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# Efficacy, Safety Profiles and Outcomes of Dual Anti Her2 Blockade in Combination with Neoadjuvant Chemotherapy in Locally Advanced (Stage II-III) Her2 Expressing Breast Cancer Patients, Middle East Experience

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## ABSTRACT

**Background** prognosis of HER2-positive breast cancer has been transformed Over the past few years, with the introduction of anti-HER2 targeted therapies.
Pertuzumab in combination with trastuzumab based chemotherapy is currently FDA- approved as a standard neoadjuvant treatment for stage II-III (HER2+) breast cancer patients. It improves pathological complete response (pCR) if used in combination with standard chemotherapy in many prospective trails. chemotherapy backbone may include: taxane (Docetaxel/paclitaxel), and/or anthracycline, or platinum .
**Methods** Forty-six HER2-positive breast cancer patients received neoadjuvant chemotherapy, with dual anti her blockade Pertuzumab and Trastuzumab from April 2013 to July 2017 in KFSHRC, Riyadh were included. patients were internally divided into 3 groups according to type of chemotherapy used, group A (sequential anthracycline/docetaxel), group B ( sequential anthracycline/paclitaxel) and group C (taxane based chemotherapy without anthracycline), Pertuzumab and Trastuzumab were given with the taxane part.
Main objective was to access pCR, Secondary endpoints included the disease-free survival (DFS), overall survival (OS), local control (LC) and toxicity profile. survival endpoints studied were pCR (defined as ypT0/is, ypN0).
**Results** Median age at diagnosis was 46.5 (23-65) years, 26(56.5%) were premenopausal. All patients had IDC [G2 (61%), G3 (39%)],36(78.3%) patients had T3/T4 and 44(95.7%) had node +ve disease. Hormone receptor was positive in 22(48%) patients. patients were internally divided into 3 groups according to type of chemotherapy used, group A (received sequential anthracycline/docetaxel), group B (received sequential anthracycline/paclitaxel) and group C (received taxane based chemotherapy without anthracycline), all

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the patients received dual anti her blockade Pertuzumab and Trastuzumab with the taxane part . MRM was done in majority of patients 39(85%), while 6(13%) had BCT. Adjuvant radiation therapy was given in 43(93.5%).
The treatment course was discontinued only in two cases (one had drop in EF>10% to <50%, second progressed while on treatment), no other reported acute or chronic G3/4 toxicity. Twenty-five (54.3%) patients achieved pathological complete response (pCR). After median follow-up of 26 months (15-59), 45(97.8%) patients were alive, only one patient died due to disease. Five (10.9%) patients developed systemic recurrences; among them 4(8.7%) had also loco-regional recurrences. The 4-year Local Control (LC) rate, disease free survival (DFS) and overall survival (OS) rate were 96%, 93% and 94% respectively. In univariable analysis, clinical response was independent prognostic factors for pCR and loco regional control (LC), while positive hormone receptor status significantly correlated with better LC and DFS.
**Conclusion** Dual anti her blockade in combination with systemic neoadjuvant chemotherapy is effective in our population, with overall observed pCR, DFS and OS rate comparable to published international studies despite the Poor prognostic features (young age, premenopausal status, high grade and large tumor size) but they achieve good disease control. There were no concerns about cardiac safety and cardio toxicity seems similar to previous reported data. Longer follow up and addressing the role of adjuvant dual blockade in such population of locally advanced breast cancer is needed for a better understanding of dual her2 blockade.

## INTRODUCTION

Breast cancer (BC) is the most commonly diagnosed cancer in women worldwide. In USA, about 30% of newly diagnosed cancers in women will be breast cancers, with estimated 266,120 new cases of invasive breast cancer are expected to be diagnosed in 2018 (1).
In Saudi Arabia, breast cancer is the most frequently diagnosed cancer among women accounting for about 21% of all cancer (2).
Management of non-metastatic breast cancer is a multimodality approach includes surgery, Chemotherapy, hormonal treatment, target therapy and radiation therapy (3).
Chemotherapy given in the adjuvant treatment or neoadjuvant setting have shown to improve overall survival. Neoadjuvant approach has several potential advantages downstage the tumor allowing less extensive surgery associated with better cosmetic outcomes (4-8), Neo adjuvant treatment also permits clinicians to monitor in vivo response to therapy, potentially allowing time and flexibility to switch therapies if patients do not respond. Pathological response post neoadjuvant approach has allowed clinician to tailor therapy post-surgery. Indeed, targeting patient with poor response with addition therapies have potentially improved outcomes (9,10).
Of all clinical breast cancer subtypes, human epidermal growth factor receptor (HER) 2–positive and triple-negative breast cancer (TNBC) are the most responsive to chemotherapy, and therefore are most likely to benefit from neo adjuvant approach (11).
Breast cancers characterized by overexpression of (HER2) receptor tyrosine kinase or amplification of *HER2* genes constitute approximately 20–25% of all breast cancers, and characterized by an aggressive clinical course with a propensity for distant metastases within 5 years of diagnosis (12, 13).
Trastuzumab is a humanized recombinant monoclonal antibody that binds to the extracellular domain of HER2 and inhibits downstream signaling, It is the first her-2 target therapy, it synergizes with many conventional cytotoxic agents with dramatic improvement in the outcomes of patients with all stages of HER2-positive breast cancer (14–20).
Pertuzumab is another HER2-directed humanized monoclonal antibody with a distinct binding site than trastuzumab. The addition of pertuzumab to taxane-based chemotherapy with trastuzumab in the preoperative setting was evaluated in in two phase II clinical trials (NeoSphere and TRYPHAENA) and resulted in significant improvement in pCR rates (defined as no residual invasive or in situ tumor in the breast and axillary lymph nodes). The overall survival benefit in the metastatic setting together with the pCR improvements in the neo adjuvant setting ultimately led to approval of neo adjuvant administration in combination with trastuzumab and taxane-containing regimens for tumors greater than 2 cm in size or node-positive disease (21 -23).
In this study we will assess efficacy and outcomes of dual Anti Her2 Blockade in combination of Neoadjuvant Chemotherapy in our patients' cohort with locally advanced Her2 Expressing Breast cancer

### Patients & Methods

Forty six HER2-positive breast cancer patients who received neoadjuvant chemotherapy, with dual anti her blockade Pertuzumab and Trastuzumab from April 2013 to July 2017, their data collected for clinic pathological characteristics, treatment and outcomes. the main objective was to access pathological response (pCR), Secondary endpoints included local control (LC) disease free survival (DFS), overall survival (OS) and toxicity
All the patients underwent complete history, physical examination, full labs, (diagnostic mammography and U/S breast), U/S guided True cut biopsy of the breast lesion with clips insertion, in addition to staging CT chest, abdomen and pelvis, Bone scan and cardiac imaging mainly echocardiogram.

Assessment of ER/PR marker and her-2 status**,** IHC test (**I**mmuno**h**isto **C**hemistry) was used to assess ER/PR marker, the threshold for a positive result for hormone receptor expression was at least 1 percent of cancer cells staining for ER or PR (ACP guidelines) (24,25). For her-2 assessment, we used both IHC and Fluorescence In Situ Hybridization (FISH test), IHC results can be 3+(positive), 0,1+(negative) and 2+ (borderline), FISH used to find out if there are too many copies of the *HER2* gene in the cancer cells.

The patients were internally divided into 3 groups according to type of chemotherapy used (group A sequential AC or EC for 4 cycles/ Docetaxel for 4cycles), group B (sequential AC or EC for 4 cycles / weekly paclitaxel for 12 weeks) and group C (Docetaxel only for 6 cycles). All the patients received HER-2neu dual target therapy (Trastuzumab (T) and pertuzumab (P).
EC therapy (epirubicin 100 mg/m² intravenously, and cyclophosphamide 600 mg/m² intravenously every 3 weeks), AC (doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² intravenously every 3 weeks), Docetaxel was given at 75-100 mg/m² every 3 weeks and paclitaxel was given at a dose of 80mg/m² weekly.

Trastuzumab was given every 3 weeks at 8 mg/kg (cycle 1), followed by 6 mg/kg. The pertuzumab loading dose was 840 mg, followed by 420 mg every 3 weeks. In all cases dual antiher2 blockade was added with Taxanes therapy
Assessment of the response to neo adjuvant treatment was done by clinical examination before each cycle. U/S breast was done if clinically indicated before surgery. Echo was repeated for every patient every 3 months to evaluate left ventricle ejection fraction (EF).

Surgery was usually done 3-4 weeks after chemo/target therapy.
Adjuvant Trastuzumab was given for all patients post operatively every 3 weeks to complete 1 year of adjuvant treatment.
Adjuvant radiation therapy was given 3-4 weeks after surgery.
Adjuvant hormonal treatment was started after end of radiation therapy in those with ER positive disease.

Regular follow up to the patients with periodic clinical examination every 3-4 months in the first 2 years and then every 4-6 months (2-5 years) post diagnosis in addition to annual mammography. We did not perform routine imaging (CT body, bone scan) unless clinically indicated. Echo was repeated every 3 months until completion of trastuzumab therapy. Patients who experience cardiac symptoms or a greater than 10% absolute asymptomatic decline in LV EF while receiving trastuzumab was continuing to undergo annual cardiac assessments following completion of trastuzumab treatment.

### Statistical analysis

Descriptive statistics was performed for all available categorical variables.

The patient and treatment characteristics were summarized as mean±SD (range) values for continuous variables, and frequency (percentage) values for categorical variables. The difference in distributions according to the chemotherapy group was tested using Pearson's chi-squared test.

**Table 1 Patients demographics and tumor characteristics**

| Characteristic | | all (n=46) | |
|---|---|---|---|
| **age at diagnosis (yrs)** | **Range** | 23-65 | |
| | **Average** | 46.5 | |
| **menopausal status** | **Pre** | 26 | 56.5% |
| | **Post** | 20 | 43.5% |
| **ECOG performance status** | **0** | 24 | 52.2% |
| | **1** | 20 | 43.5% |
| | **2** | 2 | 4.3% |
| **pre-treatment T stage** | **T1** | 1 | 2.2% |
| | **T2** | 9 | 19.6% |
| | **T3** | 21 | 45.7% |
| | **T4** | 15 | 32.6% |
| **pre-treatment N stage** | **N0** | 2 | 4.3% |
| | **N1** | 36 | 78.3% |
| | **N2** | 7 | 15.2% |
| | **N3** | 1 | 2.2% |
| **AJCC stage** | **IIa** | 4 | 8.7% |
| | **IIb** | 10 | 21.7% |
| | **IIIa** | 16 | 34.8% |
| | **IIIb** | 15 | 32.6% |
| | **IIIc** | 1 | 2.2% |
| **pre-treatment LVEF** | **50-55%** | 3 | 6.5% |
| | **>55%** | 43 | 93.5% |
| **Grade** | **G2** | 28 | 60.9% |
| | **G3** | 18 | 39.1% |
| **Hormonal receptor status** | **ER+** | 22 | 47.8% |
| | **ER-** | 24 | 52.2% |

The survival endpoints studied were pCR, LC, DFS and OS, using univariate and multivariable analyses. LC and DFS were calculated from the date of surgery, while OS was calculated from the date of diagnosis.

The Kaplan-Meier methodology was used to estimate control and survival probability (expressed as a mean with a range and two-sided 95% confidence interval) and compare between chemotherapy groups of patients, using the log-rank test.

All statistical tests were two-tailed and differences were statistically significant for a p-value less than 0.05. All statistical analyses were performed using a software package (SPSS version 20, Inc., Chicago, IL, USA).

## Results

Forty-six female patients diagnosed with her-2 positive breast cancer were included in this study, all base line and clinico pathological details are listed in table 1.
All the patients tolerate treatment well and completed all planned chemotherapy cycles except two patients in group A (one had drop in EF with >10% decrease in the EF to be < 50%, second progressed while on treatment), no grade 3 or 4 toxicity developed, list of developed toxicity table 2, Twenty five (54.3%) patients achieved pathological complete response (pCR) (of them 17(50%) in group A, 3(100%) in group B and 5 (55.6%) table 3.

**Table 2. Reported side effects and toxicity of the 3 used chemotherapy regimens**

| Toxicity | No. patients | | |
|---|---|---|---|
| | Group A (n=34) | Group B (n=3) | Group C (n=9) |
| **General** | | | |
| Fatigue | 8(23.5%) | 1(33%) | 2(22%) |
| Nausea | 9(26.4%) | 1(33%) | 3(33%) |
| Vomiting | 5(14.7%) | 1(33%) | 2(22%) |
| Myelosuppression | 7(20.5%) | 2(66%) | 3(33%) |
| Febrile neutropenia | 4(12%) | 1(33%) | 1(11%) |
| Gastrointestinal Diarrhea | 9(26.4%) | 0(0%) | 3(33%) |
| Drop in EF>10%, <50% | 1(3%) | 0(0%) | 0(0%) |

**Table 3. Response comparison between the 3 groups of patients**

| Characteristic | | Group A (n=34) | | Group B (n=3) | | Group C (n=9) | | all (n=46) | |
|---|---|---|---|---|---|---|---|---|---|
| clinical response | **CR** | 17 | 50.0% | 3 | 100.0% | 5 | 55.6% | 25 | 54.3% |
| | **PR** | 17 | 50.0% | 0 | 0.0% | 3 | 33.3% | 20 | 43.5% |
| | **PD** | 0 | 0.0% | 0 | 0.0% | 1 | 11.1% | 1 | 2.2% |
| Type of surgery | **BCT** | 2 | 5.9% | 1 | 33.3% | 3 | 33.3% | 6 | 13.0% |
| | **MRM** | 32 | 94.1% | 2 | 66.7% | 5 | 55.6% | 39 | 84.8% |
| | **No surgery** | 0 | 0.0% | 0 | 0.0% | 1 | 11.1% | 1 | 2.2% |
| Pathological response | **Breast** | 1 | 2.9% | 0 | 0.0% | 0 | 0.0% | 1 | 2.2% |
| | **Axilla** | 6 | 17.6% | 0 | 0.0% | 1 | 11.1% | 7 | 15.2% |
| | **breast & axilla** | 17 | 50.0% | 3 | 100.0% | 5 | 55.6% | 25 | 54.3% |
| | **Not achieved** | 10 | 29.4% | 0 | 0.0% | 3 | 33.3% | 13 | 28.3% |

**Table 4 pattern of recurrence and survival**

| Characteristic | | Group A (n=34) | | Group B (n=3) | | Group C (n=9) | | All (n=46) | |
|---|---|---|---|---|---|---|---|---|---|
| Recurrence | **No** | 31 | 91.2% | 3 | 100.0% | 7 | 77.8% | 41 | 89.1% |
| | **Yes** | 3 | 8.8% | 0 | 0.0% | 2 | 22.2% | 5 | 10.9% |
| site of recurrence | **ipsilateral chest wall** | 2 | 5.9% | 0 | 0.0% | 2 | 22.2% | 4 | 8.7% |
| | **ipsilateral breast** | 1 | 2.9% | 0 | 0.0% | 0 | 0.0% | 1 | 2.2% |
| | **SCV** | 1 | 2.9% | 0 | 0.0% | 0 | 0.0% | 1 | 2.2% |
| | **ipsilateral axillary node** | 1 | 2.9% | 0 | 0.0% | 0 | 0.0% | 1 | 2.2% |
| | **Lung** | 1 | 2.9% | 0 | 0.0% | 0 | 0.0% | 1 | 2.2% |
| | **Brain** | 2 | 5.9% | 0 | 0.0% | 1 | 11.1% | 3 | 6.5% |
| | **Liver** | 1 | 2.9% | 0 | 0.0% | 0 | 0.0% | 2 | 4.3% |
| | **Bone** | 0 | 0.0% | 0 | 0.0% | 1 | 11.1% | 1 | 2.2% |
| | **Other** | 0 | 0.0% | 0 | 0.0% | 1 | 11.1% | 1 | 2.2% |
| LC | **Yes** | 33 | 97.1% | 3 | 100.0% | 7 | 77.8% | 41 | 89.1% |
| | **No** | 2 | 5.9% | 0 | 0.0% | 2 | 22.2% | 4 | 8.7% |
| DFS | **Yes** | 31 | 91.2% | 3 | 100.0% | 7 | 77.8% | 41 | 89.1% |
| | **No** | 3 | 8.8% | 0 | 0.0% | 2 | 22.2% | 5 | 10.9% |
| OS | **Yes** | 33 | 97.1% | 3 | 100.0% | 9 | 100.0% | 45 | 97.8% |
| | **No** | 1 | 2.9% | 0 | 0.0% | 0 | 0.0% | 1 | 2.2% |

After median follow-up of 21 months (6-52), 45(97.8%) patients were alive, only one patient died due to disease. Five (10.9%) patients developed systemic recurrences; among them 4(8.7%) had also loco-regional recurrences. The whole patient groups 4-year Local Control (LC) rate, disease free survival (DFS) and overall survival (OS) rate were 96%, 93% and 94% respectively, with no significant difference found between the 3 groups of patients table 4 and figure 1-3

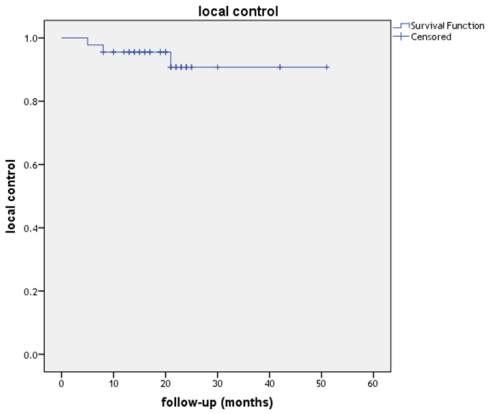


Figure 1. Loco regional control (LC) for whole group of patients

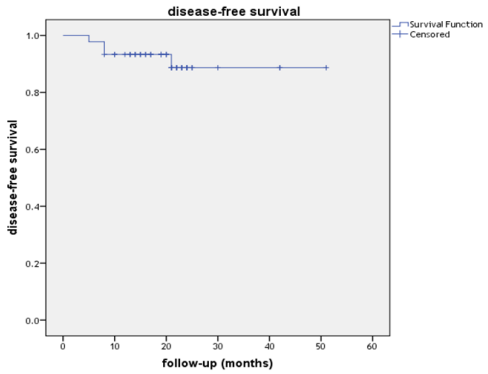


Figure 2. Disease free survival (DFS) for whole group of patients

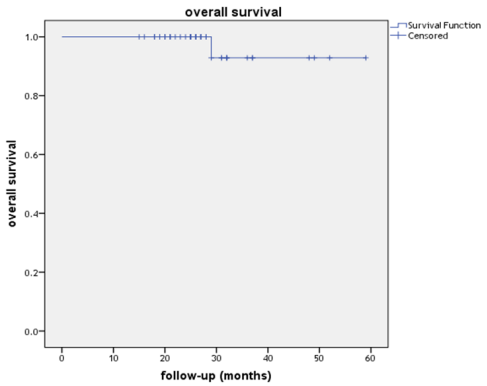


Figure 3. overall survival (OS) for whole group of patients

In univariable analysis, clinical response was independent prognostic factors for pCR while positive hormone receptor status significantly correlated with better LC and DFS. Multivariable analysis indicated pre-treatment N stage for DFS table 5.

Table 5. Prognostic factors analysis

| | | Univariate | Multivariate | | | |
|---|---|---|---|---|---|---|
| **Endpoint** | | **p** | **p** | **HR** | **95%** | |
| pCR n=13 | ECOG perfor- | 0.017 | 0.05 | -- | - | 0. |
| | Clinical response | 0.035 | | | | |
| LC n=4 | Hormone receptor status | 0.046 | | | | |
| DFS n=5 | pre-treatment N stage | 0.002 | 0.003 | 0.252 | 0.089 | 0.414 |
| | Hormone receptor status | 0.023 | | | | |
| | adj. hormonal | 0.038 | | | | |

## Discussion

Patients achieved complete pathological response (pCR) post neo adjuvant treatment have better survival than those who did not (26-32). pCR rate differs according to tumor subtype, with average rate of 18.7% (15.0-23.1%) in HER2+/HR+ vs , 38.9% (33.2-44.9%) in HER2+/HR- (33), in comparison to our study that showed higher incidence of pCR in both HER2+/HR+ and HER2+/HR-(where incidence of pCR in HER2+/HR+ was 40.9% (9/22 patients) and was 66.6% in HER2+/HR-(16/24 patients).

pCR rate in group C patients was 55.6% vs 45.8% in the comparable arm in NeoSphere study, while 50% in group A achieved pCR in comparison to 57.3% in the comparable arm in TRYPHAENA study. Comparison between the incidence of pCR in each group according to ER status revealed that for patients in group C incidence of pCR rate was 60% and 50% in those with ER negative and ER positive respectively, while those in group A (incidence of pCR rate was 64.8% and 35.3% in ER negative and ER positive respectively ,this was comparable to other studies as in the comparable arm in Neosphere study with pCR rate 26% in ER positive and 63.2% in those with ER negative disease .

In our study, median age at diagnosis in group C was 43 (32-65), in comparison to median age of 50(28-77) in the comparable arm in Neo sphere study (22) and median age at diagnosis in group A was 48 (23-63) in comparison to median age of 49.0 (24-75) in the comparable arm in TRYPHAENA study **(23).** Despite the younger age group in our study patients than other studies , the incidence of pCR rate was comparable.

Thirty two (69.5%) of our patients had AJCC stage (III) (locally advanced/inoperable disease), while 14(30.5%) has stage II

(operable cases),I n those patients in group C, 6(66.7%)patients had locally advanced/inoperable disease and 3(33.3%) had operable disease in comparison to 39% had locally advanced/ inoperable disease and 61% had operable disease in the comparable arm in Neo sphere study , while in group A, 24(70.6%) had locally advanced/inoperable disease and 10(29.4%) had operable disease while the comparable arm in TRYPHAENA study include 28%(locally advanced/inoperable disease) and 72%((operable cases). 9(100%) patients had node + disease in group C patients in comparison to 71% had node + disease in comparable arm in Neo sphere study, despite all these advanced features (higher incidence of advanced /inoperable and node positive disease in comparison to other trials) , the incidence of pCR rate was comparable.

Internal comparison between our 3 groups of patient regarding pCR rate, we found that those in group B (received sequential anthracycline/paclitaxel) achieved the highest rate(100%) of pCR , followed by group C patients (those who received taxane based chemotherapy without anthracycline) with pCR rate (55.6%),followed by those in group A(those who received sequential anthracycline/docetaxel) with pCR rate of 50%.this may raise a question regarding benefit of adding anthracycline chemotherapy in the neo adjuvant treatment for those with HER-2neu overexpressed breast cancer, however a strong recommendations cannot be concluded due to the small number of patients.

Most of our patients, 39 (86.7%) underwent mastectomy in spite of the good percentage of patients (achieving clinical and/ or pathological response), which may be attributed to the advanced stage in the majority of patients (with adverse features such as (multifocal, T4 and /or inflammatory disease) rendering it difficult to underwent BCT surgery.

The (ECOG) PS and clinical response were found to be statistically significant independent prognostic factors for pCR (as 24/25 patients who achieved pCR had ECOG 0-1, 17/25 patients who achieved pCR had clinically complete response, this may be explained by that the patient with good PS may withstand treatment cycles without significant toxicity resulting in treatment delay.

The 4 years DFS in group C was 77.8% in comparison to 5 years DFS 84%in the comparable arm in Neo sphere study . 4 years DFS and OS in group A is 91.2% and 97.1% in comparison to 3 years DFS and OAS of 88% and 94% in the comparable arm in TRYPHAENA study, the comparable results in our study came despite the previously mentioned more advanced features, however a real comparison between our study results and these study results cannot be done due to the small number of patients in our study in comparison to these studies.

ER status was found to be statistically significant independent prognostic factors for LC and DFS, as the patients who developed local and systemic recurrence had ER negative disease and no patients with ER positive disease developed local or systemic recurrence this may be explained as ER negative disease have higher incidence of recurrence that more evident in the first 3 years after diagnosis **(34)**.The site and pattern of recurrence also change with both HER-2neu and ER status, we found that the most common sites of distant metastasis were (brain in 3(60%) and liver in 2(40%) patients), that was evident before in the study conducted by kenneth et al_ they found that HR negative, HER2 positive patients have the highest incidence of brain recurrences in the first twelve years after diagnosis and liver recurrences in the first six years after diagnosis (35).

The combination of trastuzumab and pertuzumab in our patient cohort seems to be safe with no recorded G3/4 acute toxicity, the most commonly reported toxicity in group c was neutropenia in 3(33%) patients, febrile neutropenia in one patient (11.1%) in comparison to the comparable arm in Neo Sphere study( where neutropenia developed in 48 of 107 (44.8%) and five/107(4.7%) patients developed febrile neutropenia. Regarding cardiac toxicity, significant drop in EF >10%, with drop of EF <50% occurred only in one (2.2%) patient, in comparison to16% (12/75) in the comparable arm in TRYPHAENA study.

## Conclusion

Pertuzumab containing neoadjuvant chemotherapy was safe and effective in our patients population, with overall observed pCR rate comparable to international data in spite of bad prognostic features (young age, premenopausal status, high grade and large tumor size),a larger cohort of patients and longer follow up is required for better evaluation.

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