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Breast cancer – where are we standing in 2011?

Rak piersi – stan wiedzy w 2011 roku

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S u m m a r y

Breast cancer is one of the major health and social problems in women. Due to the wide application of screening programs and to improvements in treatment, breast cancer mortality in some countries has decreased by more than 30% over the last twenty years. Advances in breast cancer management include also the decreasing negative impact of therapy on patients' quality of life. This is mostly achieved by substituting major, mutilating surgery with organ-sparing or reconstructive procedures. The progress in systemic treatment of breast cancer is mostly related to the developments in molecular biology and a better understanding of breast cancer pathomechanisms, including identification of molecular subtypes of breast cancer by multigene assays. This has led to a profound modification of treatment strategies in early breast cancer. Failure risk has now been substituted as the main factor driving treatment decision-making by biology of tumor and likely sensitivity to particular treatment modalities. Most important achievements include also the development of trastuzumab and lapatinib – molecularly "targeted" compounds directed against HER2. Development of targeted therapy includes not only designing targeted agents but also identification of constitutive predictive features of particular patients, which may allow individual tailoring of systemic therapies. Among these, most interest is raised by polymorphisms of the cytochrome P450 2D6 – an enzyme involved in the metabolism of tamoxifen. Ongoing research will hopefully result in further improvements in prognosis and quality of life of breast cancer patients.

Key words: breast cancer, molecular subtypes, treatment, targeted therapy, predictive factors

S t r e s z c z e n i e

Rak piersi j jednym z najważniejszych problemów zdrowotnych i społecznych u kobiet. Dzięki upowszechnieniu programów badań przesiewowych i poprawie skuteczności leczenia, w niektórych krajach w ciągu ostatnich 20 lat udało się doprowadzić do obniżenia współczynników umieralności na ten nowotwór o około 1/3. Postępy w leczeniu raka piersi obejmują również ograniczenie niekorzystnego wpływu terapii na jakość życia chorych. Osiągane jest to głównie przez zastępowanie okaleczających procedur chirurgicznych zabiegami oszczędzającymi i rekonstrukcyjnymi. Postęp w leczeniu systemowym wiąże się przede wszystkim z osiągnięciami biologii molekularnej i lepszym zrozumieniem patomechanizmów raka piersi, w tym ze zidentyfikowaniem podtypów molekularnych raka piersi przy pomocy badań ekspresji wielogenowej. Doprowadziło to do znaczących zmian w strategii leczenia wczesnego raka piersi poprzez zastąpienie ryzyka nawrotu jako podstawowego czynnika determinującego wybór strategii leczenia charakterystyką biologiczną nowotworu i przewidywanym prawdopodobieństwem odniesienia korzyści z poszczególnych metod leczenia. Najważniejsze osiągnięcia obejmują też wprowadzenie leków ukierunkowanych molekularnie przeciwko receptorowi HER2: trastuzumabu i lapatynibu. Rozwój terapii ukierunkowanych molekularnie oznacza nie tylko tworzenie leków „celowanych", ale również identyfikację czynników predykcyjnych, pozwalających na wyodrębnienie chorych mających wysokie prawdopodobieństwo odpowiedzi na leczenie. Największe zainteresowanie budzi tutaj polimorfizm cytochromu P450 2D6 – enzymu uczestniczącego w metabolizmie tamoksyfenu. Prowadzone obecnie badania pozwalają mieć nadzieję na dalszą poprawę wyników leczenia i jakości życia chorych na raka piersi.

Słowa kluczowe: rak piersi, podtypy molekularne, leczenie, terapie ukierunkowane molekularnie, czynniki predykcyjne

Breast cancer is one of the major health and social problems in women. In 2007, almost 14,500 new cases and over 5,200 breast cancer deaths were noted in Poland, making it the most frequent female malignancy and the second most common cause of cancer death (1).

Over the last years, significant progress has been made in the management of breast cancer. The most impressive data come from the United Kingdom, where more than a 1/3 relative decrease in breast cancer mortality was noted over the last twenty years (fig. 1) (2). A similar trend can also be observed in many

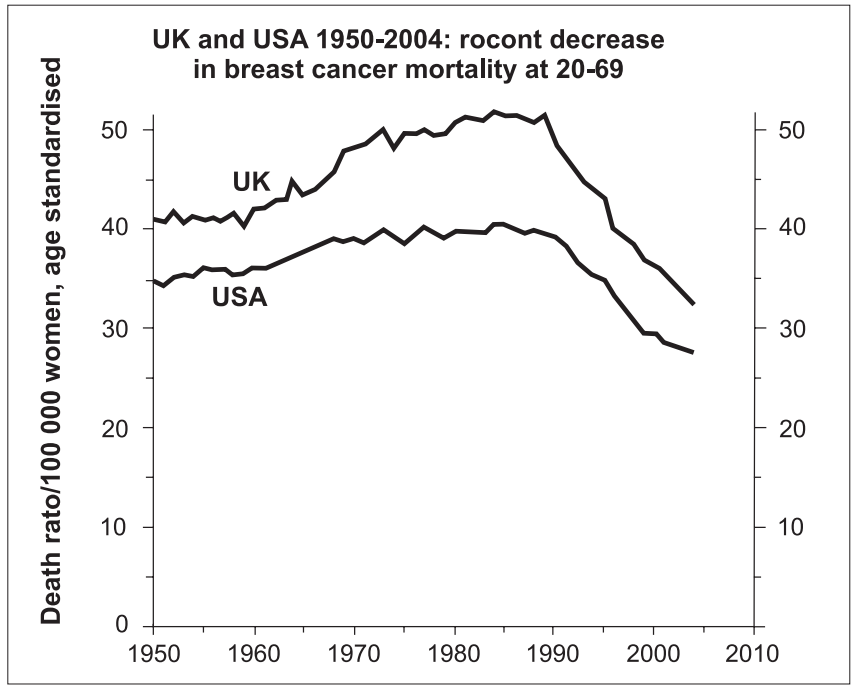

Fig. 1. Decrease in breast cancer mortality in United Kingdom and USA (based on) (2).

other countries but, unfortunately, not in Poland (1). This phenomenon is mostly related to the wide application of screening programs allowing for early diagnosis of malignancy and to improvements in the treatment of breast cancer, in particular of early disease.

Advances in breast cancer management implemented over the last years include not only improvement of treatment outcomes but also decreasing harm of anti-cancer treatment in terms of patients' quality of life. The latter may be attributed both to technological progress and to changes in the paradigms of surgical treatment, in particular substituting major, mutilating surgery with organ-sparing or reconstructive procedures. Currently, a significant fraction of early breast cancer patients undergo breast-conserving treatment and the development of oncoplastic surgical techniques allows for an effective combination of oncological safety and good cosmesis (3, 4). Patients not amenable to breast-saving therapies may benefit from a large array of breast-reconstructive surgical techniques.

A tendency to decrease the extent of surgery also applies to axillary lymph nodes. This is exemplified by the increasing use of sentinel lymph node technology, which in node negative patients allows for the omission of axillary lymph node dissection (5). As a consequence, the risk of arm lymphedema (which is a frequent complication of axillary lymphadenectomy, in particular when followed by postoperative radiotherapy) is markedly decreased.

The progress in systemic treatment of breast cancer is mostly related to the developments in molecular biology and a better understanding of breast cancer pathomechanisms. One of the most remarkable steps was the identification of molecular subtypes of breast cancer, based on multigene assays (6). These studies showed a number of distinct molecular breast cancer subtypes (luminal A, luminal B, basal, HER2+, normal breast-like) with various clinical behavior, prognosis and response to therapy. In consequence, these subtypes are currently considered separate clinical entities. Some of the multigene assays based on gene microarray technology have become commercially available and are accepted as ancillary tools in treatment decision-making in early breast cancer (7, 8). Better understanding of tumor biology has led to a profound modification of treatment strategies in early breast cancer. In particular, failure risk (which is directly related to tumor bulk and extent) has been substituted as the main factor driving treatment decision-making by biology of tumor and probability of benefit from a particular treatment modality (9).

As a result of studies on molecular pathomechanisms, a number of new "targeted" compounds have been developed and become available for breast cancer patients. **Of these, a particularly important one is trastuzumab – a humanized monoclonal antibody against HER2.** HER2 is a molecule belonging to the family of epidermal growth factor receptors and its overexpression or gene amplification in breast cancer cells (assessed by immunohistochemistry or *in situ* hybridization, respectively) is associated with shorter disease-free and overall survival (10).

Unlike most of the targeted agents, trastuzumab, when added to standard chemotherapy, was found to provide overall survival benefit in HER2 positive metastatic breast cancer patients. In the pivotal study, the median overall survival in patients treated with chemotherapy and trastuzumab was almost five months longer than with chemotherapy alone (11). In the subsequent randomized phase II study, the difference in median overall survival between chemotherapy + trastuzumab vs chemotherapy alone arms was even greater

(over eight months, p = 0.0325) (12). Trastuzumab is generally well tolerated, with the main clinically relevant toxicity being cardiac dysfunction. This side-effect was observed mostly when trastuzumab was combined with anthracyclines and, in contrast to anthracycline-related damage, it is usually reversible and probably does not lead to long term sequelae. Moreover, with proper cardiac medication, this toxicity does not preclude further treatment with trastuzumab (13).

Over the next years, the efficacy of trastuzumab was also demonstrated in a series of randomized trials in patients with early breast cancer, as an adjunct to adjuvant chemotherapy (14, 15, 16). Trastuzumab given for one year was demonstrated to decrease the risk of progression and death by almost a half (combined odds ratio 0.53 and 0.52, respectively) (17). Interestingly, although the majority of studies assessed the use of trastuzumab for one year, a similar magnitude of benefit was demonstrated in a small Finnish study employing a mere nine-week trastuzumab administration (18). Studies assessing optimal duration of adjuvant trastuzumab treatment are now under way.

HER2 pathway in breast cancer may also be targeted by other compounds, of which lapatinib is the only commercially available agent as of 2011. Lapatinib is a small molecule tyrosine kinase inhibitor of HER2 and HER1 (although the latter seems of no clinical relevance in breast cancer). It was first demonstrated to improve progression-free survival when added to capecitabine in HER2 positive advanced breast cancer patients progressing after treatment with anthracyclines, taxanes and trastuzumab (19) and became the second targeted treatment option in HER2 positive breast cancer patients. Later, the efficacy of lapatinib was also demonstrated in the first-line setting in metastatic breast cancer (20). Unfortunately, no direct comparison of trastuzumab and lapatinib efficacy has been performed but some data suggest additional benefit from combining these two compounds in advanced breast cancer patients progressing after trastuzumab treatment (21). In this study, patients progressing on prior trastuzumab-containing regimens were randomly assigned to receive either lapatinib alone or in combination with trastuzumab. Improved progression-free survival (HR 0.73, 95% CI, 0.57 to 0.93) and a trend for improved overall survival (HR = 0.75, 95% CI, 0.53 to 1.07) were observed in the combination arm.

The issue of continuing trastuzumab beyond progression remains a matter of debate. In "classical" oncology, the general rule was to terminate ineffective therapies at disease progression. This may not necessarily apply to targeted therapies, which have different modes of action. There has been a number of retrospective studies supporting the strategy of continuing trastuzumab administration in progressing patients. More recently, also the randomized German Breast Group study demonstrated a value of continuation of trastuzumab in combination with capecitabine in patients progressing while on trastuzumab (22). However, owing to the small size of this study, the real benefit of this approach and its efficacy vs switching to lapatinib remains to be determined. A number of other compounds targeting the HER2 pathway (pertuzumab, neratinib, trastuzumab-DM1) are now in advanced stages of clinical development and it is hoped they will become available in the clinic soon.

Much of clinical research in oncology focuses on inhibition of angiogenesis. Unfortunately, in contrast to some other malignancies, breast cancer studies up to date have generally been unsuccessful. Although the pivotal E2100 study showed promising doubling of median progression-free survival by the addition of bevacizumab to chemotherapy, this compound has never been demonstrated to improve overall survival in advanced breast cancer patients (23). Subsequent studies and the metaanalysis confirmed some benefit of addition of bevacizumab to chemotherapy in terms of progression-free survival (albeit of remarkably small degree), but failed to demonstrate an impact on overall survival (24, 25, 26, 27). The data on small molecule kinase inhibitors targeting angiogenesis-related pathways have been even more disappointing, with no improvement in either progression-free or overall survival from the addition of sunitinib to standard chemotherapy (28, 29).

One of the reasons for the generally disappointing results of angiogenesis inhibition in breast cancer may be the lack of predictive factors allowing for selection of patients with higher probability of benefit. The search for efficient predictive factors is, apart from the development of new drugs and treatment algorithms, one of the most important directions of clinical research in breast cancer. As of 2011, only estrogen and progesterone receptors and HER2 status are generally accepted and used for therapeutic decision-making in breast cancer (9). A number of other biomarkers, including multigene assays, have been demonstrated to correlate with prognosis and may facilitate patient selection for adjuvant treatments. Interesting data have been published on a number of putative predictive factors but further research is needed before their introduction into routine practice in breast cancer.

Among these predictive factors, the most interesting include polymorphisms of the cytochrome P450 2D6 (CYP2D6) enzyme involved in the metabolism of tamoxifen (which is a prodrug) into its active metabolite – endoxifen. In some studies, a better outcome was demonstrated in so-called "extensive metabolizers" (i.e. patients with both alleles coding for more active version of the enzyme) than in "intermediate" and "poor metabolizers" (30). Interestingly, an effect similar to that observed in "poor metabolizers" was seen in patients administered potent CYP2D6 in-

hibitors during tamoxifen treatment. The lack of consistency between studies and the unavailability of a standardized, validated test feasible for use in every-day practice preclude the use of CYP2D6 polymorphisms determination in routine care; nevertheless tamoxifen-treated breast cancer patients should be advised to avoid using strong CYP2D6 inhibitors (31).

At present, routinely available predictive factors are used in decision-making regarding the use of targeted therapy (anti-HER2 therapies) and hormonotherapy (which in fact is the oldest form of "targeted" therapy, directed against estrogen-activated pathways in cancer cells). Considerable room for improvement exists also in the more tailored use of standard chemotherapy agents. Currently, there are no accepted biomarkers which can guide chemotherapy choice in breast cancer (9). It has, however, been well documented that the expression of steroid receptors correlates negatively with overall tumor sensitivity to chemotherapy (32). **Regarding the prediction of sensitivity to particular cytotoxic agents, the greatest interest is probably focused on the potential role of topoisomerase IIα as a predictor of anthracycline sensitivity.** Topoisomerase IIα is a molecular target for anthracyclines and some studies have suggested good correlation between its alterations and favorable outcome of anthracycline treatment (33). Topoisomerase IIα amplification can probably explain the increased sensitivity of HER2 positive tumors to anthracycline treatment. As there is no plausible explanation of direct interaction between HER2 and anthracycline mode of action, most probably HER2, which gene is located on chromosome 17q in the close vicinity of topoisomerase IIα gene (and both genes are often co-amplified), is just a surrogate marker for topoisomerase IIα activity (34, 35).

Another interesting molecular mechanism which may be responsible for increased sensitivity to some cytotoxic agents and may create room for a new class of targeted drugs is related to mutation or dysfunction of *BRCA1* gene (so called "BRCAness"). *BRCA1* gene product is responsible for DNA damage repair by homologous recombination and its shortage results in alternative pathways of repair, including base excision repair pathway. Inhibition of poly(ADP-ribose) polymerase (PARP), which is an important mediator of this pathway, is a promising therapeutic opportunity in these tumors (36). Recently, compounds inhibiting PARP have demonstrated very promising activity in clinical trials (37, 38). The value of most of these new strategies and drugs warrants confirmation in well-designed prospective clinical studies.

Extensive research conducted in the field of molecular pathology and mechanisms of breast cancer has greatly improved our understanding of this disease and has resulted in significant modifications in treatment philosophy. Currently, treatment decision is dependent predominantly on tumor biology, rather than on bulk of disease and recurrence risk (9). A number of new molecularly targeted compounds have led to significant outcome improvements in many patients and it is hoped that future research will pave the way to further improvements in prognosis and quality of life of breast cancer patients.

BIBLIOGRAPHY

1. Didkowska J, Wojciechowska U, Zatoński W: Nowotwory złośliwe w Polsce w 2007 roku. Centrum Onkologii Instytut im. M. Skłodowskiej-Curie, Warszawa 2009.
2. Peto R: The worldwide overview: new results for systemic adjuvant therapies, Abstr. 30th Annual San Antonio Breast Cancer Symposium, 2007.
3. Reintgen C, Reintgen D, Solin LJ: Advances in local-regional treatment for patients with early-stage breast cancer: a review of the field. Clin Breast Cancer 2010; 10: 180-7.
4. Lebovic GS: Oncoplastic surgery: a creative approach to breast cancer management. Surg Oncol Clin N Am 2010; 19: 567-80.
5. Veronesi U, Viale G, Paganelli G et al.: Sentinel lymph node biopsy in breast cancer: ten-year results of a randomized controlled study. Ann Surg 2010; 251: 595-600.
6. Sørlie T, Perou CM, Tibshirani R et al.: Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA 2001; 98 (19): 10869-74.
7. Paik S, Shak S, Tang G et al.: A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004; 351 (27): 2817-26.
8. van de Vijver MJ, He YD, van't Veer LJ et al.: A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 2002; 347 (25):1999-2009.
9. Goldhirsch A, Ingle JN, Gelber RD et al.: Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. Ann Oncol 2009; 20: 1319-29.
10. Press MF, Bernstein L, Thomas PA et al.: HER-2/neu gene amplification characterized by fluorescence in situ hybridization: poor prognosis in node-negative breast carcinomas. J Clin Oncol 1997; 15: 2894-904.
11. Slamon DJ, Leyland-Jones B, Shak S 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, Cognetti F, Maraninchi D 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. Ewer MS, Vooletich MT, Durand JB et al.: Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. J Clin Oncol 2005; 23: 7820-6.
14. Romond EH, Perez EA, Bryant J et al.: Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005; 353: 1673-84.
15. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al.: Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005; 353: 1659-72.
16. Slamon D, Eiermann W, Robert N et al.: Phase III Randomized Trial Comparing Doxorubicin and Cyclophosphamide Followed by Docetaxel (ACT) with Doxorubicin and Cyclophosphamide Followed by Docetaxel and Trastuzumab (ACTH) with Docetaxel, Carboplatin and Trastuzumab (TCH) in Her2neu Positive Early

Breast Cancer Patients: BCIRG 006 Study. Cancer Res 2009; 69 (24 Suppl): Abstr. 62.
17. Viani GA, Afonso SL, Stefano EJ et al.: Adjuvant trastuzumab in the treatment of her-2-positive early breast cancer: a meta-analysis of published randomized trials. BMC Cancer 2007; 7: 153.
18. Joensuu H, Bono P, Kataja V et al.: Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. J Clin Oncol 2009; 27: 5685-92.
19. Geyer CE, Forster J, Lindquist D et al.: Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006; 355: 2733-43.
20. Di Leo A, Gomez HL, Aziz Z et al.: Phase III, double-blind, randomized study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer. J Clin Oncol 2008; 26 (34): 5544-52.
21. Blackwell KL, Burstein HJ, Storniolo AM 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; 28: 1124-30.
22. von Minckwitz G, du Bois A, Schmidt M et al.: Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. J Clin Oncol 2009; 27: 1999-2006.
23. Miller K, Wang M, Gralow J et al.: Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007; 357: 2666-76.
24. Miles DW, Chan A, Romieu G et al.: Final Overall Survival (OS) Results from the Randomised, Double-Blind, Placebo-Controlled, Phase III AVADO Study of Bevacizumab (BV) Plus Docetaxel (D) Compared with Placebo (PL) Plus D for the First-Line Treatment of Locally Recurrent (LR) or Metastatic Breast Cancer (mBC). Cancer Res 2009; 69 (24 Suppl): Abstr. 41.
25. Robert N, Dieras V, Glaspy J et al.: Clinical Benefit Rate and Time to Response in RIBBON-1, a Randomized, Double-Blind, Phase III Trial of Chemotherapy with or without Bevacizumab (B) for the First-Line Treatment of HER2-Negative Locally Recurrent or Metastatic Breast Cancer (MBC). Cancer Res 2009; 69 (24 Suppl): Abstr. 6084.
26. Brufsky A, Bondarenko IN, Smirnov V et al.: RIBBON-2: A Randomized, Double-Blind, Placebo-Controlled, Phase III Trial Evaluating the Efficacy and Safety of Bevacizumab In Combination with Chemotherapy for Second-Line Treatment of HER2-Negative Metastatic Breast Cancer. Cancer Res 2009; 69 (24 Suppl): Abstr. 42.
27. O'Shaughnessy J, Miles D, Gray RJ et al.: A meta-analysis of overall survival data from three randomized trials of bevacizumab (BV) and first-line chemotherapy as treatment for patients with metastatic breast cancer (MBC). J Clin Oncol 2010; 28:15s, (suppl; abstr 1005).
28. Bergh J, Greil R, Voytko N et al.: Sunitinib (SU) in combination with docetaxel (D) versus D alone for the first-line treatment of advanced breast cancer (ABC). J Clin Oncol 2010; 28: 18s, (suppl; abstr LBA1010).
29. Crown J, Dieras V, Staroslawska E et al.: Phase III trial of sunitinib (SU) in combination with capecitabine (C) versus C in previously treated advanced breast cancer (ABC). J Clin Oncol 2010; 28: 18s, (suppl; abstr LBA1011).
30. Goetz MP, Knox SK, Suman VJ et al.: The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. Breast Cancer Res Treat 2007; 101: 113-21.
31. Sideras K, Ingle JN, Ames MM et al.: Coprescription of tamoxifen and medications that inhibit CYP2D6. J Clin Oncol 2010; 28: 2768-76.
32. Berry DA, Cirrincione C, Henderson IC et al.: Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. JAMA 2006; 295: 1658-67.
33. O'Malley FP, Chia S, Tu D, Shepherd LE et al.: Topoisomerase II alpha and responsiveness of breast cancer to adjuvant chemotherapy. J Natl Cancer Inst 2009; 101: 644-50.
34. Gennari A, Sormani MP, Pronzato P et al.: HER2 status and efficacy of adjuvant anthracyclines in early breast cancer: a pooled analysis of randomized trials. J Natl Cancer Inst 2008; 100: 14-20.
35. Slamon DJ, Press MF: Alterations in the TOP2A and HER2 genes: association with adjuvant anthracycline sensitivity in human breast cancers. J Natl Cancer Inst 2009; 101: 615-8.
36. Farmer H, McCabe N, Lord CJ et al.: Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005; 434 (7035): 917-21.
37. O'Shaughnessy J, Osborne C, Pippen J et al.: 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: 18s, 2009 (suppl; abstr 3).
38. Tutt A, Robson M, Garber JE et al.: Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet 2010 Jul 5. (Epub ahead of print).

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