

# Selecting Optimal Regimen in The treatment of Metastatic Triple Negative Breast Cancer

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## 2. Keywords

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## 1. Abstract

Breast cancer is the commonest cancer and leading cause of cancer death in women. Triple negative breast cancers are ER, PR and Her 2 Neu negative. These tumors have high propensity for metastatic spread. The lack of expression of ER, PR and Her 2 Neu receptors makes chemotherapy only option available to treat these aggressive tumors. This study examines various clinical trials that will help clinicians in selecting appropriate drugs for the treatment of this subset of patients.

## 3. Introduction

Breast Cancer is the commonest cancer and leading cause of cancer death in women. In the year 2012 approximately 1,671,149 new patients were diagnosed with breast cancer and 521,907 deaths were attributed to this menace [1]. According to SEER Cancer Registry 95% of the patients have localized disease at initial presentation whereas 5% of patients present with metastatic disease [2]. About 20-30% of early stage patients develop systemic disease at some point in life [3]. In Pakistan every year approximately 90,000 women are diagnosed with breast cancer and most of these patients have either locally advanced or metastatic disease [4]. A study conducted by Gilani et al. [5] showed that 25-36% of Pakistani women present with disseminated disease.

The prognosis of patients with metastatic breast cancer is extremely poor. Despite recent advances and advent of novel therapies, the disease remains incurable with mean survival of 31.8 months [6].

Breast cancer generally comprises of 4 subgroups: ER PR positive Her 2 Neu negative; ER PR Her2 Neu positive; ER PR negative Her 2 Neu positive and ER PR Her 2 Neu negative.

Triple negative phenotype also known as Basal breast tumors are hormone receptors i.e. ER and PR and Her 2 Neu negative. Different subtypes of TNBC have been lately recognized using gene expression (GE) analysis. These subtypes include BL1 with cell cycle and DNA damage response GE signatures, BL2 with

growth factor signaling and myoepithelial markers, two mesenchymal subtypes M and MSL with high expression of genes involved in differentiation and growth factor pathways, Immunomodulatory type and luminal subtype characterized by androgen signaling [7].

Triple negative breast tumors have worst prognosis and are characterized by an aggressive disease course and propensity for visceral metastasis leading to reduction in Disease Free Survival and Overall Survival [8]. The median OS in patients with metastatic triple negative tumors is just 13.3 months [9].

The lack of expression of hormone receptors and Her 2 Neu makes chemotherapy only option available to date for the treatment of these aggressive metastatic tumors. The aim of this article is to review existing chemotherapy regimens and help clinicians in selecting appropriate chemotherapeutic drugs for the treatment of this subset of patients **Table 1**. The choice of single agent over combination chemotherapy in metastatic breast cancer depends on age, performance status, rate of tumor progression and disease burden. In patients who are elderly, have poor performance status and have slowly growing tumors, single agent chemotherapy is chosen where as in those having large tumor burden or rapidly progressing disease, combination chemotherapy is the preferred treatment modality [10]. A meta-analysis was conducted by Dear et al. [11] in 2013 comparing sequential single agent vs. combination chemotherapy in metastatic cancer. The authors concluded that there was a greater risk of progression in combination arm compared to sequential single agent arm (HR 1.16; 95% CI 1.03 to 1.31; P = 0.01), higher response

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rates were seen in combination arm at the cost of increased toxicity and no difference in overall survival was observed between the two groups (RR 1.53; 95% CI 0.71 to 3.29; P = 0.28) (11). Conversely, some of the trials have revealed superiority of combination chemotherapy over monotherapy.

## 4. Single agent Chemotherapy

### 4.1. Anthracyclines

**Table 1:** summarizes progression free survival, overall survival and response rates of various chemotherapeutic agents used as single agent in the treatment of metastatic triple negative breast cancer.

Author/Study	Trial Phase	Treatment Regimen	PFS	OS	RR
Harris et al <sup>13</sup>	Phase III	Liposomal doxorubicin vs. Doxorubicin	3.8 vs. 4.3 months	16 vs. 20 months	26%
Seidman et al <sup>14</sup>	Phase III	Weekly Paclitaxel vs. 3 weekly Paclitaxel	9 vs. 5 months	24 vs. 12 months	42 vs. 29%
Ravdin et al <sup>16</sup>	Phase III	Docetaxel vs. 3 weekly paclitaxel	5.7 vs. 3.6 months	15.4 vs. 12 months	32 vs. 25%
Gradisher et al <sup>17</sup>	Phase III	Nab Paclitaxel vs. standard paclitaxel	5.7 vs. 4.2 months	14 vs. 11.6 months	33 vs. 19%
Talbot et al <sup>21</sup>	Phase II	Capecitabine vs. paclitaxel	3.0 vs. 3.1 months	7.6 vs. 9.4 months	36 vs. 26%
PELICAN Trial <sup>23</sup>	Phase III	Capecitabine vs. Liposomal doxorubicin	6 months	26.8 vs. 23.3 mon	12.9 vs. 10.7%
Feher et al <sup>25</sup>	Phase III	Gemcitabine vs. epirubicin	3.4 vs. 6.1 months	11.8 vs. 19.1 mon	16.4 vs. 40.3%
Vogel et al <sup>27</sup>	Phase II	Vinorelbine in elderly patients	6 months	-	38%
Isakoff et al <sup>28</sup>	Phase II	Role of platinum in TNBC	89 days	-	25.60%
TNT trial <sup>29</sup>	Phase III	Carboplatin vs. Docetaxel in	6.8 vs. 4.8	-	68 vs.
		BRCA1/2 mutations	months		33.30%
Study 305 and 301 pooled analysis <sup>30</sup>	Phase III	Eribulin vs. Physicians choice chemo Eribulin vs. capecitabine	3.9 vs. 3.2 months	15 vs. 12.6 months	Similar
Perez et al <sup>32</sup>	Phase II	Ixabepilone	-	-	6-55%

These are the most ancient and most active class of chemotherapeutic drugs used in the treatment of breast cancer. The anthracyclines approved for the treatment of metastatic breast cancer are Doxorubicin, Epirubicin and Pegylated liposomal doxorubicin. Response rate achieved with doxorubicin is around 50% in chemotherapy naïve disseminated breast cancer [12].

Liposomal doxorubicin is equally effective but less cardiotoxic as compared to doxorubicin. Harris et al conducted a study comprising of 224 patients with metastatic breast cancer (34% of whom were ER negative in liposomal doxorubicin and 29% in doxorubicin group) treated first line with either liposomal doxorubicin or doxorubicin until disease progression or development of toxicity. Overall response rate was similar in both groups i.e 26%. The risk of cardiotoxicity was much higher with doxorubicin as compared to liposomal doxorubicin (29% vs. 13%) (HR = 3.56) (P = 0.0001). Median PFS was 3.8 vs. 4.3 months (p=0.59) and Overall Survival was 16 vs. 20 months (p=0.09) in liposomal doxorubicin vs. doxorubicin group respectively [13].

### 4.2. Taxanes

These are used as either first line or subsequent therapy for the management of metastatic breast cancer. Taxanes approved for the breast cancer treatment are Paclitaxel (weekly/3 weekly), Docetaxel and Nab-Paclitaxel.

Weekly paclitaxel is considered to be superior to 3 weekly schedules. A randomized phase III trial conducted by Siedman et al. [14] randomized metastatic breast cancer patients to receive paclitaxel as 175 mg/m<sup>2</sup> IV every 3 weeks or 80 mg/m<sup>2</sup> IV every week. Weekly paclitaxel was associated with superior response rates (42% vs. 29%, p=0.0004), increased progression free survival (9 vs. 5 months p < 0.0001) and better overall survival (24 vs. 12 months p=0.0092) [14].

Studies have shown that docetaxel has greater efficacy than 3 weekly paclitaxel Vu et al. [15]. Randomized 435 patients with history of disseminated disease and anthracycline resistance to docetaxel or 3 weekly paclitaxel. Twenty nine percent in paclitaxel group and 35% in docetaxel group were ER negative. Median OS was 10.9 months in docetaxel group and 8.3 months in paclitaxel group. Another trial published in 2003 demonstrated superiority of docetaxel over 3 weekly paclitaxel in terms of response rate (32 vs. 25% p=0.10), progression free survival (5.7 vs. 3.6 months p=<0.0001) and overall survival (15.4 vs. 12 months p=0.03) [16].

Nab paclitaxel demonstrates promising efficacy when compared with standard paclitaxel. It does not include solvent thus reduces the risk of hypersensitivity reactions and eliminates the need of premedication. Nab paclitaxel was compared with standard paclitaxel by Gradisher et al. [17]. The response rates and progression free survival were significantly higher for nab paclitaxel as compared to conventional paclitaxel (33% vs. 19% p=0.001) and (23 vs. 16.9 weeks p=0.006). The incidence of grade 4 neutropenia was less common and grade 3 sensory neuropathy was more common in patients receiving nab paclitaxel. Arpino et al. [18] reported a case of triple negative metastatic breast cancer patient who received nab paclitaxel as second line treatment for chest wall recurrence and regional lymphadenopathy after failure of bevacizumab. Complete response was seen after 3 cycles revealing potential role of nab paclitaxel in metastatic triple negative breast cancer [18]. Braith et al. [19] studied nab paclitaxel vs. paclitaxel in metastatic triple negative breast cancer and found that time to treatment discontinuation was significantly higher for nab paclitaxel (3.3 vs. 2.8 months) **Table 2.** Time to next treat-

ment though not statistically significant favoured nab paclitaxel (6.2 vs. 5.4 months).

2. Soria JC, Ohe Y, Vansteenkiste J. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. *N Engl J Med.* 2018; 378(2): 113-125.

**Table 2:** Summarizes progression free survival, overall survival and response rates of various chemotherapeutic agents used in different combinations in the treatment of metastatic triple negative breast cancer.

Author	Trial Phase	Treatment Regimen	PFS	OS	RR
Tannock et al <sup>34</sup>	Phase III	High dose vs. conventional dose CMF	-	15.6 vs. 12.8 months	30% vs. 11%
Lopez et al <sup>35</sup>	Phase III	FAC vs. FEC	similar	similar	46% vs. 44%
Katsumata et al <sup>37</sup>	Phase III	AC vs. Docetaxel vs. AC-T	6.4, 6.4, 6.7 months	22.6, 25.7 and 25 months	30%, 41%, 35%
Biganzoli et al <sup>38</sup>	Phase III	AT vs. AC	6 months	20.6 vs. 20.5 months	54% vs. 58%
Bontenbal et al <sup>39</sup>	Phase III	AT vs. FAC	8 vs. 6.6 months	22.6 vs. 16.2 months	58% vs. 37%
O'Shaughnessy et al <sup>42</sup>	Phase III	Capecitabine Docetaxel vs. Docetaxel alone	6.1 vs. 4.2 months	14.5 vs. 11.5 months	42% vs. 30%
Fan et al <sup>45</sup>	Phase III	Docetaxel Cisplatin vs. Docetaxel Capecitabine	10.9 vs. 4.8 months	32.8 months versus 21.5	63% vs. 15.4%
Thomas et al <sup>46</sup>	Phase III	Ixabepilone capecitabine vs. capecitabine alone	5.8 vs. 4.2 months	-	35% vs. 14%
Hu et al <sup>48</sup>	Phase III	Cisplatin Gemcitabine vs. Gemcitabine paclitaxel	7.73 vs. 6.47 months	-	-
Yardley et al <sup>49</sup>	Phase II/III	nab paclitaxel+ carboplatin or gemcitabine vs. gemcitabine carboplatin	7.4, 5.4, 6 months	-	-
Farhat et al <sup>50</sup>	Phase II	Lipoplatin + vinorelbine	8 months	21 months	53.10%

### 4.3. Capecitabine

It can be used as either first, second or third line in the management of disseminated breast cancer. Kotsori et al. [20] retrospectively analyzed 89 patients with metastatic triple negative breast cancer. Capecitabine was given as first line in 53% and as second or third line in 47% patients. An overall response rate of around 21%, median progression free survival of 11 weeks and overall survival of 39 weeks was seen. There was no difference in efficacy when used as either line.

Capecitabine when used as first line is as efficacious as paclitaxel. Talbot et al compared paclitaxel with capecitabine in patients with prior anthracycline exposure. An overall response rate of 36% was seen in capecitabine group and 26% in paclitaxel group. Median progression free survival (3.0 vs. 3.1 months) and overall survival (7.6 vs. 9.4 months) were comparable in both groups

[21].

This chemotherapeutic agent is preferred in elderly patients due to better tolerability. Dose reduction in such patients from 1250 mg/m<sup>2</sup> PO B.D to 1000 mg/m<sup>2</sup> decreases the toxicity without effecting on efficacy [22].

Capecitabine achieved equivalent results when compared with liposomal doxorubicin. PELICAN trial was the first trial to compare capecitabine and liposomal doxorubicin in terms of efficacy and toxicity. The results of this trial have been recently published. An overall response rate of 10.7 and 12.9 % was seen in liposomal doxorubicin and capecitabine arm respectively. Median overall survival was 23.3 months in liposomal doxorubicin and 26.8 months in capecitabine arm. Median progression free survival was similar i.e. 6 months in both groups [23].

Gemcitabine is not commonly used as single agent in the management of metastatic breast cancer. In heavily treated metastatic breast cancer patients, Rha et al. [24] studied the role of gemcitabine monotherapy as salvage regimen. An overall response rate of 20% was seen with two complete responses. The median response duration was 9 months whereas median overall survival was 12 months when used as third line and 7 months when used as fourth line chemotherapy.

Gemcitabine is inferior to epirubicin when used as first line in the treatment of metastatic breast cancer. Results of phase III trial comparing gemcitabine and epirubicin revealed superior response rates (40.3 vs 16.4 % p <0.001), better progression free survival (6.1 vs. 3.4 months p=0.0001) and improved overall survival (19.1 vs. 11.8 months p=0.0004) for epirubicin [25].

### 4.4. Vinorelbine

It is a vinca alkaloid used as salvage chemotherapy after failure of anthracyclines and taxanes in patients with metastatic breast cancer. An overall response rate of 25% with median time to tumor progression and overall survival of 6 months is achieved in this setting [26].

Vinorelbine due to its better toxicity profile can be given as first line in elderly patients in whom anthracyclines and taxanes are contraindicated. Vogel et al conducted a multicenter phase II trial in women aged 60 years or older

with advanced breast cancer. The objective response rate was 38% and median progression free survival was 6 months [27].

### 4.5. Platinums (Cisplatin/Carboplatin)

A number of studies with conflicting results have been carried out evaluating the role of platinums in metastatic triple negative breast cancer.

TBCRC009 was a multicenter phase II clinical trial in which metastatic triple negative breast cancer patients were enrolled to receive either cisplatin or carboplatin depending on physicians' choice. Overall response rate was 25.6% and was superior with cisplatin compared with carboplatin (32.6 vs. 18.7%). RR of 54.5% was seen in patients with BRCA1/2 mutations. In patients without germline BRCA 1/2 mutations BRCA-like genomic instability signature distinguished responding and nonresponding cases. Median PFS was 89 days but in those who responded well to treatment median PFS was 242 days. Platinums were associated with a response rate of 33% and 17% when used as first line and second line respectively [28].

TNT trial revealed no benefit of carboplatin over docetaxel in patients with triple negative breast cancer. However subgroup analyses suggested that patients with BRCA1/2 mutations demonstrated superior response rates (68 vs. 33.3%) and progression free survival (6.8 vs. 4.8 months) with carboplatin compared with docetaxel [29].

#### 4.6. Eribulin

It is a microtubule inhibitor approved for the treatment of metastatic breast cancer in patients who had received 1 or more chemotherapy regimens including an anthracycline and a taxane.

Data from two large multicenter trials (Study 305 and 301) was collectively analyzed to assess the efficacy of eribulin in various subgroups of patients with metastatic breast cancer. In study "305" patients were randomized to Eribulin or treatment of clinicians choice after failure of 2 or more chemotherapeutic agents whereas in study "301" patients were randomized to eribulin or capecitabine. There were 1644 patients in both studies combined out of which 352 were triple negative. Median overall survival (15 vs. 12.6 months  $p < 0.01$ ) and progression free survival (3.9 vs. 3.2 months  $p < 0.05$ ) was significantly longer with eribulin compared to control arm respectively. The overall response rate was same in both groups whereas clinical benefit rate was again significantly superior with eribulin (30% vs. 27%  $p < 0.05$ ). The superiority of overall survival and progression free survival with eribulin was also seen in patients with triple negative breast cancer (12.4 vs. 8.1 months  $P < 0.01$ ) (2.8 vs. 2.5 months  $p = 0.028$ ) [30].

#### 4.7. Ixabepilone

It is an Epothilone B analogue approved as single agent in patients with metastatic breast cancer resistant to anthracyclines, taxanes and capecitabine.

A retrospective analysis of 5 phase II trials was conducted by Perez et al to see its efficacy in triple negative breast cancer patients. The overall response rates in these trials with pretreatment status of no chemotherapy to progression on several lines ranged

from 6 to 55%. Median PFS was 5.7 months whereas median OS was 8.6<sub>months</sub> [31,32].

## 5. Combination Chemotherapy

### 5.1. CMF (Cyclophosphamide, Methotrexate, 5 FU)

It is one of the oldest chemotherapy protocol which lost its popularity after the introduction of anthracyclines and taxanes. Classical CMF (orally administered cyclophosphamide) was compared with intravenously administered CMF and demonstrated response rates of 44.5% and 39% respectively. PFS and OS were similar in both groups but patient's acceptance was better for intravenous CMF [33].

Superior palliation is achieved with high dose CMF at the cost of increased toxicity. A randomized trial was conducted in which 2 different dosage schemes of CMF in patients with metastatic breast cancer were evaluated. Doses on the higher-dose arm were 40 mg/m<sup>2</sup> (M) and 600 mg/m<sup>2</sup> (C,F); doses on the lower-dose arm were 20 mg/m<sup>2</sup> (M) and 300 mg/m<sup>2</sup> (C,F). Response rates were 30% vs. 11% and median survival was 15.6 months vs. 12.8 months in higher dose vs. lower dose arm [34].

CMF may have a substantial role in triple negative breast cancer. Munzone et al. [35] in their review explored the potential benefit of CMF in adjuvant setting. Cells that lack BRCA 1 have shown an *In vitro* sensitivity to chemotherapies causing double strand breaks in DNA such as 5 FU. Furthermore, antimetabolites like MTX and 5 FU are appropriate for rapid proliferation index associated with TNBC. The greater sensitivity observed with these agents' warrants further clinical studies in evaluation of its role in metastatic triple negative breast cancer.

### 5.2. FAC (5 FU, Doxorubicin, Cyclophosphamide)/ FEC (5 FU, Epirubicin, Cyclophosphamide)

FEC is therapeutically equivalent to FAC but with reduced toxicity. M Lopez et al compared FAC and FEC. The objective response rates were 46% with FAC and 44% with FEC. There was no difference in PFS and OS between the two arms. Toxicities were more frequently seen in patients receiving FAC [36].

### 5.3. Anthracyclines/Taxanes combinations

A phase III trial was designed to compare AC, single agent docetaxel and AC followed by docetaxel as first line chemotherapy in metastatic breast cancer. The overall response rates were 30% for AC, 41% for docetaxel and 35% for AC followed by docetaxel. The median PFS was 6.4, 6.4 and 6.7 months in AC, Docetaxel (D) and AC followed by docetaxel arms and median overall survival was 22.6, 25.7 and 25 months in AC, D and AC-D arms respectively.

Although there was no difference in PFS in between the three

arms, nonetheless, there was a trend favoring docetaxel alone arm in terms of RR and OS [37]. AT failed to demonstrate superiority over AC. EORTC group compared AC (doxorubicin and cyclophosphamide) with AT (doxorubicin and paclitaxel) in patients with metastatic breast cancer. The response rates were 58% vs. 54% and median overall survival was 20.6 vs. 20.5 months in AT and AC arms respectively. Median PFS was 6 months in both groups. AT regimen was more toxic with 32% incidence of febrile neutropenia in contrast to 9% seen in patients receiving AC [38].

AT is more efficacious when compared with FAC. Bontenbal et al conducted a phase III study comparing Doxorubicin and Docetaxel combination (AT) with FAC in metastatic breast cancer patients. Median time to progression and median OS were significantly longer for patients on AT compared with FAC (8.0 vs. 6.6 months  $P = .004$ ; OS: 22.6 vs. 16.2 months  $P = .019$ ). The overall response rates were also significantly higher in patients on AT regimen i.e 58 vs. 37%. The incidence of neutropenic fever was higher in patients treated with doxorubicin and Docetaxel combination (33% vs. 9%  $p < 0.001$ ) [39].

No difference in efficacy was found between EC (Epirubicin and cyclophosphamide) and ED (Epirubicin and Docetaxel) in a randomized phase III trial conducted by Blohmer et al. [40]. Similarly, in another study by Langely et al. [41] Epirubicin and Paclitaxel (EP) failed to prove its superiority over Epirubicin and Cyclophosphamide (EC) in terms of PFS and OS.

These diverse results attained for Anthracyclines vs. Taxanes combination in metastatic breast cancer patients necessitates further clinical studies.

#### 5.4. Capecitabine Combinations

Capecitabine (X) plus Docetaxel (T) is superior to Docetaxel (T) alone in metastatic breast cancer. A phase III randomized trial compared XT with T alone in patients with metastatic breast cancer previously treated with anthracyclines. The overall response rates were 42% with XT and 30% with T ( $p = 0.006$ ). The Median PFS and OS were significantly higher for XT as compared to T monotherapy (6.1 vs. 4.2 months), (14.5 vs. 11.5 months) (42). This was the first phase III clinical trial in which combination chemotherapy provided a significant survival advantage over single agent chemotherapy.

An additional randomized trial was conducted comparing concomitant administration of capecitabine and docetaxel with sequential single agent docetaxel followed by capecitabine on progression in patients with metastatic breast cancer. Combination capecitabine and docetaxel were significantly better over sequential administration of docetaxel and capecitabine [43].

A phase III study evaluated the role of maintenance capecitabine in triple negative breast cancer patients who responded to

capecitabine and docetaxel. The median PFS in the capecitabine maintenance group and non maintenance group was 10.1 vs. 6.7 months respectively ( $p = 0.003$ ). However, there was no significant difference in toxicities between the two groups [44].

Docetaxel Cisplatin may be superior to Docetaxel Capecitabine in first line treatment of metastatic triple negative breast cancer. Patients were randomized to receive either docetaxel cisplatin or docetaxel capecitabine. Overall response rates (63% vs. 15.4%  $p = 0.001$ ), PFS (10.9 vs. 4.8 months  $p < 0.001$ ) and OS (32.8 months versus 21.5 months  $P = 0.027$ ) were significantly higher in docetaxel cisplatin arm [45].

Ixabepilone and Capecitabine doublet demonstrated superior outcome in contrast to capecitabine alone in metastatic triple negative breast cancer patients previously treated with anthracyclines and taxanes. A study was designed to evaluate the efficacy of capecitabine plus Ixabepilone vs. capecitabine alone. The trial demonstrated superior PFS (5.8 vs. 4.2 months  $P < 0.0003$ ) and overall response rates (35% vs. 14%  $P < 0.0001$ ) with the doublet as compared to monotherapy. Nonetheless Grade 3/4 toxicities were more commonly seen in Ixabepilone and capecitabine arm [46].

#### 5.5. Platinum Combinations

Platinums are being extensively investigated in patients with triple negative breast cancer.

A retrospective analysis was conducted to see the response of paclitaxel and carboplatin in metastatic triple negative breast cancer patients. The overall response was 57% and median PFS was 16 weeks with this regimen [47].

CBCSG006 was a randomized open label phase III trial comparing cisplatin and gemcitabine with paclitaxel and gemcitabine as first line for patients with metastatic triple negative breast cancer. Median PFS was 7.73 months with cisplatin plus gemcitabine and 6.47 months with paclitaxel plus gemcitabine [48].

The tnAcity study is phase II/III assessing efficacy and safety of first line nab paclitaxel plus gemcitabine or carboplatin versus gemcitabine carboplatin as first line treatment of patients with metastatic triple negative breast cancer. The results of phase II portion were presented in San Antonio Breast cancer symposium in Dec 2016. The

median PFS was significantly higher with nab Paclitaxel carboplatin vs. either nab-Paclitaxel Gemcitabine or Gemcitabine Carboplatin (7.4 vs 5.4 months,  $P = 0.03$  and 7.4 vs 6.0 months,  $P = 0.02$ ) [49].

Fewer studies have been carried out evaluating the role of lipopl-

atin doublets in patients with metastatic breast cancer. One such study was conducted by Farhat et al. [50] in which patients were enrolled to receive lipoplatin and vinorelbine. The objective response rate was 53.1% with complete response seen in 3 patients (9.4%). Median PFS was 8 months and OS was 21 months.

## 6. Ongoing Chemotherapy Trials in Metastatic Breast Cancer

Platinum rechallenge in patients with platinum sensitive mTNBC. (ClinicalTrials.gov Identifier: NCT02607215)

A double blind study of Paclitaxel in combination with Reparixin or Placebo for metastatic triple negative breast cancer. (ClinicalTrials.gov Identifier: NCT02370238) Ph3 study to determine safety, tolerability & tumor response of Oraxol compared to Taxol in metastatic breast cancer. (ClinicalTrials.gov Identifier: NCT02594371) Capecitabine Maintenance Therapy Following Capecitabine Combined With Docetaxel in Treatment of mBC. (ClinicalTrials.gov Identifier: NCT01917279) A Phase Ib/II Study of Eribulin in Combination With Cyclophosphamide in Patients With Solid Tumor Malignancies.

(ClinicalTrials.gov Identifier: NCT01554371)

## 7. At Present Chemotherapy is the Mainstay of Treatment and no Targeted Agents are Approved for the Management of Patients with Triple Negative Breast Cancer

### 7.1. Below we will Highlight Investigational Agents Targeting Subtypes of Triple Negative Breast Cancer

#### 7.2. Androgen Receptor Inhibitors

Androgen receptor inhibitors under active investigation in luminal subtype characterized by androgen signaling TNBC are:

#### 7.3. Enzalutamide

The drug had been evaluated in a phase II study in patients with advanced androgen receptor positive TNBC. The clinical benefit rate was 35% at 16 weeks and 29% at 24 weeks. The overall response rate observed was 8% and median PFS was 14.7 weeks. Fatigue, nausea and anorexia were the most common treatment related adverse events [51].

An ongoing phase III ENDEAR trial will evaluate the role of enzalutamide in combination with paclitaxel or as monotherapy vs. placebo with paclitaxel in patients with advanced stage TNBC.

#### 7.4. Bicalutamide

Another drug evaluated in patients with advanced androgen receptor positive TNBC. Bicalutamide was given in a dose of 150 mg/day. The clinical benefit rate was 19% and median PFS was 12 weeks [52].

An ongoing trial at MSKCC is evaluating the role of bicalutamide in combination with CDK4/6 inhibitor Palbociclib in patients with androgen receptor positive metastatic breast cancer.

#### 7.5. Abiraterone Acetate

An additional phase II trial investigated the role of abiraterone acetate. Patients were randomized to receive abiraterone and prednisone, abiraterone, prednisone and exemestane or exemestane alone. Although not statistically significant ORR was superior in patients receiving abiraterone, prednisone and exemestane [53].

#### 7.6. Other antiandrogenic agents

Another novel agent under exploration in this subtype of triple negative breast cancer is Orteron et al. [54] a 17,20 lyase inhibitor which is a key enzyme in androgen synthesis.

## 8. Tumor Infiltrating Lymphocytes and Immunomodulatory Agents

Tumor infiltrating lymphocytes have been suggested as a marker of immune response. It predicts both prognosis and response to treatment. Increased levels of either intratumoral or stromal T cells are associated with improved OS and DFS in TNBC as compared to other subtypes of breast cancer [55]. Growing interest is seen in targeting immune system in patients with triple negative breast cancer. New immune modulatory agents including immune check point inhibitors have shown promising activity in certain subtypes of TNBC.

KEYNOTE 086 trial is a Phase II trial evaluating the role of Pembrolizumab (PD-L1 inhibitor) in heavily treated TNBC patients (Cohort A). The ORR observed was 4.7% and stable disease was seen in 20.6% patients. The median duration of response was 6.3 months. The response was independent of tumor PD-L1 expression (ORR 4.8% in PD-L1 positive patients vs. 4.7% in PD-L1 negative patients) and was relatively inferior in patients with poor prognostic factors (ORR 2% in patients with elevated LDH vs. 7% in patients with normal LDH). The median PFS was 2 months and OS was 8.9 months. Cohort B of KEYNOTE 086 trial included untreated PD-L1 expressing TNBC. The ORR observed in this cohort was 23% with complete response of 4% [56].

## 9. PARP Inhibitors

The OlympiAD Trial evaluated the role of PARP inhibitors in patients with inherited BRCA mutated metastatic breast cancer. Median PFS was 7 months with Olaparib and 4 months with standard therapy (HR for progression or death, 0.58; 95% CI, 0.43-0.8; P<0.001). The RR was 59.9% in Olaparib arm and 28.8% in standard therapy arm thus revealing the potential of this new class to deliver better results for patients with BRCA

positive breast cancer [57].

## 10. Conclusion

Metastatic triple negative breast cancer is a heterogeneous group of diseases with variable response rates.

Anthracyclines and taxanes are still preferred by many oncologists as first line whereas role of platinum in patients with BRCA mutation need to be elucidated further. Recent insight into subtypes of TNBC and selective targeted therapies may help to improve the prognosis. Participation in clinical trials should be encouraged so as to gain more understanding into this diverse group of disease.

## References

1. M Ghoncheh, Z Pournamdar, H Salehiniya. Incidence and mortality and epidemiology of breast cancer in the world. *Asian Pac J Cancer Prev*. 2016;17:S3 43-6.
2. Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Altekruse, et al. (Eds.). SEER cancer statistics review. 2012;1975-2009.
3. Clarke M, Collins R, Darby S, Davies C, Evans V, Godwin J, et al. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. *Lancet*. 2005;365:1687-717.
4. Mahmood H, Faheem M, Mehmood S. Association of menopausal status with pathological features of tumor in stage I to III A Breast Cancer patients treated with upfront modified radical mastectomy. *J Cancer PrevCurr Res*. 2016;4(1):00109.
5. Gilani GM, Kamal S, Akhter AS. A Differential Study of Breast Cancer Patients in Punjab, Pakistan. *JPMA*.2003;53(10): 478.
6. D'Hondt R, Spoormans I, Neyens N, Mortier N, Van Aelst F. Survival of patients with metastatic breast cancer-a single center experience. *ActaClin Belg*. 2014;69(3):194-9.
7. Abramson VG, Mayer IA. Molecular heterogeneity of Triple Negative Breast Cancer. *Curr Breast Cancer Rep*. 2014;6(3):154-58.
8. Kassam F, Enright K, Dent R, Dranitsaris G, Myers J, Flynn C, et al. Survival outcomes for patients with metastatic triple negative breast cancer: Implications for clinical practice and trial design. *Clin Breast Cancer*. 2009;9(1):29-33.
9. Lin NU, Claus E, Sohl J, Razzak AR, Arnaut A, Winer EP. Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer: High incidence of central nervous system metastases. *Cancer*. 2008;113(10):2638-45.
10. Milesa D, Minckwitzb GV, Seidmanc AD. Combination Versus Sequential Single-Agent Therapy in Metastatic Breast Cancer. *Oncologist*. 2002;7:13-19.
11. Dear RF, McGeechan K, Jenkins MC, Barratt A, Tattersall MH, Wilcken N. Combination versus sequential single agent chemotherapy for metastatic breast cancer. *Cochrane Database Syst Rev*. 2013;(12):CD008792.
12. Ahmann DL, Bisel HF, Eagan RT. Controlled evaluation of adriamycin (NSC-123127) in patients with disseminated breast cancer. *Cancer Chemother Rep*. 1974;58:877-82.
13. Harris L, Batist G, Belt R, Rovira D, Navari R, Azarnia N, et al. Liposome-encapsulated doxorubicin compared with conventional doxorubicin in a randomized multicenter trial as first-line therapy of metastatic breast carcinoma. *Cancer*.2002; 94:25-36.
14. Seidman AD, Berry D, Cirrincione C, Harris L, Muss H, Marcom PK, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. *J ClinOncol*. 2008;26(10):1642-9.
15. Vu T, Ellard S, Speers CH, Taylor SCM, de Lemos ML, Hu F, et al. Survival outcome and cost-effectiveness with docetaxel and paclitaxel in patients with metastatic breast cancer: a population-based evaluation. *Ann Oncol*. 2008; 9 (3): 461-464.
16. Ravdin P, Erban J, Overmoyer B et al. Phase III comparison of docetaxel and paclitaxel in patients with metastatic breast cancer. *Eur J Cancer* 2003;1(suppl 5):S201.
17. Gradishar WJ, Tjulandin S, Davidson N, Shaw H, Desai N, Bhar P, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J ClinOncol*. 2005;23(31):7794-803.
18. Arpino G, De Placido S, De Angelis C. Nab-paclitaxel for the management of triple-negative metastatic breast cancer: a case study. *Anti-cancer Drugs*. 2015;26(1):117-22.
19. Braiteh F. Nab-Paclitaxel outduels paclitaxel in HR+/Her2- and triple negative MBC. *Oncolive*. Miami Breast Cancer Conference. 2016.
20. Kotsori AA, Dolly S, Sheri A, Parton M, Shaunak N, Ashley S, et al. Is capecitabine efficacious in triple negative metastatic breast cancer. *Oncology*. 2010;79(5-6):331-6.
21. Talbot DC, Moiseyenko V, Van Belle S, O'Reilly SM, Alba Conejo E, Ackland S, et al. Randomised, phase II trial comparing oral capecitabine (Xeloda) with paclitaxel in patients with metastatic/advanced breast cancer pretreated with anthracyclines. *Br J Cancer*. 2002;86:1367-72.
22. Bajetta E, Procopio G, Celio L, Gattinoni L, Della Torre S, Mariani L, et al. Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. *J ClinOncol* 2005;23:2155-61.

23. Harbeck N, Saupé S, Jäger E, Schmidt M, Kreienberg R, Müller L, et al. A randomized phase III study evaluating pegylated liposomal doxorubicin versus capecitabine as first-line therapy for metastatic breast cancer: results of the PELICAN study. *Breast Cancer Res Treat.* 2017;161(1):63-72.
24. Rha SY, Moon YH, Jeung HC, Kim YT, Sohn JH, Yang WI, Suh CO, et al. Gemcitabine monotherapy as salvage chemotherapy in heavily pretreated metastatic breast cancer. *Breast Cancer Res Treat.* 2005;90(3):215-21.
25. Feher O, Vodvarka P, Jassem J, Morack G, Advani SH, Khoo KS, et al. First-line gemcitabine versus epirubicin in postmenopausal women aged 60 or older with metastatic breast cancer: a multicenter, randomized, phase III study. *Ann Oncol.* 2005;16(6):899-908.
26. Zelek L, Barthier S, Riofrio M, Fizazi K, Rixe O, Delord JP, et al. Weekly vinorelbine is an effective palliative regimen after failure with anthracyclines and taxanes in metastatic breast carcinoma. *Cancer.* 2001;92(9):2267-72.
27. Vogel C, O'Rourke M, Winer E, Hochster H, Chang A, Adamkiewicz B, et al. Vinorelbine as first-line chemotherapy for advanced breast cancer in women 60 years of age or older. *Ann Oncol.* 1999;10(4):397-402.
28. Isakoff SJ, Mayer EL, He L, Traina TA, Carey LA, Krag KJ, et al. TB-CRC009: A Multicenter Phase II Clinical Trial of Platinum Monotherapy With Biomarker Assessment in Metastatic Triple-Negative Breast Cancer. *Journal of Clinical Oncology.* 2015; 33 (17):1902-9.
29. Tutt A, Ellis P, Kilburn L, Gilett C, Pinder S, Abraham J, et al. The TNT trial: A randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer (CRUK/07/012) [abstract]. In: Proceedings of the Thirty-Seventh Annual CTRC-AACR San Antonio Breast Cancer Symposium: 2014 Dec 9-13; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res. 2015;75(9 Suppl):S3-01.
30. Pivot X, Marmé F, Koenigsberg R, Guo M, Berrak E, Wolfer A. Pooled analyses of eribulin in metastatic breast cancer patients with at least one prior chemotherapy. *Annals of Oncology.* 2016;27:1525-31.
31. Tkaczuk KH. Ixabepilone as Monotherapy or in Combination with Capecitabine for the Treatment of Advanced Breast Cancer. *Breast Cancer (Auckl).* 2011;5:1-14.
32. Perez EA, Lerzo G, Pivot X, Thomas E, Vahdat L, Bosserman L, et al. Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. *J Clin Oncol.* 2007;25(23):3407-14.
33. Brandi M, Demitrio A, Ditunno P, Catino A, Lorusso V, Delena M. Oral versus intravenous CMF in metastatic breast-cancer - a randomized study. *Int J Oncol.* 1994(3):559-65.
34. Tannock IF, Boyd NF, DeBoer G, Erlichman C, Fine S, Larocque G, et al. A randomized trial of two dose levels of cyclophosphamide, methotrexate, and fluorouracil chemotherapy for patients with metastatic breast cancer. *J Clin Oncol.* 1988;6(9):1377-87.
35. Munzone E, Curigliano G, Burstein HJ, Winer EP, Goldhirsch A. CMF revisited in the 21st century. *Ann Oncol.* 2012;23:305-11.
36. Lopez M, Papaldo P, Di Lauro L, Vici P, Carpano S, Conti EM. 5-Fluorouracil, adriamycin, cyclophosphamide (FAC) vs. 5-fluorouracil, epirubicin, cyclophosphamide (FEC) in metastatic breast cancer. *Oncology.* 1989;46(1):1-5.
37. Katsumata N, Watanabe T, Minami H, Aogi K, Tabei T, Sano M, et al. Phase III trial of doxorubicin plus cyclophosphamide (AC), docetaxel, and alternating AC and docetaxel as front-line chemotherapy for metastatic breast cancer: Japan Clinical Oncology Group trial (JCOG9802). *Ann Oncol.* 2009;20:1210-5.
38. Biganzoli L, Cufer T, Bruning P, Coleman R, Duchateau L, Calvert AH, et al. Doxorubicin and Paclitaxel Versus Doxorubicin and Cyclophosphamide as First-Line Chemotherapy in Metastatic Breast Cancer: The European Organization for Research and Treatment of Cancer 10961 Multicenter Phase III Trial. *Clinical Oncology.* 2002; 20 (14): 3114-21.
39. Bontenbal M, Creemers GJ, Braun HJ, de Boer AC, Janssen JT, Leys RB, et al. Phase II to III Study Comparing Doxorubicin and Docetaxel With Fluorouracil, Doxorubicin, and Cyclophosphamide As First-Line Chemotherapy in Patients With Metastatic Breast Cancer: Results of a Dutch Community Setting Trial for the Clinical Trial Group of the Comprehensive Cancer Centre. *J Clin Oncol.* 2005;23(28):7081-8.
40. Blohmer JU, Schmid P, Hilfrich J, Friese K, Kleine-Tebbe A, Koelbl H, et al. Epirubicin and cyclophosphamide versus epirubicin and docetaxel as first-line therapy for women with metastatic breast cancer: Final results of a randomised phase III trial. *Ann Oncol.* 2010;21(7):1430-5.
41. Langley RE, Carmichael J, Jones AL, Cameron DA, Qian W, Uscinska B, et al. Phase III Trial of Epirubicin Plus Paclitaxel Compared With Epirubicin Plus Cyclophosphamide As First-Line Chemotherapy for Metastatic Breast Cancer: United Kingdom National Cancer Research Institute Trial AB01. *J Clinical Oncology.* 2005;23(33):8322-30.
42. O'Shaughnessy J, Miles D, Vukelja S et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol.* 2002;20:2812-23.
43. Beslija S, Obralic N, Basic H. A single institution randomized trial of Taxotere (T) and Xeloda (X) given in combination vs. Taxotere (t) followed by Xeloda (x) after progression as first line chemotherapy (CT) for metastatic breast cancer (MBC). *EJC Suppl.* 2005;3:114.
44. Liang X, Di L, Song G, Yan Y, Wang C, Jiang H, et al. Capecitabine



- maintenance therapy for XT chemotherapy-sensitive patients with metastatic triple-negative breast cancer. *Chin J Cancer Res.* 2014; 26(5):550-7.
45. Fan Y, Xu BH, Yuan P, Ma F, Wang JY, Ding XY, et al. Docetaxel–Cisplatin Might Be Superior to Docetaxel–Capecitabine in the First-line Treatment of Metastatic Triple-negative Breast Cancer. *Ann Oncol.* 2013;24(5):1219-25.
46. Thomas ES, Gomez HL, Li RK, Chung HC, Fein LE, Chan VF, et al. Ixabepilone Plus Capecitabine for Metastatic Breast Cancer Progressing After Anthracycline and Taxane Treatment. *Journal of Clinical Oncology.* 2007;25(33):5210-7.
47. Chia JW, Ang P, See H. Triple Negative Metastatic/Recurrent Breast Cancer: Treatment with Paclitaxel/Carboplatin Combination Chemotherapy. *Journal of Clinical Oncology.* 2007;25:1086.
48. Hu XC, Zhang J, Xu BH, Cai L, Ragaz J, Wang ZH, et al. Cisplatin plus gemcitabine versus paclitaxel plus gemcitabine as first line therapy for metastatic triple negative breast cancer CBCSG006: a randomized open label multicenter phase III trial. *The Lancet Oncology.* 2015;16(4):436-46.
49. Yardley DA, Coleman RE, Conte PF, Cortes J, Brufsky A, Shtivelband M, et al. Nab-paclitaxel + carboplatin or gemcitabine vs gemcitabine/carboplatin as first-line treatment for patients with triple-negative metastatic breast cancer: Results from the randomized phase 2 portion of the tnAcity trial [abstract]. In: *Proceedings of the 2016 San Antonio Breast Cancer Symposium; 2016 Dec 6-10; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res* 2017;77(4 Suppl):Abstract nr P5-15-03.
50. Farhat F, Temraz S, Kattan J. Preliminary Results of a Phase II Study of Lipoplatin (Liposomal Cisplatin)/Vinorelbine Combination as First Line Treatment in HER2/Neu Negative Metastatic Breast Cancer (MBC). *Clinical Breast Cancer.* 2011;11(6):384-9.
51. Traina TA, Miller K, Yardley DA. Results from a phase 2 study of enzalutamide, an androgen receptor inhibitor, in advanced AR+ triple-negative breast cancer. *J Clin Oncol.* 2015;33(suppl):1003.
52. Gucaip A, Tolaney S, Isakoff SJ, Ingle JN, Liu MC, Carey LA, et al. Phase II trial of bicalutamide in patients with androgen receptor positive, estrogen receptor-negative metastatic Breast Cancer. *Clin Cancer Res.* 2013;19(19):5505-12.
53. O'Shaughnessy J, Campone M, Brain E. Randomized phase 2 study of abiraterone acetate with or without exemestane in postmenopausal patients with estrogen receptor-positive metastatic breast cancer. *J Clin Oncol.* 2014;32:5.
54. [ClinicalTrials.gov](https://clinicaltrials.gov). Orteronel as monotherapy in patients with metastatic breast cancer (MBC) that expresses the androgen receptor (AR). 2016.
55. Disis ML, Stanton SE. Triple-Negative Breast Cancer: Immune Modulation as the New Treatment Paradigm. *ASCO Educational Book.* 2015.
56. Adams S, Schmid P, Rugo HS, et al. Phase 2 study of pembrolizumab (pembro) monotherapy for previously treated metastatic triple-negative breast cancer (mTNBC): KEYNOTE-086 cohort A. *J Clin Oncol.* 2017;35.
57. Robson M, Im SA, Senkus E. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med.* 2017;377:523-33.