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REVIEW OF CLINICAL RESPONSE IN LOCALLY ADVANCED AND ADVANCED STAGE BREAST CANCER ON VARIOUS REGIMENTS OF CHEMOTHERAPY AND SUBTYPES: A HOSPITAL BASED STUDY IN TERTIARY CARE HOSPITAL, INDONESIA

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Background: Chemotherapy is the most commonly used systemic therapy for locally advanced and advanced-stage breast cancer, not only for TNBC, HER-2 type, and luminal B, but also partly for luminal A. In Haji Adam Malik (HAM) Hospital, a tertiary care hospital, most breast cancer patients are in stages III and IV; hence, most patients receive chemotherapy. In this review, we examine the clinical response of breast cancer according to various chemotherapy regimens and subtypes of breast cancer.

Methods: A review of medical records and clinical examinations was conducted in the Surgical Oncology Division of the Department of Surgery at HAM Hospital in Medan, Indonesia, using a cross-sectional study design. Response Evaluation Criteria in Solid Tumors/RECIST was used to assess clinical response.

Result: In 2022, 107 patients met the criteria for this study, including 56 Luminal B, 23 Luminal A, 19 HER-2 type, and 9 TNBC. General clinical responses: CR(complete response), PR(partial response), SD(stable disease), and PD(progressive disease) were as follows: 2 cases(1,9%), 55 cases(51,4%), 20 cases(18,7%), and 30(28%) cases, respectively. A total of 13 chemotherapy regimens were administered; AT (Paclitaxel/Doxorubicin), TP (Docetaxel/Cisplatin), CEF (Cyclophosphamide/ Epirubicin/5FU), and AC (Doxorubicin/Cyclophosphamide) were given the most. Cumulative complete and partial response for AT:64,5%,TP:28,6%,CEF:53%,and AC:58,3%. Based on subtype, the cumulative complete and partial response for TNBC 66,7%, Luminal A 60%, HER-2 type 52,6%, and Luminal B 48,2%. On regiments AT,TP,CEF,AC consecutively, benefit response (CR+PR+SD) of luminal A: 9/9(100%), 2/5(40%), 3/5(60%), 2/2(100%); luminal B: 9/11(81,8%), 8/15(53,3%), 2/4(50%), 4/6(66,7%); TNBC: 5/5(100%), 3/3(100%), 1/1(100%), 0% and HER-2 type: 5/6(83,3%), 1/1(100%), 4/4(100%), 2/3(66,7%).

Conclusion: Paclitaxel plus doxorubicin had the highest cumulative complete and partial responses and also the highest benefit response in all subtypes of breast cancer, including TNBC.

Keywords: Clinical Response; Breast Cancer; Chemotherapy

INTRODUCTION

Chemotherapy is the main treatment modality for locally advanced (stage III) and advanced (stage IV) breast cancer. Chemotherapy is administered as neoadjuvant chemotherapy (NAC) for stage III disease and as primary therapy for stage IV disease. Various chemotherapy regimens are recommended for breast cancer treatment, generally based on anthracycline and/or taxane. Different chemotherapy regimens may give different responses and subtypes of breast cancer may elicit different responses.[1-3]

According to GLOBOCAN data (2020), there were 396,941 new cancer cases in Indonesia out of a total population of 273,523,621. The most common type of cancer in Indonesia is breast cancer.[4] The majority of patients with breast cancer who seek treatment at tertiary referral hospitals are in stages IIIB and IV.

At Haji Adam Malik Hospital, a tertiary referral hospital and the main teaching hospital in Medan, Indonesia, the majority of breast cancer patients who seek treatment are in stages III and IV; therefore, chemotherapy is commonly administered as part of the treatment. Based on this, the researcher aimed to evaluate the response to various chemotherapy regimens and breast cancer subtypes in stages III and IV at Haji Adam Malik Hospital.

[Breast Cancer Chemotherapy]

Chemotherapy is a cancer treatment that involves the administration of cytostatic drugs to kill cancer cells. This therapy has systemic effects in terms of both drug response and side effects. To achieve an optimal chemotherapy response with tolerable side effects, chemotherapy administration should follow the guidelines for calculating chemotherapy doses, which include:[5]

1. Do not use Body Surface Area (BSA) as the sole parameter for dose calculation.
2. Do not use extreme BSA values for dose calculation (e.g., BSA of 2). Cachexia and obesity also affect drug doses
3. Use BSA to figure out the typical absolute dose range for the therapy protocol (e.g., the dose of doxorubicin is 80 to 120 mg, not 60mg/m2). The best dose is within that range and not solely dependent on BSA.
4. Round off calculated doses. Do not order fractional doses. (e.g., 102 mg of doxorubicin should be rounded to 100 mg). This has safety, compounding, and financial implications.
5. Always consider parameters other than BSA when calculating doses (see points 6-9).
6. Know how the drug is eliminated. Adjust the dose based on drug elimination tests, such as serum creatinine, GFR, bilirubin, transaminase, or other drug elimination tests.
7. Check other drugs that can inhibit or increase cytostatic drug elimination (inhibit: erythromycin, fluconazole, cimetidine, diltiazem, etc. Increase: rifampicin, dexamethasone, spironolactone, phenytoin, etc.).
8. Check other parameters that affect drug disposition, such as albumin, ascites, cachexia, obesity, and performance status.
9. Check other factors that affect normal tissue sensitivity, which is necessary for dose reduction, such as previous chemotherapy or radiation therapy history, performance status, and cachexia.
10. Note that chemotherapy doses are inaccurate by up to 40%. About 10% of patients overdosed and 30% are underdosed.
11. Measure biological endpoints, such as the impact of myelosuppression. Adjust the next dose (increase or decrease). The minimum neutrophil count for myelosuppressive drugs is 1,5x109 per liter.
12. Always check the dose calculation made for other parties.

Chemotherapy for breast cancer can be administered as adjuvant, neoadjuvant, or primary therapy. The recommended chemotherapy regimens for breast cancer are generally based on anthracycline and taxane, either alone or in combination. The combination of frequently used chemotherapy regimens includes: AT (paclitaxel + doxorubicin), AC-T (doxorubicin + cyclophosphamide-paclitaxel), CAF (cyclophosphamide + doxorubicin + 5FU), CEF (cyclophosphamide + epirubicin + 5FU), TCH (docetaxel + carboplatin + trastuzumab), TP (docetaxel + cisplatin), docetaxel + cyclophosphamide, paclitaxel + cisplatin, vinorelbine + 5-fluorouracil + leucovorin, gemcitabine, and eribulin.[3]

- Adjuvant Chemotherapy

Adjuvant chemotherapy is primarily administered to patients with early stage breast cancer who are considered high-risk. Risk stratification was based on clinicopathological parameters and the biological nature of the cancer (Table 1). Patients classified as low risk are recommended to receive endocrine therapy alone. For intermediate-risk patients, chemotherapy should also be administered if all criteria are met. For the intermediate-risk group, which is still indeterminate, genetic mutation testing (MammaPrint, oncotype DX) can be conducted if available. Chemotherapy is also indicated for patients with TNBC (Triple Negative Breast Cancer) subtype.[6]

The goal of adjuvant chemotherapy is to eradicate microscopically visible cancer cells and reduce the risk of local, regional, and systemic recurrences. This, in turn, can increase the disease-free interval and improve overall survival.[7]

- Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy is administered before definitive surgery. This approach aims to reduce tumor size, control micrometastasis, convert inoperable cases to operable ones, convert cases that supposedly require MRM to BCS, and determine the chemotherapy response to a specific regimen.[8,9]

Neoadjuvant chemotherapy is given in breast cancer:[1,3]

- Advanced local stage (Stage III)
- Stage II with triple-negative subtype or HER-2 overexpression
- Early-stage breast cancer that will undergo BCS (Breast Conserving Surgery) and meets all the criteria for BCS, except for tumor size

- Primary/Palliative Chemotherapy

Chemotherapy is the primary therapy for breast cancer with distant metastases. Chemotherapy is administered in this condition with the aim of prolonging survival, alleviating or preventing symptoms or complications, and improving quality of life.[10]

[Chemotherapy Response Evaluation and Surgery Timing]

Chemotherapy response is evaluated after 3 cycles using the Response Evaluation Criteria in Solid Tumor (RECIST) or World Health Organization (WHO) criteria. Chemotherapy response consists of complete response, partial response, stable disease or unresponsive, and progressive disease. The criteria for evaluating chemotherapy response according to RECIST are as follows:[11]

1. Complete response (CR): disappearance of the tumor lesion measured at the second observation conducted at an interval of not less than four weeks from the first observation.
2. Partial response (PR): a decrease in tumor size by 30% or more was measured at the second observation conducted at an interval of not less than four weeks from the first observation.

3. Progressive disease (PD): an increase in tumor size by 20% or more or the appearance of new lesions.
4. Stable disease (SD): The tumor shrinks but does not meet the PR criteria, or grows but does not meet the PD criteria.

According to the WHO criteria, the evaluation of chemotherapy response is as follows:[12]

1. Complete response (CR): Disappearance of the tumor lesion measured at the second observation conducted at an interval of not less than four weeks from the first observation.
2. Partial response (PR): A decrease in tumor size of 50% or more was measured at the second observation conducted at an interval of not less than 4 weeks from the first observation.
3. Progressive disease (PD): An increase in tumor size by ≥ 25% or the appearance of new lesions.
4. Stable disease (SD): Does not meet the PR and PD criteria.

Patients with partial or complete response undergo definitive surgery, followed by three cycles of chemotherapy or continuation of chemotherapy until full dose (4-8 cycles) before definitive surgery is performed. Switching to a different chemotherapy regimen is recommended for patients with minimal response or progression.[1,3,13]

METHODS

This was an observational study conducted on a population of breast cancer patients treated at Haji Adam Malik (HAM) General Hospital. The inclusion criteria were all patients with stage III and IV breast cancer who were treated at the Surgical Oncology Division Ward in 2022 and had complete data, including the type and subtype of breast cancer, stage, and all parameters for evaluating chemotherapy response. Patients who died before completing all cycles of chemotherapy and those who had communication difficulties were excluded from the study. Data were obtained from medical records and direct clinical examinations of the patients. Direct clinical examination was mainly performed on patients with data that required confirmation of accuracy.

The clinical response to chemotherapy was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST), where the response was grouped into four criteria: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). A response assessment was conducted after the third cycle of chemotherapy.

Breast cancer subtypes were grouped into four subtypes: luminal A, luminal B, HER-2 positive, and Triple Negative Breast Cancer (TNBC). The criteria for the breast cancer subtypes were as follows:[14]

1. Luminal A: ER and/or PR (+), HER-2 (-), Ki 67 < 20%
2. Luminal B: ER and/or PR (+), HER-2 (+) or HER-2 (-), Ki 67 > 20%
3. HER -2 type: ER (-) dan PR (-), HER-2 (+)
4. TNBC (Basal like): ER (-) dan PR (-), HER-2 (-).

*ER, estrogen receptor; PR, progesterone receptor; HER, human epidermal growth factor receptor.

This study is registered with the ResearchRegistry and the unique identifying number is: researchregistry9692.

RESULTS

A total of 107 patients met the inclusion criteria for the study, with a mean age of 51.2 years, range: 26–77 years). The majority of the histopathological types were invasive breast carcinoma of no special type (83%), followed by invasive lobular and mucinous carcinomas. The distribution according to breast cancer subtype was as follows: Luminal B subtype was found in 56 patients (52%), Luminal A 23 patients (21%), HER-2 type in 19 patients (18%), and TNBC in 9 patients (8%). The most commonly used chemotherapy regimen was AT in 31 patients (29%), followed by TP in 21 patients (20%), CEF in 13 patients (12%), and AC in 12 patients (11%); 30 patients received other regimens. Patient characteristics are shown in Table 2.

Overall, the highest response to chemotherapy was PR (partial response) in 55 (51,4%) patients, while CR (complete response) was only found in 2 (1,9%) patients, each with AT (doxorubicin+paclitaxel) and TP (docetaxel+cisplatin) regimens. A benefit response (CR + PR + SD) to chemotherapy was observed in 77 (72%) patients (Table 3).

The cumulative complete and partial response (CCP) of chemotherapy regimens was 20/31 patients or 64.5% for the AT regimen, 7/12 patients or 58.3% for the AC regimen, 7/13 patients or 53.8% for the CEF regimen, and 6/21 patients or 28.6% for the TP regimen. Overall, the AT regimen exhibited the highest cumulative response rate. No complete or partial response was found for the EC and VLF regimens, but there was only 1 for each regimen. For the combination of Docetaxel and Trastuzumab (TH), of the three patients who experienced progressive disease, two had a partial response and one had progressive disease (see Table 4).

Based on breast cancer subtype, the cumulative complete and partial response for TNBC was 6/9 patients (66.7%), Luminal A was 14/23 patients (60%), HER-2 type was 10/19 patients (52.6%), and Luminal B was 27/56 patients (48.2%). Therefore, the cumulative complete and partial responses for TNBC were highest (see Table 5).

Based on the four most commonly used regimens, AT, TP, CEF, and AC, the benefit response (CR + PR + SD) for each breast cancer subtype was as follows:

- Luminal A: 9/9 (100%), 2/5 (40%), 3/5 (60%), 2/2 (100%)
- Luminal B: 9/11 (81,8%), 8/15 (53,3%), 2/4 (50%), 4/6 (66,7%)
- TNBC: 5/5 (100%), 3/3 (100%), 1/1 (100%), 0%
- HER-2 type: 5/6 (83,3%), 1/1 (100%), 4/4 (100%), 2/3 (66,7%)

The AT regimen had a very good benefit response (100%) for both Luminal A and TNBC, and a

good response for Luminal B (82%) and HER-2 type (83%). TP and CEF have a 100% benefit response for TNBC and the HER-2 type, but with a limited number of patients. The AC regimen is superior for Luminal A, but also with a limited number of patients (see Table 4).

DISCUSSIONS

Among 107 patients who received various chemotherapy regimens, the highest clinical response observed was partial response (PR) at 51%, followed by progressive disease (PD) at 28%, stable disease (SD) at 19%, and complete response (CR) at 2%. This differs from the results of Sivasanker's study, which found the highest response to SD (38%), followed by PR (34%), CR (24%), and PD (4%) among 50 patients receiving the AT regimen [2]. This discrepancy may be due to differences in the chemotherapy regimens used and the timing of administration, as this study included patients receiving first-line, second-line, and third-line chemotherapy.

The combination of anthracycline and taxane (AT) is a commonly used chemotherapy regimen as neoadjuvant therapy for early and locally advanced breast cancer.[15] The AT regimen is also recommended as a primary therapy for advanced breast cancer.[16] In this study, the AT regimen showed a better overall response rate (complete and partial response) than TP, CEF, AC, and other regimens. This is consistent with Sivasanker et al.'s study, which found better clinical and pathological responses with the AT regimen compared to CAF and recommended it as first-line neoadjuvant therapy for locally advanced breast cancer.[2]

Based on the breast cancer subtype, the highest cumulative complete and partial response rates were observed in TNBC (66,7%), followed by luminal A (60%), HER2 type (52,6%), and luminal B (48,2%). This differs from Sharma et al.'s study of 31 patients, which found the highest cumulative complete and partial response rates in HER2 type (87,5%), followed by luminal A/B (80%) and TNBC (77,5%). This difference may be due to the smaller sample size and differences in the chemotherapy regimens used, as Sharma et al. only used the AC regimen. However, it is interesting to note that a good response was observed for the luminal A subtype in both studies. This suggests that the luminal A subtype should receive chemotherapy in addition to endocrine therapy, especially for locally advanced and advanced breast cancers.[17]

Based on breast cancer subtypes, generally (without evaluating chemotherapy regimens), the highest cumulative complete and partial responses were found in the TNBC subtype. This is consistent with several studies indicating good responses to chemotherapy in TNBC, whether as adjuvant, neoadjuvant, or metastatic therapy. Studies evaluating neoadjuvant chemotherapy consistently report higher responses in TNBC compared to non-TNBC.18 Currently, the NCCN guidelines recommend the use of pembrolizumab + chemotherapy as first-line systemic therapy for TNBC with PD-L1 (+), using taxane, anthracycline, and platinum-based chemotherapy.[1]

For benefit response, the AT regimen was superior to other regimens for luminal A and TNBC, with a benefit response of 100%, while the benefit response for luminal B and HER2 type was 82-83%. The TP and CEF regimens also showed a good benefit response in TNBC and HER2 types, but with fewer patients. A meta-analysis conducted by Vidra et al. found an increase in the complete pathological response in TNBC patients receiving platinum-based NAC, regardless of the type of platinum used, but did not evaluate the efficacy of other chemotherapy regimens.[19]

The limitations of this study include the non-uniform setting of chemotherapy administration, with some patients receiving first-, second-, and third-line chemotherapy, which may affect the chemotherapy response. Another limitation is that the sample size of patients was inadequate to conduct a comprehensive evaluation of various chemotherapy regimens based on the subtypes.

CONCLUSION

The combination of Paclitaxel and Doxorubicin (AT) had the highest cumulative complete and partial responses and also benefit response in all subtypes of breast cancer, including TNBC. Therefore, the AT regimen may be considered the first-line chemotherapy option for locally advanced and advanced-stage breast cancer in all breast cancer subtypes.

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TABLES FOOTNOTES & CAPTIONS

Table 1. Risk Stratification based on Clinical-pathological parameters [6].

Risk Category	Clinical-pathological Parameters	Adjuvant Therapy
Low-risk	Negative lymph node and normal all clinical-pathological parameters: - pT < 2 cm - Grade 1 - peritumoral lymphovascular invasion (-) - ER and/or PR (+) - low Ki-67 (< 10 %) - HER-2 overexpression (-) - >35 years old	Chemotherapy not recommended Endocrine therapy
Intermediate-risk	Negative lymph node and min. one of poor prognostic features: - pT > 2 cm - Grade 2-3 - LVE (+) - ER and/or PR (-) / weak positive (1-9%) - Intermediate Ki-67 (10 - 20%) - HER2 overexpression (+) - <35 years old - Positive lymph node (1-3), with good prognostic features (HER2 (-), ER and/or PR positive)	Chemotherapy is given if all criteria are met
High-risk	- Positive lymph node (1-3) and HER-2 (+), ER and PR (-), high Ki-67 > 20% - Positive lymph node (4 or more)	Chemotherapy

*pT, pathological tumor size; LVE, lymphovascular extension; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2

Table 2. Patients characteristic before receiving chemotherapy

Variable	Frequency (N=107)
Age	
• Average	51,2 years old
• Range	26-77 years old
Menstrual Status	
• Premenopause	37
• Perimenopause	27
• Post-menopause	41
• Unknown	2
Histology Type	
• IDC/NST	89
• ILC	12
• Mucinous	2
• others	4
Grade	
• I	15
• II	48
• III	23
• Unknown	21
Cancer Subtype	
• Luminal B	56
• Luminal A	23
• Her-2 Type	19
• Triple Negative	9

Stage	
• III	46
• IV	61
ER/PR Status	
• Positive	82
• Negative	25
HER-2 Status	
• Positive	47
• Negative	60
Chemotherapy Regimen	
• Paclitaxel + doxorubicin (AT)	31
• Docetaxel + Cisplatin (TP)	21
• Cyclophosphamide + Epirubicin + 5FU (CEF)	13
• Doxorubicin + Cyclophosphamide (AC)	12
• Other regimens	30

*IDC, invasive ductal carcinoma; NST, invasive carcinoma of no special type; ILC, invasive lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2

Table 3. Total Chemotherapy Response

Chemotherapy Response	Frequency (N=107) (100%)
Complete response (CR)	2 (1,9%)
Partial response (PR)	55 (51,4%)
Stabile disease (SD)	20 (18,7%)
Progressive disease (PD)	30 (28%)

Table 4. Chemotherapy response of various subtypes according to chemotherapy regimen

Chemotherapy Regimen	All Subtypes (N=107)	Luminal A (N=23)	Luminal B (N=56)	HER-2 (N=19)	TNBC (N=9)
Paclitaxel + Doxorubicin (AT)	N=31(29%)→CCP: 64,5% (20/31)	n=9	n=11	n=6	n=5
• Complete Response (CR)	1	1	-	-	-
• Partial Response (PR)	19	6	7	3	3
• Stable Disease (SD)	8	2	2	2	2
• Progressive Disease (PD)	3	-	2	1	-
Docetaxel + Cisplatin (TP)	N=21(19,6%)→CCP: 28,6% (6/21)	n=5	n=15	n=1	n=3
• Complete Response (CR)	1	-	1	-	-
• Partial Response (PR)	5	1	4	-	2
• Stable Disease (SD)	5	1	3	1	1
• Progressive Disease (PD)	10	3	7	-	-
Cyclophosphamide + Epirubicin + 5FU (CEF)	N=13(12,1%)→CCP: 53,8% (7/13)	n=5	n=4	n=4	n=1
• Complete Response (CR)	-	-	-	-	-
• Partial Response (PR)	7	2	2	2	1
• Stable Disease (SD)	2	1	-	2	-
• Progressive Disease (PD)	4	2	2	-	-
Doxorubicin + Cyclophosphamide (AC)	N=12(11,2%)→CCP: 58,3% (7/12)	n=2	n=6	n=3	
• Complete Response (CR)	-	-	-	-	
• Partial Response (PR)	7	2	3	2	
• Stable Disease (SD)	1	-	1	-	
• Progressive Disease (PD)	4	-	2	1	
Paclitaxel + epirubicin (EP)	N:7 (6,5%)	n=1	n=5	n=1	
• Complete Response (CR)	-	-	-	-	
• Partial Response (PR)	5	1	3	1	
• Stable Disease (SD)	-	-	-	-	

• Progressive Disease (PD)	2	-	2	-
Cyclophosphamide + Doxorubicin + 5FU (CAF)	N:7 (6,5%)	n=1	n=5	n=1
• Complete Response (CR)	-	-	-	-
• Partial Response (PR)	4	1	3	-
• Stable Disease (SD)	-	-	-	-
• Progressive Disease (PD)	3	-	2	1
Paclitaxel + Cisplatin (TP)	N: 6 (5,6%)		n=3	
• Complete Response (CR)	-		-	
• Partial Response (PR)	4		2	
• Stable Disease (SD)	1		-	
• Progressive Disease (PD)	1		1	
Docetaxel + Trastuzumab (TH)	N: 3 (2,8%)		n=1	n=2
• Complete Response (CR)	-		-	-
• Partial Response (PR)	1		-	1
• Stable Disease (SD)	-		-	-
• Progressive Disease (PD)	2		1	1
Docetaxel + Cisplatin + Trastuzumab (TCH)	N: 2 (1,9%)		n=2	
• Complete Response (CR)	-		-	
• Partial Response (PR)	1		1	
• Stable Disease (SD)	1		1	
• Progressive Disease (PD)	-		-	
Docetaxel + Epirubicin (TE)	N: 2 (1,9%)		n=1	n=1
• Complete Response (CR)	-		-	-
• Partial Response (PR)	2		1	1
• Stable Disease (SD)	-		-	-
• Progressive Disease (PD)	-		-	-
Epirubicin + Cyclophosphamide (EC)	N: 1 (0,9%)		n=1	
• Complete Response (CR)	-		-	
• Partial Response (PR)	-		-	
• Stable Disease (SD)	1		1	
• Progressive Disease (PD)	-		-	
Vinorelbine + Leucovorin + 5FU (VLF)	N: 1 (0,9%)		n=1	
• Complete Response (CR)	-		-	
• Partial Response (PR)	-		-	
• Stable Disease (SD)	-		-	
• Progressive Disease (PD)	1		1	
Docetaxel + Cyclophosphamide (TC)	N: 1 (0,9%)		n=1	
• Complete Response (CR)	-		-	
• Partial Response (PR)	-		-	
• Stable Disease (SD)	-		-	
• Progressive Disease (PD)	1		1	

*CCP, cumulative complete and partial response (CR+PR); HER-2, HER-2 type breast cancer; TNBC, triple negative breast cancer

Table 5. Total chemotherapy response according to subtype

Chemotherapy Response	Subtype			
	Luminal A (n=23)	Luminal B (n=56)	HER-2 (n=19)	TNBC (n=9)
Complete Response (CR)	1	1	-	-
Partial Response (PR)	13	26	10	6
Stabile Disease (SD)	4	8	5	3
Progressive Disease (PD)	5	21	4	-
CCP	*14/23 (60%)*	*27/56 (48,2%)*	*10/19 (52,6%)*	*6/9 (66,7%)*

*CCP, cumulative complete and partial response (CR+PR); HER-2, HER-2 type breast cancer; TNBC, triple negative breast cancer