Tips and tricks in triple-negative breast cancer: how to manage patients in real-life practice?

M Piccart¹,², G Viale³,⁴, P Ellis⁵,⁶, M Abramowicz⁷,⁸ and L Carey⁹

¹Free University of Brussels, Brussels, Belgium
²Department of Medicine, Jules Bordet Institute, Brussels, Belgium
³University of Milan School of Medicine, Milan, Italy
⁴Division of Pathology and Laboratory Medicine, European Institute of Oncology, Milan, Italy
⁵Guy’s Hospital, London, UK
⁶Cancer Medicine, King’s College, London, UK
⁷Department of Genetics, Centre of Human Genetics, Hôpital Erasme, Brussels, Belgium
⁸Human and Medical Genetics, Free University of Brussels, Belgium
⁹Department of Medicine, Division of Hematology/Oncology, University of North Carolina, Chapel Hill, North Carolina, USA

Correspondence to Martine Piccart. Email: martine.piccart@bordet.be

Published: 19/07/2011
Received: 04/07/2011

eccancer 2011, 5:217 DOI: 10.3332/ecancer.2011.217

Copyright: © the authors; licensee ecancermedicalscience. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
Introduction

This article has been developed following, and drawing on the content of, a satellite meeting at the fifth International Breast Cancer Conference, held in Paris, France, on 29 January 2011. The purpose of the meeting was to examine several questions relating to triple-negative breast cancer (TNBC):

- How should TNBC be defined?
- Are there clinically important TNBC subtypes?
- Should patients be given adjuvant or neoadjuvant treatment for TNBC?
- Should patients with TNBC and their families have genetic tests?
- How should relapsing or metastatic TNBC be treated?

Using a real-life case study, at each stage of the patient care pathway from diagnosis through assessment to treatment, the audience was encouraged to vote on potential decisions, before an expert panel on which we all sat discussed the evidence and presented what we consider constitutes best clinical practice.

In this article we share the proceedings of the meeting, which we believe contained valuable educational content of potential interest to the wider healthcare community.

Case study

Carole is a 37-year-old primary school teacher, with a husband and two young children (a 7-year-old daughter and a 3-year-old son). She presented, in January 2010, with a palpable large tumour mass (6 cm) in her right breast. She was diagnosed with a right mammary tumour (T4N2), with carcinomatous mastitis and four suspicious lymph nodes. Biopsy confirmed a grade 3 invasive ductal carcinoma that was negative for oestrogen receptors (ER), progesterone receptors (PgR) and human epidermal growth factor receptor 2 (HER2).

How should TNBC be defined?

Audience voting

When offered potential definitions for ER or PgR negativity, most of the audience (58%) agreed on a cutoff of 1% positive cells, although around a third would use 10% as a cutoff. Most participants (89%) would use fluorescence in situ hybridization (FISH) to confirm HER2 status if the immunohistochemistry (IHC) test was 2+; in some countries (such as Belgium), FISH testing is mandatory for trastuzumab reimbursement, regardless of IHC score.

Expert opinion of Professor Giuseppe Viale

Concordance on thresholds for defining ER and PgR negativity is vital to ensure that pathologists and clinicians describe and treat patients consistently. The joint American Society of Clinical Oncology (ASCO) and College of American Pathologists guidelines on IHC testing in breast cancer [1] have specified a cutoff of 1% immunoreactive cells.
There is a concern that patients with 1–10% immunoreactive cells are not responsive to endocrine therapy; however, review of patients recruited into clinical trials of tamoxifen and aromatase inhibitors has shown that these patients have a greater benefit from endocrine treatment than those who have less than 1% immunoreactive cells. The question should not be “Is it worth treating this patient?” but rather “Am I sure I can deny this patient the possible benefit of endocrine treatment?”

Pathologists need to confirm the lack of immunoreactive cells (negative ER status) in the tissue sample by a positive control in normal ducts to avoid any false negative reports and to be assured of the sensitivity and specificity of the assay. Evidence shows that there is much room for improvement in accuracy, with up to 20% false-negative results for ER/PgR, more than 12% false-positive results for PgR, and up to 15% false-positive results for HER2 [2].

Are there clinically important TNBC subtypes?

Audience voting

Most participants would not request additional tumour analyses (e.g. epidermal growth factor receptor (EGFR), cytokeratin 5/6, 14 and 17). The audience was divided almost equally over the issue of histological subtyping for patients who have been classified as having TNBC.

Expert opinion of Professor Giuseppe Viale

Patients with TNBC have some typical features, as shown in Table 1 [3,4], but there is a great heterogeneity in the underlying pathological tumour type (Table 2). The vast majority of tumours (70–85% [5,6]) are invasive ductal carcinomas not otherwise specified, but there are many other TNBC tumour subtypes and prognosis varies greatly. The answer to the question “Are you interested in subtyping TNBC?” should be “yes!”

Around 80% of TNBC has a basal-like gene expression [7]. Basal-like breast cancer is defined by expression of around 500 different messenger RNA molecules. At the messenger RNA level, such tumours have a relatively high expression of a number of markers, including cytokeratin 5 and 17, EGFR, KIT, laminin, collagen type XVII, calponin 1 and calveolin 2, and a relatively low expression of ER or HER2. Currently, assessment of these markers has no impact on clinical treatment decisions, although the potential prognostic implications of surrogate markers is being investigated.

When confronted with an apparently triple-negative tumour, pathologists should follow a hierarchical approach to assessment, focusing first on morphology to identify the subtypes with a good prognosis (i.e. adenoid-cystic, medullary, metaplastic low-grade, apocrine

| Table 1: Typical clinical and pathological features of triple-negative breast cancer (ref. [3,4]). |
|---------------------------------------------------------------|---------------------------------------------------------------|
| Clinical | Younger patients (47–55 years) |
|          | African-American women |
|          | BRCA1 mutations |
| Pathological features | High grade, high mitotic count |
|          | Pushing borders (recalls medullary cancer of breast) |
|          | Geographic necrosis, central fibrosis |
|          | Stromal lymphocytic infiltrate |
|          | Metaplasia |
|          | Prevalence of brain and lung metastases even if the patient has negative lymph nodes |
low-grade). They should then confirm that the immunophenotype is truly nonendocrine-responsive (with <1% ER/PgR immunoreactive cells, and no false-negative results) and reassess equivocal IHC results. Further phenotyping could be performed for investigational purposes.

In summary, the definition of TNBC needs to be standardized and agreed by the international community. Clinicians need to understand the differences between TNBC and basal-like breast cancer and the importance of using a hierarchical approach to diagnosis, focusing on thorough evaluation of morphological features, followed by accurate assessment of receptor status (ER, PgR and HER2), with use of surrogate IHC markers or gene expression profiling assays to identify basal-like carcinomas if deemed appropriate.

**Should patients be given adjuvant or neoadjuvant chemotherapy for TNBC?**

**Audience voting**

Given a choice of potential treatments for Carole, the patient in this case study, 40% of the audience opted for neoadjuvant chemotherapy alone and 38% would consider additional adjuvant chemotherapy depending on pathological response to neoadjuvant treatment. The most popular selection of neoadjuvant chemotherapy was a sequential regimen of anthracycline followed by taxane (48%) or combination of these agents (38%). Around 13% of participants would consider neoadjuvant platinum-based treatment.

**Case study**

In January 2010, the patient was started on a dose-dense epirubicin + cyclophosphamide regimen followed by weekly paclitaxel 80 mg/m². After four cycles of the anthracycline treatment, there was evidence of a slight decrease in tumour size but lymph nodes were still palpable. After 12 weeks of paclitaxel, the patient had clinical and radiological improvement (no lymph nodes, no measurable disease). After tumorectomy and axillary lymph-node dissection in June 2010, the patient had no residual tumour and no lymph-node involvement (pT0N0).

| Tumour description                                      | Prognosis              |
|----------------------------------------------------------|------------------------|
| Invasive ductal carcinoma not otherwise specified, high grade | Poor                   |
| Invasive lobular carcinoma, pleomorphic type, high grade  | Poor                   |
| Metaplastic or myeloblastic carcinoma, high grade         | Poor                   |
| High-grade oat-cell neuroendocrine tumours               | Poor                   |
| Apocrine breast cancers (some may be HER2⁺)              | Depends on grade:      |
|                                                           | Grade 1 = good         |
|                                                           | Grade 2 = intermediate  |
|                                                           | Grade 3 = poor         |
| Medullary                                                | Good                   |
| Adenoid-cystic                                           | Good                   |
| Metaplastic low-grade (low-grade adenosquamous, fibromatosis like) | Good |
**Expert opinion of Professor Paul Ellis**

Using pathological complete response (pCR) as a surrogate endpoint, there is evidence that TNBC is a chemo-responsive disease, with pCR rates of 20–45% after anthracycline or anthracycline/taxane-based treatments [8–11]. These rates are similar to those achieved in women with HER2* disease, and substantially better than in endocrine-responsive disease. However, as Figure 1 shows, although patients with TNBC who achieve a pCR have a good prognosis, those without a pCR have a poor outcome, with a higher risk of relapse [10].

Neoadjuvant therapy may not have a role in all patients (e.g. those with small tumours that can be treated with surgery and standard adjuvant chemotherapy) but its use in many patients makes sense—in particular those in whom breast conservation is not possible or who have clinically involved nodes. In clinical trials, neoadjuvant therapy helps to address questions about treatment choices—an example would be the use of different chemotherapy backbones to support novel therapeutic approaches such as inhibitors of poly-(ADP) ribose polymerase (PARP)—and to use translational research to identify subgroups of TNBC patients who might benefit from different treatments.

Anthracyclines are commonly used in TNBC, and there is clinical trial evidence of a survival benefit versus no treatment (hazard ratios ranging from 0.35 (95% confidence interval 0.18–0.68) for nonbasal subtypes to 0.54 (0.27–1.08) for basal subtypes [12].) Furthermore, compared with cyclophosphamide + methotrexate + 5-fluorouracil, patients with TNBC achieved a superior benefit from anthracyclines [13], although the MA5 study [14] found the opposite result in a relatively small group of patients receiving cyclophosphamide + methotrexate + 5-fluorouracil or cyclophosphamide + epirubicin + 5-fluorouracil.

A meta-analysis of randomized trials has shown docetaxel to be as effective in TNBC as in non-TNBC patients in terms of disease-free survival (Figure 2) [15]: the hazard ratios for docetaxel versus no docetaxel were 0.67 (95% confidence interval 0.50–0.90) in 2,296
TNBC patients (five studies) and 0.73 (0.61–0.88) in 2,089 non-TNBC patients (three studies). A similar benefit has been confirmed for paclitaxel [16]. Therefore, it seems reasonable that full-dose anthracycline/taxane-based therapy should be the standard of care for TNBC patients.

Data for platinum agents are less mature, although a number of studies in the neoadjuvant setting suggest a benefit in terms of pCR rates, particularly in patients with BRCA mutations (72% pCR with cisplatin [17]). However, in less selected TNBC patients, the pCR rates are only around 15–30% with cisplatin [18,19] and 22–40% with carboplatin [19–22]. A number of questions about platinum agents remain to be answered, such as the choice of agent and the relative benefit versus nonplatinum chemotherapies. For the time being, although they show promise, they should not yet be considered the standard of care in the neoadjuvant or adjuvant setting.

The potential impact of targeted therapies is being explored in TNBC. Evidence suggests that the addition of bevacizumab to an anthracycline/taxane combination may be beneficial in ER-negative patients, although there is no benefit in the whole breast cancer population [23]. The addition of bevacizumab to chemotherapy is also being explored in the BEATRICE study [24]. A range of PARP inhibitor studies, being developed by different cooperative groups, could provide information on ways to optimize chemotherapy in the neoadjuvant treatment of TNBC.

In summary, the evidence supports anthracycline/taxane combination therapy for early TNBC. The patient should receive a full course of treatment, whether in the neoadjuvant or the adjuvant setting. If she has received the full course before surgery, there is no need for further adjuvant chemotherapy outside a clinical trial. Our challenge is to help those patients who we know will do badly if they do not achieve a pCR, ideally exploring the use of new therapies with minimal use of cytotoxic agents.

Should patients and their families have genetic tests?

**Case study**

The familial history should be assessed in all young women with breast cancer. In this case study, Carole’s mother was diagnosed with hormone-sensitive breast cancer at the age of 56 years but there is no other confirmed case in the maternal family.
**Audience voting**

Two thirds of the audience would look for a genetic mutation (specifically BRCA1 and possibly BRCA2) in this patient. Assuming a genetic mutation was found, around a quarter of participants would screen the patient's sisters as well, although very few would screen further family members.

**Expert opinion of Professor Marc Abramowicz**

Only a small minority of breast cancers are due to a hereditary mutation in a single gene (perhaps 5% [25]). Inherited mutations usually involve the BRCA1 or BRCA2 gene. Some families, however, have other mutations, which may not always be easy to identify with existing techniques.

When deciding whether to test a woman for a hereditary mutation, it must be borne in mind that other members of the family will be affected too, although it may not be feasible to test everyone at first. Furthermore, the result of the test does not guarantee that breast cancer will or will not develop. A sister without the mutation may still have breast cancer by chance, whereas many women with mutations do not develop the disease [26]. Nonetheless, women can be assigned to risk categories to determine appropriate risk-reducing and management strategies.

Only a minority of TNBC patients are BRCA1 carriers, even in conspicuous familial cases when both the mother and daughter had onset in their early 30s [27]. As a result, it would be inappropriate to assess all TNBC patients for BRCA1 mutations: such testing would be labour-intensive and expensive, and would result in too many false-negatives and false-positives (i.e. genetic variants that do not result in disease), with associated mistaken reassurances or psychological impact on family members. Therefore, ASCO recommends that genetic testing should be performed in selected patients with personal or family history features suggesting a genetic cancer susceptibility (Table 3), with appropriate genetic counselling [28]. The test needs to be adequately interpreted and must be able to provide results that can guide diagnosis or treatment decisions for the patient or family members.

For Carole, in this case study, her father’s family history should be reviewed too, as men can also transmit mutations. As she had TNBC before the age of 50 years, she should be considered for BRCA1 testing. If she is found to have a BRCA1 mutation, her sisters should be offered testing, as should her daughter when she is an adult (i.e. around 20 years old). Her mother should also be tested, even though she has a history of ER-positive disease.

**How should recurring or metastatic TNBC be treated?**

| Features suggestive of hereditary cancer among first-degree relatives (second-degree if paternal) |
| --- |
| • Two women with breast cancer diagnosed before the age of 50 years |
| • One woman with breast cancer diagnosed before 50 years + one woman with ovarian cancer at any age or + one woman with bilateral breast cancer at any age |
| • Four women with breast cancer only |
| • One woman with breast + ovarian cancer |
| • One woman with breast cancer diagnosed before the age of 30 years |
| • One woman with triple-negative breast cancer diagnosed before 50 years |

| Offer genetic counselling before testing |
| Test affected family members first (i.e. those with history of breast cancer) |

---

Table 3: Personal or familial features suggestive of hereditary cancer, as a guide for genetic testing (adapted from ASCO 2003 [26]).
Case study

Despite having achieved a pCR in June, Carole experienced a rapid cutaneous relapse and neuropathic pain. On clinical examination in October 2010, she was found to have skin infiltration and a right axillary mass. Imaging showed right diffuse carcinomatous mastitis, and there was evidence of axillary and retroperitoneal para-aortic lymph-node involvement.

Audience voting

More than half of the audience suggested entering her into a clinical trial of a PARP inhibitor. Other options included platinum-based or taxane-based (docetaxel + capecitabine or gemcitabine; paclitaxel + bevacizumab) chemotherapy.

Expert opinion of Professor Lisa Carey

The heterogeneity described earlier for TNBC continues to manifest when the disease progresses to the metastatic stage. Slowly progressive or asymptomatic patients with small metastases present a different challenge from those with rapidly progressive, symptomatic disease, although in all cases the disease is not curable.

In asymptomatic patients, the goals of treatment are to control disease (i.e. to stop the tumour from growing, rather than trying to reduce tumour size) without exposing the patient to undue toxicity. In such patients, sequential single agents are the norm (if there is no appropriate clinical trial), and the choice depends on patient convenience, comorbidities and previous toxicities (95% of patients have already received neoadjuvant or adjuvant chemotherapy [29]). Possible treatments include taxanes, anthracyclines (e.g. liposomal doxorubicin), capecitabine, platinum agents, other microtubule-directed agents, vinorelbine and gemcitabine.

In patients with rapidly progressive and symptomatic metastatic disease, there is little need to balance efficacy and tolerability of treatments, because the disease is likely to cause more toxicity than therapy would. The goal of treatment is to achieve a tumour response, and combination regimens always have higher response rates than single agents. Options include combinations involving bevacizumab, docetaxel + capecitabine, paclitaxel + gemcitabine, and ixabepilone + capecitabine.

As with the neoadjuvant and adjuvant settings, the jury is still out on the benefit of platinum-based treatments in the metastatic setting. Cisplatin monotherapy achieved only a 10% response rate in largely treatment-naive patients [30]. Carboplatin monotherapy achieved a 17% response rate in patients who were largely pretreated with an EGFR inhibitor [31]. Until the results of further clinical trials are available, platinum-based treatment should probably not be a standard of care, although it could be considered in later lines of treatment for metastatic TNBC.

Novel anticancer agents such as PARP inhibitors and iniparib are eliciting a great deal of interest currently, although none is yet available outside clinical trials. Most data are available for iniparib, which is provoking most excitement in the setting of sporadic (i.e. not BRCA1-associated) TNBC. Iniparib does not possess characteristics typical of the PARP inhibitor class and investigations are currently in progress to elucidate its main mechanism of action. The recently published phase II study demonstrated that the addition of iniparib to gemcitabine + carboplatin improved the clinical benefit and survival of patients with metastatic TNBC, compared with chemotherapy alone, without significantly increased toxic effects (Figure 3) [32]. However, in the pivotal phase III trial, iniparib demonstrated activity but did not meet the statistically rigorous primary endpoint [33], although it is possible that subsets within the larger trial will demonstrate benefit; those analyses are ongoing.

Questions that remain to be answered include: Is DNA damage stimulus needed in non-BRCA+ tumours? Might PARP inhibitors and iniparib work in any breast cancer or will the benefit be seen only in TNBC patients? What secondary effects might occur with prolonged prevention of DNA damage repair?
Conclusions

In the opinions of this expert panel, three factors are critical when considering a patient with TNBC and deciding how best to manage her disease:

- The quality of the initial pathology
- The possibility of a genetic mutation, and the impact on the wider family
- The challenges posed by the heterogeneity of the disease and the range of treatment options available

Breast cancer mortality is decreasing [34], but most benefits are seen in patients with ER-positive or HER2-positive disease. The only way that treatment for TNBC can improve is through clinical trials of new agents and new strategies. Therefore all patients should be encouraged to participate in clinical trials.

Acknowledgements

The authors thank Succinct Healthcare Communications for medical writing support, which was funded by Sanofi. The authors retain full control of content.

References

1. Hammond ME, Hayes DF, Dowsett M et al (2010) American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version) Arch Pathol Lab Med 134 e48–e72 PMID: 20586616
2. McCullough AE, Dell’Orto P, Reinholz MM et al (2010) Concordance of HER2 central assessment by two international central laboratories: a ring study within the framework of the adjuvant HER2-positive ALTTO trial (BIG2-06/N063D/EGF106708) Cancer Res 70 (Suppl) Abstract P3-10-36

3. Reis-Filho JS, Tutt AN (2008) Triple negative tumours: a critical review Histopathology 52 108–118 PMID: 18171422

4. Diaz LK, Cryns VL, Symmans WF, Sneige N (2007) Triple negative breast carcinoma and the basal phenotype: from expression profiling to clinical practice Adv Anat Pathol 14 419–430 PMID: 18049131

5. Oakman C, Viale G, Di Leo A (2010) Management of triple negative breast cancer Breast 19 312–321 PMID: 20382530

6. American Cancer Society. Breast cancer. Available at: <http://www.cancer.org/acs/groups/cid/documents/webcontent/003090-pdf.pdf> (accesses June 2011).

7. Nielsen TO, Hsu FD, Jensen K et al (2004) Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma Clin Cancer Res 10 5367–5374 PMID: 15328174

8. Rouzier R, Perou CM, Symmans WF et al (2005) Breast cancer molecular subtypes respond differently to preoperative chemotherapy Clin Cancer Res 2005 11 5678–5685 PMID: 16115903

9. Carey LA, Dees EC, Sawyer L et al (2007) The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes Clin Cancer Res 13 2329–2334 PMID: 17438091

10. Liedtke C, Mazouni C, Hess KR et al (2008) Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer J Clin Oncol 26 1275–1281 PMID: 18250347

11. Straver ME, Glas AM, Hannemann J et al (2010) The 70-gene signature as a response predictor for neoadjuvant chemotherapy in breast cancer Breast Cancer Res Treat 119 551–558 PMID: 19214742

12. Conforti R, Boulet T, Tomasic G et al (2007) Breast cancer molecular subclassification and estrogen receptor expression to predict efficacy of adjuvant anthracyclines-based chemotherapy: a biomarker study from two randomized trials Ann Oncol 18 1477–1483 PMID: 17515403

13. Di Leo A, Isola J, Piette F et al (2008) A meta-analysis of phase III trials evaluating the predictive value of HER2 and topoisomerase II alpha in early breast cancer patients treated with CMF or anthracycline-based adjuvant therapy Poster presented at the 31st Annual San Antonio Breast Cancer Symposium, San Antonio, Texas, USA, December 2008; Abstract 705

14. Cheang M, Chia SK, Tu D et al (2009) Anthracyclines in basal breast cancer: the NCIC-CTG trial MA5 comparing adjuvant CMF to CEF J Clin Oncol 27 (Suppl) Abstract S19

15. Laporte S, Jones S, Chapelle C, Jacquin J, Martin M (2009) Consistency of effect of docetaxel-containing adjuvant chemotherapy in patients with early stage breast cancer independent of nodal status: meta-analysis of 12 randomized clinical trials Cancer Res 69 (Suppl 3) Abstract 605

16. Hayes DF, Thor AD, Dressler LG et al (2007) HER2 and response to paclitaxel in node-positive breast cancer N Engl J Med 357 1496–1506 PMID: 17928597

17. Gronwald J, Byrski T, Huzarski T et al (2009) Neoadjuvant therapy with cisplatin in BRCA1-positive breast cancer patients J Clin Oncol 27 (Suppl) Abstract 502

18. Ryan PD, Tung NM, Isakoff SJ et al (2007) Neoadjuvant cisplatin and bevacizumab in triple negative breast cancer (TNBC): safety and efficacy J Clin Oncol 27 (Suppl) Abstract 551

19. Leone JP, Guardiola V, Venkatraman A et al (2009) Neoadjuvant platinum-based chemotherapy (CT) for triple-negative locally advanced breast cancer (LABC): retrospective analysis of 125 patients J Clin Oncol 27 (Suppl) Abstract 625
20. Sikov WM, Dizon DS, Strenger R et al (2009) *Frequent pathologic complete response in aggressive stages II to III breast cancers with every-4-week carboplatin and weekly paclitaxel with or without trastuzumab: a Brown University Oncology Group Study* J Clin Oncol 27 4693–4700 PMID: 19720916

21. Torrisi R, Balduzzi A, Ghisini R et al (2008) *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 62 667–672 PMID: 18064460

22. Silver DP, Richardson AL, Eklund AC et al (2010) *Efficacy of neoadjuvant cisplatin in triple-negative breast cancer* J Clin Oncol 28 1145–1153 PMID: 20100965

23. von Minckwitz G, Eidtmann H, Loibl S et al (2011) *Integrating bevacizumab, everolimus, and lapatinib into current neoadjuvant chemotherapy regimen for primary breast cancer. Safety results of the GeparQuinto trial* Ann Oncol 22 301–306 PMID: 20624784

24. ClinicalTrials.gov (2010) *BEATRICE study: a study of Avastin (bevacizumab) adjuvant therapy in triple negative breast cancer* Available at: http://www.clinicaltrials.gov/show/NCT00528567 (accessed June 2011)

25. Wooster R, Weber BL (2003) *Breast and ovarian cancer* N Engl J Med 348 2339–2347 PMID: 12788999

26. Struewing JP, Hartge P, Wacholder S et al (1997) *The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews* N Engl J Med 336 1401–1408 PMID: 9145676

27. Mavaddat N, Pharoah PD, Blows F et al (2010) *Familial relative risks for breast cancer by pathological subtype: a population-based cohort study* Breast Cancer Res 12 R10 PMID: 20482762

28. American Society of Clinical Oncology (2003) *American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility* J Clin Oncol 21 2397–2406

29. Koshy N, Quispe D, Shi R, Mansour R, Burton GV (2010) *Cisplatin-gemcitabine therapy in metastatic breast cancer: improved outcome in triple negative breast cancer patients compared to non-triple negative patients* Breast 19 246–248 PMID: 20227277

30. Baselga J, Gomez P, Awada A et al (2010) *The addition of cetuximab to cisplatin increases overall response rate and progression-free survival in metastatic triple-negative breast cancer: results of a randomized phase II study (BALI) Ann Oncol 21* (Suppl 8) Abstract 2740

31. Carey LA, O'Shaughnessy JA, Hoadley K et al (2009) *Potential predictive markers of benefit from cetuximab in metastatic breast cancer: an analysis of two randomized phase 2 trials* Cancer Res 69 (Suppl 3) Abstract 2014

32. O'Shaughnessy J, Osborne C, Pippen JE et al (2011) *Iniparib plus chemotherapy in metastatic triple-negative breast cancer* N Engl J Med 364 205–214 PMID: 21208101

33. O'Shaughnessy J, Schwartzberg LS, Danso MA et al (2011) *A randomized phase III study of iniparib (BSI-201) in combination with gemcitabine/carboplatin (G/C) in metastatic triple-negative breast cancer (TNBC)* J Clin Oncol 29 (Suppl) Abstract 1007

34. Peto R, Boreham J, Clarke M, Davies C, Beral V (2000) *UK and USA breast cancer deaths down 25% in year 2000 at ages 20-69 years* Lancet 355 1822