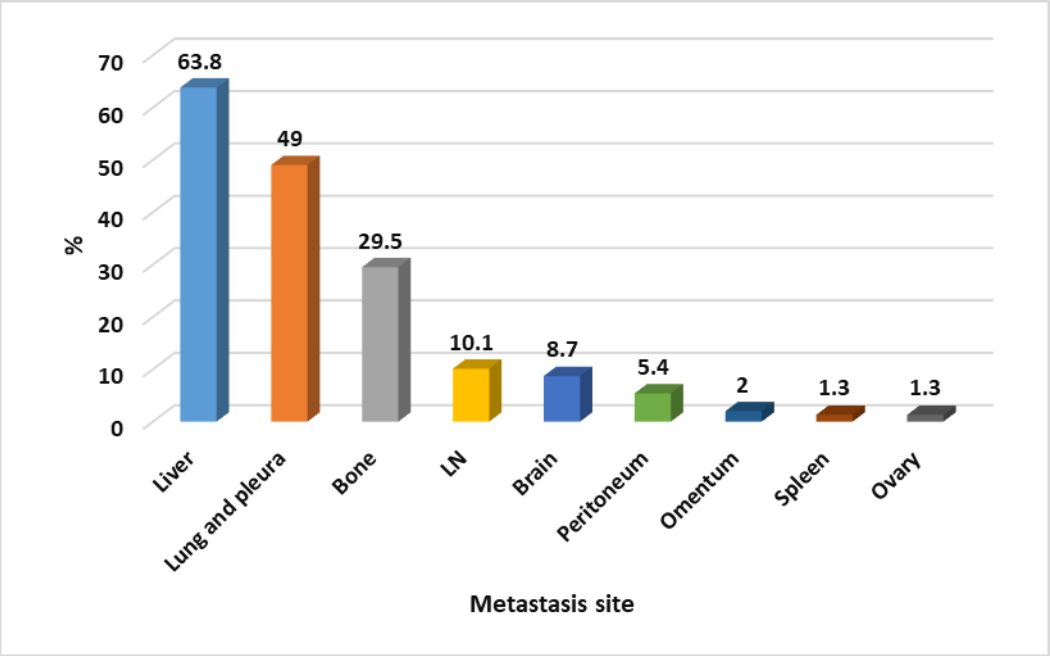

Figure (1): Metastatic sites

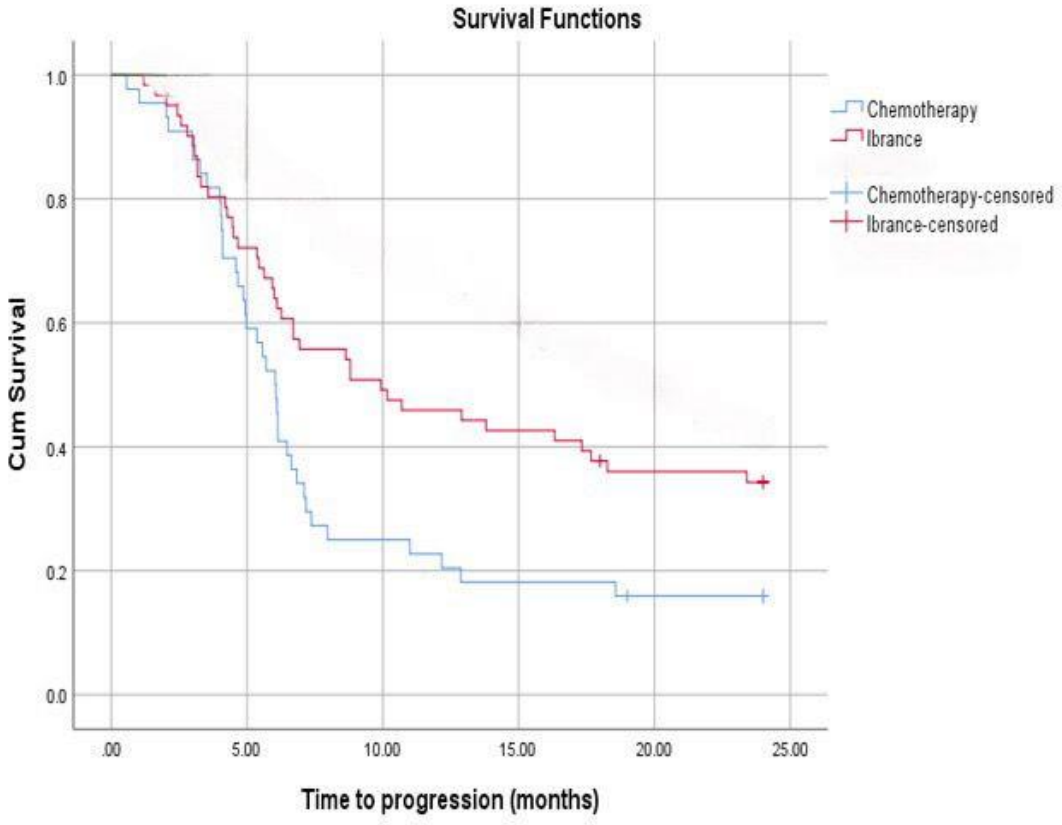

Figure (2): PFS between Palbociclib+ET vs combined chemotherapy

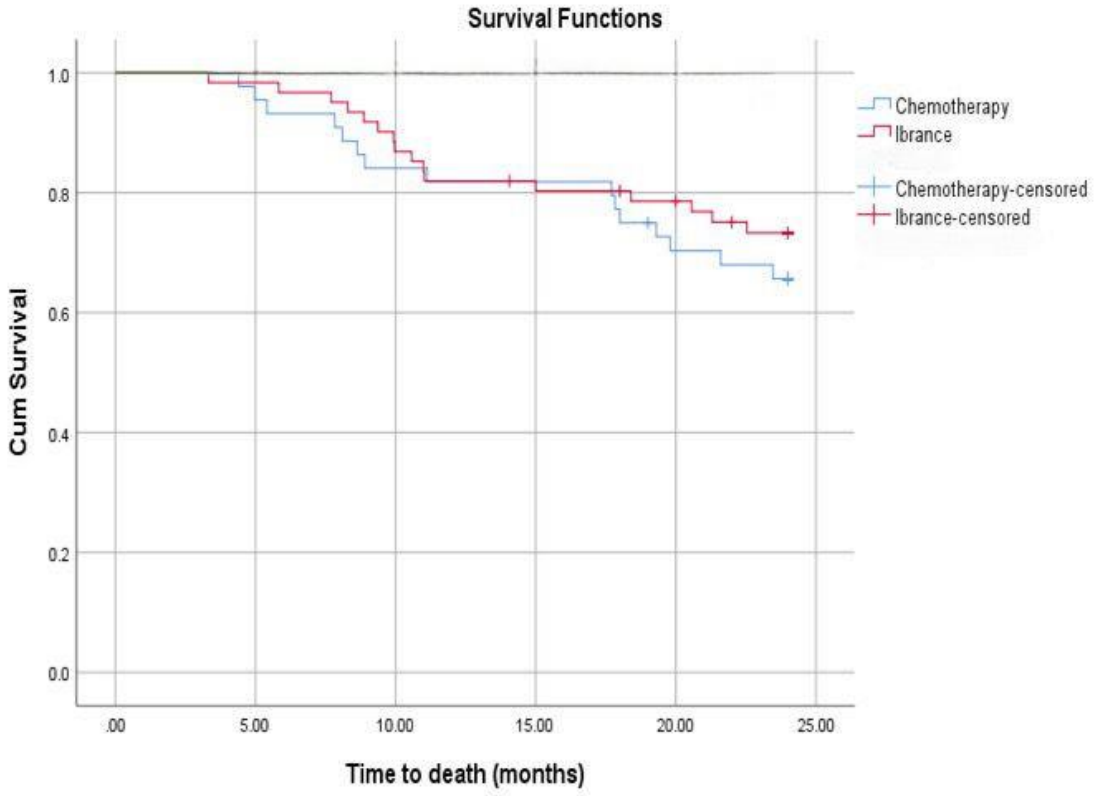

Figure (3): OS between Palbociclib+ET vs combined chemotherapy