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Response assessment in triple positive breast cancer with neoadjuvant chemotherapy and targeted therapy: A case report and its literature review of different regimes, targeted drugs, immune therapies, bispecific antibodies which are under trials

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Abstract

Background: Triple positive breast cancer expresses the human epidermal growth factor receptor (Her 2 neu), estrogen and progesterone receptor. It is well known that Her 2 neu expression is associated with a more aggressive subtype of breast cancer and is associated with reduced mortality. It has less response to hormonal therapy. Neoadjuvant chemotherapy and targeted therapy have become the new standard of treating Her 2 expressive or Triple positive breast cancer.

Introduction: Triple positive breast cancer is a subtype of breast cancer having expression of Estrogen receptors, progesterone and Her 2 neu receptors. The current standard of this in localized disease (stage I, II and III) includes neo adjuvant targeted along with chemotherapy. The response rate of different regimens in neo adjuvant settings varies widely. Choosing of neo adjuvant treatment depends on patient performance status, comorbidities and socio-economic status.

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Objective: To find the percentage of size reduction in triple positive breast cancer, in neo adjuvant Chemotherapy and targeted agents and assess for pathological complete response rates.

Study Design: Case report and its systematic review.

Methodology: Got the patient data with informed consent from patients treated at Khyber Teaching hospital Peshawar, and compared with the data already published in PubMed library, Google scholar. Up to date chemotherapy protocols have been followed as advised in the national comprehensive care network (NCCN). Extensive Literature search has been mentioned with sophisticated drugs and under trials regimen with referencing done.

Results: Her 2 expressive disease or triple positive breast cancer is one of the aggressive histological subtypes and its treatment is one of the most costly treatments due to the involvement of the targeted therapy against Her 2 neu receptors. In our case we had a very huge left breast cancer which was Her 2 neu positive. She received neo adjuvant chemotherapy along with Herceptin and perjeta, to which the cancer had responded very well, and down staged the disease from in operable to make it operable and the patient underwent surgery followed by adjuvant radiation therapy and Hormonal as well as chemotherapy and targeted therapies as received in neo adjuvant setting. As per the different trials the pathologic complete responses (p CR) have been found to be different like Neosphere the pCR was 46%, TRYPHAENA showed pCR rates in all treatment arms ranging from 57% to 66%, ACOSOG (p CR= 55%), NSABP (p CR= 49%), GBG (p CR= 45%), DAPHNE (p CR= 56.7%), ADAPT (p CR= 40%), PAMEL (p CR= 30%), GEPARSEPTO (p CR= 60%). In targeted agents Trustuzumab DM TDM 1, PERTUZUMAB showed 43.6% (95% CI, 33-52%) overall response rate, DHP regimen in CLEOPTRA shows PFS of 18 months and median OS of 57 months. Trastuzumab Deruxtecan and DS-8201 showed 59.5% (95%CI, 49.7–68.7) over all response rate, The PFS was 19.4 months (95%CI, 14.1–not reached), 24.6 months (95%CI 23.1 months-not reached) of median OS. ARX788 showed PFS of 17 months if use as monoclonal agent in met breast Cancer. Neratinib showed PFS of 22.2 weeks if used trustuzumab if no trustuzumab than 39 week PFS and OR rate of 24% if previously trustuzumab used if no trustuzumab used than ORR of 54 %. Pyrotinib and poziotinib showing PFS of 14.1 months, ORR of 27%, PFS of 4 months (95% CI, 3.0-4.4) respectively.

CDK4/6 inhibitors showed no objective response if used as a mono therapy Monarch Her trial showed ORR (35.4% vs. 22.8% with chemotherapy plus trastuzumab) and median PFS with the endocrine/targeted therapy triplet (8.3 vs. 5.7 months; HR = 0.673, 95%CI, 0.451–1.003; p = 0.0253) but no significant response difference with no chemo arm and and PI3K Inhibitors Llike Alpelisib with TDM 1 shows response in pre-treated HER2-positive patients, an ORR of 43% and a median PFS of 8.1 months (95%CI 3.9–10.8) were reported. In the BOLERO-3 trial, the combination of everolimus with trastuzumab and vinorelbine was evaluated in patients with trastuzumab-resistant ABC, and a small but statistically significant benefit in PFS was reported: median PFS 7.0 vs. 5.78 months (HR = 0.78; 95%CI, 0.65–0.95; p = 0.0067). Margetuximab plus chemotherapy generated handsome amount of 24% relative risk reduction in the hazard of progression vs trastuzumab plus chemotherapy, median OS was 21.6 months with margetuximab vs 19.8 months with trastuzumab, and the final analysis of OS will be reported.

Conclusion: The results of all the trials have been discussed briefly along with a case report to signify the treatment in aggressive type of breast cancer. The treatment has been standardized, for tumors of size less than 2 cm shall undergo upfront surgery, followed by adjuvant treatment. If it is pathologically T1 with no nodal metastasis then the patient is advised to receive HP for 12 cycles as per Tolaney study, but if it is p T2 or N+ than the patient will be treated by chemotherapy along with HP for 12 cycles as per Aphinity trial. Those patients having tumor size greater than 2 cm or having nodal metastasis shall receive neo adjuvant chemotherapy and targeted therapy followed by surgery. Adjuvant treatment is based on the final histology of pCR than HP for one year as per Aphinity trial. If no p CR then the patient is advised to receive radiation therapy along with Trastuzumab emtansine (TDM-1) for one year as per Katheriene trial or shall receive HP for 6-12 cycles followed by Neratinib for one year as per Extenet trial.

Keywords: Breast Cancer; Neo adjuvant chemotherapy; Response assessment; Anti her 2 therapy; Tryphaena Trial; Aphinity trial; ExteNet trial; Katherine Trial

1. Introduction

Breast cancer is one of the most common cancers diagnosed among women in the majority of the countries [1]. In 2022 there were 2.3 million newly diagnosed cases of breast cancer, out of whom 670,000 deaths occurred throughout the world [2]. Breast cancer is classified into subtypes based on the presence of estrogen receptors, progesterone receptors and human epidermal growth factor receptor 2 (HER2) [3]. Triple negative breast cancer (TNBC) occurs more in premenopausal patients and it usually presents at an advanced stage. It has also been found that TNBC patients have

high tumor grading, locoregional recurrence, and metastasis rate as compared to TPBC. The prognosis of triple positive breast cancer (TPBC) is usually better which is mostly due to the role of hormonal treatment and targeted therapy [4].

For HER2+ breast cancer, the availability of targeted therapy in the form of monoclonal antibodies that targets HER2 receptors like trastuzumab has significantly improved the survival rates [5]. The treatment of metastatic HER2-positive breast cancer can still be challenging. The primary treatment goal revolves around extending survival while enhancing the quality of life. However, newer agents like neratinib are showing favorable results in metastatic HER2 positive breast cancer patients as well. Several other agents, such as tucatinib, ado-trastuzumab emtansine, and trastuzumab deruxtecan, are now available in this context [6].

In this article we discuss a case report of a triple positive breast cancer patient who was given neoadjuvant chemotherapy and targeted therapy followed by surgery followed by adjuvant treatment. Chemotherapy medications used for breast cancer and various clinical trials evaluating the effects of neoadjuvant chemotherapy on triple positive breast cancer are discussed and pathological complete responses to various neoadjuvant regimens are compared.

2. Case Presentation:

A 42-year-old female patient, who was married and had one child, presented with the history of a mass in her left breast for three months. On physical examination, her right breast had no abnormalities, while her left breast showed a large mass occupying the lateral side. The rest of the physical examination was normal. She had normal baseline blood tests, as shown in Table 1. She was advised to have a mammogram shown, and the report revealed a normal breast parenchyma and a normal breast skin on the right side (BI-RADS category I). A large, irregular, ill-defined, lobulated, and high-density mass involving the left breast parenchyma and extending outside the confines of the breast parenchyma was noted. It also involved nipple areolar complexes with diffuse skin thickening and internal pleomorphic calcifications (BI-RADS Category V). Multiple enlarged ipsilateral axillary lymph nodes were present, the largest measuring up to 1 cm on the left side. She underwent a core needle biopsy, which showed Grade II invasive ductal carcinoma. Modified Nottingham Score was 06 out of 09, tubule formation was <10% (Score: 03 out of 03), nuclear pleomorphism was moderate (Score: 02 out of 03), and mitosis was 6-8/10 HPF (Score: 01 out of 03). The immunohistochemical profile revealed estrogen receptor status 4/8, progesterone receptor status 4/8, and HER2 Neu 3+. Ki-67(PROLIFERATIVE INDEX) was 30%. p63 was negative while GATA3 was positive.

Table 1 Baseline Hematologic Investigations

Test Name	Result	Reference Range
WBC Total	4,130	(4000/UL -11000/UL)
RBC, Total	3.47	M(4.5 - 6.5)m/UL F(3.8 - 5.8)m/UL
Hemoglobin	11.3	M(13.0-18.0)g/dL F(11.6-16.5)g/dL
HCT	34.4	M(40 - 54)% F(38 - 47)%
MCV	99.1	(80 - 90)fL
MCH	32.6	(27 - 32)pg
MCHC	32.8	(33 - 38)g/dL
Platelet Count	124,000	(150,000-400,000)/UL
Neutrophils	59	(40 - 75)%
Lymphocytes	32	(20 - 45)%
Monocytes	6	(2 - 10)%
Eosinophils	3	(1 - 6)%
Basophil	0	(0 - 1)%
RDW	12.1	(11.5 - 13.6)%

Total Bilirubin	0.18	Adult upto 1.2 mg/dL, Neonatal: 0-2 Days 2.0-7.0 mg/dL 3-5 Days 4.0-12.0 mg/dL
Creatinine	0.80	Male 0.72 - 1.25 mg/dL Female 0.57 - 1.11 mg/dL
Estimated GFR using CKD-EPI equation	81.46	> 60 ml/min/1.73m^2
AST	22	Female: up to 32 U/L, Male: up to 40 U/L
ALT	24	Female: up to 33 U/L, Male: up to 41 U/L
Alkaline Phosphatase	97	Adult: 40-130 U/L, Children: 1-10 Years up to 335 U/L 11-15 Years up to 468 U/L
GGT	16	M: up to 60 U/L, F: up to 40 U/L
Hepatitis C Virus Antibody	Non Reactive	Non-Reactive 0.90 S/Co Borderline 0.90-0.99 S/Co Reactive >= 1.0 S/Co
Human Immunodeficiency Virus Antigen / Antibody Combo	Non Reactive	Non-Reactive 0.90 S/Co Borderline 0.90-0.99 S/Co Reactive >= 1.0 S/Co
Hepatitis B core Antibody (Total)	Non Reactive	Non-Reactive > 1.0 S/CO Reactive = 1.0 S/CO

WBCs: White blood cells; RBCs Red blood cells; HCT: hematocrit; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; RDW: Red cell distribution width; GFR; Glomerular filtration rate; CKD-EPI: Chronic kidney disease epidemiology collaboration; AST: aspartate aminotransferase; ALT: Alanine transaminase; GGT: Gamma glutamyl transferase; M: Male; F: Female; g/dL: Gram per decilitre; fL: Femtoliter; pg: Picogram; dL: decilitre; U/L: Unite per liter; mg/dL: milligram per decilitre; ml/min/m^2: milliliter per minute per meter square; S/Co: Signal to cut-off

Her computed tomography scan of chest, abdomen and pelvis (CT CAP) showed a large, lobulated, confluent, enhancing, and fungating mass on the lateral side of the left breast. Multiple confluent and infiltrative lesion components protruded into the breast parenchyma surrounding the retroareolar area as shown in Figure 1. Additionally, multiple smaller satellite lesions were seen in the left breast, extending inferiorly near the diaphragm. Diffuse left breast skin thickening and extensive perilesional congestive changes were also present. The lesion was also abutting the posterior chest wall. Multiple mildly enlarged ipsilateral axillary lymph nodes were also shown. The CT scan did not show any pulmonary nodules. However, a tiny, too small to characterize, hypodensity was seen in segment II of the liver. There were no other liver lesions or abdominopelvic lymph nodes. A non-obstructive 12 x 11mm calculus was seen in the lower pole of the right kidney.

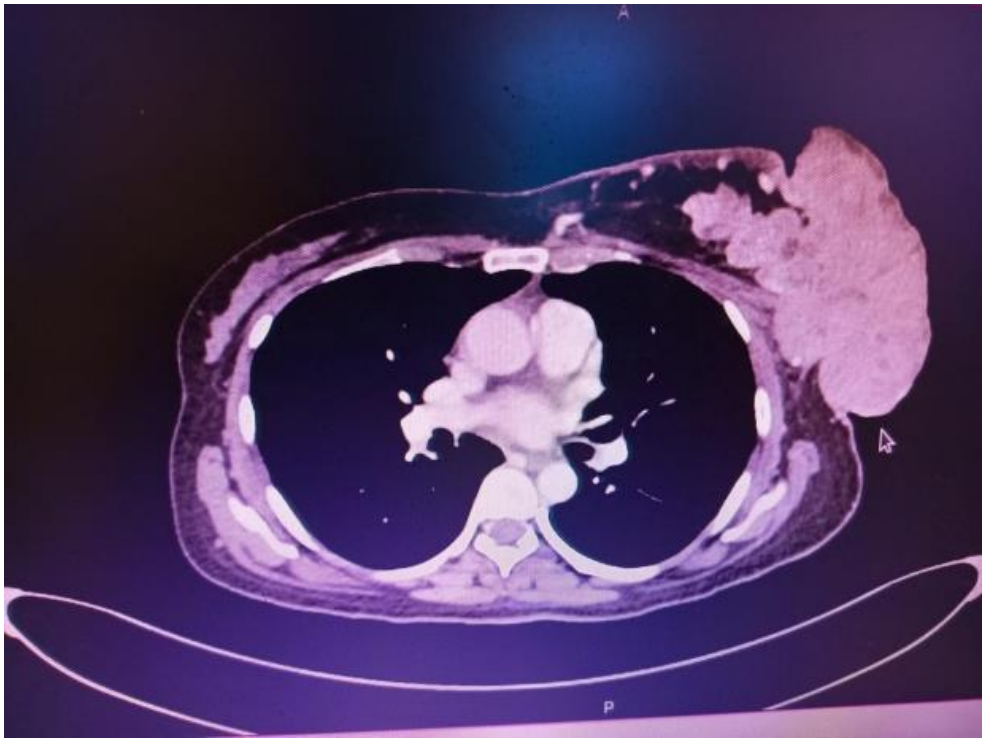

Figure 1 A CT scan of the patient. A large, lobulated, confluent, and fungating mass on the lateral side of the left breast abutting the posterior chest wall can be seen

Her Technetium 99m-methylene diphosphonate whole body bone scan revealed no evidence suggestive of metastatic bone disease. The ECHO report revealed an ejection fraction of 50 %. Her viral profile was negative.

She was started on the standard first-line chemotherapy and targeted regimen as a neoadjuvant treatment, which was composed of docetaxel, cyclophosphamide, trastuzumab, and pertuzumab explained in Table 2.

Table 2 Chemotherapy and targeted therapy given to the patient

Serial Number	Drug name	Dose	Route	Duration	Any major side effects
1	HERCEPTIN (TRASTUZUMAB)	510 mg	IV	STAT for one day	Cardio toxicity
2	CARBOSOL (CARBOPLATIN)	750 mg	IV	STAT For 1 Day	Hand foot syndrome, bone marrow suppression, nephron toxcity
3	DEXAMETHASONE (DEXAMETHASONE)	0.5 mg	Orally	3 tablets TDS	Metabolic syndrome
4	AVIL (PHENIRAMINE-MALEATE)	50 mg	Orally	OD	None
5	ZOFRAN (ONDANSETRON)	8 mg	IV	OD	None
6	NOCID (FAMOTIDINE)	20 mg	Orally	OD	None
7	TAXOTERE (DOCETAXEL)	140 mg	IV	OD	Hand foot syndrome, bone marrow suppression.
8	DECADRON (DEXAMETHASONE)	16 mg	IV	OD	None
9	PERJETA (PERTUZUMAB)	420	IV	STAT	Cardio toxicity

10	APREON KIT (APREPITANT)	285 mg	Orally	OD	None

mg: milligram; IV: Intravenous; STAT: immediately; OD: once a day; BD: two times a day; TDS: three times a day; ml: milliliter

After 6 cycles of treatment her CT scan was repeated as shown in Figure 2 and a comparison with the prior scan was done. There was marked interval reduction in heterogeneous, enhancing, ulcerating, and lobulated lesions in the left breast measuring approximately 2.3 x 3.5 cm from the prior size of 12 cm. Overlying skin thickening, architectural distortion and surrounding stranding changes were also noted. Multifocal and multicentric disease process was noted with viable tumors in the axillary tail region and central lower breast abutting the pectoralis muscle. Skin deposits were seen which showed interval reduction as well. The largest lymph node measured 6 mm in size. There was no suspicious lesion in the right breast or lymphadenopathy in the right axilla. Liver was 16 cm in craniocaudal dimension. Liver and kidneys were normal having no hypodensities.

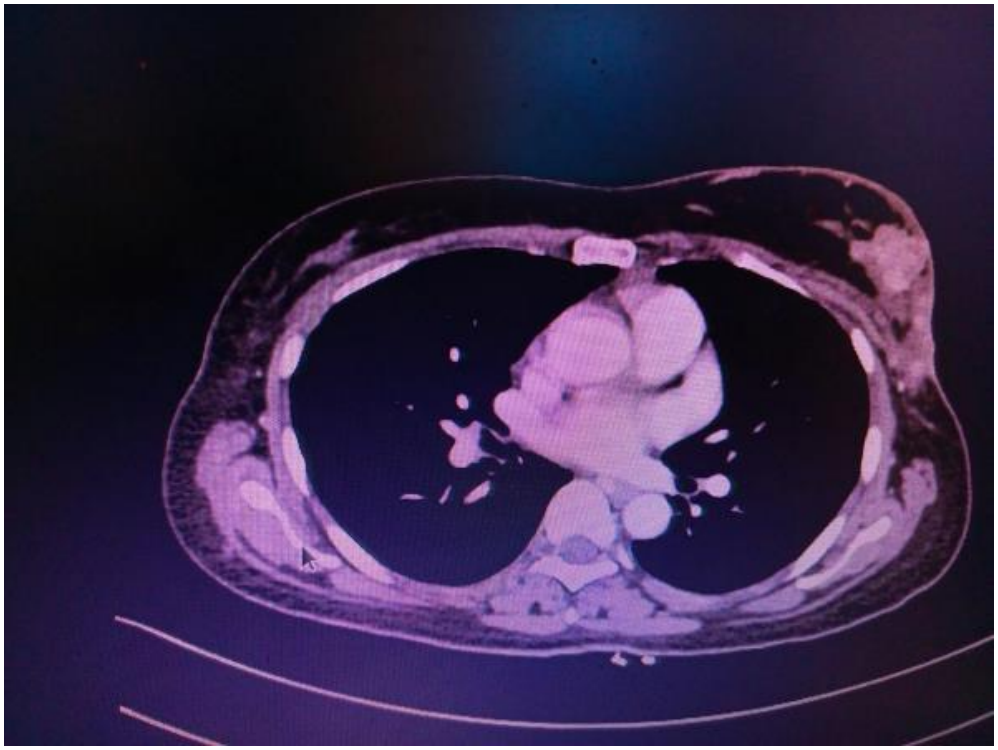

Figure 2 CT Scan chest with contrast after neo adjuvant chemo and immunotherapy. A heterogeneous, ulcerating, and lobulated lesion in the left breast which has decreased in size as compared to the previous CT scan of the chest. Overlying skin thickening, architectural distortion and surrounding stranding changes can also be seen

After the neo adjuvant chemotherapy and targeted therapy the patient has underwent left modified radical mastectomy, the CT scan figure 3 showing the chest wall explained.

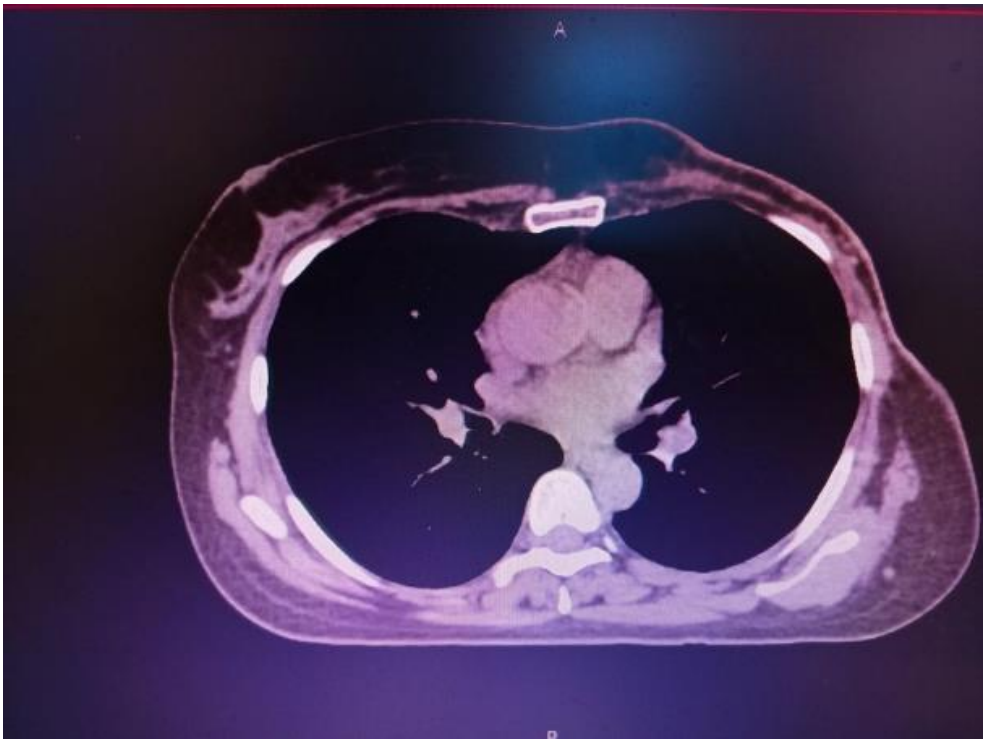

Figure 3 Post left modified radical mastectomy CT Chest with contrast: no residual disease seen.

2.1. Literature review for Breast Cancer (Triple Positive Breast Cancer) in term of response assessment in patients who have received NACT:

Table 3 Sophisticated Therapies and new drugs discovered or under trials for human epidermal growth receptors, Anti Her therapies and other used in Her 2 expressive breast Cancer

Drug type and class	Drug name	Linker drug cleavable or not	Trial phase status	Reported results or efficacy And overall survival rate	Side effects
Anti her 2 Monoclonal antibodies/Her 2 directed ADCs	Trustuzumab DM TDM 1, PERTUZUMAB	Non clevable	FDA Approved	43.6% (95% CI, 33-52%) overall response rate, DHP regimen in CLEOPTRA shows PFS of 18 months and median OS of 57 months.	Nausea, vomiting and Cardiomyopathy [7]
	Trastuzumab Deruxtecan,DS-8201	Cleavable	Phase II/III	59.5% (95%CI, 49.7–68.7) over all response rate, The PFS was 19.4 months (95%CI, 14.1–not reached), 24.6 months (95%CI 23.1 months-not reached) of median OS.	Neutropenia, nausea, interstitial lung disease [8]
	SYD985	Cleavable	Phase III	33% over all response rate.	
	XMT-1522	Cleavable	Phase I	Unknown	
	ARX788	Non Cleavable	Phase II	PFS of 17 months if use as monoclonal agent in met breast Cancer	Pneumonitis , neutropenia and ocular abnormalities

					reversible with steroids
	DHES0815A	Non cleavable linker	Phase I	PFS of 3.2 months with ORR of 20%.	Rash, hyperpgmentation, eye lid edema, pneumothorax, keratitis, wheeze
HER2-directed TKIs in clinical development.	Neratinib		PhaseIII	PFS of 22.2 weeks if used trustuzumab if no trustuzumab than 39 week PFS. and OR rate of 24% if previously trustuzumab used if no trustuzumab used than ORR of 54 %	Diarrhea, xerostomia, nose bleed, stomach pan [9]
	Tucatinib		Phase III	Tucatinib plus TDM 1 shows median PFS of 9.5 months (95% CI, 7.4-10.9), only tucatinib PFS in patients receiving tucatinib only was 7.8 months (95% CI: 7.5, 9.6)	Diarrhea, stomatitis, hepatotoxicity, rash and anorexia [10]
	Pyrotinib		Phase II	PFS OF 14.1 months,	Diarrhea , vomiting and Hand foot syndrome [11]
	Poziotinib		PhaseII	ORR of 27%, PFS of 4 months (95% CI, 3.0-4.4)	Diarrhea, rash, stomatitis and paronychia [12]
CDK4/6 inhibitors	Palbociclib Ribociclib Abemaciclib		Phase III Phase III Phase III	No objective response if used as a mono therapy Monarch Her trial showed ORR (35.4% vs. 22.8% with chemotherapy plus trastuzumab) and median PFS with the endocrine/targeted therapy triplet (8.3 vs. 5.7 months; HR = 0.673, 95%CI, 0.451–1.003; p = 0.0253) but no significant response difference with no chemo arm.	Neutropenia, leukopenia, QT prolongation, diarrhea, hepato toxicity and headache [13]
PI3K Inhibitors	Alpelisib Taselisib Copanlisib			Alpelisib with TDM 1 shows response in pre-treated HER2-positive patients, an ORR of 43% and a median PFS of 8.1 months (95%CI 3.9–10.8) were reported.	Rash, GI toxicity, transaminitis, hyperglycemia [14]
mTOR inhibitors	Everulimus			In the BOLERO-3 trial, the combination of everolimus with trastuzumab and vinorelbine was evaluated	Stomatitis, anorexia, anemia, and fatigue [15]

				in patients with trastuzumab-resistant ABC, and a small but statistically significant benefit in PFS was reported: median PFS 7.0 vs. 5.78 months (HR = 0.78; 95%CI, 0.65–0.95; *p* = 0.0067)	
Biospecific Anti bodies and fusion proteins	Zenucutuzumab Azymetric ZW25 PRS 343 TPl P95Her2TCB			TPL is Superior blocking agent as compared to Trustuzumab and pertzumab [16]	
Other drugs Mergetuximab			Phase III	Margetuximab plus chemotherapy generated handsome amount of 24% relative risk reduction in the hazard of progression vs trastuzumab plus chemotherapy, median OS was 21.6 months with margetuximab vs 19.8 months with trastuzumab, and the final analysis of OS will be reported [17]	

2.2. Increased *MET* and *HGF* gene copy numbers are associated with trastuzumab failure in HER2-positive metastatic breast cancer:

Pathologic complete response (pCR) is one of the most favorable predictive criteria for knowing the survival rate, and disease free survival when treatment is done before the surgery. Preoperative systemic treatment helps breast conservation and makes the huge inoperable tumor to be operable by down staging the disease. Pre-operative therapy helps to determine the percentage of risk of recurrence in patients with residual tumors after neoadjuvant treatment. It allows the patient and oncologist to think over the option of breast conservation surgery versus mastectomy. It may allow the patient to have limited radiation fields in patients with cT1, 2, 3, 4 with cN+ who become pT 0 /pN 0. The patients which are selected for pre-operative therapy usually have one of these features such as inoperable tumor, invasive breast cancer with bulky lymph nodes, or tumors with skin or chest wall involvement, large tumor size as compared to breast size, and extra nodal extension. The different food and drugs regulatory authorities have approved some regimens tested in different well established, popular trials which have been discussed in Table 4 and Table 5.

Table 4 There are different regimens FDA approved used in Her 2 positive cancers in perioperative setting

Serial number	Regimen
1	Neosphere: TCH+P: docetaxel 75 mg/m^2, carboplatin AUC 6, Trastuzumab 6 mg/kg, and pertuzumab of 840 mg intravenously every 3 weekly for 6 cycles.
2	PHP: Paclitaxel 80 mg/m2 every week for 12 cycles with pertuzumab 840 mg followed by 420 mg, and trastuzumab 8 mg/kg in first followed by 6 mg/kg for 1 year
3	TCH: docetaxel 75 mg/m2 with cyclophosphamide 600 mg/m2, for 4 cycles with 3 weekly with 1 year of 3 weekly trastuzumab 2-6 mg/kg.
4	TRYPHAENA: AC followed by TH: doxorubicin 60 mg /m2 with cyclophosphamide 600 mg/m2 every three weekly for 4 cycles followed by docetaxel 100mg/m2 for 4 cycles and trastuzumab 4-6 mg/kg every 3 weekly for 1 year.
5	Katherine Trial: Neratinib completion of 12 cycles, taken per oral, initiating dose from 120 mg daily increasing the dose up to 240 mg daily from 2^{nd}, 3^{rd} cycle.

6	ddAC followed by THP: doxorubicin 60 mg /m2 with cyclophosphamide 600 mg/m2 every three weekly for 4 cycles followed by docetaxel 100mg/m2 for 4 cycles with pertuzumab 840 mg followed by 420 mg, and trastuzumab 8 mg/kg in first followed by 6 mg/kg for 1 year
7	ddAC followed by PH: doxorubicin 60 mg /m2 with cyclophosphamide 600 mg/m2 every two weekly for 4 cycles followed by paclitaxel 175 mg/m2 every two weekly with trastuzumab 4-6 mg/kg every 3 weekly for 1 year.
8	PH: paclitaxel weekly for 12 weeks 80 mg/m2 with Trastuzumab 6 mg/kg 3 weekly for 1 year
9	Pacli/carbo + HP: paclitaxel 80 mg/m2 on day 1 and day 8, with Carboplatin on day 1 AUC 6, with trastuzumab 8 mg/kg and pertuzumab 840 mg on day followed by Trastuzumab 6 mg/kg and pertuzumab 420 mg/kg.
10	Ado-trastuzumab emtansine (T-DM1): T-DM1 3.6mg /kg 3 weekly for one year

T= taxotere or docetaxel, P =pertuzumab, H= Herceptin, C= carboplatin, TDM-1 = Ado-trustuzmab emtansine (T-DM1), A= Adriamycin or doxorubicin, pacli/carbo=paclitaxel/carboplatin.

Table 5 Studies showing different regimens used in Her 2 neu + breast cancer, with its pathological responses explained

Serial No.	**Studies and Patients age, sex**	**Stage: Tumor size and nodal status**	**Receptor Status**	**Type of Neoadjuvant therapy and number of cycles**	**Percentage of Response radio logically noted**	**Side effect, lost to follow up and any adverse event in NeoAdjuvant chemo.**
	NeoSphere trial, 417 patients	Stage II and stage III	HER 2 Neu +	12 weeks of neoadjuvant therapy composed of four cycles of either a combination of docetaxel and trastuzumab (TH) or docetaxel, trastuzumab, and pertuzumab (THP) or trastuzumab and pertuzumab (HP) or docetaxel and pertuzumab (TP).	pCR was 45.8% for THP, 29% for TH, 24% for TP, and 16% for HP.	Most common side effects included neutropenia, febrile neutropenia, and leukopenia [18]
	American College of Surgeons Oncology Group (ACOSOG) Z1041 study, 282 patients	Operable locally advanced cancer with lymph node involvement	Her 2 Neu +,	Fluorouracil, epirubicin, and cyclophosphamide (FEC) followed by paclitaxel and trastuzumab versus paclitaxel and trastuzumab followed by FEC with trastuzumab	pCR was 52.9% in the first treatment group and 50% in the second group and the difference was not statistically different.	Tolerated chemotherapy well [19]
	National Surgical Adjuvant Breast and Bowel Project (NSABP) B-	Locally advanced breast cancer with lymph node involvement	Her Neu 2+	four cycles of doxorubicin and cyclophosphamide (AC) followed by paclitaxel and trastuzumab (Group 1) or paclitaxel and lapatinib (Group 2) or paclitaxel, trastuzumab, and lapatinib (Group 3).	pCR rate was 62.0% in group 3, 53.2% in group 2, and 52.5% in group 1. The difference was not	Most common side effects included neutropenia and diarrhea. Adverse event included congestive

	41 study, 529 patients				statistically significant.	heart failure [20]
	German Breast Group (GBG-44) Gepar Quinto study, 309 patients in ECU-TH group and 311 in ECl-TL group	Locally advanced breast cancer with lymph node involvement.	Her 2 Neu +	Four cycles of epirubicin, cyclophosphamide, and docetaxel with trastuzumab (ECH-TH) or four cycles of epirubicin, cyclophosphamide, and docetaxel with lapatinib (ECL-TL).	pCR was 30.3% in ECH-TH group and 22.7% in ECL-TL group. The difference was statistically significant.	Patients in ECH-TH group experienced edema and dyspnea while patients in ECL-TL group experienced diarrhea and skin rash [21]
	WSG ADAPT trial, 92 patients in HP group and 42 in THP group.	Stage II and III	Her 2 Neu + and HR -	12 weeks of either trastuzumab and pertuzumab (HP) or trastuzumab, pertuzumab, and docetaxel (THP).	pCR was 90.5% in THP group and 36.3% in HP group	Tolerated well [22]
	PAMELA study, a multicenter phase II trial on 151 patients	Stage I to stage IIIA	Her2+	18 weeks of trastuzumab and lapatinib, with concurrent endocrine therapy in HR-positive patients	pCR was achieved in 30% of the patients.	Tolerated well [23]
	GeparSepto (GBG 69) trial, 1229 patients	Stage II and III		Neoadjuvant nabpaclitaxel or solvent based paclitaxel followed by epirubicin and cyclophosphamide (EC), with concurrent trastuzumab and pertuzumab	pCR rates were 38% in nab-paclitaxel group and 29% in solvent based paclitaxel group.	Tolerated well with cardio toxicity in some patients [24]
8.	TRYPHAENA Trial	Stage I, II, III		AC x 4 cycle along with HP 3 weekly for 1 year	It showed pCR rates in all treatment arms ranging from 57% to 66%	Tolerated well [25]

2.3. The pathological complete responses of different regimens have been compared in Figure 4, used in different trials

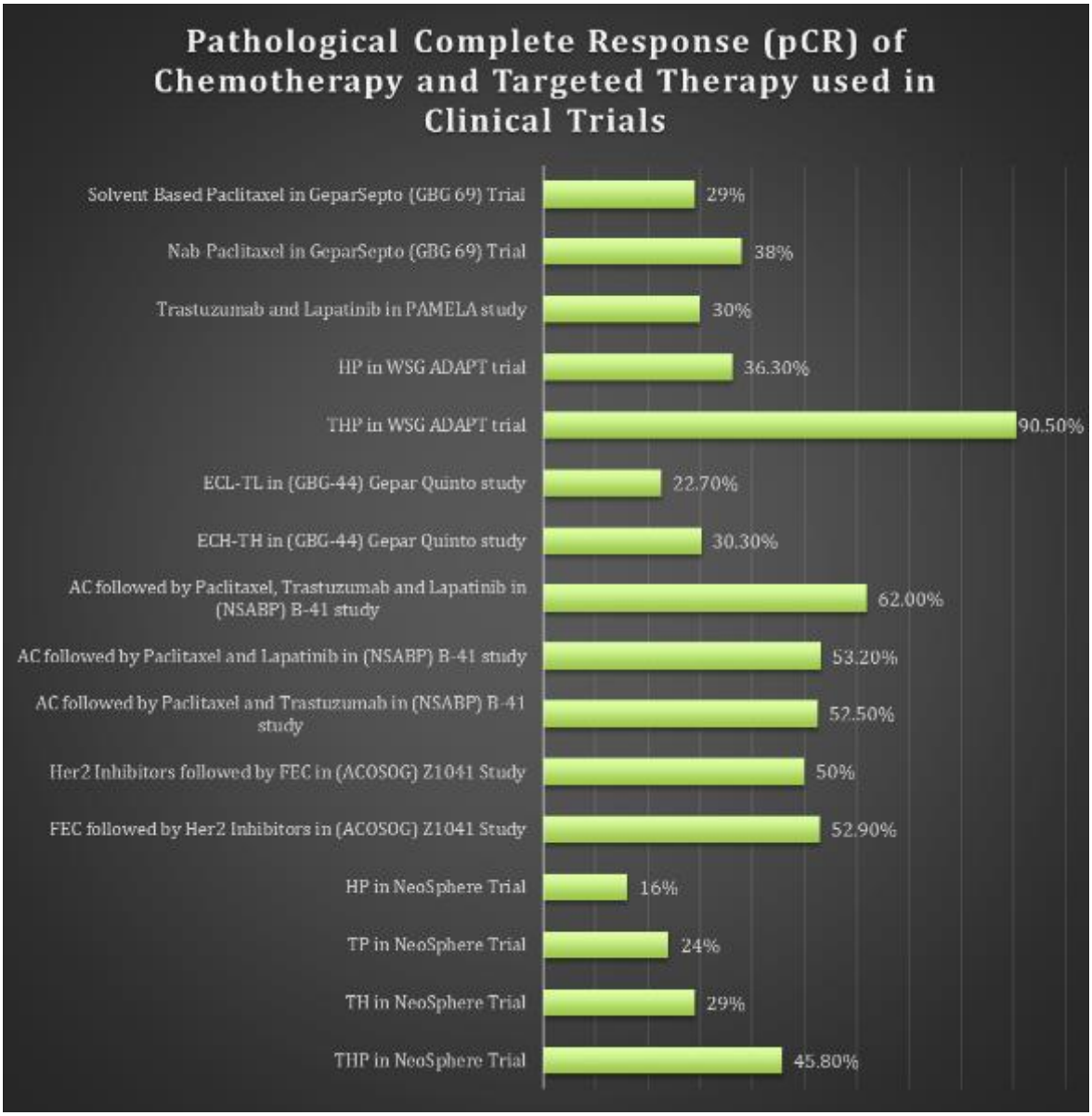

Figure 4 Graphical representation of various chemotherapy and targeted agents in breast cancer used in Neo adjuvant setting, the Y axis shows the chemotherapy regimens briefly with name of the trial done, the X axis represent the pathological complete response percentage

2.4. Recommendations for neo adjuvant and adjuvant therapy for HER 2 positive breast cancer

TCHP and THP have become the basic choices for the patients receiving the neo adjuvant therapy. The Chinese society of clinical oncology has designed the treatment in her 2 neu + breast cancer in the following way. If the cancer is c T1 N0 than upfront surgery is indicated, followed by adjuvant Herceptin and trastuzumab therapy for 12 cycles if the cancer is p T1 N0, if it is p T2 or node positive than adjuvant chemotherapy is indicated along with HP. For patients achieving the PCR they recommend to continue the same targeted treatment as used in neo adjuvant setting, if only trastuzumab have been used than dual targeted agents shall be used as indicated in the affinity trial. For patients having no PCR after neo adjuvant therapies trastuzumab emtansine (TDM -1) or dual target therapy are recommended. No available study currently is present to show which one is better, the HP vs. TDM-1. If there is good regression in the tumor (miller and Payne grade 3,4) then continue same dual HP but if less response to neoadjuvant dual targeted therapy than switch to TDM-1 [26] explained in figure 5.

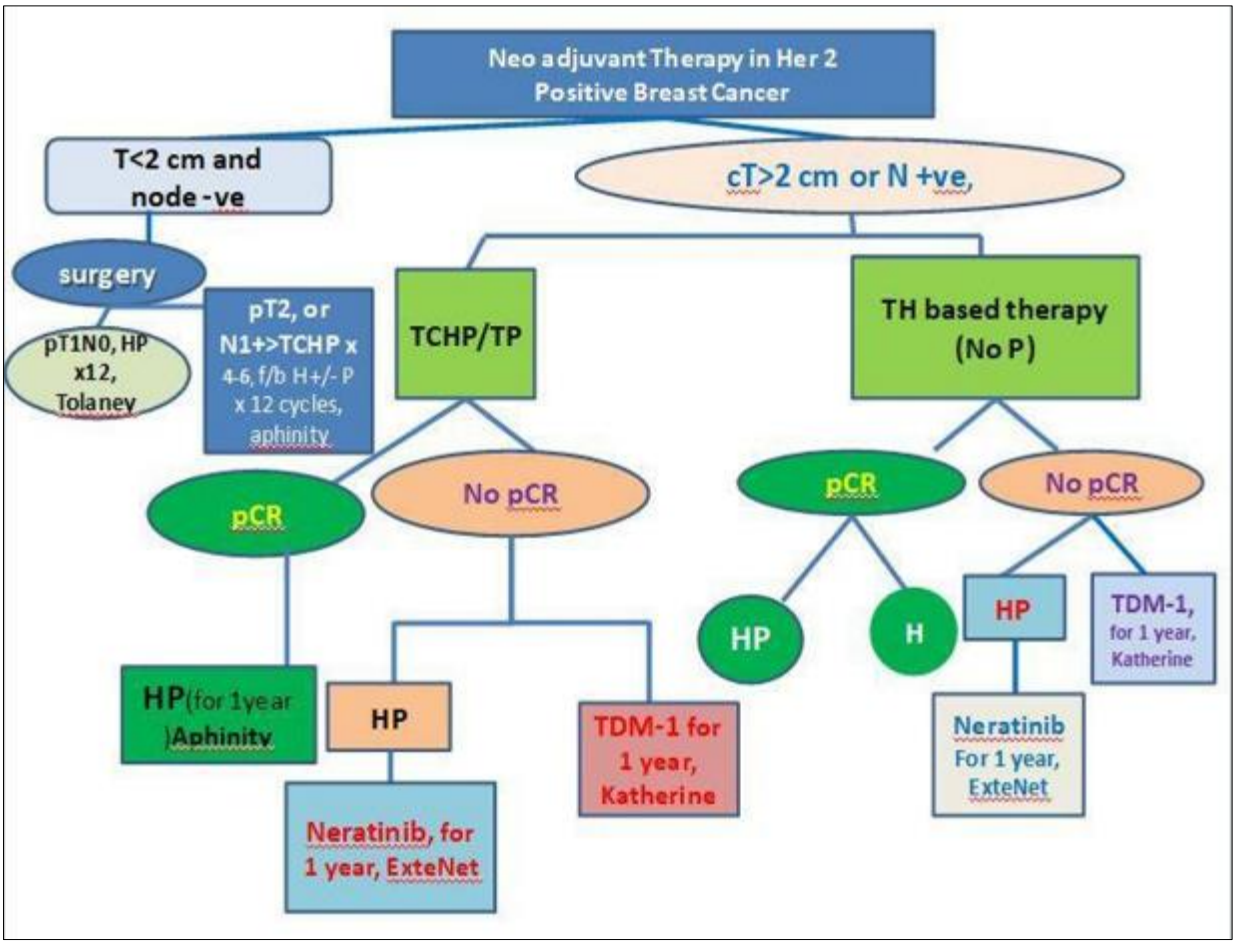

Figure 5 Recommendations for neoadjuvant and adjuvant therapy for HER2 positive breast cancer. pCR, pathological complete remission; TCHP, taxane, carboplatin, trastuzumab and pertuzumab; THP, taxane, trastuzumab and pertuzumab; HP, trastuzumab and pertuzumab; T-DM1, trastuzumab emtansine

3. Discussion

In this article, we discuss a case of a 42 years old female patient, who presented with a mass in her left breast. She was then found to have a grade II invasive ductal carcinoma on histopathology. The immunohistochemical profile revealed triple positive breast cancer. This subtype of breast cancer is marked by the coexistence of hormone receptor (HR) expression, specifically estrogen receptor (ER) and/or progesterone receptor (PR), and overexpression of the human epidermal growth factor receptor 2 (HER2) gene, as determined by immunohistochemistry (IHC) staining. Triple-positive breast cancer is a diverse sub-type of breast cancer characterized by various histological differentiations, including mucinous, lobular, or micro papillary features [27].

HER2 overexpression is a significant factor in determining the response to therapy in triple-positive breast cancer. Research suggests that the presence of HER2 overexpression is associated with a more favorable response to treatment. However, it's important to note that HER2 overexpression is found in approximately 15% to 25% of invasive breast carcinomas, and historically, it has been linked to aggressive histopathologic characteristics and poor clinical outcomes [28].

Our patient was treated with neo adjuvant chemotherapy and targeted therapy consisting of docetaxel, cyclophosphamide, trastuzumab, and pertuzumab. No significant difference in pCR of HER2 positive breast cancer patients was found when they were given either sequential or concurrent chemotherapy and anti HER2 antibodies in (ACOSOG) Z1041 study [29]· Trastuzumab has shown a pCR of 45.8% in HER2 positive breast cancer patients, when combined with pertuzumab and docetaxel in the NeoSphere trial. The usage of HER1 and HER2 inhibitors like lapatinib instead of trastuzumab in combination with chemotherapy has shown good results in terms of pCR in (NSABP) B-41 study but on other hand Gepar Quinto GBG-44 study showed statistically lower pCR when lapatanib was substituted for trastuzumab[30]. Taxanes like docetaxel, when added to dual HER2 inhibitors such as a combination of trastuzumab and

pertuzumab has shown significant improvement in pCR.[31] There are four different molecular subtypes of HER2 positive breast cancer. Among them, HER2 enriched subtype has significantly increased chances of having a higher pCR when dual HER2 inhibitors are used[32]. In neoadjuvant studies the TCHP regimen is considered as the basis of therapy for localized her 2+ ve breast cancer. If the cancer is c T1 N0 than upfront surgery is indicated, followed by adjuvant Herceptin and trastuzumab therapy for 12 cycles if the cancer is p T1 N0, if it is p T2 or node positive than adjuvant chemotherapy is indicated along with HP. If the tumor is c T2 or greater, or node positive clinically then the patient is supposed to receive TCH +- /P in Neo adjuvant therapy followed by surgery, if there is complete pathologic response then HP for one year is advised as per Aphinity trial[33]. If there is no p CR then the patient is supposed to receive 1 year of TDM -1 as per Katherine trial or HP for 6 to 12 cycles followed by Neratinib for one year[33]. The different FDA approved regimens in Her 2 + breast cancers are explained in Table 3 and the different trials have been summarized in Table 4. The different response rates after one year of treatment have been explained in Figure 5. In the case of metastatic HER2-positive breast cancer, the prognosis is generally poor, and effective targeted therapies are limited. Nevertheless, there is hope in emerging anti-HER2 agents, especially when combined with chemotherapy, as they hold promise for increasing pathological complete response rates. For instance, margetuximab has demonstrated significant improvements in progression-free survival, particularly in pretreated patients[34]. Surgical intervention, in addition to systemic therapy (ST), offers survival benefits for stage IV breast cancer patients, particularly those with known hormone receptor and HER2 status. It is a consideration, especially after neoadjuvant chemotherapy, for patients with ER+, PR+, or HER2+ disease[35]. Notably, patients with triple-negative and HER2-positive breast cancers exhibit higher rates of breast-conserving surgery and pathological complete response (pCR) after neoadjuvant chemotherapy, making them suitable candidates for less invasive surgical approaches following chemotherapy[36]. Additionally, the management of contralateral axillary lymph node metastasis (CAM) involves comprehensive treatment, including chemotherapy and radiotherapy, to achieve better control. However, axillary lymph node dissection (ANLD) alone is generally considered insufficient, and mastectomy is not commonly recommended[37]. Survival rates in breast cancer patients are influenced by several factors, including the number of positive nodes, the extension of metastases beyond their capsule, and age. These criteria independently impact survival rates, leading to the identification of subgroups with varying prognoses, particularly among patients older than 40[38]. In targeted agents Trustuzumab DM TDM 1, PERTUZUMAB showed 43.6% (95% CI, 33-52%) overall response rate, DHP regimen in CLEOPTRA shows PFS of 18 months and median OS of 57 months. Trastuzumab Deruxtecan and DS-8201 showed 59.5% (95%CI, 49.7–68.7) over all response rate, The PFS was 19.4 months (95%CI, 14.1–not reached), 24.6 months (95%CI 23.1 months-not reached) of median OS. ARX788 showed PFS of 17 months if use as monoclonal agent in met breast Cancer. Neratinib showed PFS of 22.2 weeks if used trustuzumab if no trustuzumab than 39 week PFS and OR rate of 24% if previously trustuzumab used if no trustuzumab used than ORR of 54 %. Pyrotinib and poziotinib showing PFS of 14.1 months, ORR of 27%, PFS of 4 months (95% CI, 3.0-4.4) respectively. CDK4/6 inhibitors showed no objective response if used as a mono therapy Monarch Her trial showed ORR (35.4% vs. 22.8% with chemotherapy plus trastuzumab) and median PFS with the endocrine/targeted therapy triplet (8.3 vs. 5.7 months; HR = 0.673, 95%CI, 0.451–1.003; p = 0.0253) but no significant response difference with no chemo arm and and PI3K Inhibitors Llike Alpelisib with TDM 1 shows response in pre-treated HER2-positive patients, an ORR of 43% and a median PFS of 8.1 months (95%CI 3.9–10.8) were reported. In the BOLERO-3 trial, the combination of everolimus with trastuzumab and vinorelbine was evaluated in patients with trastuzumab-resistant ABC, and a small but statistically significant benefit in PFS was reported: median PFS 7.0 vs. 5.78 months (HR = 0.78; 95%CI, 0.65–0.95; p = 0.0067). Margetuximab plus chemotherapy generated handsome amount of 24% relative risk reduction in the hazard of progression vs trastuzumab plus chemotherapy, median OS was 21.6 months with margetuximab vs 19.8 months with trastuzumab, and the final analysis of OS will be reported.

4. Conclusion

The results of all the trials have been discussed briefly along with a case report to signify the treatment in aggressive type of breast cancer. The treatment has been standardized, for tumors of size less than 2 cm shall undergo upfront surgery, followed by adjuvant treatment. If it is pathologically T1 with no nodal metastasis then the patient is advised to receive HP for 12 cycles as per Tolaney study, but if it is p T2 or N+ than the patient will be treated by chemotherapy along with HP for 12 cycles as per Aphinity trial. Those patients having tumor size greater than 2 cm or having nodal metastasis shall receive neo adjuvant chemotherapy and targeted therapy followed by surgery. Adjuvant treatment is based on the final histology of pCR than HP for one year as per Aphinity trial. If no p CR then the patient is advised to receive radiation therapy along with Trastuzumab emtansine (TDM-1) for one year as per Katheriene trial or shall receive HP for 6-12 cycles followed by Neratinib for one year as per Extenet trial.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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