Standard therapy of HER2-positive and triple negative metastatic breast cancer – present and future

Jasna Trifunović, Jasna Pešić

Arch Oncol 2013;21(3-4):163-7.
UDC: 618.19-006:615-085:577.112.4
DOI: https://doi.org/10.2298/AOO1304163T

Oncology Institute of Vojvodina, Sremska Kamenica, Serbia

Correspondence to:
Prof. Dr. Jasna Trifunović,
Oncology Institute of Vojvodina,
Put dr Goldmana 4,
21204 Sremska Kamenica, Serbia
trifunovic.jasna@onk.ns.ac.rs

Received: 10.12.2013
Accepted: 26.12.2013

TREATMENT OF HER2-POSITIVE METASTATIC BREAST CANCER

The treatment of HER2-positive metastatic breast cancer (MBC) has been improved. The HER family consists of four transmembrane receptors that mediate in a complex network of signaling pathways (1). HER1, HER2, and HER3 are all implicated in the development and progression of cancer (2, 3). The HER1 and HER2 receptors are perhaps the best known HER family members. The HER3 receptor is gaining increasing importance in cancer research. The role of the HER4 receptor in breast cancer is unclear (4). Human epidermal growth factor receptor 2 (HER2) is a transmembrane protein and the part of HER family of growth factor receptors. However, there is no known ligand for HER2. After dimerization, intracellular signaling is activated through transphosphorylation reactions by the tyrosine kinase located at the cytoplasmic domain. HER2 plays a key role in the regulation of normal cell survival, proliferation, and differentiation (5-8). HER2 is a very significant to target therapy.

Overexpression of the HER2 protein, usually as a result of HER2 gene amplification, can result in malignant transformation of cells and it is seen in about 18%-20% patients with breast cancer (7). Women with HER2-positive breast cancer usually have tumors that are more aggressive, shorter time to relapse at all stages of the disease, and a poor prognosis (9). HER2 positivity is a negative prognostic marker (10).

HER2 positive patients have lower survival rate. Breast cancer patients have different disease profiles, which are categorized by HER2 and HR status. Subgroups of patients with breast cancer have different disease prognosis. About 50% of HER2-positive patients are also HR-positive, and have a better prognosis. Patients with HER2-positive/HR-positive disease have a better prognostic outcome regarding time to distant metastasis and overall survival in comparison to HER2-positive/HR-negative patients. HER2 overexpression in patients with breast cancer is associated with an increased risk of disease progression and death.

Treatments that suppress HER2 signaling improve disease control in patients with HER2-positive metastatic breast cancer. HER2-targeted therapy contributes to a more favorable treatment outcome in HER2-positive patients with metastatic breast cancer (9). Paul Ehrlich (1854-1915), Nobel Prize Winner (1908), introduced the word chemotherapy and set the concept of "magic bullet" which was the basis for target therapy.

Today many opportunities exist to target the HER2 receptor and downstream pathways: on extracellular domain there are monoclonal antibodies (i.e. trastuzumab, pertuzumab, T-DM 1), and on intracellular domain there are tyrosine kinase inhibitors like (lapatinib, neratinib, afatinib) and downstream inhibitors (i.e. everolimus, mTOR, BKM120, BEZ-235).

Trastuzumab is the first oncogene-targeted therapy that changes the prognosis of HER2-positive BC. The effect of trastuzumab is achieved through four mechanism of action:

- Activation of ADCC
- Prevention of the formation of $p95^{HER2}$, a truncated but very active form of HER2,
- Inhibition of cell proliferation, and
- Inhibition of HER2-regulated angiogenesis

One of the major mechanisms of action of trastuzumab is its ability to activate the body's own immune response, resulting in apoptosis of tumor cell via antibody-dependent cellular cytotoxicity (ADCC).

Anti-HER2 therapy (trastuzumab) in combination with chemotherapy, endocrine therapy or alone should be offered early to all HER2-positive MBC patients, who do not have contra-indications for these therapies (11, 12, 13, 14). Addition of trastuzumab to chemotherapy (paclitaxel and docetaxel) improves progression-free survival (PFS) and overall survival (OS) in the first-line treatment of HER2-positive MBC. With docetaxel, overall survival is prolonged for 8.5 months. Twenty-two percent of these patients lived longer than 4 years.

The best option for patients with HR+/HER2+ MBC is anti-HER2 therapy in combination with hormone therapy. Lapatinib in combination with letrozole improved PFS in HR-positive patients compared with letrozole alone (EGF30008) 8.2 months versus 3 months. In those patients, the response rate and clinical benefit were significantly greater than in patients treated in the control arm. According to the study TAnDEM, trastuzumab in the combination with anastrozole prolongs PFS in HR-positive patients, compared with anastrozole alone (TAnDEM).

On the bases of those facts, endocrine therapy alone is suboptimal, and these patients are often treated with chemotherapy and anti-HER2 therapy. However, the treatment approach should consider following:

- Patient characteristics (age, performance status)
- Tumor characteristics (ER, PR and HER2 status)
- Prognosis (slow, rapid progression)
- Metastasis status (visceral, non-visceral crisis)
- Patient's preference

The best option for the treatment of no visceral crisis and slow progression is anti-HER2 therapy and aromatase inhibitor, and for visceral crisis and rapid progression, it would be anti-HER2 therapy and chemotherapy. Despite the proved efficacy of the standard therapy, trastuzumab and chemotherapy, a proportion of patients with HER2-positive breast cancer will not respond, while the majority of HER2-positive patients responding to first- line therapy, trastuzumab, and chemotherapy, will progress within 1 year (11).

What are the options if a patient is progressed on trastuzumab? Continue anti-HER2 suppression.

For the second-line treatment, there are lapatinib in combination with capecitabine, trastuzumab in combination with other chemotherapy, and

treatment with new agents TDM1 and new combination lapatinib and trastuzumab.

Can we do more for the treatment of HER2-positive MBC in the future?

There is a great improvement in treatment of HER2 positive BC, which includes combining anti-HER2 agents; it allows a better potential for more complete treatment because of better blockade of HER2 receptor with two agents compared with a single agent alone.

This strategy includes:

- Combining agents targeting the extracellular domain on the HER2 receptor with Trastuzumab and Pertuzumab
- Combining agents targeting intra- and extracellular domains of the HER2 receptor – with trastuzumab and lapatinib (vertical dual blockade)

Trastuzumab and pertuzumab bind to different regions on HER2 and have synergistic activity. HER2 dimerizes preferentially with HER3 drive to downstream signaling. Pertuzumab is the first in a new class of targeted anticancer agents it prevents the formation of HER2:HER3 receptor. In addition, it is the inhibitor of HER2 dimerization. In the treatment of HER2-positive MBC, we target the HER2 receptor with two monoclonal antibodies in combination with chemotherapy.

Addition of pertuzumab to first-line chemotherapy-trastuzumab combination was associated with improved response rate, (PFS) and (OS) (15). Pertuzumab-trastuzumab and docetaxel is approved for patients with HER2-positive MBC who have not received previous anti-HER2 therapy or chemotherapy for metastatic breast cancer disease (CLEOPATRA study).

There are more options in the second-line treatment. There is the benefit of continuing anti-HER2 therapy after progression of disease. Continuing trastuzumab in combination with different chemotherapy regiment after the first disease progression is superior to chemotherapy alone. Lapatinib in combination with capecitabine for second-line treatment is approved for use in patients with HER2-positive MBC previously treated with anthracycline, taxane, and trastuzumab (16).

There are some other options in the second-line treatment of metastatic disease: vertical dual blockade (trastuzumab and lapatinib) or treatment with new agent trastuzumab-emtansine (T-DM1). Antibody-drug conjugate (ADC) is a unique combination of monoclonal antibody with targeted effect. ADC is designed to have a selective effect to malignant cells and kills them with a minimal damage for healthy tissue. T-DM1 was associated with improved progression-free survival (PFS) and overall survival (OS) (EMILIA study). A clinical benefit of trastuzumab-lapatinib combination (vertical dual blockade) has been confirmed; it prolongs progression-free survival and it has a significant benefit in overall survival (EGF-104900 study) (17, 18).

However, making treatment decisions is individual and it is driven by multiple factors: HER2 and HR status, symptoms, location of metastasis, previous treatment, disease free interval (DFI), adverse event (AE), patient preferences, and other.

Conclusion

HER2 targeted therapy in combination with standard therapy (chemotherapy and hormone therapy) prolongs survival in HER2-positive MBC. Anti-HER2 therapy should always be a part of each treatment line of MBC, including treatment beyond disease progression, which is recommended in ESMO treatment guidelines and NCCN guidelines from 2014.

Some questions remain open, including optimal duration of anti-HER2 therapy and the best treatment option at the time of disease progression on trastuzumab plus a cytotoxic agent.

In the end, I would like to remind to the words of professor Hordobghyi: "Our realistic expectation from existing treatments today is to stop the progression of disease and perhaps reduce tumor burden for some period. We can also control symptoms in the majority of patients – at least for some time. There is a small minority of patients in whom we can achieve a complete remission. Some patients remain without a recurrence for very long period of time."

TREATMENT OF METASTATIC TRIPLE NEGATIVE-BREAST CANCER

The triple negative breast cancer (TNBC) is a type of aggressive breast cancer that is characterized by the absence of the estrogen (ER), progesterone (PR) and human epidermal growth factor receptors 2 (HER2). About 10% to 25% of all breast cancers are TNBC (1, 19).

TNBC subgroups

At the molecular level, the TNBC is a heterogeneous tumor and it is comprised of six subgroups: basal like 1 (BL1), basal like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem cell (MSL), luminal androgen receptor (LAR) (2, 3, 20, 21).

Histopathological division

In the histopathological terms, the TNBC is invasive ductal carcinoma, not otherwise specified, in about 50% to 80% of the cases, lobular cancer in about 5% to 15%. The remaining 10% to 25% of the cases are less common subtypes such as mucinous, apocrine, metaplastic, medullar, and neuroendocrine. Most of these cancers are the grade 3 cancers (4, 5, 22, 23).

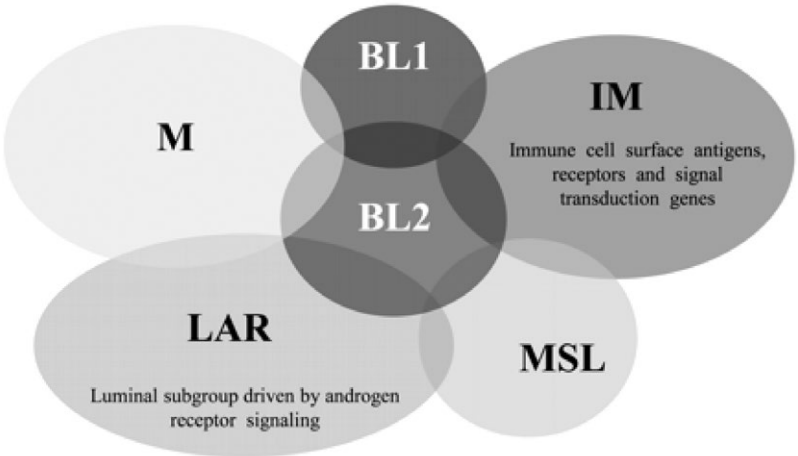

Figure 1. TNBC subgroups (2, 3)

Epidemiology and risk factors

TNBC accounts for approximately 15%-25%of all breast cancer cases. This type of cancer occurs more frequently with premenopausal women, African American women and women that had early menarche, multiparas, who breastfed their children for a short period. It occurs also in high body mass index women. In those who have poor socioeconomic status (6, 24).

Clinical characteristics

The disease relapse occurs most frequently between the first and third year from the time it was diagnosed. However, late relapses are rare. TNBC have greater hematogenous than lymphatic metastatic potential. More frequently affects parenchymatous organs, particularly the lungs, and the brain, with a more aggressive course in comparison to the non-TNBC (7, 25). The hormone and the target therapy with HER2 antagonists are not possible due to lack of the ER, PR, and HER2 receptors.

Gene aberrations

Different types of gene aberrations can be present in the TNBC, e.g. TP53, BRCA1, PIK3CA, *RB1, PTEN, MYO3A*, and *GH1* (6, 24).

EGFR and the androgen receptor expression are also present. These findings have made an implementation of the target therapy possible, primarily in the clinical trials that gave certain results.

STANDARDIZED THERAPY

According to Sledge, there is no standardized target therapy for the metastatic TNBC (mTNBC/) and currently, the standardized treatment for this kind of breast cancer is chemotherapy. Overall survival of mTNBC has not significantly improved in recent years. Conventional treatments for mTNBC are limited, particularly, because standard chemotherapeutic regimens containing anthracyclines and taxanes have usually been given in the adjuvant and neoadjuvant settings.

The cause of metastatic treatments failure is multidrug resistance to standardized therapy regimens (8, 26).

Trial pegylated liposomal doxorubicin (PLD) plus docetaxel (D) or docetaxel groups

The results (9, 27) of these trials can be summarized as:

- TTP 10 versus 7 months for docetaxel pegylated liposomal doxorubicin
- ORR 35% vs. 26% PLD/D vs. D
- OS similar between the two groups 20.6 months for the docetaxel monotherapy arm and 20.5 months for combination arm

Capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients

RR significantly superior: 42% of patients in the combination arm compared with 30% in the single-agent arm

OS 14.5 of patients in the combined arm compared with 11.5 months

Trials with gemcitabine-based regimen are presented in Table 1 (10)

Table 1. Results

TRIALS	ORR	Median survival Times/months/
Gemcitabine/Vinorelbine	39%	17.5
Gemcitabine/Cisplatin	48%	13.0
Gemcitabine/Capecitabine	35%	19.4

Platinum-based regimens:

Their use has been supported by the strong association of TNBC with germline mutations in the BRCA 1 gene. About 10% of TNBC are having BRCA 1 mutation**.** BRCA 1 mutation compromises the ability of the tumor to recover from DNA damaging agents by reducing their capacity for DNA repair by homologous recombination**.** Some trial showed efficacy in mTNBC (10, 11, 28, 29).

Table 2. Results

TRIALS	RR	OS
Platinum/Taxane	39% similar tonon TNBC	worse than non TNBC
Cisplatin/Gemcitabine	48%	13.0
Carboplatin/Cetuximab	17%	12.0

CMF regimen in mTNBC

Cyclophosphamide, methotrexate, and fluorouracil (CMF) regimen is rarely administered for metastatic breast cancer because it appears to produce the same response rate when compared to oral capecitabine 20% in one trial.

CMF results in a shorter OS (median, 22 vs. 18 months; HR 0.72; 95% CI, 0.55-0.94). CMF may be indicated in patients who cannot tolerate capecitabine or for patients in whom an oral regimen is not feasible for whatever reason (12, 30).

High-dose, dose-dense, and metronomic therapies

These therapy types have shown a certain benefit in mTNBC treatment in comparison to the response rate, but without significant effect to OS (13, 31).

Chemotherapy recommendations

Due to aggressive nature of the mTNBC, consensus groups recommend combined chemotherapeutic regimens in its treatment

Prognosis for patients with relapsed TNBC is very poor if they are treated with the conventional cytotoxic therapy, because the response duration in that case is usually short

Median OS for patients with mTNBC was 13 months, in comparison to median OS for the general metastatic breast cancer population that is 2.0 to 35 years.

Median response time to used chemotherapy is significantly decreased with the class of used therapeutic measure: first-line medications -12 weeks, second-line medications – 9 weeks, third-line medications - 4 weeks.

Molecularly targeted therapy

The findings of the molecular analysis in high expression level of the different genes linked to the growth and survival pathways like EGFR, VEGFR, and FGFR and increased activation of Akt that led to the set up of the different studies targeting these receptors and pathways (13, 31).

Bevacizumab

Angiogenesis inhibition

VEGF genotype for selected polymorphisms in VEGF and VEGF2 was found to be predictive of outcome to bevacizumab therapy

Bevacizumab therapy is, so far, the only target therapy that has been proven effective in mTNBC treatment.

Meta-analysis in 3 randomized trials (RIBBON-1, AVADO, ECOG 2100) of first-line bevacizumab and chemotherapy (docetaxel, paclitaxel, capecitabine) in mTNBC reported significant increase in PFS with the addition of the bevacizumab from 5.4 to 8.1 months. However, the statistically significant difference in OS in comparison to the patients that were not treated with bevacizumab has not been proven (14, 32).

Two non-interventional studies in patients with TNBC support these findings. ATHENA study results for TTP is 7.2 month and for median OS it is 18.3 months. GERMAN observational study group results for median PFS is 7.3 months (15, 33).

SURVIVAL BENEFIT

These trial studies could not show significant survival benefit in patients treated with Bevacizumab. Therefore, the FDA has not approved its use in metastatic breast cancer treatment. However, the European Medicines Agency and the NCCN, have approved the Bevacizumab as the First choice medication in the treatment of the MBC.

EGFR inhibition

Approximately 60% of basal like TNBC express EGFR. Cetuximab /Ct/ is a monoclonal antibody that binds to EGFR (16, 17, 34, 35).

Table 3. EGFR inhibition

TRIALS	First or second line	
Ct_+ Carboplatin	TBCRC001	RR 6% vs. 16%
Cisplatin +_Ct	BALI-1	PFS 1.5 vs. 3.7 OS 9.4 vs. 12.9
Irinotecan+carboplatin+-cetuximab	USOR 04070	RR 30% vs. 49% PFS 5.1 m vs. 4.7 m OS 12.3 m vs. 15.5 m

m - Months

As low as 25% of all tumors that express the EGFR, are sensitive to cetuximab. Accordingly, those patients should be identified prior to the beginning of the treatment. Those are the patients with a high expression of the PTEN, or lack of the KRAS, or low expression of the alpha crystal B chain.

mTOR inhibition

PTEN is protein that inhibits activation of the AKT/mTOR pathaway. mTOR activation could lead to cisplatin resistance.

Trial RAD001 with everolimus reported ORR of 12%. Ongoing trials define the role of the everolimus as a single therapy or combined with lapatinib or carboplatin (18, 36).

PARP Inhibitors

PARP1 is a gene that encodes an enzyme involved in the molecular reactions leading to cell recovery from DNA damage, but when inhibited, leads to the accumulation of double stranded DNA breaks.

Cells deficient in BRCA1and BRCA2 are exquisitely sensitive to PARP1 inhibition. Synergy action of the PARP1 inhibitors, iniparib /In/, with gemcitabine /G/ and cisplatin /C/ was the foundation for the trial research as a second- and a third-line medication in mTNBC treatment. The results for PFS per months are G/C 3.3% vs. G/C/In 6.9% and for OS per months they are G/C 7.7% vs. G/C/In 12.2%.

However, in case of the first-line medications, the results of the overall survival were not promising.

There is possibility of the efficient treatment if the iniparib is administered as the second- and third-line medication in the mTNBC treatment accompanying the chemotherapy (19, 37).

Ongoing researches of the potential new inhibitors FGFR, JAK2, and AR2 are aimed at targeting stem cells (20, 21, 38, 39).

Ongoing researches of the potential new inhibitors

New researches are focused to FGFR inhibitors, JAK2 inhibitors, AR2 inhibitors, and targeting stem cells (20, 21, 38, 39).

Conclusion

Due to molecular heterogeneity in the breast cancer of this kind, it is clear that there is no adequate therapy that would benefit all mTNBC patients.

Significant efforts are being made in the field of the TNBC research, in order to identify potential target cells and adequate target therapy (22, 40).

Due to the lack of the adequate target therapy, for now, the clinicians rely to chemotherapy.

Accordingly, we may quote Sledge: ''Chemotherapy, for now, is the sole standard in the mTNBC treatment'' (8, 26).

However, a significant effort is being made in the field of predicative markers, TNBC subgroups, research that could help in the choice of the adequate target therapy.

The combined therapy could possibly lead to a better disease control and consequently to an increase in the survival rate of the mTNBC patients.

Consequently, the mTNBC target therapy regimens could be standardized in the future.

Conflict of interest

We declare no conflicts of interest.

REFERENCES:

1 Yarden Y, Sliwkowski MX. Untangling the ErbB signaling network. *Nat Rev Mol Cell Biol*. 2001;2:127–37.

2 Gullick WJ. The type 1 growth factor receptors and their ligands considered as a complex system. *Endocr Relat Cancer*. 2001;8:75–82.

3 Rowinsky EK. Signal events: cell signal transduction and its inhibition in cancer. *Oncologist*. 2003;8:5–17.

4 Hsieh AC, Moasser MM. Targeting HER proteins in cancer therapy and the role of the non-target HER3. *Br J Cancer*. 2007;97:453–7.

5 Slamon DJ, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science.* 1989;244:707–12.

6 Sliwkowski MX. In: Harris JR, Lippman ME, Morrow M, Osborne CK, editors. Diseases of the breast. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 415–26.

7 Wolff AC, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol.* 2007;28(1):118–45.

8 Prenzel N, et al. The epidermal growth factor receptor family as a central element for cellular signal transduction and diversification. *Endocr Relat Cancer.* 2001;8:11–31.

9 Dawood S, et al. Prognosis of women with metastatic breast cancer by *HER2* status and trastuzumab treatment: an institutional-based review. *J Clin Oncol.* 2010;28:92–8.

10 Goldhirsch A, et al. Strategies for subtypes – dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann Oncol*. 2011;22:1736-47.

11 Slamon DJ, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med.* 2001;344:783-92.

12 Marty M, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol.* 2005;23:4265-74.

13 Mackey J. Trastuzumab prolongs progression-free survival in hormone-dependent and HER2-positive metastatic breast cancer. Presented at the 29th SABCS, San Antonio, Texas, USA, 14-17 December, 2006.

14 Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E. Locally recurrent or metastatic breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;23(7):11-9.

15 Baselga J, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366:109-19.

16 Geyer CE, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med*. 2006;355:2733-43.

17 Blackwell KL, Burstein HJ, Sledge GW, Stein S, Ellis C, Casey M, et al. Updated survival analysis of a randomized study of lapatinib alone or in combination with trastuzumab in women with HER2-positive metastatic breast cancer progressing on trastuzumab therapy. Oral presentation at the 32nd Annual SABCS, San Antonio, Texas, USA, 9-13 December 2009.

18 Blackwell KL, Burstein HJ, Storniolo AM, Rugo H, Sledge G, Koehler M, et al. Randomized study of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. *J Clin Oncol*. 2010.

19 Aysola K, et al. Triple Negative Breast Cancer - An Overview. *Hereditary Genetics*. 2013: S2.

20 Williams N. TNBC in post genomic era. *Oncol J*. 2013;27(9):859-64.

21 Perou CM. Molecular stratification of triple negative breast cancers. *Oncologist*. 2011;Suppl 1:61-70.

22 Penault F, et al. Pathological and molecular diagnosis of triple-negative breast cancer: a clinical perspective. *Ann Oncol.* 2012;23.

23 Dreyer G, et al. Triple Negative Breast Cancer: Clinical characteristics in the different histological subtypes. *The Breast*. 2013;16.

24 Aysal, et al. Hereditary Triple Negative Breast Cancer-An Overview. *Hereditary Genetics.* 2013; S2.

25 Foulkes W, et al. Triple-Negative Breast Cancer. *N Engl J Med*. 2010;363:1938-48.

26 Sledge G. Advances in Advanced TNBC. *Breast.* 2013;ABC2:22

27 Sparano J, et al. Pegylated Liposomal Doxorubicin Plus Docetaxel Significantly Improves Time to Progression Compared With Docetaxel Monotherapy in Patients With Advanced Breast Cancer Previously Treated With Neoadjuvant-Adjuvant Anthracycline: Results From a Phase III Study, San Antonio Breast Cancer Symposium, December 10-14, 2008.

28 Koshy N, et al. Cisplatin- gemcitabine therapy in metastatic breast cancer: Improved outcome in triple negative breast cancer patients compared to non-triple negative patients. *Breast*. 2010;19(3):246-8.

29 Fan Y, et al. Docetaxel/Cisplatin vs. Docetaxel/Capecitabine. *Ann Oncol.* 2013;24:1219-25.

30 Joensuu H, Gligorov J. Adjuvant treatments for triple – negative breast cancers. *Ann Oncol*. 2012; 23 Suppl 6:40–5.

31 Nieto Y, et al. High dose chemotherapy for high risk primary and metastatic breast cancer is another look waranted? *Curr Opin Oncol.* 2009;21.

32 O'Shaughnessy J, et al. Meta-analysis of patients with triple-negative breast cancer (TNBC) from three randomized trials of first-line bevacizumab (BV) and chemotherapy treatment for metastatic breast cancer (MBC). Proceedings of the 33rd Annual CTRC-AACR San Antonio Breast Cancer Symposium. December 8–12, 2010, San Antonio, TX; AACR Philadelphia, PA: Abstr P6-12-03.

33 Thomssen C, et al. First-line bevacizumab combination therapy in triple-negative locally recurrent/metastatic breast cancer; subpopulation analysis of study MO19391 (ATHENA) in 2000 patients. Proceedings of the 32nd Annual CTRC-AACR San Antonio Breast Cancer Symposium. December 9–13, 2009, San Antonio, TX; AACR Philadelphia, PA: Abstr 6093.

34 Baselga J, et al. Cetuximab + cisplatin in estrogen receptor-negative, progesterone receptor-negative, HER2-negative (triple-negative) metastatic breast cancer: results of the randomized phase II BALI-1 trial. Proceedings of the 33rd Annual CTRC-AACR San Antonio Breast Cancer Symposium. December 8–12, 2010, San Antonio, TX; AACR Philadelphia, PA: Abstr PD01-01.

35 Carey LA, et al. TBCRC 001: EGFR inhibition with cetuximab added to carboplatin in metastatic triple-negative (basal-like) breast cancer. *J Clin Oncol.* 2008;26. Abstr 1009.

36 Singh J, et al. RAD001-Carboplatin combination in TNBC. *J Clin Oncol.* 2013;31:Abstr.1042.

37 O' Shaughnessy, et al. Randomised phase III study iniparib in combination with gemcitabine/carboplatin in metastatic TNBC. *J Clin Oncol*. 2011;29.

38 Niemeier LA, et al. Androgen receptor in breast cancer: expression in receptor positiveand receptor negative tumors with apocrine differentiation. *Modern Pathol J UD Can Acad Pathol Inc.* 2010;205-12.

39 Bayraktar S, et al. Molecularly targeted therapies for metastatic triple- negative breast cancer. *Breast Cancer Res Treat.* 2013:138(1):21-35.

40 Arnedos M, et al. Triple Negative Breast Cancer Are We Making Headway at least, *Ther Adv Med Oncol*. 2012;4:195-210.