ISSN 0975-6299 Vol 3/Issue 2/April – June 2012

International Journal of Pharma and Bio Sciences

REVIEW ARTICLE CELL BIOLOGY

TRIPLE-NEGATIVE BREAST CANCER AND IT'S THERAPEUTIC OPTIONS

C.B.S. DANGI* AND A. FIRODIYA

Human Genetic Lab., C.S.R.D., Peoples Group, Bhopal, India.

C.B.S. DANGI
Human Genetic Lab., C.S.R.D., Peoples Groups, Bhopal, India.

ABSTRACT

Triple-negative breast cancer (TNBC) is subtype, accounts 15-20% of breast cancers, which does not express estrogen receptor (ER), progesterone receptor (PR) or human epidermal growth factor 2 (HER2). *BRCA*1 related pathway significantly contributes in the development of TNBC. Premenopausal African-American women are majorly associated and unique molecular features, aggressive behaviors, early pattern of metastatis and poor prognosis are characteristics of it. Eventhough, better results observed through chemotherapy in neoadjuvant, adjuvant and metastatic treatment of TNBC, role of specific chemotherapy agents was not completely understood. Currently different therapeutic agents for TNBC are platinum agents, signaling pathway inhibitors, Poly-(ADP-ribose)-polymerase inhibitors, antiangiogenic agents, microtubule inhibitors, androgen receptor based therapy, histone deacetylase inhibitors and heat shock protein 90 inhibitors. Further molecular insight will optimize therapeutic strategies for TNBC patients.

KEYWORDS

Basal-like breast cancer, Chemotherapy, Triple-negative breast cancer.

INTRODUCTION

Breast cancer (BC), a malignant heterogeneous disease associated with specific morphological, immunohistochemical features and clinical behaviors proves vast global impact.[1-3]. In the United States (U. S.) BC is a most common cancer among women. In 2011, an estimated 1,596,670 women were diagnosed with BC and 5,71,950 will die of disease[4]. Amongst 1 million cases of BC are diagnosed annually worldwide, 1,70,000 are of the triple-negative phenotype approx[5].

Triple-negative breast cancer (TNBC) is clinical entity referring to tumors that do not express estrogen receptor (ER), progesterone receptor (PR), or human epidermal growth factor 2 (HER2)[6]. TNBC (ER-, PR-, HER2-) accounts for 10-15% of BCs approx (Figure 1)[7]. Disease-free survival (DFS) and overall survival (OS) is a poor prognostic factor for TNBC. Premenopausal women and women with African descent express clustering of TNBC. There is no effectual specific targeted therapy readily available for TNBC. Therefore, the heterogeneity of the disease underscores need for treatment to be tailored for a specific patient, depending on the molecular characteristics.

This review focuses on epidemiology, risk factors, molecular features, prognosis and pattern of recurrence, and therapeutic options for this heterogeneous aggressive entity. Ongoing research of TNBC would lead to strategies improving outcomes for patients.

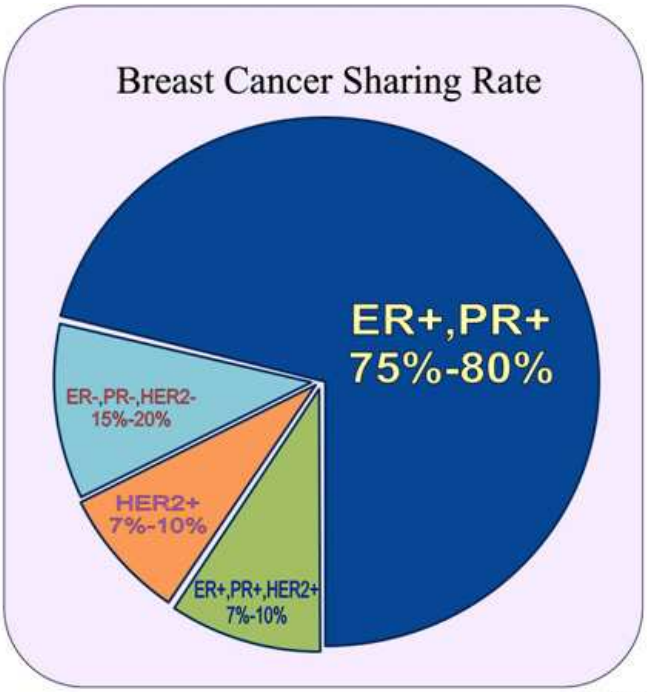

Figure 1 Expression of receptor in breast tumors[15,62,73]. Approximately among breast cancer 15-20% cancers are triple negative for hormonal and HER2 receptors[20,31,68].

TRIPLE-NEGATIVE BREAST CANCER AND BASAL-LIKE BREAST CANCER:

Triple-negative breast cancer (TNBC) and basal-like breast cancer (BLBC) are two different entities, eventhough used interchangeably (Figure 2). These subgroups share significant similarities[8,9]. About 15% basal-like phenotype exhibits BC possessing low expression of ER and HER2[10]. 123 samples out of 172 triple-negative (TN) tumors (71%) were determined to cluster with BLBC, signifying that not all TNBC are of the basal-like subtypes. Whereas, gene expression profiling of 123 (77%) out of the 160 tumors were defined as BLBC, but proved to be TN in histological staining, indicating that not all BLBC are TN[11]. Basal-like subtypes form a homogeneous group of tumors with a similar gene expression profile related to prognosis and therapy response whereas, TNBC do not form so. [8,11,12,13].

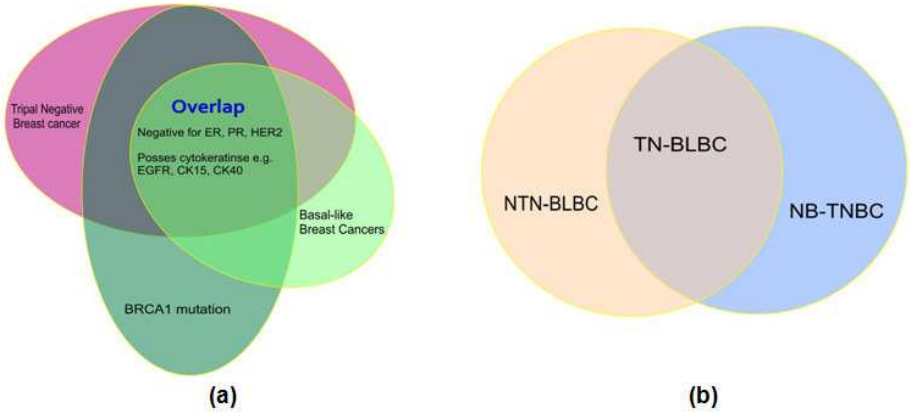

Figure 2

Interrelation of triple-negative breast cancer (TNBC), basal-like breast cancer (BLBC) and BRCA deficient breast cancer patient.

(a) TNBC as well as BLBC shares major properties. In addition, most cancers with BRCA1 mutation are TNBC and BLBC.

(b) BLBC gives birth to non-triple negative basal-like breast cancer (NTN-BLBC) and triple negative basal like breast cancer (TN-BLBC). Non-basal-like breast cancer (N-BLBC) gives birth to non-basal-like triple negative breast cancer (NB-TNBC).

Basal-like cancer is associated with p53 mutation and *BRCA1* gene[10,14,16,17,18]. Analysis exhibits 88% of 17 subjects with *BRAC1* mutation, identified as basal-like cancers (OR = 9.9; 95% confidence interval [CI], 1.9-43; *P* = 0.002)[18]. Mutation in *BRCA1* might have similar etiology to BLBC[12]. Basal-like cancers showed high nuclear and mitotic grade and high mitotic index with poor differentiation[19]. There are 31% of basal-like cancers stained positive for c-KIT, however only 11% with other subgroups (*P* = 0.001). Expression of cytokeratin 5/6 (CK5/6) and /or the epidermal growth factor receptor (EGFR) in tumors exhibited by most widely used panel are TN[20]; whereas no consistent consent exists as to what is the best possible immunohistochemical panel to identify BLBC[8,11,14].

Triple-negative group of BC is not a homogeneous disease entity. However, a significant fraction of TN tumors related to the basal-like tumor type forms a homogeneous group. Therefore, basal-like subgroup provides the overall poor prognosis of TNBC. Triple negativity is more as a symptom than as an entity of BC.

MOLECULAR FEATURES:

TN term defined ER, PR, and HER2 based on clinical assays, whereas basal-like defined using cDNA micrsoarrays[10,15]. TN and basal-like terms are not identical, as most triple-negative breast tumors do cluster within the basal-like subgroup[11,14]. Molecular classification through gene expression profiling showed differences between hormone receptor (HR)-positive and HR-negative tumors[15]. BC subtypes classified

into five distinct subgroups (intrinsic subtypes) based on gene expression or molecular phenotypes (DNA microarray analysis).

- Luminal A (ER+/PR+/HER2-)
- Luminal B (ER+/PR+/HER2+)
- HER2+/ER- (ER-/PR-/HER2+)
- Basal-like (ER-/PR-/HER2-)(Positive for either cytokeratin 5/6 and HER1 or both)
- Normal breast-like

Another subtype, luminal C distinguished from luminal A and luminal B by elevated expression of particular sets of genes[10].

Expression of selected immunohistochemical markers can combine to estimate the different breast cancer phenotypes (Figure 3). These subgroups behave differently in terms of prognosis, outcomes, and therapeutic targets[10,14]. Profile defined by ER-, HER2-, cytokeratin 5/6+, and/or HER1+ constantly associate with BLBC, the survival outcomes of patients with this immunohistochemical profile correlated with the poorer survival outcomes.[14]

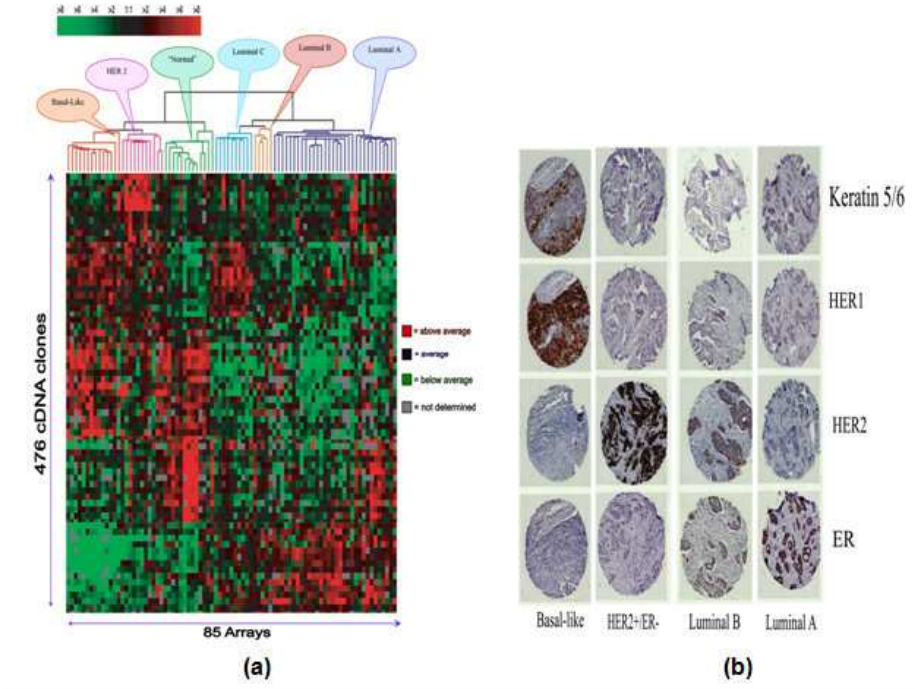

Figure 3

Genetic expression of breast cancer subtypes.

(a) Breast cancer are separated into 5 or 6 distinct subtypes by DNA microarray analysis[10].

Sorlie T, Perou CM, Tibshirani R, et al., Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications, Proc Natl Acad Sci USA, 98(19): 10869-10874, (2001).

(b) Immunohistochemical profile of tissue sample from microarray results[21].

Schneider BP, Winer EP, Foulkes WD, et al., Triple-negative breast cancer: risk factors to potential targets, Clin Cancer Res, 14(24): 8010-8018 (2008).

Microarray study in series (n = 21) ascertained, basal-like subtype was negative for ER and HER2, but high expression for basal cytokeratin 5/6, HER1 and c-kit[14]. Low disease-specific survival outcome resulted from 930 cases, express basal CK5/6, and CK17. HER1 expression was significantly independent negative prognostic factor (relative risk [RR], 154; P = 0.017) with tumor size (RR, 1.12) and nodal status (RR, 2.10).

Carolina Breast Cancer study (CBCS) provided immunophenotypic classification of several aggressive pathological features of TNBC. It showed BC subtypes are associated with tumor size, axillary lymph node status, combined grade, nuclear pleomorphism, and p53 mutation status[20]. Luminal A harbored greater number of *TP53* mutations (44% vs 15%; *P* □ 0.001), higher mitotic index (odd ratio [OR], 11.0; 95% CI, 5.6-21.7), more marked nuclear

pleomorphism (OR, 9.7; 95% CI, 5.3-18.0), and higher combined grade (OR, 8.3; 95% CI, 4.4-15.6) when compared with BLBC.

Low molecular weight cytokeratin as CK7, CK8, CK18, and CK19, MUC1 alpha-6 integrin, BCL1, ER, PR, and GATA3 expressed by central luminal cells. Myoepithelial cells consist of basal cell layer which direct outward toward basement membrane, express high molecular weight-cytokeratin including CK5, CK14, and CK17; also smooth muscles specific marker, caldesman, calponin, p63, laminin, maspin, beta-4 integrin, CD10, S100 and nerve growth factor receptor[22-27].

A microarray profiling[28] among 56 tumors, 23 provide basal-like tumor were grade 3, ductal (21/23) or metastatic (2/23) carcinomas and oftenly demonstrated geographic necrosis (17/23), a pushing border of invasion (14/23), and stromal lymphocytic response (13/23).

EPIDEMIOLOGY AND RISK FACTORS:

BC is group of heterogeneous disease that varies in incidence and mortality across demographic groups. These differences underscored in TNBC women. Younger age and lower socioeconomic status are common characteristics reported among large cohorts of TNBC patients. When TNBC compared with HR-positive luminal breast tumors, it shows common pattern of molecular and histological characteristics with distinct patterns of epidemiology and risk factors[5].

Epidemiology and risk factors associated with TNBC disease, relates to age and race. A population based, case control, CBCS determining clinical association and distribution across BC among 500 women evaluated with basal-like tumors (ER/PR/HER2-negative, CK5/6-positive, and/or HER1-positive) were more likely to be African-American (prevalence of 26 % vs 16% in non African-Americans) and premenopausal (24% vs 15% postmenopausal)[19]. Study revealed that basal-like breast tumors occurred at a higher prevalence among premenopausal patient than postmenopausal African-American and non-African American patients[29,30]. In the United Kingdom, African-American women with BC have a substantially higher mortality rate than Caucasian women (33.5 vs 22.4 per 1,00,000)[31]. California Cancer Registry data showed African-American women with late stage TNBC had the poorest survival than any BC subgroup[29]. There is slightly better prognosis with TNBC among Asian women than Caucasian women[32,33]. Hispanic women among TNBC exhibit relatively high prevalence rate (24%)[34].

Table 1

Distrribution of Risk Factor Of selected TNBC

Table 1: Distribution of Risk Factor of selected TNBC

Risk element	African American Age < 40 yr		White Aged <40yr	African American Aged 40-49 yr		White Aged 40-49 yr
Parity ≥ 3	24%	*P* = 0.45	13%	41%	*P* = 0.0001	19%
Never breastfed	82%	*P* = 0.01	61%	75%	*P* =0.0003	61%
Parity ≥3 and never breastfed	18%	*P* = 0.002	5%	30%	*P* = 0.0001	7%
Lactation suppressants, ever use	34%	*P* = 0.06	19%	61%	*P* = 0.0003	42%
Parous women: age at first-term pregnancy < 26 years	78%	*P* = 0.04	59%	86%	*P* = 0.0001	61%
Parous women ≥2 children breastfed	9%	*P* =0.0001	37%	14%	*P* = 0.0001	27%
Parous women ≥4 months breastfeeding per child	9%	*P* =0.0001	39%	10%	*P* = 0.0001	26%
Waist-to-hip ratio ≥ 0.77	61%	*P* = 0.31	46%	80%	*P* = 0.0001	55%

The risk factor associated with BC subtypes (luminal A, luminal B, basal-like and EGFR2-positive/ER-negative) of 1424 BC cases were found out in CBCS[35]. Basal like breast tumor were more likely to arise among premenopausal women with higher parity, younger age at menarche, higher body mass index, younger age at full term pregnancy, shorter duration of breast-feeding and waist to hip ratio. Women who did not breast feed and used medication to suppress lactation have increased risk of BLBC in comparison with luminal-A breast cancer. Study indicates BLBC could prevent among younger African-American women by promoting breast-feeding and decreasing abdominal fattiness. When the women subdivided into two age groups, differences in risk factors between African-American and white women were particularly strong (Table 1).

Population-based case-control study analyzed reproductive and hormonal risk factors in BC women[36]. Younger age women with HER2-overexpressing disease are associated with risk (OR = 2.7, 95% CI: 1.4-5.5), those who breast-feed for more than 6 months was shielded for luminal (OR = 0.8, 95% CI: 0.6-1.0) and TN disease (OR = 0.5, 95% CI: 0.3-0.9). Postmenopausal age (OR = 1.6, 95% CI: 1.1-2.2) and use of estrogen and progesterone hormone therapy associated with luminal disease (OR = 1.7, 95% CI: 1.3-2.1).

Polish breast cancer studies exhibit increasing age at menarche reduces the risk for basal-like cancer, when compared with luminal A-type breast cancer[37]. In addition, increasing body mass index was associated with a reduced risk of luminal BCs among premenopausal women. It reveals BC risk may vary by molecular subtypes. Therefore, prevention strategies planned accordingly.

PROGNOSIS AND PATTERN OF RECURRENCE:

TNBC is more aggressive with inferior outcomes and have higher percentage of distant metastasis. It relapses more rapidly with worse DFS in comparison with other BC subtypes[6,38,39,40]. Clinical nomograms and gene expression strategies provide prediction of higher risk patients for subsequent BC related brain relapse[41,42]. TN breast tumor type could detect through clinical examination, which may act like "interval cancers" between regular mammograms[6].

Population based studies show patients with TN disease had reduced BC specific survival as compared with luminal phenotypes[6,20]. TN cancer and those negative for the expression of EGFR and CK5/6 showed a lower incidence of locoregional relapse when compared to basal-like subtype[43]. A recent study of Canadian series depicts, among 1601 BC patients 180 (11.25%) had TN breast tumors, both the likelihood of distant recurrence (HR, 2.6; $P < 0.0001$) and death from BC within 5 years of diagnosis (HR, 3.2; $P < 0.0001$) which are higher compared to non-triple negative subtypes. Recurrence risk of TNBC rose sharply after diagnosis, peaking at approximately 3 years and then declined rapidly. Subsequently follow up reduces recurrence of TNBC (figure 4)[6,20].

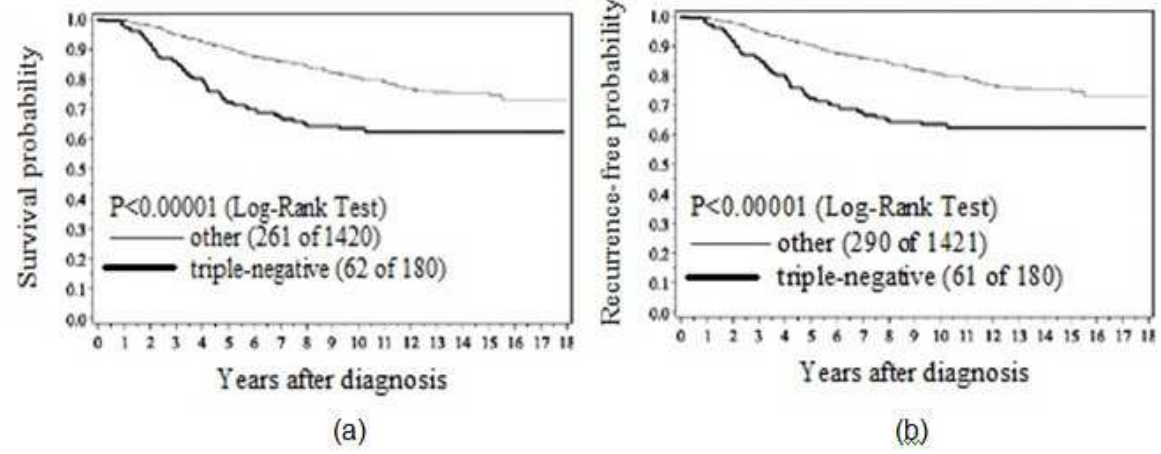

Figure 4

Overall survival and distant recurrence-free survival rates in triple negative and other breast cancers
(a) Breast-specific survival rates in triple-negative and other breast cancers.
(b) Distance recurrence rates in triple-negative and other breast cancers.

Biological features characterize location of TNBC metastasis and pathways that are specific to basal-like subtypes[44,45]. Signaling pathways and chemokines lend to survival and proliferation of tumor cells in new areas, which alleviate metastasis to specific areas. Aggressiveness in soft tissues and visceral organ relapse are more common than bone relapse, when these diagnosed with TN vs. estrogen receptor positive disease[44,46]. Women with TNBC have shorter median survival time, when recurrence takes place. TNBC and other subtype had different recurrence location as lung, visceral and CNS metastases, as distant metastases. Recurrence takes place in patient with aggressive subtypes and patients with bone metastases are less likely to relapse[44,46,47,48].

There are higher risks of death earlier after diagnosis in women with TNBC in comparison with other subtype. Death related to TNBC occurred within first 10 years, while other subtypes continued to live upto 18 years after diagnosis[6,46]. Distant recurrence experiences lately than local recurrence in TNBC[6]. The site-specific patterns of relapse determined among 344 patients with lymph node-negative breast tumors, which treated solely with local therapy by the intrinsic gene list describing molecular subtypes (i.e. luminal, basal, HER2-positive etc.). Lung metastasis was often observed in basal-like subtype (P = 0.01) and less likely among luminal subtype, while in case of bone metastasis basal phenotypes are less likely occur (P = 0.0001) and more likely to occur in luminal subtypes (luminal A, P = 0.056).

CNS metastasis:

Among patients diagnosed with BC, 15% would develop brain metastasis. There is poor survival, 6 month to 1 year for approx 20% brain metastasis to occur following a diagnosis with currently available therapies such as surgical resection, whole brain radiotherapy, corticosteroid, stereoactive radiosurgery and supportive care[49,50]. The lapatinib (Tykerb) has promising results in treatment with increased incidence of brain metastasis among patients with HER2-positive metastasis BC[51,52].

A study at Dana-Farber Cancer Institute from January 2000 to June 2006 characterizes the outcomes of 116 patients with TN metastatic BC having risk and clinical consequences of CNS relapse[53]. At initial metastatic course, 14% patients diagnosed with CNS metastases while 46% diagnosed during their metastatic course. Median survival with subsequent diagnosis of CNS metastasis was 4.9 months. The patients with CNS metastasis at first presentation of age-and race-adjusted death rate were 3.4 times than that of those with no CNS lesion at first metastatic presentation.

The incidence and aggressiveness of intracranial metastasis in TNBC are recently highlighted, although similar systemic strategies are not yet available. Multivariate analysis among 3,193 patients with brain metastasis arising from BC treated between 1989 to 2006 shows TN condition was greater risk factor for development of cerebral metastasis (OR = 4.16; P = 0.001), compared to HER2-positive status (O.R. = 3.43; P = 0.005). TNBC has shorter median interval between primary diagnosis and cerebral relapse than non-triple-negative (22 vs. 51 months, O.R. = 2.7; P<0.0001). There is worse survival after diagnosis of brain metastasis (4 vs.8 months, P = non-significant)[14]. Another study between 2003 to 2006 in series of 222 patients with brain metastasis also found a petty median survival for TN patient (3.7 months) compared with HER2-positive (9 months) and ER/PR/HER2-positive (15 months) disease[54]. The above studies gave abundant example of prognostic, preventive, and therapeutic strategies, are major problem in TN tumor settings with intracranial relapse.

THERAPEUTIC OPTIONS

TNBC is not acquiescent to either hormonal therapies ER or HER2 approaches. There were neither established guidelines for specific agent nor standard regimen available for TNBC women[55,56,57]. Several approaches are currently under investigation (Figure 5). However, two therapeutic options for management of TN tumors are chemotherapy and targeted therapy. Cytotoxic agents bestow a DNA-damaging effect in generally all dividing

cells. Fast dividing cancer cells are more susceptible to cytotoxic therapy, but with numerous adverse effects. In contrast, targeted therapies interfere with a specific biomolecule to which their effect directed. This target is specific characteristic of the cancerous cell, e.g. an overexpressed receptor, providing certain selectivity against malignant cells, thereby being ineffective or less effective on normal cells[58]. Clinical judgment and individual patient consideration are helpful in making decision during treatment of TNBC patients

.

Figure 5
Different types of currently available therapeutic options for TNBC.

CHEMOTHERAPY

Although scanty evidences combinational and sequential chemotherapeutic regimens are probable strategies for TNBC[55]. One study demonstrated, those with TNBC were likely to receive aggressive adjuvant (postoperative) chemotherapy, eventhough with small tumors (> 0.5 cm to ≤ 1 cm)[59]. TNBC had high chemosensitivity with short time of progression and survival. Anthracyclin and taxane are currently used cytotoxic therapies in TNBC patients. Pathologic complete response (pCR) rate to anthracycline and taxane has increased in patients with TNBC[60,61]. The good overall outcomes found in subjects who accomplish pCR. When treated with anthracycline agents in combination with taxane found a pCR of 38% compared to 14% in non-triple negative breast cancer[62]. A latest study of about 300 patient with TNBC showed significantly higher pCR in p53 positive tumors than in p53 negative (22% vs 10%; $P = 0.09$)[63].

A study of Cancer and Leukemia Group B (CALGB) in 9344 patients with

positive axillary node compared different anthracycline doses with paclitaxel in adjuvant therapy, shows good benefits ($P = 0.002$), although independent of HER2 status[64]. Other group studied the same kind of combination instead of comparing paclitaxel every 21 days versus paclitaxel once a week after four courses of adriamycin-paclitaxel every three weeks. A 378 TN patients treated with paclitaxel once a week exhibit statistically significant results ($P = 0.037$)[65]. Another study of 82 subjects based on molecular classification using anthracycline and taxane combination gave 45% pCR for HER2-positive and basal-like tumors, versus 6% for luminal tumors[66], emphasizing benefits of chemotherapy in harmone independent tumor.

As TN tumors are heterogeneous, *BRCA*1 associated TNBC is functionally similar to sporadic TNBC, remain ambiguous with regard to anthracycline sensitivity. Study suggests that *BRCA*1 associated TNBC may be less responsive to anthracycline-based therapy[67]. There were 12 *BRCA*1 carriers identified among 55 TNBC patients who received 6 cycles of FEC 100 (florouracil/epirubicin100mg/m2/cyclophosphamide). The pCR rate was 17% in 12 TN *BRCA*1 carriers and 42% in 55 sporadic TN non-carriers. However, other studies suggested, patient with *BRCA*1/2 mutation carriers have high pCR rates to anthracyclines[68]. A recent study of MA5 revealed an improvement in 5-year OS in adjuvant cyclophosphamide, methotrexate, fluorouracil (CMF) for TNBC (71% vs 51%) when compared cyclophosphamide, epirubicin, fluorouracil (CEF) arm. CEF arm was superior in all other subgroups[69]. Early Breast Cancer Trialist Collaborative Group (EBCTCG) in 2005 overviewed ER-poor BC was benefited by polychemotherapy[70].The study of more than 6000 patients with ER poor BC are exposed to 46 polychemotherapy trials which show significantly reduction in recurrence risk and death in younger (10 yr. HR 0-73 and 0.73 respectively) and older patients (10 yr. HR 0-82 and 0.86 respectively). Study reveals that eventhough lack of data on HER2 status in older patients, TNBC derives significant benefit from chemotherapy.

Trial name	Regimen	Status	*N*	Start	Sponcer	NCI ID
Neoadjuvant/Adjuvant clinical trials for patients with triple-negative breast cancer						
Randomized phase II 2 × 2 factorial trial of the addition of Carboplatin +/− Bevacizumab to neoadjuvant weekly Paclitaxel followed by dose-dense AC hormone receptor-/HER2-Negative resectable breast Cancer.	Arm A: Paclitaxel D1 weekly × 12 weekly → ddAC D1 × 4 cycles Arm B: Arm A+ bevacizumab q2wks (weeks 1, 3, 5, 7, 9, 10, 11, 13, 15, 17) Arm C: Arm A + Carboplatin q3wks (wks 1, 4, 7, 10 Arm D:Arm A + Bevacizumab as in Arm B + Carboplatin as in Arm C.	Recruiting	362	May 2009	Cancer and Leukemia Group B	NCT00861705
A phase 1 study of neoadjuvant chemotherapy with the gamma Secretase inhibitor RO4929097 in combination with Paclitaxel and Carboplatin in patients with clinical stage II-III Triple Negative breast cancer.	RO4929097 D1-3, 8-10, 15-17 & Paclitaxel D1, 8, 15 & Carboplatin D1 × 6 cycles (cycle = 21 days)	Recruiting	18	Dec 2010	Arthur G. James Cancer Hospital & Richard J. Solove Research Institute (Columbus, OH)	NCT01238133
Effect of neoadjuvant Platinum-based chemoradiation therapy for locally advanced Triple negative breast cancer: clinical outcome and correlation to biological parameters.	Cisplatin 75mg/m2 IV or Carboplatin AUC = 6 IV, at physician discretion) + XRT × 6 weeks (50–60Gy to breast/CW; 45–50Gy to internal mammary nodes, supraclavicular fossa nodes and axillary nodal basins)	Recruiting	53	Dec 2010	Washington University School of Medicine (St. Louis, MO)	NCT01167192
A prospective, open and unicentric phase II clinical trial of Docetaxel combined with Oxaliplatin for Triple Negative local advanced breast cancer patients (TNLABC).	Docetaxel 75mg/m2 D1 & Oxaliplatin 130 mg/m2 D2 × 6 cycles (cycle = 21 days)	Available		Oct 2010	Fudan University (Shanghai, China)	NCT01216124
A prospective, randomized, open-label, multicentric, phase III clinical trial compared with PC and CEF100 followed by Docetaxel as adjuvant chemotherapy. Regimen for Chinese primary Triple Negative breast cancer patients.	Paclitaxel 100 mg/m2 & Cisplatin AUC = 2 D1, 8, 15 × 6 cycles (cycle = 28 days)	Available		Oct 2010	Fudan University (Shanghai, China)	NCT01216111
Phase IIb trial of Paclitaxel plus Carboplatin versus Paclitaxel plus Epirubicin as neoadjuvant treatment in locally advanced Triple Negative breast cancer.	Arm A: Paclitaxel 175 mg/m2 D3 & Epirubicin 75 mg/m2 D 1, 2 × 2–6 cycles (cycle = 21 days) Arm B: Paclitaxel 175 g/m2 D1 & Carboplatin AUC = 5 D2 × 2–6 cycles (cycle = 21 days)	Recruiting	80	Oct 2010	Chinese Academy of Medical Sciences	NCT01276769
Phase II trial of neoadjuvant metronomic	DOXORUBICIN 24 mg/m2 IV plus	Recruiting	28	July	Leo W. Jenkins	NCT00542191

chemotherapy in Triple Negative breast cancer.	CYCLOPHOSPHAMID E 60mg/m2 PO weekly x 12 successive weeks followed by PACLITAXEL 80mg/m2 IV over 1 hour plus CARBOPLATIN AUC 2 IV weekly x 12 successive weeks			2007	Cancer Center	
A Multi-Center, randomized study of Docetaxel, Anthracycline and Cyclophosphamide (TAC) versus Docetaxel and Cyclophosphamide (TC) in neoadjuvant treatment of Triple Negative or Her2 positive breast cancer.	Arm A: Docetaxel 75mg/m2 & Doxorubicin 50mg/m2 OR Epirubicin 60 mg/m2 & Cyclophosphamide 500 mg/m2 D1 × 6 cycles (cycle = 21 days) Arm B: Docetaxel 75mg/m2 & Cyclophosphamide 500 mg/m2 D1 × 6 cycles (cycle = 21 days)	Recruiting	600	July 2009	Shanghai Jiao Tong University School of Medicine	NCT00912444
Phase III study of adjuvant Capecitabine metronomic chemotherapy in Triple Negative operable breast cancer.	Arm A: Standard adjuvant chemotherapy followed by capecitabine 650mg/m2 BID × 1 yr Arm B: standard adjuvant chemotherapy	Recruiting	684	Apr 2010	Sun Yat-sen University	NCT01112826
Phase III study of Doxorubicin/Cyclophosphamide (AC) followed by Ixabepilone vs. AC followed by Paclitaxel in patients with Triple-Negative early-stage breast cancer.	Arm A: Doxorubicin 60 mg/m2 & cyclophosphamide 600 mg/m2 D1 × 4 cycles (cycle = 21 days) → Ixabepilone at 40mg/m2 D1 × 4 cycles (cycle = 21 days) Arm B: Doxorubicin 60 mg/m2 & Cyclophosphamide 600 mg/m2 D1 × 4 cycles (cycle = 21 days) →Paclitaxel at 80 mg/m2 D1 weekly ×12 weeks	Active/Not recruiting	1800	Jan 2009	Sarah Cannon Research Institute	NCT00789581
Randomized, open label, multicentric phase III evaluating the benefit of a sequential regimen associating FEC 100 and Ixabepilone in adjuvant treatment of non metastatic, poor prognosis breast cancer defined as Triple-Negative tumors [HER2-negative ER- negative PR-Negative]or [HER2 negative and PR negative] tumors in node positive or node negative patients.	Arm A: Epirubicin & 5-Fluorouracil & Cyclophosphamide D1 × 3 cycles (cycle = 21 days) → Docetaxel D1 × 3 cycles (cycles = 21 days) Arm B: Epirubicin & 5-Fluorouracil & Cyclophosphamide D1 × 3 cycles (cycle = 21 days) → Ixabepilone D1 × 3 cycles (cycles = 21 days)	Active/Not recruiting	2500	Sep 2007	Federation Nationale des Centres de Lutte Contre le Cancer	NCT00630032
Docetaxel plus Carboplatin versus Epirubicin plus Cyclophosphamide followed by Docetaxel as adjuvant treatment in Triple Negative breast cancer.	Arm I: epirubicin(90mg/m2 d1) plus cyclophosphamide(600mg/m2 d1),21 days a cycle, for 4 cycles followed by docetaxel 75mg/m2 d1,21 days a cycle, for 4 cycles Arm II: Docetaxel(75mg/m2,d1)plus carboplatin(AUC=6d1),21days a cycle,for 6 cycles	Recruiting	500	Jun 2010	Chinese Academy of Medical Sciences	NCT01150513

A phase III, multicenter, open-label, randomized study of Gemcitabine plus Cisplatin (GP) versus Gemcitabine plus Paclitaxel (GT) as first-line treatment in patients with advanced Triple Negative breast cancer.	Arm I: Gemcitabine 1250 mg/m2, IV drip 30 minutes, D1, D8 Cisplatin 75 mg/m2, IV drip 120 minutes, D1 Arm II: Gemcitabine 1250 mg/m2, IV drip 30 minutes, D1, D8 Paclitaxel 175 mg/m2, IV, 3h,D1	Recruiting	232	Jan 2011	Fudan University	NCT01287624
A phase II neo-adjuvant study of Cisplatin, Paclitaxel with or without RAD001 in patients With Triple Negative locally advanced breast Cancer.	Arm I: Patients receive cisplatin IV over 1 hour and oral everolimus once weekly in weeks 1-12 and paclitaxel IV over 1 hour once weekly in weeks 4-12 in the absence of disease progression or unacceptable toxicity. Arm II: Patients receive cisplatin IV over 1 hour and oral placebo once weekly in weeks 1-12 and paclitaxel IV over 1 hour once weekly in weeks 4-12 in the absence of disease progression or unacceptable toxicity.	Recruiting	96	Jun 2009	Vanderbilt-Ingram Cancer Center	NCT00930930
Open label randomized clinical trial of standard neoadjuvant chemotherapy (Paclitaxel Followed by FEC) versus the combination of Paclitaxel and RAD001 followed by FEC in women with Triple receptor-negative breast cancer (CRAD001C24101).	Arm A: Drug: Paclitaxel 80mg/m2 D1 weekly & RAD001 30 mg D1, 8,15 × 12 cycles (cycle = 21 days) →5-Fluorouracil 500 mg/m2 & Epirubicin100 mg/m2 & cyclophosphamide 500 mg/m2 D1 × 4 cycles (cycle = 21 days) Arm B: Paclitaxel 80mg/m2 D1 weekly × 12 cycles (cycle =21 days) → 5-Fluorouracil 500 mg/m2 & epirubicin100 mg/m2 & yclophosphamide 500mg/m2 D1 × 4 cycles (cycle = 21 days)	Active/Not Recruiting	50	July 2007	M.D. Anderson Cancer Center	NCT00499603
A phase II neo-adjuvant study of Cisplatin, Paclitaxel with or without RAD001 in patients with Triple-Negative locally advanced breast cancer.	Arm A: Cisplatin & Everolimus D1 weekly × 12 weeks & Paclitaxel D1 weekly in weeks 4–12 Arm B: Cisplatin & Placebo D1 weekly × 12 weeks & Paclitaxel D1 weekly in weeks 4–12	Recruiting	96	Jun 2009	Vanderbilt-Ingram Cancer Center	NCT00930930
Poly(ADP-ribose) polymerase (PARP) inhibitors						
A phase 2 study of standard chemotherapy plus BSI-201 (a PARP Inhibitor) in the neoadjuvant treatment of Triple Negative breast cancer.	Gemcitabine & Carboplatin & BSI-201 q3wks	Recruiting	36	Dec 2008	Sanofi-Aventis	NCT00813956
Randomized, open-label, phase 2 study of the efficacy and safety of weekly Paclitaxel single-agent and two different regimens of the PARP-1 inhibitor SAR240550 (BSI-201) in	Arm A: Iniparib 5.6mg/kg D1, 4 &Paclitaxel 80mg/m2 D1 weekly ×12 weeks Arm B: Iniparib 11.2 mg/kg D1 &Paclitaxel 80mg/m2 D1 weekly × 12 weeks	Recruiting	135	Sep 2010	Sanofi-Aventis	NCT01204125

combination with weekly Paclitaxel, as neoadjuvant therapy in Patients with stage II-IIIA Triple Negative breast cancer (TNBC).	Arm C: Paclitaxel 80mg/2 D1 weekly × 12 weeks					
PARP inhibition after preoperative chemotherapy in patients with Triple Negative breast cancer or ER/PR +, HER2 negative with known BRCA1/2 Mutations: Hoosier Oncology Group BRE09-146.	Arm A: PF-01367338 D1-3 C1:30mg C2-4: 24 mg & Cisplatin 75 mg/m2 D1 × 4 cycles (cycle = 21 days) Arm B: Cisplatin 75 mg/m2 D1 × 4 cycles (cycle = 21 days)	Recruiting	135	Feb 2010	Hoosier Oncology Group	NCT01074970
Phase I study of ABT-888 in combination with Cisplatin and Vinorelbine for patients with advanced Triple negative breast cancer and/or BRCA-mutation associated breast cancer.	Veliparib PO BID on days 1-14 (days 0-13 of course 1 only) and Cisplatin IV over 1 hour on day 1 & Vinorelbine ditartrate IV over 5-10 minutes on days 1 and 8. Treatment repeats every 21 days for 6-10 courses in the absence of disease progression or unacceptable toxicity. Treatment with veliparib alone may continue in the absence of disease progression or unacceptable toxicity.	Recruiting	36	July 2010	Fred Hutchinson Cancer Research Center	NCT01104259
A phase I, open-label study to assess the safety and tolerability of KU-0059436 in combination with Carboplatin, KU-0059436 in combination with a Paclitaxel/Carboplatin T/C doublet and KU-0059436 in combination with Paclitaxel in the treatment of patients with advanced solid tumors.	Arm I: Carboplatin (I.V.)+ KU-0059436(oral) Arm II: Paclitaxel (I.V.) + KU-0059436 (oral) Arm III: Paclitaxel, Carboplatin (I.V.)+ KU-0059436 (oral)	Recruiting	190	Jun 2007	AstraZeneca	NCT00516724
Antiangiogenic agents						
Randomized phase II 2 x 2 factorial trial of the addition of Carboplatin +/- Bevacizumab to neoadjuvant weekly Paclitaxel followed by dose- dense AC in hormone receptor-poor/HER2-negative resectable breast cancer.	Arm A: Paclitaxel D1 weekly × 12 weekly → dd AC D1 × 4 cycles Arm B: Arm A+bevacizumab q2wks (weeks 1, 3, 5, 7, 9, 10, 11, 13, 15, 17) Arm C: Arm A + Carboplatin q3wks (wks 1, 4, 7, 10 Arm D:Arm A+bevacizumab as in Arm B + Carboplatin as in Arm C.	Recruiting	362	May 2009	Cancer and Leukemia Group B	NCT00861705
A Phase II trial of neoadjuvant Bevacizumab, Docetaxel and Carboplatin for Triple Negative breast cancer (Neat Trial).	Bevacizumab & Docetaxel & Carboplatin D1 × 5 cycles (cycle = 21 days → Docetaxel & Carboplatin C6D1	Recruiting	45	Sep 2010	Severance Hospital	NCT01208480
Neoadjuvant weekly Nab-paclitaxel (Abraxane®) plus Carboplatin followed by Doxorubicin plus Cyclophosphamide with	Nab-paclitaxel D1, 8, 15 & Carboplatin D1 & Bevacizumab D1,15 × 4 cycles (cycle = 28 days) → ddAC × 4 cycles (cycle = 14 days) &	Recruiting	60	Oct 2008	University of TennesseeCancer Institute	NCT00777673

bevacizumab added concurrently to chemotherapy for palpable and operable Triple Negative invasive breast cancer.	Bevacizumab D1 × 2 cycles (cycle = 14 days) >4 weeks postoperative: Bevacizumab D1, 15 × 8 cycles (cycle = 28 days)					
An open label 2-arm study to evaluate the impact of adjuvant Bevacizumab on invasive disease free survival in Triple Negative breast cancer.	Arm A: Standard adjuvant chemotherapy (anthracycline ± taxane or taxane only) & 1 yr of Bevacizumab 5mg/kg/week dosing equivalent Arm B: Standard adjuvant chemotherapy (anthracycline ± taxane or taxane only)	Active,not recruiting	2581	Dec 2007	Hoffmann-La Roche	NCT00528567
Phase I/II trial of neoadjuvant Sunitinib administered with weekly Paclitaxel/Carboplatin in patients with locally advanced Triple Negative breast cancer.	Paclitaxel D1, 8, 15 & Carboplatin D1 & Sunitinib D1-21 × 6 cycles (cycle = 28 days)	Recruiting	53	Jun 2009	Sarah Cannon Research Institute	NCT00887575
WCI1590-08: Phase II neoadjuvant trial of Sorafenib in combination with Cisplatin followed by dose dense Paclitaxel for ER-, PR-, Her2-(Triple Negative) early-stage breast cancer.	Sorafenib 400 mg BID throughout the study: single agent for weeks 1–4, then in combination with cisplatin followed by dose dense paclitaxel	Recruiting	50	Jun 2010	Emory University	NCT01194869
A phase II trial of RAD001 in Triple negative metastatic breast cancer.	RAD001-10 mg O.D. orally	Unknown	6	Jun 2009	Penn State University	NCT00827567
Randomized phase II 2 x 2 factorial trial of the addition of Carboplatin +/- Bevacizumab to neoadjuvant weekly Paclitaxel followed by dose- dense AC in hormone receptor-Poor/HER2-negative resectable breast cancer.	Arm I: Patients receive paclitaxel IV over 60 minutes once weekly in weeks 1-12. Patients then receive dose-dense doxorubicin hydrochloride IV over 5-10 minutes and cyclophosphamide IV over 5-30 minutes (ddAC) once in weeks 13, 15, 17, and 19. Arm II: Patients receive paclitaxel and ddAC as in arm I. Patients also receive bevacizumab IV over 30-90 minutes in weeks 1, 3, 5, 7, 9, 11, 13, 15, and 17. Arm III: Patients receive paclitaxel and ddAC as in arm I. Patients also receive carboplatin IV over 30 minutes once in weeks 1, 4, 7, and 10. Arm IV: Patients receive paclitaxel and ddAC as in arm I, bevacizumab as in arm II, and carboplatin as in arm III.	Recruiting	362	May 2009	Cancer and Leukemia Group B	NCT00861705
EGFR inhibitors						

A Phase II trial of Panitumumab, Gemcitabine, and Carboplatin in Triple-Negative metastatic breast cancer.	Panitumumab: 6 mg/kg IV on Day 1 of each 2-week treatment cycle for 3 cycles (6 weeks) Carboplatin: AUC=2.5 IV, Day 1 of each 2-week treatment cycle for 3 cycles (6 weeks) Gemcitabine : 1500 mg/m2 IV, Day 1 of each 2-week treatment cycle for 3 cycles (6 weeks)	Recruiting	98	Feb 2010	Sarah Canon Research Institute	NCT00894504
Randomized open-label neo-adjuvant phase II study comparing Ixabepilone (I) Vs. Ixabepilone plus Cetuximab (IC) in Triple Negative breast cancer patients.	Arm A: Cetuximab 400 mg/m2 D1 then weekly 250mg/m2 & Ixabepilone 40mg/m2 D1 1 × 4 cycles (cycle = 21 days) Arm B: Ixabepilone 40mg/m2 D1 1 × 4 cycles (cycle = 21 days)	Recruiting	116	Oct 2008	The Methodist Hospital System	NCT01097642
Phase II pilot study evaluating the neoadjuvant combination "Taxotere (Docetaxel) and Erbitux (Cetuximab) in operable and "Triple Negative" breast cancer patients. TENEO Study.	Cetuximab : dosage : 5mg/ml one administration per week: 400 mg/m2 then 250 mg/m2 during 18 weeks Docetaxel : 100mg/m2 every 21 days 6 cycles of 21 days	Recruiting	35	Jan 2008	Centre Jean Perrin	NCT00600249
Phase II trial of neoadjuvant Erlotinib Plus chemotherapy for treatment of ER negative, PgR negative and HER-2 negative primary breast cancer.	Adjuvant chemotherapy given at the discretion of treating physician followed by 1 yr of maintenance erlotinib 150 mg daily	Active/Not Recruiting	30	July 2007	University of Kansas	NCT00491816
A phase II neo-adjuvant study of Cisplatin, Paclitaxel with or without RAD001 in patients with Triple-Negative locally advanced breast cancer.	Arm A: Cisplatin & Everolimus D1weekly × 12 weeks & Paclitaxel D1 weekly in weeks 4–12 Arm B: Cisplatin & Placebo D1 weekly × 12 weeks & Paclitaxel D1 weekly in weeks 4–12	Recruiting	96	Jun 2009	Vanderbilt-Ingram Cancer Center	NCT00930930
Open label randomized clinical trial of standard neoadjuvant chemotherapy (Paclitaxel followed by FEC) versus the combination of Paclitaxel and RAD001 followed by FEC in women with Triple receptor-negative breast cancer (CRAD001C24101).	Arm A: Drug: Paclitaxel 80mg/m2 D1 weekly & RAD001 30 mg D1, 8, 15 × 12 cycles (cycle = 21 days) → 5-Fluorouracil 500 mg/m2 & Epirubicin100 mg/m2 & Cyclophosphamide 500 mg/m2 D1 × 4 cycles (cycle = 21 days) Arm B: Paclitaxel 80mg/m2 D1 weekly × 12 cycles (cycle = 21 days) → 5-Fluorouracil 500	Active/Not Recruiting	50	July 2007	M.D. Anderson Cancer Center	NCT00499603

	mg/m2 & Epirubicin100 mg/m2 & Cyclophosphamide 500mg/m2 D1 × 4 cycles (cycle = 21 days)					
Androgen receptor (AR) based therapy						
Bicalutamide for the treatment of androgen receptor positive (AR(+)) metastatic breast cancer patients: A phase II feasibility study.	Oral bicalutamide O.D. for 4 weeks. Treatment repeats every 4 weeks for 6 months in absence of disease progression or unacceptable toxicity.	Recruiting	28	March 2007	Memorial Sloan-Kettering Cancer Center	NCT00468715
Src kinase inhibitor						
A phase I/II trial of Dasatinib in combination with Trastuzumab and Paclitaxel in the first line treatment of Her2-positive metastatic breast cancer patients.	treated with 4-week cycles of trastuzumab 2 mg/kg IV weekly (following a loading dose of 4 mg/kg in cycle 1) and paclitaxel 80 mg/m2 weekly x 3 weeks followed by a rest period of 7 days. Dasatinib will be administered orally in two dose levels 100 and 140 mg QD (a -1 dose level is included just in case dose de-escalation is needed). Treatment will be repeated on Day 1 of a 28-day cycle until radiographic or symptomatic progression or unacceptable toxicity occurs. Only in the phase I, the first cycle will last 38 days.	Recruiting	60	July 2011	Spanish Breast Cancer Research Group	NCT01306942
DNA binding agent						
Phase II, multicenter, open-label, clinical trial of Trabectidin (Yondelis) in metastatic breast cancer patients With Triple Negative profile (ER-, PR-, HER2-), HER2 overexpressing tumors and *BRCA*1 or *BRCA*2 mutation carriers.	Trabectedin, 1.3mg/m2 3-hr iv infusion on Day 1 of every 21-day treatment cycle. Dexamethasone, 4mg, PO 24h and 12h before trabectedin followed by dexamethasone 20 mg, iv 30 minutes before trabectedin, followed by dexamethasone, 4mg, PO 24h,36h,48h,60h,and 72h after the start of trabectedin	Not yet recruting		Jun 2007	Johnson & Johnson Pharmaceutical Research Development, L.L.C.	NCT00580112
Other target						
A phase II, randomized, multicenter study of CDX-011 in patients with advanced GPNMB-expressing breast cancer.	CDX-011 (1.88 mg/kg) administered as an intravenous infusion on Day 1 of each 21 day cycle.	Recruiting	120	July 2010	Celldex Therapeutics	NCT01156753

Study of low dose cyclophosphamide, doxorubicin, fluorouracil (CAF) regimen from CALGB8541 compared with dose dense regimen of doxorubicin, cyclophaphamide followed by paclitaxel in CALGB9741[71], exhibits reduction in risk of recurrence for ER-negative and ER-positive tumors was 55% and 26% respectively. Improvement in risk of recurrence with 5 years tamoxifen treatment for ER-negative and ER-positive tumors was 22.8% and 7% respectively. A retrospective study of 236 high-risk patients in WSG AM-01 study demonstrated that dose intensive regimens improve outcomes in TNBC patient who treated for four cycles of epirubicin and cyclophasphamide followed by three cycles of CMF, which compared to high dose with peripheral stem cell support[72]. TNBC patients who received high dose of chemotherapy have an improved OS of 76% compared to 61% in the dose dense arm, supporting the benefit of chemotherapy.

Neoadjuvant (preoperative) chemotherapy for TNBC:

As compared to HR-positive BC, TNBC has significantly increased pCR rates and improve outcome when treated with neoadjuvant chemotherapy. An 1118 TNBC and non-TNBC patients treated with neoadjuvant therapy from 1985 to 2004 studied at the MD Anderson Cancer Centre. The pCR rate in 23% of TNBC patients was double compared to non-TNBC subgroup (22% versus 11%)[46]. The overall 3-year freedom from progression in TNBC and non-TNBC groups was 63% and 76% respectively. In addition, the 3 year OS was 74% in TNBC and 89% in non-TNBC confirmed by poor progression. TNBC patients show excellent long-term outcomes who achieved a pCR. A neoadjuvant chemotherapy of 1731 patients in retrospective study from 1988 to 2005 found 13% an overall pCR rate[73]. HR-positive (67%) patients achieved a pCR rate of 8% while HR- negative patients achieved 24%. The prospective study of 190 patients who received neoadjuvant anthracycline and taxane based therapy in I-SPY trial indicate 33% TNBC patients achieve pCR rate compared to HER2 patients, while HR-positive had only 10% response rate[74].

A retrospective study between 1985 to 2003 in 435 subjects, who received neoadjuvant therapy for BC depicts ER-negative tumors were more likely to achieve pCR than ER-positive (26.6% vs 8.1%)[75]. A 5 years survival was higher in the ER-negative subgroup who achieved a pCR compared to those who did not (90% vs. 52%). An overall 15.7% had a pCR in 399 patients treated preoperatively between 1994 and 2002[76]. Among them 129 HR-negative patients has 33% pCR rate compared to 7.6% in the HR-positive group. This study reported dissimilarly to other studies as patients achieved a pCR with slightly worse prognosis than those who did not achieve pCR. It reflects the worse overall prognosis of the HR-negative group. Therefore, pCR can describe as a complete or nearly complete response in breast only, excluding the nodes.

A neoadjuvant chemotherapy study in BLBC treated with 12 weeks of weekly paclitaxel followed by 4 cycles of fluorouracil, doxorubicin, cyclophosphamide (FAC) provide a 45% pCR rate[66]. Among basal-like tumors, 95% are ER-negative and 96% are HER2-negative. The pCR rate of molecular subgroups as, Luminal A/B (n = 30), normal breast like (n = 10), HER2+ (n = 20) were 7%, 0% and 45% respectively, indicating BLBC is highly sensitive to paclitaxel and doxorubicin chemotherapy and correlates with similar results in histological markers for TNBC. Study indicates TNBC has superior response to neoadjuvant chemotherapy resulting in momentous improvements in pCR compared to HR-positive tumors. It signifies that TNBC has good response to neoadjuvant chemotherapy with improvement in pCR rate. It may vary with different chemotherapeutic agents. There is necessity of new specific target therapy over today's conventional chemotherapy in poor outcome TNBC.

NEWER TREATMENT APPROACHES:

TNBC may normally display chemosensitivity in clinics due to its proliferative biology. Even though recent advances in BC treatment, relapse rates in

TNBC remains high, with poor OS. Such outcomes underscore the need for better treatment options. Several newer treatment strategies are under clinical investigation. Targeted therapies intervene with specific biomolecules e.g. overexpressed protein, selective cancerous cells that are less harmful on normal cells. Cytotoxic agents have greater short-term effect in TNBC than any other BC subgroup. Prognosis of TNBC is worse eventhough better response to chemotherapy due to relapse in patients.

Platinum agents:

Platinum agent causes interstrand DNA break in *BRCA*1 mutated cancer cell, which produce good response in TNBC than non-TNBC disease with neoadjuvant and adjuvant therapy[77,78]. Cisplatin and carboplatin is a platinum containing agent having good cytotoxic activity[58]. Neoadjuvant treatment with platinum containing agent in TNBC shows 88% clinical response with worse five-year survival and 55% in other subtypes[79]. Currently, a molecular pathway for cisplatin to induce cell death in TNBC patients has found out. Inhibition of this pathway increases 10 to 100 folds IC50 value in BC cell[80].

A group of 28 TNBC patients with stage II or III BC treated with cisplatin therapy studied in neoadjuvant setting[81], showing 6 (22%) patients with *BRCA*1 germline mutation achieve a pCR and 18 (64%) received complete or partial response. About 14 (50%) subjects exhibit good pathological responses with younger age (P = 0.001), low mRNA expression (P = 0.03), *BRCA*1 promoter methylation (P = 0.04), p53 nonsense or frameshift mutations (P = 0.01), and gene expression signature of E2F3 activation (P = 0.03) are factors associated with it. It revealed cisplatin sensitive TNBC subsets decreases *BRCA*1 expression. However, till to date there is no randomized, controlled study to facilitate the benefit of platinum versus other agents.

Cisplatin in neoadjuvant treatment achieved 40% pCR rate when coupled with epirubicin and 5-FU[82]. A high rate of pCR (65%) seen in 74 patients when treated in combination of cisplatin, epirubicin, paclitaxel with G-CSF support[83]. The role of platinum agent in early stage treatment of TNBC studied in CALGB 40603 and Spanish Breast Cancer Research Group, evaluating addition of carboplatin and bevacizumab to preoperative weekly paclitaxel followed by dose dense doxorubicin+/-cyclophosphamide in HR poor HER2-breast cancer. The Spanish Breast Cancer Research Group evaluating neoadjuvant epirubicin, cyclophosphamide for 4 cycles followed by docetaxel+/-carboplatin in TNBC[84]. These studies provide importance of platinum in prediction of DFS, OS and an opportunity to assess prognostic biomarkers of platinum sensitivity.

A retrospective study of 541 subjects in neoadjuvant, adjuvant and metastatic settings observed platinum based chemotherapy in TNBC and non-TNBC patient outcomes[78]. There were superior complete response rate obtained in platinum based neoadjuvant therapy in TNBC versus non-TNBC patients (88% vs 51%; P= 0.005), but insignificantly in TNBC with regard to 5 years OS (65% vs 80%). There is decrease in 5 years PFS (57% vs 72%) and OS rate (64% vs 88%), who took adjuvant and neoadjuvant platinum based therapy, which compared to non-TNBC diseases. Advanced BC patients with TNBC group treated with the platinum-based regimens showed non-significant trends toward improved overall response rate (ORR; complete response plus partial response; 41% vs 31%) and 5-year OS (11 months vs 7 months), as well as a significantly longer median PFS (6 months vs 4 months; P = 0.05).

Metastatic TNBC patients with platinum agents have less satisfactory prognosis outcomes. One retrospective study of 106 patients who took taxane/platinum chemotherapy in metastatic BC as first or second line treatment gave unchanged pattern of ORR between those with TNBC (37.5%), HER2 positive (35.7%) or HR positive (41.4%)[85,86]. Above all results were justify exploring therapeutic combination of platinum in TNBC patients and need of discovering biomarkers predictive response.

***PARP inhibitors**:*

Poly (adenosine diphosphate-ribose) polymerase (PARP), a nuclear protein involved in molecular pathways leading to cell recovery from DNA damage. Inhibition of PARP1 leads to accumulation of double-strand DNA break in cell lacking *BRCA*1 and *BRCA*2, which repaired via DNA-break repair and homologous recombination pathway[87,88]. Therefore, *BRCA*1 or *BRCA*2 deficient cells are sensitive to PARP1 inhibitior, leads to cell death. *In vitro*, *BRCA*1 or *BRCA*2 deficient cells exhibits 1000 times more sensitivity to PARP inhibitors than normal cells[88,89,90]. PARP inhibitor shows significant tumor regression, longer DFS and OS in mice[91]. Phase I and phase II clinical trials of PARP inhibitors with *BRCA*1 mutation provide significant anti-tumor activity with less side effects. Expression of PARP inhibitor commonly occurs in TNBC than other BC subgroup[90]. Latest study shows that TNBC have elevated frequency of BRCA1 methylation, and the inhibition of PARP in BRCA1 methylated and *BRCA*1 mutated BC cell line is similar one[93].

Olaparib (AZD2281), a PARP inhibitor in phase I trial illustrates selective activity against *BRCA*1/2-mutated breast cancer, whereas others are unaffected[94]. It evaluated in phase I study of BC patients (n = 60), among them 9 had an objective responder with *BRCA* gene abnormalities. Three women with BC had *BRCA*2 mutation. A complete response remains for more than 60 weeks in one of the *BRCA* carriers and another one had stable disease for 7 months. The higher dose of olaparib in phase II trial for efficacy, safety and tolabarity in *BRCA*1/2 mutation are associated with an enhanced objective response rate. The patients with *BRCA*1/2 mutation carrier and with without *BRCA* mutation have similar low toxicity[95]. Another study of olaparib evaluated in phase II trial on 54 patients with *BRCA* mutation and BC. Among them, 27 received 400 mg twice daily doses, of which 11 (41%) have a response with a median PFS of 5.7 months. A second cohort of 27 women received 100 mg of olaparib twice per day, of which 6 patients (22%) experience response with a median PFS of 3.8 months. A latest phase I trial report at American Society of Clinical Oncology (ASCO) presented daily dose of 200 mg for olaparib with weekly paclitaxel combination leads to myelosupression[96].

Iniparib (BSI-201) evaluated in randomized phase II trial in about 120 patients with combination of gemcitabine and carboplatin exhibit notably increase in overall survival, when compared to standard regimen alone and with heavily pretreated patients. Iniparib may improve response rate (16% vs 48%; *P* = 0.002), PFS (3.3 vs 6.9 months, *P* = 0.0001) and OS (12.2 vs 7.7 months; *P* = 0.005; HR = 0.5; CI, 0.30-0.082). A confirmatory data of phase III trial (NCT00938652) for the same above regimen has expected to be in coming year[92,97,98]. A Spanish phase II neoadjuvant trial studied paclitaxel as alone or in combination with iniparib (NCT01204125).

Veliparib (ABT-888) is another PARP inhibitor, evaluated in clinical trials. When used with temozolamide, dose may need to reduce from 40 mg to 30 mg twice daily due to thrombocytopenia. Activity is restricted to *BRCA* deficient women. Stable disease lasting for longer than 4 months was seen in 4 patients, of which 2 have *BRCA*2 mutation. Median PFS was 1.9 months in all patients and 5.5 months in those with *BRCA* mutations[99]. One question may arise in such condition that if patient treated intravenously with iniparib with no toxicity, but toxicity may arise in oral PARP inhibitors. A clinical trial (NCT01042379) assessed in neoadjuvant TNBC subject with multiarm study. One arm may study regimen with combination of paclitaxel, carboplatin and veliparib. One phase II randomized clinical trial (NCT01149083) associated *BRCA* BC evaluated for combination of veliparib with carboplatin or alone. Analysis of PARP expression via IHC in phase III GeparTrio trial with taxane-anthracyclin neoadjuvant therapy showed high expression of PARP was associated with higher incidence of pCR rate[100].

PTEN (phosphate and tensin homolog) is useful in cell cycle progression, proliferation and DNA repair. Deficiency of PTEN leads to impaired homologous

recombination and might elevated toxicity to PARP inhibitors[101]. Deregulation of DNA repair mechanism and genomic instability is not only present in TNBC or basal-like but also in luminal B and HER2 amplified tumors[102]. Proper selection of patients among population of TNBC subtypes which respond to PARP inhibitor are the major problems. Still there are some doubts regarding use of PARP inhibitors. Therefore, newly translational clinical trial should be planned and projected.

***DNA binding agent**:*

A new molecule trabectidin (Yondelis ET-743), which are under evaluation in phase II trial prospectively designed to assess in TNBC. It binds to minor groove of DNA and disrupts cellular function with inducing apoptosis. (NCT00580112)

Microtubule inhibition:

In the study of CALGB9344/INT1048, randomized 3121 patients on adjuvant therapy with taxane exhibit, TNBC derives substantial benefit from addition of different doses of paclitaxel in adjuvant setting[64,103]. A randomized adjuvant therapy of doxorubicin and cyclophosphamide followed by docetaxel/paclitaxel given weekly or once every three weeks in trial of 4950 patients shows an overall improvement in 5 years DFS and OS, which are 27% and 32% respectively[104]. Eventhough there is nonspecific benefit of taxane for TNBC in metastatic settings, sensitivity influenced by *BRCA* function contributes to antimicrotubule sensitivity[105]. In the recent study Caveolin-1 marker frequently expressed in TNBC, which tested for cellular uptake of nonoparticle-albumin bound paclitaxel via caveolin-1 dependent receptor mediated transcytosis. Therefore, paclitaxel may further investigate for TNBC treatment[106,107].

Ixabepilone (Ixempra), first epithilone that inhibit microtubule, causes cell cycle arrest and apoptosis[108]. Two phase III clinical trials studied in combination of Ixabepilone with capecitabine versus ixabepilone alone. Resistance mechanism lowered when ixabepilone combined with capecitabine. It has observed that patients with TNBC had improved overall response for their combination of 31% vs 15% and PFS 4.2 vs 1.7 months (HR, 0.63; 95% CI, 0.52-0.77)[109]. Expression of β III tubulin correlated with resistance to taxane. Patients with basal-like tumor have higher expression of β III tubulin, which gave predictive response to therapy in overall population[110]. Potential markers needed for further study. Eribulin (Halaven, E7389), a nontaxane microtubule dynamics inhibitor approved for metastatic BC treatment by U.S. Food and Drug Administration. A number of women with refractory metastatic BC treated with eribulin in phase III trial demonstrated median OS 13.1 vs 10.7, HR 0.81, CI 0.66-0.99[111].

Antiangiogenesis (multikinase) therapy:

Angiogenesis is requisite for development, invasion and metastasis of BC. Vascular endothelial growth factor (VEGF) is key factor for angiogenesis, which is highly expressed within the tumor of TNBC than other subtypes[112].

Bevacizumab (Avastin), a humanized monoclonal antibody is approved by U.S. Food and Drug Administration as a first line treatment in metastatic BC. Combination therapy of bevacizumab with paclitaxel in phase III study (E2100) gave significant response rate than paclitaxel monotherapy (36.9% vs 21.2%) with time to progression (8.8 vs 4.6 months). This study exhibit addition of bevacizumab benefited in HER2-negative patients as well TN subgroups[113]. There is an increase in objective response rate in phase III AVADO study which combines bevacizumab with docetaxel in metastatic cancer[114] and in RIBBON-1 trial bevacizumab along with combination of different drugs as paclitaxel, docetaxel, anthracycline or capecitabine[115]. Meta-analysis depicted statistically significant improvement in one-year survival for patient assigned to chemotherapy, also bevacizumab versus chemotherapy and placebo. It evaluated in phase II trial CALGB40803 (NCT008617705) with neoadjuvant study undergoing randomized paclitaxel with or without carboplatin and combination of this with or without bevacizumab. Another study, BEATRICE (NCT00528567) in phase II

adjuvant study evaluated with several chemotherapy regimens along with different doses of bevacizumab.

Sunitinib (Sutent), a new antiangiogenic molecule exhibiting antitumor activity in several preclinical BC studies, alone or along with other drugs. It is tyrosine kinase inhibitor, which target vascular endothelial growth factor 1, 2 and 3, platelet-derived growth factor alpha and beta, c-kit and colony-stimulating factor 1[116,117,118]. Patient pretreated with HER2-negative advanced BC evaluated in phase III randomized trial with sunitinib versus capecitabine[119]. In this study, primary end-point and DFS not desired but median DFS was good with capecitabine (4.2 months vs 2.8 months). Therefore, independent data committee recommended, sunitinib cannot be used as monotherapy in advanced metastatic breast cancer.

Sorafenib (Nexavar), another antiangiogenic and antiproliferative molecule depicts potent multikinase inhibitor. Two phase IIb trials represented at San Antonio Breast Cancer Symposium 2009 evaluating efficacy and safety of sorafenib with chemotherapy or placebo[120,121]. Combination of sorafenib with capecitabine or placebo in patients with metastatic BC in SOLIT-0701 trial exhibit extended median PFS with statistically significant results (HR, 0.57; *P* = 0.0006). The occurrence of grade III hand-foot was 45% vs 13% in placebo group[120]. Another study trial in patients with locally recurrent or metastatic BC in combination of sorafenib with paclitaxel exhibited HR for PFS was 0.78 (*P* = 0.08) and occurance of grade III hand-foot was 30% vs 3% in placbo group. In grade III hand-foot syndrome, occurrence of toxicity was unacceptable, so it recommended reducing the dose of sorafenib[121].

***mTOR inhibitors**:*

Mammalian target of rapamycin protein that downstream phosphatidyl inositol 3-phosphatase and PTEN/AKT pathways leads to loss of PTEN tumor suppressor gene in TNBC[122]. Everolimus (Afinitor), an oral mTOR inhibitor evaluated in two-phase II randomized regimen in 59 metastatic BC in which 20 are HER2-negative. A study of 10 mg/day or 70 mg/week regimen is compared with 12% response in daily versus 0% weekly[123]. Temsirolimus (Torisel), an intravenous mTOR inhibitor is currently evaluated in phase II nonrandomized trial in metastatic TNBC patients (NCT00827567), and phase III randomized study evaluating everolimus in combination with anthracycline and taxane in neoadjuvant settings (NCT00930930).

***Src kinase inhibitor**:*

Src kinase is a non-receptor signaling pathway including PDGFR, EGFR, IGF-1R and HGFR which downregulate growth factor receptors. Dasatinib (Sprycel), an oral Src tyrosine kinase inhibitor, acts on proteins src and abl, which overexpressed in BC and associated with metastatic disease progression. It inhibits BLBC cell line in preclinical studies[124,125]. Phase II trial has 9% clinical benefit rate in triple-negative metastatic BC[126]. Studies are being evaluated for monotherapy or combination therapy regimen. KX01, a Src kinase inhibitor studied in phase I clinical trial with good preliminary results in petri dishes and animal tumor models. It has currently studied in phase II trial. Kinex using Mimetica and Opal (optimized photo-affinity labeling) platforms formulates KX01. A phase I trial of KX02 will expect to start in early 2012[127].

Heat shock protein 90 inhibitor:

Heat Shock Protein 90 (HSP90) is cellular chaperone protein, which facilitates maturation and stabilization of protein receptors RAF1, CDK4, AKT and other signal transducing proteins. The client protein HSP90 is downregulated by proteosome, as function of HSP90 inhibitor[128].

Geldanamycin and tanespimycin have evaluated activity in HER2-positive metastatic BC[129]. In preclinical studies, PU-H71 inhibitor demonstrated activity against TNBC[130]. αβ-crystallin, a small heat shock protein usually expressed in basal like breast tumor (45%), observed by microarray analysis[131]. Induction of neoplastic changes in mammary acini by αβ-crystallin that transform immortalized human mammary epithelial cells, and increases cell migration and invasion. It

helps in downregulating the MEK/ERK pathway, which is effective for BLBC. Effectiveness of MEK inhibitors are presently being evaluated in phase I trial.

***Histone deacetylase inhibitor**:*

Histone deacetylase **(**HDAC) inhibitor (Scriptaid), plays a role in growth inhibition and reexpression of estrogen–responsive gene by epigenetic mechanism[132,133]. A combination of tamoxifen with HDAC inhibitor vorinostat (suberoylaniline hydroxamic acid; SAHA) restored sensitivity in selecting patients with endocrine resistant disease[134], illustrating 4 major responses and 5 patients with SD for >12 months. Vorinostat (Zolina), currently evaluated in combination with capecitabine in the setting of advanced BC. Another molecule trichostactin A, butyrate derivative was studied for HDAC inhibitor. Another placebo-controlled study is evaluating in the neoadjuvant setting with combination of carboplatin and albumin-bound paclitaxel with or without vorinostat.

Androgen receptor (AR) based therapy:

A genome wide gene expression profiling study was carried out in 99 subjects. Among them 41 had TNBC and 9 with TNBC, cluster together with ER-positive group[135]. Characterization of TNBC subtype showed molecular similarity to ER-positive tumors, which expresses gene to target ER. Half of the tumors expressed androgen receptor. MDA-MB-453 cell line has a similar molecular phenotype with subtypes of TNBC. This cell line had proliferative effect with androgen stimulation in ER-independent but AR-dependent manner. Study demonstrates 10-35% of TNBC express androgen receptor[136,137,138]. A bicalutamide, an antiandrogen AR-positive evaluated in phase II trial for treatment of TNBC (NCT00468715).

Other targets:

Epidermal growth factor receptor (EGFR) are actively expressed in TNBC than other subtypes[14,20,140,141,142]. Inhibition of *EGFR* results in tumor growth arrest. *EGFR* inhibitor utilizes two agent to target molecule as monoclonal antibody (MAb) and small molecule, tyrosine kinase inhibitor (TKI). MAb target receptor internalization and target extracellular domain of receptor, blocking ligand to inhibit function and triggering immune reaction against *EGFR* cells. TKI's inhibit tyrosine kinase activity by targeting intracellular domain receptor and depicting it ineffective[143]. Around 85% of TNBC is of the basal-like subtype and 60% of basal-like tumors overexpress *EGFR*[4,12,144]. So, *EGFR* targeted tyrosine could potentially be benefited for patient with TNBC. However, overexpression of *EGFR* is a negative prognostic factor in TNBC, indicating less favorable response to chemotherapy and poorer survival; these observations provide a rationale for *EGFR*-targeted intervention[145,146].

Cetuximab (Erbitux) in phase II trial of 102 pretreated subjects with metastatic TNBC gave promising preliminary data[147]. Monotherapy of cetuximab has low activity. The significant improvement in ORR and an overall clinical benefit rate (partial response or stable disease ≥ 6 months) was 18% and 27% respectively, when cetuximab combined with carboplatin. Panitumumab (Vectibix), fully humanized anti-EGFR MAb used in treatment of metastatic TNBC in combination with gemcitabine (Gemzar) and carboplatin (NCT00894504). Erlotinib (Tarceva) and gefitinib (Iressa) in combination of docetaxel and carboplatin were used patients with metastatic TNBC. These EGFR inhibitors are under phase II investigation for treatment of TNBC.

Fibroblast growth factor receptor (*FGFR*) is a part of signaling pathway, which downregulated in several malignancies[148]. *FGFR1* gene overexpressed upto 5.5% in TNBC patients[149], whereas 5% *FGFR2* gene overexpressed in TNBC patients with postmenopausal BC[150]. Other agent TKI258, which target *FGFR* receptor, evaluated in phase II study of women with HER2-negative BC (NCT000958971). Mitogen activated protein kinase (MAPK), an important signaling pathway that regulates neoplastic cells. A number of inhibitor of this pathway are in clinical trials[151]. Inhibition of mitogen activated protein kinase (*MEK*) leads to activation of the phoshphatidyl 3-kinase (*PI3K*) pathway. It

downregulated in 30% BLBC, exhibited in preclinical studies[152,153]. The combination of *MEK* and *PI3K* inhibitors needed to evaluate further in TNBC population.

Low-density lipoprotein receptor-related protein 6 (LRP6), a newly identified biomarker, defined a new subtype of BC as well as offer a potential way to treat it. It stimulates cell growth regulation through Wnt signaling pathway[154]. Its expression increased more frequently in TNBC patients. Study showed Extracellular Mesoderm development protein (Mesd) or Mesd-based peptide inhibit Wnt signaling through LRP6, which had currently evaluated in preclinical studies. Microarray analysis of frizzled homolog 7 (FZD7), a Wnt pathway genes shown reduced cell proliferation, suppressed invasiveness and colony formation in MDA-MB-231 and BT-20 cells via FZD7shRNA knock down expression[155]. Thus, FZD7 may promise as a biomarker and potential therapeutic target for TNBC. Another research by scientist at Dana-Farber Cancer Research Institute succeeded in identifying a pool of 15 genes associated with TNBC. Genetic analysis found that these genes associated with Jak2/Stat3 signaling pathways. TNBC contains a large number of 'Stem-like' BC cells, CD44+ CD24- cells, referring to identifying markers on their surfaces. Knocking out these cells with activated Jak2/Stat3 signaling could be useful in combating TNBC[156].

Research at University of Maryland and Steward Greenebaum Cancer Centre led a multicenter clinical trial to determine an experimental drug Entinostat. It can reprogramme tumor cell to express a protein called an estrogen receptor to make them sensitive to harmone therapy. When combined with an aromatase inhibitor, it sensitizes TNBC cells and reduces growth and spread of tumors in animal model (NCT01234532). ABT-737, a BH3 mimetics targets on Bcl-2 protein in cancer cells[157]. Combination of ABT-737 and docetaxel in mice transplanted with human BC cells improved tumor response and survival rates, when compared to docetaxel as a single agent. Good outcomes in preclinical studies may hope to be use in human. Glembatumumab vedontin (CDX-011), novel antibody-drug conjugate targets on cancer cells expressing transmembrane glycoprotein NMB (GPNMB)[158]. A Phase 2b clinical study of CDX-011 carried out in 120 patients with GPNMB-expressing TNBC (NCT01156753). Another Phase I/II clinical trial with CDX-011 is shown good clinical activity in patients whose tumor expresses GPNMB with longer PFS (NCT00704158).

One retrospective study of about 1413 subjects with neoadjuvant chemotherapy exhibit, use of beta-blocker is associated with improved relapse-free survival (RFS) in patients with TNBC (HR, 0.30; 95% CI, 0.10 to 0.87; $P = 0.027$) but not OS (HR, 0.35; 95% CI, 0.12 TO 1.00; $P = 0.05$)[159]. Research at McGill University shown antidiabetic drug metformin (Glucophase) holds promise for treatment of TNBC. Antineoplastic activity of metformin via growth inhibition of BC epithelial cells; indeed high mammographic breast density known to predict increased BC risk which is associated with higher concentrations of circulating insulin-like growth factor-I (IGF-I). It also plays a critical role in carcinogenesis and tumorigenesis. Epidemiologic and preclinical laboratory studies indicated that metformin has anti-tumor effects, via activation of AMP-activated protein kinase (AMPK)[160,161]. Large-scale phase III trials of metformin in adjuvant BC settings have been planned.

Transcriptional profiling data evaluate differentially expressed human kinome and growth of ER-negative BC[162]. Kinases such as *CHK1, BUB1, TTK* and *AK2* are involved in cell cycle checkpoint control and mitogenesis. Another kinases involved in S6 kinase signaling pathway include *RPS6KA3, SMG-1* and *RPS6KA1*. Signaling pathways determined by siRNA knockdown experiment. These kinases could be potential target for therapeutic treatment. PTPN12 is a tyrosine phosphatase acting as a tumor suppressor in TNBC[163]. It suppresses mammary epithelial cell proliferation and transformation. It is to identify that PTPN12 is commonly inactivated tumor suppressor and provide a rationale for combinatorially targeting in TNBC. PTPN12 inhibit multiple oncogenic tyrosine kinases including HER2, EGFR and

PDGFR-β, which could be target for activation for their intractable cancer. Gene expression and genomic copy number variation provides insight into heterogeneity of TNBC with potential new target.

CONCLUSION

TNBC is a clinical entity that does not express ER, PR, or HER2 receptors, also a heterogeneous nature with difficult-to-define subtypes. It is a discrete BC subtype based on its unique profile in terms of poor prognosis, aggressive metastatic behavior, and its unique molecular and genetic features. Although a large proportion of TNBCs are 'basal-like', not all TNBCs are 'basal-like', with the reverse also being true. A Gene expression study has enable to classify breast cancers into at least five intrinsic subtypes: luminal A, luminal B, HER2 positive, basal-like, and normal breast-like. Women with TNBC have a higher likelihood of relapse and a poorer prognosis than, women with other subtypes. TNBC patient not achieving pCR with adjuvant chemotherapy have a high likelihood of relapse and poor survival. TNBC majorly occurred in African-American premenopausal women with higher parity, higher body mass index, younger age at menarche, shorter duration of breast-feeding and waist to hip ratio are common risk factors associated with it. Attention of clinicians toward this aggressive breast cancer subtype increased with its potential for earlier recurrence patterns and predisposition for distant metastasis to the brain, lung, and other visceral sites.

TNBC patient's pretense significant clinical management challenges, as no targeted therapy is available for them. They achieve relatively good chemotherapy response rates, compared to patients with luminal subtypes in early-stage disease, and chemotherapy-based regimens that maximize the rate of pCR, currently offer the best treatment approach for TNBC. The only systemic therapy currently available is chemotherapy and prognosis remains poor; hence, new tailored treatment regimens urgently needed. An introduction of novel strategies into the treatment paradigm of women with these tumors allowed proper patient selection to maximize therapeutic benefit. Several targets are currently under clinical investigation for the treatment of TNBC, including EGFR, DNA repair enzyme PARP1, angiogenesis (via VEGF), HDAC, Src and so on. Discovering new markers expressed in basal-like and TN breast cancer will allow for the use of other therapeutic targets, as αβ-crystallin, phoshorylated glycoprotein. Markers such as ceveolin 1, caveolin 2, p63, p73 exhibit predictive treatment responses. In addition, a CD44/CD24 phenotype shows significant therapeutic alternative, as it reported in breast cancer with unfavorable prognosis. Recently, research on PTPN12 will open a new avenue for treatment of TNBC. It is hoping that ongoing progress in understanding molecular biology of TNBC will have better impact in optimizing outcomes for women with prognostically poor subtype of breast cancer.

ACKNOWLEDGMENT

The authors are thankful to Shri. S.N. Vijaywargia and Capt. Ruchi Vijaywargia for providing laboratory facilities and Sarvajanik Jankalyan Parmarthik Nyas, People's Group for granting financial assistance to carry out the present research work.

REFFERENCES

1. Lacroix M, Toillon RA, and Leclercq G, Stable 'portrait' of breast tumors during progression: data from biology, pathology and genetics, Endocr Relat Cancer, 11(3): 497–522, (2004). [Pubmed:15369451]
2. Simpson PT, Reis-Filho JS, Gale T, and Lakhani SR, Molecular evolution of breast cancer, J Pathol, 205(2): 248–254, (2005). [Pubmed:15641021]
3. Siegel R, Ward E, Brawley O, and Jemal A, Cancer statistic, 2011: The impact of

eliminating socioeconomic and racial disparities on premature cancer deaths, CA Cancer J Clin, 61(4): 212–236, (2011). [Pubmed:21685461]
4. Anders CK, and Carey LA, Biology, metastatic patterns, and treatment of patients with triple- negative breast cancer, Clin Breast Cancer, 9(2): S73-S81, (2009). [Pubmed: 19596646]
5. Reis-Filho JS, Simpson PT, Gale T, and Lakhani SR, The molecular genetics of breast cancer: the contribution of comparative genomic hybridization, Pathol. Res. Pract, 201(11): 713–725, (2005). [Pubmed:16325514]
6. Dent R, Trudeau M, Pritchard KL, Hanna WM, Kahn HK, Sawka CA, Lickley LA, Rawlinson E, Sun P, and Narod SA, Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res, 13(15): 4429-4434, (2007). [Pubmed:17671126]
7. Kaplan HG, and Malmgren JA, Impact of triple negative phenotype on breast cancer prognosis, Breast J, 14(5): 456-463, (2008). [Pubmed:18657139]
8. Rakha EA, Tan DS, Foulkes WD, Ellis IO, Tutt A, Nielsen TO, and Reis-Filho JS, Are triple-negative tumors and basal-like breast cancer synonymous? Breast Cancer Res, 9(6): 404, author reply 405, (2007). [Pubmed:18279542]
9. Bosch A, Eroles Pk, Zaragoza R, Vina JR, and Lluch A, Triple-negative breast cancer: molecular features, pathogenesis, treatment and current lines of research, Cancer Treat Rev, 36(3): 206-215, (2010). [Pubmed:20060649]
10. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen MB, van de Rijn M, Jeffrey SS, Thorsen T, Quist H, Matese JC, Brown PO, Botstein D, Eystein Lønning P, and Børresen-Dale AL, Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications, Proc Natl Acad Sci U S A, 98(19): 10869-10874, (2001). [Pubmed:11553815]
11. Bertucci F, Finetti P, Cervera N, Esterni B, Hermitte F, Viens P, and Birnbaum D, How basal are triple-negative breast cancer? Int J Cancer, 123(1): 236-240, (2008). [Pubmed:18398844]
12. Rakha EA, Elsheikh SE, Aleskandarany MA, Habashi HO, Green AR, Powe DG, El-sayad ME, Enhasouna A, Brunet JS, Akslen LA, Evans AJ, Blamey R, Reis-filho JS, Foulkes WD, and Ellis IO, Triple-negative breast cancer: distinguishing between basal and nonbasal subtypes, Clin Cancer Res, 15(7): 2302-2310, (2009). [Pubmed:19318481]
13. Morris SR, and Carey LA, Gene expression profiling in breast cancer, Curr Opin Oncol, 19(6): 547-551, (2007). [Pubmed:17906450]
14. Nielsen TO, Hsu FD, Jensen K, Cheang M, Karaca G, Hu Z, Hernandez-Boussard T, Livasy C, Cowan D, Dressler L, Akslen LA, Ragaz J, Gown AM, Gilks CB, van de Rijn M, and Perou CM, Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma, Clin Cancer Res, 10(16): 5367-5374, (2004). [Pubmed:15328174]
15. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeff rey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenchikov A, Williams C, Zhu SX, Lønning PE, Børreson-Dale AL, Brown PO, and Botstein D, Molecular portraits of human breast tumours, Nature, 406(6797): 747-752, (2000). [Pubmed: 10963602]
16. Korsching E, Packeisen J, Agelopoulos K, Eisenacher M, Voss R, Isola J, van Diest PJ, Brandt B, Boecker W, and Buerger H, Cytogenetic alterations and cytokeratin expression patterns in breast cancer: Integrating a new model of breast differentiation into cytogenetic pathways of breast carcinogenesis, Lab Invest, 82(11):1525-1533, (2002). [Pubmed: 12429812]
17. Foulkes WD, Stefansson IM, Chappuis PO, Begin LR, Goffin JR, Wong N, Trudel M, and Akslen LA, Germline BRCA1 mutations and basal epithelial phenotype in breast cancer, J Natl Cancer Inst,

95(19):1482-1485, (2003). [Pubmed: 14519755]
18. Sorlie T, Tibshirani R, Parker J, Hastie T, Marron JS, Nobel A, Deng S, Johnsen H, Pesich R, Geisler S, Demeter J, Perou CM, Lønning PE, Brown PO, Børresen-Dale AL, and Botstein D, Repeated observation of breast tumor subtypes in independent gene expression data sets, Proc Natl Acad Sci U S A, 100(14): 8418-8423, (2003). [Pubmed: 12829800]
19. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, Troester MA, Tse CK, Edmiston S, Deming SL, Geradts J, Cheang MC, Nielsen TO, Moorman PG, Earp HS, and Millikan RC, Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study, JAMA, 295(21): 2492–2502, (2006). [PubMed: 16757721]
20. Cheang MC, Voduc D, Bajdik C, Leung S, McKinney S, Chia SK, Perou CM, and Nielsen TO, Basal-like breast cancer defined by five biomarkers has superior prognostic value than triple negative phenotype, Clin Cancer Res, 14(5):1368–1376, (2008). [Pubmed: 18316557]
21. Schneider BP, Winer EP, Foulkes WD, Garber J, Perou CM, Richardson A, Sledge GW, and Carey LA, Triple-negative breast cancer: risk factors to potential targets, Clin Cancer Res, 14(24): 8010-8018 (2008). [Pubmed: 19088017]
22. Bocker W, Bier B, Freytag G, Brommelkamp B, Jarasch ED, Edel G, Dockhorn-Dworniczak B, and Schmid KW, An immunohistochemical study of the breast using antibodies to basal and luminal keratins, alpha-smooth muscle actin, vimentin, collagen IV and laminin. Part I: Normal breast and benign proliferative lesions, Virchows Arch A Pathol Anat Histopathol, 421(4): 315–322, (1992). [PubMed: 1384226]
23. Gottlieb C, Raju U, Greenwald K, and Myoepithelial cells in the differential diagnosis of complex benign and malignant breast lesions: An immunohistochemical study, Mod Pathol, 3(2):135–140, (1990). [PubMed: 1691493]
24. Lazard D, Sastre X, Frid MG, Glukhova MA, Thiery JP, and Koteliansky VE, Expression of smooth muscle-specific proteins in myoepithelium and stromal myofibroblasts of normal and malignant human breast tissue, Proc Natl Acad Sci U S A, 90: 999–1003, (1993). [PubMed: 8430113]
25. Nakano S, Iyama K, Ogawa M, Yoshioka H, Sado Y, Oohashi T, and Ninomiya Y, Differential tissular expression and localization of type IV collagen alpha1(IV), alpha2(IV), alpha5(IV), and alpha6(IV) chains and their mRNA in normal breast and in benign and malignant breast tumors, Lab Invest, 79(3): 281–292, (1999). [PubMed: 10092064]
26. Nayar R, Breland C, Bedrossian U, Masood S, DeFrias D, and Bedrossian CW, Immunoreactivity of ductal cells with putative myoepithelial markers: A potential pitfall in breast carcinoma, Ann Diagn Pathol, 3(3):165–173, (1999). [PubMed: 10359852]
27. Rudland P, Histochemical organization and cellular composition of ductal buds in developing human breast: Evidence of cytochemical intermediates between epithelial and myoepithelial cells, J Histochem Cytochem, 39(11):1471–1484, (1991). [PubMed: 1918925]
28. Livasy CA, Karaca G, Nanda R, Tretiakova MS, Olopade OI, Moore DT, and Perou CM, Phenotypic evaluation of the basal-like subtype of invasive breast carcinoma, Mod Pathol, 19(2): 264–271, (2006). [PubMed: 16341146]
29. Bauer KR, Brown M, Cress RD, Parise CA, and Caggiano V, Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple negative phenotype: A population-based study from the california cancer registry, Cancer, 109(9):1721–1728, (2007). [PubMed: 17387718]
30. Morris GJ, Naidu S, Topham AK, Guiles F, Xu Y, McCue P, Schwartz GF, Park PK, Rosenberg AL, Brill K, and Mitchell EP, Differences in breast

carcinoma characteristics in newly diagnosed African-American and Caucasian patients: A single-institution compilation compared with the National Cancer Institute's Surveillance, Epidemiology, and End Results database, Cancer, 110(4): 876–884, (2007). [PubMed: 17620276]

31. Ries LAG, SEER Cancer Statistics Review, 1974-2004. Bethesda, MD: National Cancer Institute, (2009).
32. Iwase H, Yamamoto Y, Kurebayashi J, Tsuda H, Ota T, Kurosumi M, Miyamoto K, and Iwase T, Clinicopathologic and prognostic features of triple-negative breast cancer analyzed in registration data of the Japanese Breast Cancer Society, 11705 cases, J Clin Oncol, 27(15S): abstract 22122, (2009).
33. Yin WJ, Lu JS, Di GH, Lin YP, Zhou LH, Liu GY, Wu J, Shen KW, Han QX, Shen ZZ, and Shao ZM, Clinicopathological features of the triple-negative tumors in Chinese breast cancer patients, Breast Cancer Res Treat, 115(2):325–333, (2009). [Pubmed: 18563552]
34. Khan A, Tovar YE, Rodriguez C, Huerta AL, Rajabi B, Hakim MN, and Mulla ZD, Incidence of triple negative breast cancer phenotype in a predominantly Hispanic cohort, J Clin Oncol, 27(15S): abstract 22188, (2009).
35. Millikan RC, Newman B, Tse CK, Moorman PG, Conway K, Dressler LG, Smith LV, Labbok MH, Geradts J, Bensen JT, Jackson S, Livasy C, Carey L, Earp HS, and Perou CM, Epidemiology of basal-like breast cancer, Breast Cancer Res Treat, 109(1):123–139, (2008). [PubMed: 17578664]
36. Phipps AI, Malone KE, Porter PL, Daling JR, and Li CI, Reproductive and hormonal risk factors for postmenopausal luminal, HER-2-overexpressing, and triple-negative breast cancer, Cancer, 113(7):1521–1526, (2008). [PubMed: 18726992]
37. Yang XR, Sherman ME, Rimm DL, Lissowska J, Brinton LA, Peplonska B, Hewitt SM, Anderson WF, Szeszenia-Dabrowska N, Bardin-Mikolajczak A, Zatonski W, Cartun R, Mandich D, Rymkiewicz G, Ligaj M, Lukaszek S, Kordek R, and Garcia-Closas M, Differences in risk factors for breast cancer molecular subtypes in a population-based study, Cancer Epidemiol Biomarkers Prev, 16(3): 439–443, (2007). [PubMed: 17372238]
38. Haffty BG, Yang Q, Reiss M, Kearney T, Higgins SA, Weidhaas J, Harris L, Hait W, and Toppmeyer D, Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer, J Clin Oncol, 24(36):5652-5657, (2006). [Pubmed: 17116942]
39. Onitilo AA, Engel JM, Greenlee RT, and Mukesh BN, Breast cancer subtypes based on ER/PR and Her2 expression: comparison of clinicopathologic features and survival, Clin Med Res, 7(1-2): 4-13, (2009). [Pubmed: 19574486]
40. Kassam F, Enright K, Dent R, Dranitsaris G, Myers J, Flynn C, Fralick M, Kumar R, and Clemons M, Survival outcomes for patients with metastatic triple negative breast cancer: implications for clinical practice and trial design, Clin Breast Cancer. 9(1): 29-33, (2009). [Pubmed: 19299237]
41. Duchnowska R, Jassem J, Thorat MA, Morimiya A, Sledge GW, Li L, Biernat W, Szczylik C, Steeg PS, and Badve SS, Gene expression analysis for prediction of early brain metastasis (BM) in HER2-positive (HER2+) breast cancer patients, J Clin Oncol, 26: abstract 1019, (2008).
42. Tham Y, Creighton C, Gutierrez C, Osborne CK, Brown P, and Chang JC, A gene expression signature of eventual brain metastases in patients with breast cancer, J Clin Oncol, 25(18S):36s, abstract 1019, (2007).
43. Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO, and Kennecke H, Breast cancer subtypes and the risk of local and regional relapse, J Clin Oncol,

28(10):1684-1691, (2010). [Pubmed: 20194857]
44. Smid M, Wang Y, Zhang Y, Sieuwerts AM, Yu J, Klijn JG, Foekens JA, and Marten JW, Subtypes of breast cancer show preferential site of relapse, Cancer Res, 68(9): 3108-3114, (2008). [Pubmed: 18451135]
45. Minn AJ, Gupta GP, Siegel PM, Bos PD, Shu W, Giri DD, Viale A, Olshen AB, Gerald WL, and Massague J, Genes that mediate breast cancer metastasis to Lung, Nature, 436(7050): 518-524, (2005). [Pubmed: 16049480]
46. Liedtke C, Mazouni C, Hess KR, Andre F, Tordai A, Mejia JA, Symmans WF, Gonzalez- Angulo AM, Hennessy B, Green M, Cristofanilli M, Hortobagyi GN, and Pusztai L, Response to neoadjuvant therapy and long-term survival in patients with triple negative breast cancer, J Clin Oncol, 26(8):1275-1281,(2008). [Pubmed: 18250347]
47. Heitz F, Harter P, Traut A, Lueck HJ, Beutel B, and du Bois A, Cerebral metastases (CM) in breast cancer (BC) with focus on triple negative tumors, J Clin Oncol, 26: abstract1010, (2008).
48. Rodriguez-Pinilla SM, Sarrio D, Honrado E, Hardisson D, Calero F, Benitez J, and Palacios J, Prognostic significance of basal-like phenotype and fascin expression in node negative invasive breast carcinomas, Clin Cancer Res, 12(5):1533-1539 (2006). [Pubmed: 16533778]
49. Boogerd W, Vos VW, Hart AA, and Baris G, Brain metastases in breast cancer; natural history, prognostic factors and outcome, J Neurooncol, 15(2):165–174, (1993). [PubMed: 8509821]
50. Lin N, Bellon J, and Winer E, CNS metastases in breast cancer, J Clin Oncol, 22(17):3608– 3617, (2004). [PubMed: 15337811]
51. Bendell JC, Domchek SM, Burstein HJ, Harris L, Younger J, Kuter I, Bunnell C, Rue M, Gelman R, and Winer E, Central nervous system metastasis in women who receive trastuzumab-based therapy for metastatic breast carcinoma, Cancer, 97(12): 2972–2977, (2003). [PubMed: 12784331]
52. Lin NU, Carey L, Liu MC, Younger J, Come SE, Ewend M, Harris GJ, Bullitt E, Van den Abbeele AD, Henson JW, Li X, Gelman R, Burstein HJ, Kasparian E, Kirsch DG, Crawford A, Hochberg F, and Winer EP, Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer, J Clin Oncol, 26(12):1993– 1999, (2008). [PubMed: 18421051]
53. Lin NU, Claus E, Sohl J, Razzak AR, Arnaout A, and 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, 113:2638–2645, (2008). [PubMed: 18833576]
54. Niwinska A, and Murawska M, Brain metastases in breast cancer patients: Differences in survival depending on biological subtype and RPA RTOG prognostic class, J Clin Oncol, 26(15S):55s, (2008).
55. Cleator S, Heller W, and Coombes R, Triple negative breast cancer: Therapeutic options, Lancet Oncol, 8(3):235-244, (2007). [Pubmed: 17329194]
56. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology™ Breast Cancer.v1.2010. http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf. Accessed August 14, 2010.
57. Aebi S, Davidson T, Gruber G, and Castiglione M, Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up, Ann Oncol, 21(5):v9-v14, (2010).
58. Tan AR, and Swain SM, Therapeutic strategies for triple-negative breast cancer, Cancer J, 14(6): 343–351, (2008). [Pubmed: 19060597]
59. Kaplan HG, Malmgren JA, and Atwood M, T1N0 triple negative breast cancer: risk of

recurrence and adjuvant chemotherapy, Breast J, 15(5): 454-460, (2009). [Pubmed: 19671105]

60. Carey LA, Dees EC, Sawyer L, Gatti L, Moore DT, Collichio F, Ollila DW, Sartor CI, Graham ML, and Perou CM, The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes, Clin Cancer Res, 13(8): 2329–2334, (2007). [Pubmed: 17438091]
61. Hugh J, Hanson J, Cheang MC, Nielsen TO, Perou CM, Dumontet C, Reed J, Krajewska M, Treilleux I, Rupin M, Magherini E, Mackey J, Martin M, and Vogel C, Breast cancer subtypes and response to docetaxel in node-positive breast cancer: use of an immunohistochemical definition in the BCIRG 001 trial, J Clin Oncol, 27(8):1168–1176, (2009). [Pubmed: 19204205]
62. Wang S, Yang H, Tong F, Zhang J, Yang D, Liu H, Cao Y, Liu P, Zhou P, Cheng L, Liu M, and Guo J, Response to neoadjuvant therapy and disease free survival in patients with triple- negative breast cancer, Gan To Kagaku Ryoho, 36(2): 255–258, (2009). [Pubmed: 19223741
63. Bidard FC, Matthieu MC, Chollet P, Raoefils I, Abrial C, Domont J, Spielmann M, Delaloge S, Andre F, and Penault-Llorca J, p53 status and efficacy of primary anthracyclines/alkylating agent-based regimen according to breast cancer molecular classes, Ann Oncol, 19(7):1261– 1265, (2008). [Pubmed: 18325917]
64. Hayes DF, Thor AD, Dressler LG, Weaver D, Edgerton S, Cowan D, Broadwater G, Golstein LJ, Martino S, Ingle JN, Henderson IC, Norton L, Winer EP, Hudis CA, Ellis MJ, and Berry DA, HER2 and response to paclitaxel in node-positive breast cancer, N Engl J Med, 357(15):1496-1506, (2007). [Pubmed: 17928597]
65. Loesch D, Greco F, and O'Shaughnessy J, A randomized, multicenter, phase III trial comparing regimens of doxorubicin + cyclophosphamide (AC) followed by paclitaxel to doxorubicin + paclitaxel (AP) followed by weekly paclitaxel (wP) as adjuvant therapy for patients with high-risk, operable breast cancer, J Clin Oncol, 25(18): abstract 517, (2007).
66. Rouzier R, Perou CM, Symmans WF, Ibrahim N, Cristofanilli M, Anderson K, Hess KR, Stec J, Ayers M, Wagner P, Morandi P, Fan C, Rabiul I, Ross JS, Hortobagyi GN, and Pusztai L, Breast cancer molecular subtypes respond diff erently to preoperative chemotherapy, Clin Cancer Res, 11(16): 5678-5685, (2005). [Pubmed: 16115903]
67. Petit T, Wilt M, Rodier J, Muller D, Ghnassia J, Dufour P, Fricker J, Are BRCA1 mutations a predictive factor for anthracycline-based neoadjuvant chemotherapy response in triple-negative breast cancers? J Clin Oncol, 25(18), abstract 580, (2007).
68. Chappuis PO, Goffin J, Wong N, Perret C, Ghadirian P, Tonin PN, and Foulkes WD, A significant response to neoadjuvant chemotherapy in BRCA1/2 related breast cancer, J Med Genet, 39(8): 608–610, (2002). [PubMed: 12161606]
69. Cheang M, Chia SK, Tu D, Jiang S, Shepherd LE, Pritchard KI, Nielsen TO, Anthracyclines in basal breast cancer: The NCIC-CTG trial MA5 comparing adjuvant CMF to CEF, J Clin Oncol, 27(15) , abstract 519, (2009).
70. Clarke M, Coates AS, Darby SC, Davies C, Gelber RD, Godwin J, Goldhirsch A, Gray R, Peto R, Pritchard KI, and Wood WC, Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: patient-level meta-analysis of randomised trials, Lancet, 371(9606):29–40, (2008). [PubMed: 18177773]
71. Citron ML, Berry DA, Cirrincione C, Hudis C, Winer EP, Gradishar WJ, Davidson NE, Martino S, Livingston R, Ingle JN, Perez EA, Carpenter J, Hurd D, Holland JF, Smith BL, Sartor CI, Leung EH, Abrams J, Schilsky RL, Muss HB, and Norton L, Randomized trial of dose-dense versus conventionally scheduled and

sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741, J Clin Oncol, 21(8):1431–1439, (2003). [PubMed: 12668651]

72. Gluz O, Nitz UA, Harbeck N, Ting E, Kates R, Herr A, Lindemann W, Jackisch C, Berdel WE, Kirchner H, Metzner B, Werner F, Schütt G, Frick M, Poremba C, Diallo-Danebrock R, and Mohrmann S, Triple-negative high-risk breast cancer derives particular benefit from dose intensification of adjuvant chemotherapy: results of WSG AM-01 trial, Ann Oncol, 19 (5):861–870, (2008). [PubMed: 18174609]
73. Guarneri V, Broglio K, Kau SW, Cristofanilli M, Buzdar AU, Valero V, Buchholz T, Meric F, Middleton L, Hortobagyi GN, and Gonzalez-Angulo AM, Prognostic value of pathologic complete response after primary chemotherapy in relation to hormone receptor status and other factors, J Clin Oncol 24 (7):1037– 1044, (2006). [PubMed: 16505422]
74. Esserman LJ, Perou C, Cheang M, DeMichele A, Carey L, van't Veer LJ, Gray J, Petricoin E, Conway K, Hylton N, Berry D, Breast cancer molecular profiles and tumor response of neoadjuvant doxorubicin and paclitaxel: The I-SPY TRIAL (CALGB 150007/150012, ACRIN 6657), J Clin Oncol, 27:18s, abstract LBA515, (2009).
75. Ring AE, Smith IE, Ashley S, Fulford LG, and Lakhani SR, Oestrogen receptor status, pathological complete response and prognosis in patients receiving neoadjuvant chemotherapy for early breast cancer, Br J Cancer, 91(12): 2012–2017 (2004). [PubMed: 15558072]
76. Colleoni M, Viale G, Zahrieh D, Pruneri G, Gentilini O, Veronesi P, Gelber RD, Curigliano G, Torrisi R, Luini A, Intra M, Galimberti V, Renne G, Nolè F, Peruzzotti G, and Goldhirsch A, Chemotherapy is more effective in patients with breast cancer not expressing steroid hormone receptors: a study of preoperative treatment, Clin Cancer Res, 10 (19): 6622–6628, (2004). [PubMed: 15475452]
77. Frasci G, Comella P, Rinaldo M, Iodice G, Di Bonito M, D'Aiuto M, Petrillo A, Lastoria S, Siani C, Comella G, and D'Aiuto G, Preoperative weekly cisplatin-epirubicin-paclitaxel with G-CSF support in triple-negative large operable breast cancer, Ann Oncol, 20(7):1185–1192, (2009). [Pubmed: 19218307]
78. Sirohi B, Arnedos M, Popat S, Ashley S, Nerurkar A, Walsh G, Johnston S, and Smith IE, Platinum-based chemotherapy in triple-negative breast cancer, Ann Oncol, 19(11):1847–1852, (2008). [Pubmed: 18567607]
79. Sobin LH, Gospodarowicz MK, and Wittekind CH, UICC: TNM classification of malignant tumors. Wiley-Blackwell, Oxford, (2009).
80. Leong CO, Vidnovic N, Deyoung MP, Sgroi D, and Ellisen LW, The p63/p73 network mediates chemosensitivity to cisplatin in a biologically defined subset of primary breast cancers, J Clin Invest, 117(5): 1370-1380, (2007). [Pubmed: 17446929]
81. Silver DP, Richardson AL, Eklund AC, Wang ZC, Szallasi Z, Li Q, Juul N, Leong CO, Calogrias D, Buraimoh A, Fatima A, Gelman RS, Ryan PD, Tung NM, De Nicolo A, Ganesan S, Miron A, Colin C, Sgroi DC, Ellisen LW, Winer EP, and Garber GE, Efficacy of neoadjuvant Cisplatin in triple-negative breast cancer, J Clin Oncol, 28(7):1145-1153, (2010). [Pubmed: 20100965]
82. Torrisi R, Balduzzi A, Ghisini R, Rocca A, Bottiglieri L, Giovanardi F, Veronesi P, Luini A, Orlando L, Viale G, Goldhirsch A, and Colleoni M, Tailored preoperative treatment of locally advanced triple negative (hormone receptor negative and HER2 negative) breast cancer with epirubicin, cisplatin, and infusional fluorouracil followed by weekly paclitaxel, Cancer Chemother

Pharmacol, 62(4): 667-672, (2008). [Pubmed: 18064460]
83. Frasci G, Comella P, Rinaldo M, Iodice G, Di Bonito M, D'Aiuto M, Petrillo A, Lastoria S, Siani C, Comella G, and D'Aiuto G, Preoperative weekly cisplatin-epirubicin-paclitaxel with G-CSF support in triple-negative large operable breast cancer, Ann Oncol, 20(7):1185-1192, (2009). [Pubmed: 19218307]
84. Isakoff SJ, Triple-negative breast cancer: role of specific chemotherapy agents, Cancer J, 16(1): 53-61, (2010). [Pubmed: 20164691]
85. Uhm JE, Park YH, Yi SY, Cho EY, Choi YL, Lee SJ, Park MJ, Lee SH, Jun HJ, Ahn JS, Kang WK, Park K, and Im YH, Treatment outcomes and clinicopathologic characteristics of triple-negative breast cancer patients who received platinum-containing chemotherapy, Int J Cancer, 124(6):1457–1462, (2009). [Pubmed: 19065658]
86. Smith JW 2nd, McIntyre KJ, Acevedo PV, Encarnacion CA, Tedesco KL, Asmar L, and O'Shaughnessy JA, Results of a phase II open-label, nonrandomized trial of oral satraplatin in patients with metastatic breast cancer, Breast Cancer Res Treat, 118(2): 361–367, (2009). [Pubmed: 19459042]
87. Tentori L, and Graziani G, Chemopotentiation by PARP inhibitors in cancer therapy, Pharmacol Res, 52(1): 25–33, (2005). [PubMed: 15911331]
88. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, Kyle S, Meuth M, Curtin NJ, and Helleday T, Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase, Nature, 434(7035): 913–917, (2005). [PubMed: 15829966]
89. Farmer H, McCabe N, Lord CJ, Tutt AN, Jonson DA, Richardson TB, Santatosa M, Dillon KJ, Hickson I, Knights C, Martin NM, Jackson SP, Smtih GC, and Ashworth A, Targeting the DNA repair defect in BRCA1 mutant cells as a therapeutic strategy, Nature, 434(7035): 917- 921, (2005). [Pubmed: 15829967]
90. Evers B, Drost R, Schut E, de Bruin M, van der Burg E, Derksen PW, Holstege H, Liu X, van Drunen E, Beverloo HB, Smith GC, Martin NM, Lau A, O'Connor MJ, and Jonkers K, Selective inhibition of BRCA-2 defi cient mammary tumor cell growth by AZD2281 and cisplatin, Clin Cancer Res, 14(12): 3916-3925, (2008). [Pubmed: 18559613]
91. Rottenberg S, Jaspers JE, Kersbergen A, van der Burg E, Nygren AO, Zander SA, Derksen PW, de Bruin M, Zevenhoven J, Lau A, Boulter R, Cranston A, O'Connor MJ, Martin NM, Borst P, and Jonkers J, High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs, Proc Natl Acad Sci U S A, 105(44):17079–17084, (2008). [Pubmed: 18971340]
92. von Minckwitz G, Jonat W, Fasching P, du Bois A, Kleeberg U, Luck HJ, Luck HJ, Kettner E, Hilfrich J, Eiermann W, Torode J, and Schneeweiss A, A multicentre phase II study on gefitinib in taxane- and anthracycline-pretreated metastatic breast cancer, Breast Cancer Res Treat, 89(2):165–172, (2005). [Pubmed: 15692759]
93. Veeck J, Ropero S, Setien F, Gonzalez-Suarez E, Osorio A, Benitez J, Herman JG, and Esteller M, BRCA1 CpG Island Hypermethylation Predicts Sensitivity to Poly (Adenosine Diphosphate)-Ribose Polymerase Inhibitors, J Clin Oncol, 28(29):e563-564; author reply e565-566, (2010). [Pubmed: 20679605]
94. Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, Mortimer P, Swaisland H, Lau A, O'Connor MJ, Ashworth A, Carmichael J, Kaye SB, Schellens JH, and de Bono JS,Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers, N Engl J Med, 361(2):123–134, (2009). [Pubmed: 19553641]

95. Tutt A, Robson M, Garber JE, Domchek SM, Audeh MW, Weitzel JN, Friedlander M, Arun B, Loman N, Schmutzler RK, Wardley A, Mitchell G, Earl H, Wickens M, and Carmichael J, Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial, Lancet, 376(9737): 235–244, (2010). [Pubmed: 20609467]
96. Dent R, Lindeman G, Clemons M, Wildiers H, Chan A, McCarthy N, Singer C, Lowe E, Kemsley K, and Carmichael J, Safety and efficacy of the oral PARP inhibitor olaparib (AZD2281) in combination with paclitaxel for the firstor second-line treatment of patients with metastatic triple-negative breast cancer: Results from the safety cohort of a phase I/II multicenter trial, J Clin Oncol, 28(15): abstract 1018, (2010).
97. O'Shaughnessy J, Osborne C, Pippen J, Patt D, Rocha C, Ossovskaya V, Sherman B, and Bradley C, Final Results of a Randomized Phase II Study Demonstrating Efficacy and Safety of BSI-201, a Poly (ADP-Ribose) Polymerase (PARP) Inhibitor, in Combination with Gemcitabine/Carboplatin (G/C) in Metastatic Triple Negative Breast Cancer (TNBC), Cancer Res, 69:686S-687S, (2009).
98. O'Shaughnessy J, Osborne C, Pippen J, Yoffe M, Patt D, Monaghan G, Rocha C, Ossovskaya V, Sherman B, and Bradley C, Efficacy of BSI-201, a poly (ADP-ribose) polymerase-1 (PARP1) inhibitor, in combination with gemcitabine/carboplatin (G/C) in patients with metastatic triple-negative breast cancer (TNBC): Results of a randomized phase II trial, J Clin Oncol, 27:3-3, (2009).
99. Isakoff SJ, Overmoyer B, Tung NM, Gelman RS, Giranda VL, Bernhard KM, Habin KR, Winer EP, and Goss PE, A phase II trial of the PARP inhibitor veliparib (ABT888) and temozolomide for metastatic breast cancer, J Clin Oncol, 28: abstract 1019, (2010).
100. Loibl S, Mueller B, von Minckwitz G, Blohmer JU, du Bois A, Huober J, Fend F, Budczies J, and Denkert C, PARP expression in early breast cancer and its predictive value for response to neoadjuvant chemotherapy, J Clin Oncol, 28: 15s, abstract 10511, (2010).
101. Pandolfi PP, Breast cancer–loss of PTEN predicts resistance to treatment, N Engl J Med, 351(22):2337-2338, (2004). [Pubmed: 15564551]
102. Kwei KA, Kung Y, Salari K, Holcomb IN, and Pollack JR, Genomic instability in breast cancer: Pathogenesis and clinical implications, Mol Oncol, 4(3):255-266, (2010). [Pubmed: 20434415]
103. Henderson IC, Berry DA, Demetri GD, Cirrincione CT, Goldstein LJ, Martino S, Ingle JN, Cooper MR, Hayes DF, Tkaczuk KH, Fleming G, Holland JF, Duggan DB, Carpenter JT, Frei E 3rd, Schilsky RL, Wood WC, Muss HB, and Norton L, Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer, J Clin Oncol, 21(6): 976–983, (2003). [PubMed: 12637460]
104. Sparano JA, Wang M, Martino S, Jones V, Perez EA, Saphner T, Wolff AC, Sledge GW Jr, Wood WC, and Davidson NE, Weekly paclitaxel in the adjuvant treatment of breast cancer, N Engl J Med, 358(16):1663–1671, (2008). [PubMed: 18420499]
105. Quinn JE, Kennedy RD, Mullan PB, Gilmore PM, Carty M, Johnston PG, and Harkin DP, BRCA1 functions as a differential modulator of chemotherapy-induced apoptosis, Cancer Res, 63(19): 6221–6228, (2003). [PubMed: 14559807]
106. Pinilla SM, Honrado E, Hardisson D, Benitez J, and Palacios J, Caveolin-1 expression is associated with a basal-like phenotype in sporadic and hereditary breast cancer, Breast cancer Res Treat, 99(1):85–90, (2006). [PubMed: 16541313]

107. Altundag K, Harputluoglu H, Aksoy S, and Gullu IH, Potential chemotherapy options in the triple negative subtype of breast cancer, J Clin Oncol, 25(10):1294–5, author reply 5-6, (2007). [PubMed: 17401026]
108. Rivera E, Lee J, and Davies A, Clinical development of ixabepilone and other epothilones in patients with advanced solid tumors, Oncologist, 13(12):1207–1223, (2008). [Pubmed: 19088324]
109. Rugo HS, Roche H, Thomas ES, Blackwell K, Chung HC, Lerzo G, Volles LA, Poulart V, Perez E, Ixabepilone plus capecitabine vs capecitabine in patients with triple negative tumors: a pooled analysis of patients from two large phase III clinical studies. Presented at the 31st Annual San Antonio Breast Cancer Symposium; December 10–14, San Antonio, TX. Abstract 3057, (2008).
110. Horak CE, Lee FY, Xu L, Galbraith S, and Baselga J, High {beta}-III tubulin expression in triple-negative (TN) breast cancer (BC) subtype, 27: abstract 3587, (2009).
111. Cortes J, and Lorca R, Eribulin mesylate: a promising new antineoplastic agent for locally advanced or metastatic breast cancer, Future Oncol, 7(3):355-64, (2011). [Pubmed:21375468]
112. Linderholm BK, Hellborg H, Johansson U, Elmberger G, Skoog L, Lehtio J, and Lewensohn R, Significantly higher levels of vascular endothelial growth factor (VEGF) and shorter survival times for patients with primary operable triple-negative breast cancer, Ann Oncol, 20(10):1639-1646, (2009). [Pubmed: 19549711]
113. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, Shenkier T, and Cella D, Davidson NE, Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer, N Engl J Med, 357(26):2666-2676, (2007). [Pubmed: 18160686]
114. Miles D, Chan A, Romieu G, Dirix LY, Cortes J, Pivot X, Tomczak P, Taran T, Harbeck N, and Steger GG, Randomized, doubled-blind, placebo controlled, phase III study of bevacizumab (BV) with docetaxel (D) or docetaxel with placebo (PL) as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO, J Clin Oncol, 26(15S): abstarct1008s, (2008).
115. Robert NJ, Dieras V, Glaspy J, Brufsky A, Bondarenko I, Lipatov O, Perez E, Yardley D, Zhou X, and Phan S, Ribbon-1: randomized, double-blind, placebo controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer, J Clin Oncol, 29(10): 1252-1260, (2011). [Pubmed: 21383283]
116. Mendel DB, Laird AD, Xin X, Louie SG, Christensen JG, Li G, Schreck RE, Abrams TJ, Ngai TJ, Lee LB, Murray LJ, Carver J, Chan E, Moss KG, Haznedar JO, Sukbuntherng J, Blake RA, Sun L, Tang C, Miller T, Shirazian S, McMahon G, and Cherrington JM, In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet derived growth factor receptors: determination of pharmacokinetic/ pharmacodinamic relationship, Clin Cancer Res, 9(1):327-337, (2003). [Pubmed: 12538485]
117. Abrams TJ, Lee LB, Murray LJ, Pryer NK, and Cherrington JM, SU 11248 inhibits KIT and platelet-derived growth factor receptor beta in preclinical models of human small cell lung cancer, Mol Cancer Ther, 2(5):757-766, (2003). [Pubmed: 12748309]
118. Murray LJ, Abrams TJ, Long KR, Ngai TJ, Olson LM, Hong W, Keast PK, Brassard JA, O'Farrell AM, Cherrington JM, and Pryer NK, SU 11248 inhibits tumor growth-and CSF-1R-dependent osteolysis in an experimental breast cancer bone metastasis model, Clin Exp Metastasis, 20(8):757-766, (2003). [Pubmed: 14713109]

119. Barrios C, Liu M, and Lee S, A phase III randomized trial of sunitinib versus capecitabine in patients with previously treated HER 2 negative advanced breast disease (SUN 1107) [abstract 46]. In *Proceedings of the San Antonio Breast Cancer Symposium*: 32nd Annual San Antonio Breast Cancer Symposium [www.sabcs.org], (2009).
120. Baselga J, Roche H, and Costa F, SOLTI 0701: a multinacional double-blind, randomized phase 2b study evaluating the effi cacy and safety of sorafenib compared to placebo when administered in combination with capecitabine in patients with locally advanced or metastatic breast cancer [abstract 45]. In *Proceedings of the San Antonio Breast Cancer Symposium*: 32nd Annual San Antonio Breast Cancer Symposium [www.sabcs.org], (2009).
121. Gradishar W, Kaklamani V, Prasad Sahoo T, Lokanatha D, Raina V, Bondarde S, and Jain M, A double-blind, randomized, placebo-controlled, phase 2b study evaluating the efficacy and safety of sorafenib in combination with paclitaxel as a first line therapy in patients with locally recurrent or metastatic breast cancer, Cancer Research, 69(24), In *Proceedings of the San Antonio Breast Cancer Symposium*: 32nd Annual San Antonio Breast Cancer Symposium [www.sabcs.org], (2009).
122. Meric-Bernstam F, and Gonzalez-Angulo AM, Targeting the mTOR signaling network for cancer therapy, J Clin Oncol, 27(13): 2278-2287, (2009). [Pubmed: 19332717]
123. Ellard SL, Clemons M, Gelmon KA, Norris B, Kennecke H, Chia S, Pritchard K, Eisen A, Vandenberg T, Taylor M, Sauerbrei E, Michaeli M, Huntsman D, Walsh W, Olivo M, McIntosh L, and Seymour L, Randomized phase II study comparing two schedules of everolimus in patients with recurrent/metastatic breast cancer: NCIC clinical trials group IND.163, J Clin Oncol, 27(27):4536-4541, (2009). [Pubmed: 19687332]
124. Verbeek BS, Vroom TM, Adriansen-Slot SS, Ottenhoff -Kalff AE, Geertzema JG, Hennipman A, and Rijksen G, c-Src protein expression is increased in human breast cancer. An immunohistochemical and biochemical analysis, J Pathol, 180(4):383-388, (1996). [Pubmed: 9014858]
125. Finn RS, Dering J, Ginther C, Wilson CA, Glaspy P, Tchekmedyian N, and Slamon DJ, Dasatinib, an orally ative small molecule inhibitor of both the src and abl kinases, selectively inhibits growth of basal-type triple negative breast cancer cell lines growing in vitro, Breast Cancer Res Treat, 105(3):319-326, (2007). [Pubmed: 17268817]
126. Finn R, Bengala C, Ibrahim N, Strauss LC, Fairchild J, Sy O, Roche H, Sparano J and Goldstein LJ, Phase II trial of dasatinib in triple-negative breast cancer: results of study CA 180059, Cancer Res, 69(2), abstract 2015, (2009).
127. Anbalagan M, Carrier L, Glodowski S, Hangauer D, Shan B, and Rowan BG, KX-01, a novel Src kinase inhibitor directed toward the peptide substrate site, synergizes with tamoxifen in estrogen receptor α positive breast cancer, [Epub ahead of print], (2011), [Pubmed: 21509526]
128. Whitesell L, Mimmaugh E, De Costa B, Myers CE, and Neckers LM, Inhibition of heat shock protein HSP90–pp60v-src heteroprotein complex formation by benzoquinone ansamycins: essential role for stress proteins in oncogenic transformation, Proc Natl Acad Sci USA, 91(18):8324-8328, (1994). [Pubmed: 8078881]
129. Modi S, Heat shock protein 90 inhibition: a novel strategy for the treatment of HER2-positive breast cancer. In *Proceedings of the San Antonio Breast Cancer Symposium*; 32nd Annual San Antonio Breast Cancer Symposium, (2009). [www.sabcs.org]
130. Caldas-Lopez E, Cerchietti L, Ahn J, Clement CC, Robles AI, Rodina A, Moulick K, Taldone T, Gozman A, Guo Y,

Wu N, de Stanchine E, White J, Gross SS, Ma Y, Varticovski L, Melnick A, and Chiosis G, Hsp90 inhibitor PU-H71, a multimodal inhibitor of maliganancy induces complete responses in triple negative breast cancer models, Proc Natl Acad Sci USA, 106(20):8368-8373, (2009). [Pubmed: 19416831]

131. Moyano JV, Evans JR, Chen F, Lu M, Werner ME, Yehiely F, Diaz Lk, Turbin D, Karaca G, Wiley E, Nielsen TO, Perou CM, and Cryns VL, αB-crystallin is a novel oncoprotein that predicts poor clinical outcome in breast cancer, J Clin Invest, 116:261–270, (2006). [PubMed: 16395408]
132. Keen JC, Yan L, Mack KM, Pettit C, Smith D, Sharma D, and Davidson NE, A novel histone deacetylase inhibitor, scriptaid, enhances expression of functional estrogen receptor α (ER) in ER negative human breast cancer cells in combination with 5-aza 2'-deoxycytidine, Breast Cancer Res Treat, 81:177–186, (2003). [PubMed: 14620913]
133. Sabnis GJ, Gediya LK, Njar VCO, and Brodie AMH, HDAC inhibitors sensitize ER negative breast cancer cells to AIs, Breast Cancer Res Treat, 106(1):S117, abstract 2096, (2007).
134. Lacevic M, Minton SE, Schmitt ML, Bicaku E, Marchion DC, and Munster PN, Phase II trial of the HDAC inhibitor, vorinostat, in combination with tamoxifen for patients with advanced breast cancer who have failed prior antihormonal therapy, Breast Cancer Res Treat, 106 (1):S117, abstract 2097, (2007).
135. Doane AS, Danso M, Lal P, Donaton M, Zhang L, Hudis C, and Gerald WL, An estrogen receptor-negative breast cancer subset characterized by a hormonally regulated transcriptional program and response to androgen, Oncogene, 25(28):3994-4008, (2006). [Pubmed: 16491124]
136. Gonzalez-Angulo AM, Stemke-Hale K, Palla SL, Carey M, Agarwal R, Meric-Berstam F, Traina TA, Hudis C, Hortobagyi GN, Gerald WL, Mills GB, and Hennessy BT, Androgen receptor levels and association with PIK3CA mutations and prognosis in breast cancer, Clin Cancer Res, 15(7):2472-2478, (2009). [Pubmed: 19276248]
137. Niemeier LA, Dabbs DJ, Beriwal S, Striebel JM, and Bhargava R, Androgen receptor in breast cancer: Expression in estrogen receptor-positive tumors and in estrogen receptor-negative tumors with apocrine differentiation, Mod Pathol, 23(2):205-212, (2010). [Pubmed: 19898421]
138. Park S, Koo J, Park HS, Kim JH, Choi SY, Lee JH, Park BW, and Lee KS, Expression of androgen receptors in primary breast cancer, Ann of Oncol, 21(3):488-492, 2009. [Pubmed: 19887463]
139. www.clinicaltrials.org
140. Collins LC, Martyniak A, Kandel MJ, Stadler ZK, Masciari S, Miron A, Richardson AL, Schnitt SJ, and Garber JE, Basal Cytokeratin and epidermal growth factor receptor expressionare not predictive of BRCA1 mutation status in women with triple-negative breast cancers, Am J Surg Pathol, 33(7):1093–1097, (2009). [Pubmed: 19390427]
141. Meche A, Cimpean AM, and Raica M, Immunohistochemical expression and significance of epidermal growth factor receptor (EGFR) in breast cancer, Rom J Morphol Embryol, 50(2): 217–221, (2009). [Pubmed: 19434314]
142. Nalwoga H, Arnes JB, Wabinga H, and Akslen LA, Expression of EGFR and c-kit is associated with the basal-like phenotype in breast carcinomas of African women, APMIS 116(6):515–525, (2008). [Pubmed: 18754326]
143. Harari PM, Epidermal growth factor receptor inhibition strategies in oncology. Endocr Relat Cancer, 11(4):689–708, (2004). [Pubmed: 15613446]
144. Rakha E, Ellis I, and Reis-Filho J. Are triple-negative and basal-like breast cancer synonymous? Clin Cancer Res, 14(2):618; author reply 618–619, (2008). [Pubmed: 18223240]

145. Corkery B, Crown J, Clynes M, and O'Donovan N, Epidermal growth factor receptor as a potential therapeutic target in triple-negative breast cancer, Ann Oncol, 20(5):862–867, (2009). [Pubmed: 19150933]
146. Nogi H, Kobayashi T, Suzuki M, Tabei I, Kawase K, Toriumi Y, Fukushima H, and Uchida K, EGFR as paradoxical predictor of chemosensitivity and outcome among triple-negative breast cancer, Oncol Rep, 21(2): 413–417, (2009). [Pubmed: 19148516]
147. Carey LA, Rugo HS, Marcom PK, Irvin W, Ferraro M, Jr, Burrows E, He X, Perou CM, Winer EP, TBCRC 001: EGFR inhibition with cetuximab added to carboplatin in metastatic triple-negative (basal-like) breast cancer (abstract 1009), J Clin Oncol, 26(15S): abstract 1009, (2008).
148. Turner N, and Grose R, Fibroblast growth factor signalling: from development to cancer, Nat Rev Cancer, 10(2):116-129, (2010). [Pubmed: 20094046]
149. Elsheikh SE, Green AR, Lambros MB, Turner NC, Grainge MJ, Powe D, Ellis IO, and Reis-Filho JS, *FGFR1* amplification in breast carcinomas: a chromogenic in situ hybridisation analysis, Breast Cancer Res, 9(2):R23, (2007). [Pubmed: 17397528]
150. Hunter DJ, Kraft P, Jacobs KB, Cox DG, Yeager M, Hankinson SE, Wacholder S, Wang Z, Welch R, Hutchinson A, Wang J, Yu K, Chatterjee N, Orr N, Willett WC, Colditz GA, Ziegler RG, Berg CD, Buys SS, McCarty CA, Feigelson HS, Calle EE, Thun MJ, Hayes RB, Tucker M, Gerhard DS, Fraumeni Jr JF, Hoover RN, Thomas G and Chanock SJ, A genome-wide association study identifies alleles in *FGFR2* associated with risk of sporadic postmenopausal breast cancer, Nat Genet, 39(7): 870-874, (2007). [Pubmed: 17529973]
151. Sebolt-Leopold JS, and Herrera R, Targeting the mitogen-activated protein kinase cascade to treat cancer, Nat Rev Cancer, 4(12):937-947, (2004). [Pubmed: 15573115]
152. Saal LH, Johansson P, Holm K, Gruvberger-Saal SK, She QB, Maurer M, Koujak S, Ferrando AA, Malmstrom P, Memeo L, Isola J, Bendahl P-O, Rosen N, Hibshoosh H, Ringner M, Borg A, and Parsons R, Poor prognosis in carcinoma is associated with a gene expression signature of aberrant PTEN tumor suppressor pathway activity, Proc Natl Acad Sci USA, 104(18):7564-7569, (2007). [Pubmed: 17452630]
153. Saal LH, Gruvberger-Saal SK, Persson C, Lovgren K, Jumppanen M, Staaf J, Jo¨nsson G, Pires MM, Maurer M, Holm K, Koujak S, Subramaniyam S, Vallon-Christersson J, Olsson H, Su T, Memeo L, Ludwig T, Ethier SP, Krogh M, Szabolcs M, Murty VV, Isola J, Hibshoosh H, Parsons R, and Borg A, Recurrent gross mutations of the PTEN tumor suppressor gene in breast cancers with deficient DSB repair, Nat Genet, 40(1):102-107, (2008). [Pubmed: 18066063]
154. Liua C-C, Priorb J, Piwnica-Wormsb D, and Bua G. LRP6 overexpression defines a class of breast cancer subtype and is a target for therapy, Proc Natl Acad Sci USA, 107(11): 5136-5141, (2010). [Pubmed: 20194742]
155. Yang L, Wu X, Wang Y, Zhang K, Wu J,Yuan Y-C, Deng X, Chen L, Kim C C H, Lau S, Somlo G and Yen Y, FZD7 has a critical role in cell proliferation in triple negative breast cancer, Oncogene, 30(43): 4437-4446,(2011). [Pubmed: 21532620]
156. 156. Marotta LL, Almendro V, Marusyk A, Shipitsin M, Schemme J, Walker SR, Bloushtain- Qimron N, Kim JJ, Choudhury SA, Maruyama R, Wu Z, Gönen M, Mulvey LA, Bessarabova MO, Huh SJ, Silver SJ, Kim SY, Park SY, Lee HE, Anderson KS, Richardson AL, Nikolskaya T, Nikolsky Y, Liu XS, Root DE, Hahn WC, Frank DA and Polyak K, The JAK2/STAT3 signaling pathway is required for growth of $CD44^{+}CD24^{-}$ stem

cell–like breast cancer cells in human tumors, J Clin Invest, 121(7): 2723–2735, (2011). [Pubmed: 21633165]

157. van Delft MF, Wei AH, Mason KD, Vandenberg CJ, Chen L, Czabotar PE, Willis SN, Scott CL, Day CL, Cory S, Adams JM, Roberts AW, and Huang DC, The BH3 mimetic ABT-737 targets selective Bcl-2 proteins and efficiently induces apoptosis via Bak/Bax if Mcl-1 is neutralized, Cancer Cell, 10(5): 389-99, (2006). [Pubmed: 17097561]
158. Rose AA, Grosset AA, Dong Z, Russo C, Macdonald PA, Bertos NR, St-Pierre Y, Simantov R, Hallett M, Park M, Gaboury L, and Siegel PM, Glycoprotein nonmetastatic B is an independent prognostic indicator of recurrence and a novel therapeutic target in breast cancer, Clin Cancer Res, 16(7): 2147-2156, (2010). [Pubmed: 20215530]
159. Melhem-Bertrandt A, Chavez-MacGregor M, Lei X, Brown EN, Lee RT, Meric-Bernstam F, Sood AK, Conzen SD, Hortobagyi GN, and Gonzalez-Angulo A-M, Beta-Blocker Use Is Associated With Improved Relapse-Free Survival in Patients With Triple-Negative Breast Cancer, J Clin Oncol, 29(19): 2645-2652, (2011). [Pubmed: 21632502]
160. Goodwin PJ, Ligibel JA, and Stambolic V, Metformin in breast cancer: time for action, J Clin Oncol, 27(20): 3271-3273, (2009). [Pubmed: 19487373]
161. Liu B, Fan Z, Edgerton SM, Deng XS, Alimova IN, Lind SE, and Thor AD, Metformin induces unique biological and molecular responses in triple negative breast cancer cells, Cell Cycle, 8(13): 2031-2340, (2009). [Pubmed: 19440038]
162. Speers C, Tsimelzon A, Sexton K, Herrick AM, Gutierrez C, Culhane A, Quackenbush J, Hilsenbeck S, Chang J, and Brown P, Identification of novel kinase targets for the treatment of estrogen receptor-negative breast cancer, Clin Cancer Res, 15(20):6327-6340, (2009).[Pubmed: 19808870]
163. Sun T, Aceto N, Meerbrey KL, Kessler JD, Zhou C, Migliaccio I, Nguyen DX, Pavlova NN, Botero M, Huang J, Bernardi RJ, Schmitt E, Hu G, Li MZ, Dephoure N, Gygi SP, Rao M, Creighton CJ, Hilsenbeck SG, Shaw CA, Muzny D, Gibbs RA, Wheeler DA, Osborne CK, Schiff R, Bentires-Alj M, Elledge SJ, and Westbrook TF, Activation of multiple proto-oncogenic tyrosine kinases in breast cancer via loss of the PTPN12 phosphatase, Cell, 144(5):703-718, (2011). [Pubmed: 21376233]