Breast Cancer 2012 – New Aspects

Mammakarzinom 2012 – neue Aspekte

Authors

H.-C. Kolberg¹, D. Lüftner², M. P. Lux³, N. Maass⁴, F. Schütz⁵, P. A. Fasching⁶, T. Fehm⁷, W. Janni⁸, S. Kümmel⁹

Affiliations

The affiliations are listed at the end of the article

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- GAIN

Schlüsselwörter

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Correspondence

Prof. Peter A. Fasching, MD
University Hospital Erlangen
Department of Gynecology
and Obstetrics
Universitätsstraße 21–23
91054 Erlangen
peter.fasching@uk-erlangen.de

Abstract

Treatment options as well as the characteristics for therapeutic decisions in patients with primary and advanced breast cancer are increasing in number and variety. New targeted therapies in combination with established chemotherapy schemes are broadening the spectrum, however potentially promising combinations do not always achieve a better result. New data from the field of pharmacogenomics point to prognostic and predictive factors that take not only the properties of the tumour but also inherited genetic properties of the patient into consideration. Current therapeutic decision-making is thus based on a combination of classical clinical and modern molecular biomarkers. Also health-economic aspects are more frequently being taken into consideration so that health-economic considerations may also play a part. This review is based on information from the recent annual congresses. The latest of these are the 34th San Antonio Breast Cancer Symposium 2011 and the ASCO Annual Meeting 2012. Among their highlights are the clinically significant results from the CLEOPATRA, BOLERO-2, EMILIA and SWOG S0226 trials on the therapy for metastatic breast cancer as well as further state-of-the-art data on the adjuvant use of bisphosphonates within the framework of the ABCSG-12, ZO-FAST, NSABP-B34 and GAIN trials.

Introduction

Therapy for breast cancer has undergone appreciable changes in the past decades [1,2]. The conscientious assessment of the invasiveness of an intervention in the human body and the benefit with regard to reduced mortality and recurrence

Zusammenfassung

Die Behandlungsoptionen und auch die Charakteristika zur Therapieentscheidung der Patientin mit einem primären und fortgeschrittenen Mammakarzinom werden immer vielfältiger. Neue zielgerichtete Therapien in Kombination mit etablierten Chemotherapien erweitern das Spektrum, doch potenziell vielversprechende Kombinationen bringen nicht immer ein besseres Ergebnis. Neueste Daten aus der Pharmakogenomik weisen auf Prognose- und Prädiktivfaktoren hin, die nicht nur die Eigenschaften des Tumors, sondern auch die vererbten genetischen Eigenschaften der Patientin berücksichtigen. Die aktuelle Therapieentscheidung ist somit mittlerweile eine Kombination aus klassischerweise klinischen und modernen molekularen Biomarkern. Immer häufiger werden auch gesundheitsökonomische Aspekte berücksichtigt, sodass auch gesundheitspolitische Überlegungen eine Rolle spielen können. Dieser Übersichtsartikel baut auf den aktuellen Kongressen auf, die jedes Jahr stattfinden. Die letzten berücksichtigten sind hierbei das 34. San Antonio Breast Cancer Symposium und das ASCO Annual Meeting 2012. Zu deren Highlights zählen die klinisch bedeutsamen Ergebnisse der Studien CLEOPATRA, BOLERO-2, EMILIA und SWOG S0226 zur Therapie des metastasierten Mammakarzinoms sowie weitere aktuelle Daten zum adjuvanten Einsatz der Bisphosphonate im Rahmen der Studien ABCSG-12, ZO-FAST, NSABP-B34 und GAIN.

rates has been even further refined since the introduction of breast-conserving therapy with radiotherapy of the breast and since the introduction of chemotherapy. Nowadays, the aims of modern therapy are an exact adaptation of the therapy not only towards the aggressiveness of the disease but also towards the individual thera-

peutic response of the patients as well as possible undesired side effects. This is being realised not only by the development of new drugs but also by the integration into modern study designs of individual biomarkers that can predict the efficacy and side effects of a drug. This review considers recent congresses, e.g., the San Antonio Breast Cancer Symposium in December 2011 and the ASCO Annual Meeting 2012 as a basis to reflect upon the current status of breast cancer therapy and to report on recent developments.

Local Therapies

Sentinel node biopsy and axillary staging

The introduction of breast-conserving therapy with subsequent radiotherapy was one of the major successes in local therapy that markedly improved the patients' quality of life without jeopardising oncological safety [3,4]. Similarly, the introduction of the sentinel lymph node biopsy technique clearly reduced [6] the previously high prevalence of lymph oedema accompanying breast cancer [5]. Since then there has been a paradigm change in the management of axillary lymph nodes that is still a subject of controversial discussion [7]. In the guidelines of Commission Mamma of the working committee for gynaecological oncology [Arbeitsgemeinschaft für Gynäkologische Onkologie (AGO; www.ago-online.de)] there is a recommendation to avoid completion of axillary staging in favour of a systematic dissection of levels I and II, both in cases of micrometastases in sentinel lymph nodes and in cases with less than 3 lymph nodes with macrometastases in those patients in whom a breast-conserving therapy with subsequent whole-breast radiation is planned.

It has not yet been finally clarified whether the lack of a therapeutic effect of axillary dissection is a result of the systemic therapy decision or an unplanned therapeutic effect of the tangential radiation, more data are required [7].

In the IBCSG 23-01 trial, 931 patients with micrometastases in sentinel lymph nodes were randomised into a wait-and-see group and to a systematic axillary dissection group [8]. 75% of the patients received breast-conserving therapy and about 90% received postoperative radiotherapy. Unfortunately recruitment was terminated prematurely (recruitment target was 1960 patients) because it proceeded too slowly and less events occurred than expected. At the time point of evaluation the median follow-up period amounted to 49 months. The disease-free survival (DFS) after 5 years showed no differences and amounted to 88.4% for the group without axillary dissection ($n=467$) and 87.3% for the group with axillary dissection ($n=464$). The overall survival was excellent and the same in both groups with 98% after 5 years [8]. In spite of the poor recruitment and the lack of stratification according to the type of breast operation and radiotherapy performed, these data impressively demonstrate that in cases of micrometastases in sentinel lymph nodes a systematic axillary dissection is not indicated [9–12]. When these results are considered in the light of the data from the NSABP-B32 trial [12], the question arises as to which patients – if any – after SNLB with affected sentinel lymph nodes require an axillary dissection. In NSABP-B32 with over 4000 patients no differences in recurrence rate or overall survival were found between patients with affected sentinel lymph nodes and those with free sentinel lymph nodes [12]. Data from Guiliiano also did not reveal any differences between patients with affected and free sentinel lymph nodes [11]. The discussion on the therapeutic value of axillary dissec-

tion is not new [10], however, one should remember that the value of axillary staging lies above all in triage. Patients with 3 and more affected lymph nodes benefit from a dose-dense chemotherapy [9]. In so far the recommendation of AGO not to undertake an axillary dissection in cases with up to 2 affected SLN is a consequent and reasonable guideline for routine daily counselling of patients (www.ago-online.de).

Radiotherapy: partial breast radiation with brachytherapy

According to the Commission Mamma of the AGO whole-breast radiotherapy with or without boost is the current standard treatment after breast-conserving surgery for invasive breast cancer [13]. The external boost is more and more being replaced by intraoperative irradiation with an electron beam or X-rays or by interstitial brachytherapy. Radiation with these techniques alone is still an experimental procedure since no robust data on the long-term results are available [14, 15].

Even so, the techniques of partial breast radiation, especially in older patients, are in use in the USA also outside of clinical trials [16]. In a retrospective study the data from a statutory health insurance (Medicare) of patients after whole breast irradiation (WBI) were compared with those of patients after accelerated partial breast brachytherapy (APBB) [16]. Altogether 130,535 women over 66 years of age were identified for whom costs of one of the above-mentioned therapy options were reimbursed by public health insurances between 2000 and 2007. In 2000 the proportion of APBB amounted to only about 1%, but rose to 13% in 2007. On average patients receiving APBB were older, more ill and less frequently had affected lymph nodes or received chemotherapy. The authors defined the rate of secondary mastectomies as parameter for the failure of local therapy. After 5 years the rate for the APBB group was significantly higher than that for the WBI group (APBB: 4.0% WBI: 2.2%, $p < 0.001$). Also acute complications were less favourable for the APBB group than for the group with whole breast irradiation (hospitalisation for APBB: 9.6%; for WBI: 5.7%, $p < 0.001$; infection for APBB: 8.1%; for WBI: 4.5%, $p < 0.001$). The same picture is seen on considering the long-term complications which were also less favourable for the brachytherapy group (rib fractures for APBB: 4.2%; for WBI: 3.6%; necrosis of adipose tissue for APBB: 9.1%; for WBI: 3.7%; pain for APBB: 14.9%; for WBI: 11.7%; p for all comparisons < 0.001). Only the incidence of pneumonitis was more favourable for the APBB group, 0.1%, than that for the WBI group, 0.8% ($p < 0.001$). Because of the retrospective design and the poorly balanced groups, Smith et al. did not interpret their data as evidence for the inferiority of brachytherapy but rather as an urgent appeal to await the results of randomised trials before widely using such methods outside of an experimental setting [16].

This needs to be emphasised with all due clarity. It is disturbing that in the USA 13% of the investigated patients were treated by a method for which practically no data are available. There is a danger that promising therapeutic options may thus be discredited even before their efficacy and risks can be assessed.

DCIS: assessment of prognosis

The standard in the local treatment of ductal carcinoma in situ (DCIS) is the breast-conserving operation with subsequent whole breast irradiation without boost or mastectomy. After it had been attempted for many years to identify a group of patients who would not benefit from irradiation, in the current guidelines of the Commission Mamma of the AGO there is a general recom-

mendation for irradiation without identification of various different risk groups. According to the currently available data the omission of irradiation generally increases the risk of recurrence without compromising the overall survival [17–19]. However, for a meaningful counselling of patients with DCIS about their risk of recurrence and the absolute risk of doing without radiotherapy, the necessary robust data are still lacking.

In the trial E5194 of ECOG, 670 patients in whom a DCIS had been operated by a breast-conserving method were examined. The cancer-free margins were defined as ≥ 3 mm, 228 patients were given tamoxifen, and no patient was irradiated. The recurrence rates found in this group varied widely in dependence on age, size of the lesion and its stage. Only for the group with high-grade-DCIS could it be shown independently that the recurrence risk in the absence of radiotherapy was unacceptably high [20]. In a more recent analysis by the same research group, 327 patients of the main trial were examined with regard to molecular markers. Using paraffin block techniques, molecular markers were examined for expression by means of PCR. A modified Recurrence score® (Oncotype DX®) in order to predict the recurrence risk for DCIS was developed with these markers [21]. The 10-year risk for a local recurrence for the entire cohort was 15.4% (invasive: 5.6%) for well or moderately differentiated DCIS and 5.1% (invasive: 9.8%) for poorly differentiated DCIS whereby the results of grading between local and central pathology exhibited large differences. The results modified according to the new DCIS score after a median follow-up of 8.8 years are presented in the following **Table 1**.

The significant relationship presented in the **Table 1** between the risk groups and recurrence risk was independent of the use of tamoxifen and the size of the disease-free margins. The classic Recurrence score® did not show any relationship with the local events.

The new DCIS score consists of the prospectively investigated test that quantitatively assesses the recurrence risk and complements classic prognostic factors. However, at first it has only been examined for patients who did not receive any radiotherapy. Accordingly, it is a new option for risk assessment in breast-conserving DCIS surgery that can be used for patient counselling prior to surgery.

Neoadjuvant Therapy

After the establishment of neoadjuvant therapy for the treatment of breast cancer in the 1990s, German trial groups in particular contributed to the integration of this therapy concept into the routine management of patients and to the fact that the results obtained thereby could be used for research purposes. This is reflected in the multitude of large, randomised trials [22–27]. Also,

Table 1 Probability for a local recurrence (LRFS) after DCIS in dependence on the expression of several genes [21] (* p = 0.02; ** p = 001).

DCIS score risk group	n	LRFS for ipsilateral local recurrence (invasive or DCIS)*	LRFS for ipsilateral invasive local recurrence**
Low (< 39)	246	12%	5.1%
Intermediate (39–54)	45	24.5%	8.9%
High (≥ 55)	36	27.3%	19.1%

the establishment of pathologically complete remission (pCR) as an extremely strong surrogate marker for the prognosis of patients in some molecular subgroups clearly illustrated the strength of this therapy concept in the identification of resistance to chemotherapy and its significance for prognostic assessment [27]. In addition, important information on the use of new drugs in this therapeutic situation was gathered.

Anti-HER2-therapy with pertuzumab in the neoadjuvant situation

In the four-armed NeoSphere trial the neoadjuvant dual HER2-antibody blockade with pertuzumab (P) and trastuzumab (T) as well as docetaxel (D) was compared with the dual blockade alone or the respective antibody alone in combination with docetaxel in patients with HER2-positive breast cancer [28]. The dual blockade in combination with docetaxel exhibited a significant improvement in the pCR rate without any relevant differences in toxicity (pCR for P+T+D 45.8%; 95% CI: 36.1–55.7 vs. pCR for T+D 29.0%; 95% CI: 20.6–38.5; p=0,0141). The combination of pertuzumab and trastuzumab without chemotherapy surprisingly reached a pCR rate of 16.8% (95% CI: 10.3–25.3) with a favourable tolerance profile [29].

Unfortunately, a comprehensive search for biomarkers to demonstrate a response to the therapy presented in San Antonio 2011 failed to yield any convincing data. All parameters proved to be inadequate in clinical routine and were unable to provide a supplement or alternative to the usual determination of HER2 by means of immunohistochemistry or FISH testing and so could not serve as good surrogate markers for a response to therapy. Even the great expectations that had been placed on the marker p95 could not be fulfilled.

It is well known that cardiac safety is of particular interest in an anti-HER2-targeted therapy. The cardiac safety of the combination of the two substances (trastuzumab and pertuzumab) was examined more closely in the neoadjuvant Tryphaena trial (phase II study) on 225 HER2-positive patients. The presented trial results revealed a low incidence of symptomatic and asymptomatic left ventricular systolic dysfunction (LVSD) and, with regard to a decrease of the left ventricular ejection fraction (LVEF), no significant differences were found between the 3 treatment groups A–C (arm A: 3 × FEC + H + P followed by 3 × Doc + H + P; arm B: 3 × FEC followed by Doc + H + P; arm C: 6 × docetaxel + carboplatin + H + P) (**Fig. 1**) [30].

At the time of the presentation merely 16% of the study population had completed the adjuvant part of the treatment. Concerning toxicity, more grade 3 and higher toxicities were observed in arm C, even when the differences with regard to the respective symptom did not appear to be large. The pCR rate is a component of the secondary trial objective of this study, defined as ypT0/is, i.e., in-situ residues were allowed. Here pCR rates of ca. 60% were achieved (arm A: 61.6%, arm B: 57.3%, arm C: 66.2%). Especially the group of hormone receptor-positive patients, who otherwise usually exhibit poorer pCR rates, profited from these combinations with a pCR rate of up to 50%. The results of the further follow-up with survival data as well as an evaluation of the biomarker results are awaited. Ultimately, large phase III trials are needed to confirm these very good and for the patients highly promising data. The ongoing phase III Aphinity trial is already evaluating the dual blockade in combination with a standard chemotherapy in the adjuvant situation.

Fig. 1 Tryphaena trial – median changes in the left ventricular ejection fraction (LVEF) of the treatment groups A–C (arm A: $3 \times \text{FEC} + \text{H} + \text{P}$ followed by $3 \times \text{Doc} + \text{H} + \text{P}$; arm B: $3 \times \text{FEC}$ followed by $\text{Doc} + \text{H} + \text{P}$; arm C: $6 \times \text{Docetaxel} + \text{Carboplatin} + \text{H} + \text{P}$) [30].

Prognostic relevance of the pCR after neoadjuvant chemotherapy

It was shown for triple negative breast cancer some years ago that patients with pCR have a markedly better prognosis [31, 32]. Recent work has now shown that this is also the case for HER2-positive breast cancer under trastuzumab therapy [25]. The large numbers of patients encompassed within the framework of the studies of the AGO and GBG make it possible today to undertake a comprehensive analysis of these data. In a meta-analysis 4387 patients were examined with regard to the question of the prognostic relevance of pCR in HER2-negative patients undergoing chemotherapy in comparison to HER2-positive patients who received only neoadjuvant chemotherapy or a combination of neoadjuvant chemotherapy with trastuzumab [33]. It was found that, in general, patients with HER2-positive breast cancer treated with the combination of trastuzumab and chemotherapy could achieve a higher pCR rate (defined as ypT0, ypN0) than HER2-negative patients (27.3 vs. 14.8%) (• Fig. 2). For all 3 subgroups (HER2-negative, HER2-positive with and without trastuzumab), significant improvements in distant metastasis-free survival (DDFS) and overall survival (OS) were found for those patients who achieved pCR.

The OS showed a tendency for improvement ($p = 0.058$) when trastuzumab was added to the treatment of HER2-positive patients in comparison to that of HER2-positive patients who did not receive trastuzumab and was similar to the OS of HER2-negative patients ($p = 0.134$). In particular, HER2-positive, hormone receptor-negative patients after trastuzumab therapy reach a significantly better DDFS ($p = 0.012$) in comparison to HER2-positive patients who did not receive trastuzumab. With regard to OS and

Fig. 2 Comparison of survival according to pathological complete response (pCR) in patients with HER2-positive breast cancer receiving neoadjuvant chemotherapy with and without Trastuzumab compared to patients with HER2-negative tumours [33].

hormone receptor status, there was a significant advantage only for the HER2-positive, hormone receptor-negative subgroup ($p = 0.029$) in comparison to HER2-negative patients.

Thus, pCR can serve as a surrogate marker in this assessment. According to this meta-analysis those HER2-positive patients in all 3 subgroups for whom no pCR could be achieved have a significantly higher risk of disease recurrence and a poorer prognosis for overall survival independent of whether or not they received trastuzumab. An alternative treatment option is urgently needed for these patients. In such cases dual blockade of the HER2 receptors may help.

Molecular markers for identification of therapy response

Through the neoadjuvant trial design we have learnt in the past few years to identify which patients will respond to chemotherapy and which will not. Thus, hormone receptor-positive patients have a poorer response than hormone receptor-negative patients [26, 31]. Also, patients with a higher grading and a higher proliferation rate exhibit a better response to neoadjuvant chemotherapy. With the many possible multigene tests for the prognosis in breast cancer patients, the question naturally arises as to whether these tests not only predict the prognosis but also act as predictors for the response to therapy. One trial recently presented results in this direction [34]. In patients undergoing neoadjuvant treatment the so-called PAM50 risk score was examined. This score is calculated from the gene expression values of 50 genes and is able to define a so-called HER2-enriched (HER2-E) subgroup within the clinically HER2-positive tumours that cannot be determined with the classic markers (IHC, FISH). Two independent patient groups were examined: (i) 67 patients who received a neoadjuvant, anthracycline- and taxane-containing chemotherapy without trastuzumab and (ii) 27 patients from the so-called XeNA trial who received neoadjuvant treatment consisting of a combined therapy with trastuzumab + docetaxel/

capecitabine (without anthracyclines). Clinically HER2-positive and PAM50-HER2-E tumours reached higher pCR rates with both mentioned therapy regimens [34]. For confirmation of the possible predictive role of the PAM50-HER2-E distinction further studies with larger patient numbers are needed. An explanation for the possible predictive value of this gene signature with regard to trastuzumab-containing regimens consists of the fact that tumours with both clinically HER2-positive and PAM50-HER2-E status show an activation of the EGFR-HER2 signalling pathway.

Procedure for non-responsiveness to neoadjuvant chemotherapy

In the course of neoadjuvant therapy the response of the tumour to the therapy can be monitored by imaging procedures such as mammography or sonography. In general patients who demonstrate no response on such controls also have no pCR at the time of surgery. Thus, the question arises whether an improvement in therapy response and prognosis can be achieved in these non-responding patients by using substances with different mechanisms of action in their therapy. The GeparTrio trial was one of the first studies to investigate this prospectively in a larger patient sample. After sonographic evaluation of the response to neoadjuvant chemotherapy consisting of 2 cycles of TAC, the patients were divided into so-called responders (defined as a reduction in size of at least 50% of the primary tumour size) and non-responders. Patients with partial or complete remission received an intensification of therapy by addition of 2 therapy cycles with in total 8 × TAC and the patients in a no-change situation after 2 × TAC as experimental arm were changed to a presumably non-cross resistant regimen with 4 × NX (vinorelbine 25 mg/m² d1 + 8 i.v. q3w + capecitabine 1000 mg/m² 2 × daily. d1–14 p.o. q3w). Both the responder and the non-responder groups were integrated into a standard arm with in total 6 × TAC for comparison [35].

The pCR rates (defined as ypT0, ypN0) as primary endpoint showed no significant differences on comparison between the standard arm with 6 × TAC and the prolonged therapy with 8 × TAC ($p = 0.27$) [35]. The same situation was also observed for the non-responders with regard to 6 × TAC in comparison with 2 × TAC followed 4 × NX ($p = 0.73$). The recently presented analysis of the secondary endpoints, disease-free survival (DFS) and OS, however, showed a significant difference between the conventionally treated patients with 6 × TAC and the patients receiving the so-called response-controlled treatment [change depending on response to the longer arm with 8 × TAC for responders or other substances (vinorelbine/capecitabine) for non-responders (DFS: HR 0.71; 95% CI: 0.6–0.85; $p < 0.001$; OS: HR 0.79; 95% CI: 0.63–0.99; $p = 0.048$)].

Within the responder group the prolonged TAC administration proved to be significantly better for DFS (HR 0.78; 95% CI: 0.62–0.97; $p = 0.026$) and among the non-responders DFS was also improved significantly by the change to a non-cross-resistant chemotherapy (NX) (HR 0.59; 95% CI: 0.49–0.82; $p = 0.001$). In the subgroup analysis it was found that the effect in DFS of the response-controlled therapy turns out to derive from the luminal tumour as defined according to the current St. Gallen criteria (HR-positive, HER2-positive or -negative) [36] (HR 0.40–0.56) (● Fig. 3). Here the therapy change after 2 × TAC and insufficient responses gave a positive effect whereas in contrast for the triple-negative or HER2-positive non-luminal tumours no improvement in DFS could be achieved through response-controlled therapy (HR 1.01; 95% CI: 0.61–1.67 and HR 0.87; 95% CI: 0.61–1.25).

Fig. 3 GeparTrio analysis: pCR rate according to subtype and supplemented according to Minckwitz G et al. [77].

Also the more actual GeparQuinto trial of the AGO and GBG study groups was designed to determine whether a response could be achieved in patients with HER2-negative tumours who did not respond to a neoadjuvant, anthracycline-based therapy ($\pm$ bevacizumab). The results of the main trial, which has checked the addition of bevacizumab to anthracycline- and taxane-based neoadjuvant chemotherapy, were published recently [23,24] and showed that the pCR could be increased by the addition of bevacizumab from 14.9% (95% CI: 12.5–17.3%) to 18.4% (95% CI: 16.0–21.0%) (odds ratio 1.29; 95% CI: 1.02–1.65; $p = 0.04$) [23,37].

For those patients who did not respond to the neoadjuvant therapy with 4 × EC $\pm$ bevacizumab, the therapeutic strategy was changed and now 4 cycles of paclitaxel (Pw) 80 mg² d1 + 8 q3w $\pm$ RAD001 (5 mg/d from day 13 after start with dose escalation from 2.5 mg to 5 mg/day) were administered. Altogether, 395 patients were enrolled in this non-responder arm of the trial.

The addition of RAD001 to 12 weeks of paclitaxel did not improve the pCR rate (defined as primary endpoint with ypT0, ypN0) but did show increased toxicity for all symptoms (Pw 5.6% vs. Pw + RAD001 3.6%; $p = 0.476$) [38]. However, the pCR could be the wrong marker for the effect of RAD001. DFS and OS data for this must be awaited. A large biomarker programme for the identification of possible predictive markers is underway.

Adjuvant Therapy

Whereas the past years were characterised by a multitude of classic chemotherapy trials, comparative studies between aromatase inhibitors and tamoxifen and adjuvant trastuzumab trials, hardly any comparable studies can be found in the last 12 months that have been concerned with the pure comparison of therapy arms in this study design. Attention has rather been directed to other substance classes and molecular tests intended to examine the responses to established substances. One of these groups of substances is the bisphosphonates that have been approved for the treatment of osteoporosis and bone metastases, and are now under discussion as to whether they can improve the prognosis or for which groups of patients they can do so, also in the adjuvant situation (● Table 2). The relationships between the female breast, the disease breast cancer and bone health have

Table 2 Comparison of adjuvant therapy trials with bisphosphonates in different patient collectives.

Trial	n	Patient description	CHT	Bisphosphonate therapy	Median FU	HR for DFS	HR for OS	Reference
AZURE all patients	3 360	stage II/III	95%	zoledronate 4 mg, 6 × q3-4w, 8 × q3m, 5 × q6m	60 m	0.98 (p = 0.79)	1.01 (p = 0.93)	Coleman, 2011 [42]
AZURE post- menopausal patients	1 101	stage II/III postmenopausal	95%	zoledronate 4 mg, 6 × q3-4w, 8 × q3m, 5 × q6m	60 m	0.71 (p = 0.0017)	0.71 (p = 0.017)	Coleman, 2011 [42]
ABCSG-12	1 803	premenopausal	< 5%	zoledronate 4 mg, 6 × q6m	84 m	0.72 (p = 0.014)	0.63 (p = 0.0049)	Gnant, 2009 [41]
ZOFAST	1 065	postmenopausal	0%	zoledronate 4 mg, 6 × q6m	60 m	0.66 (p = 0.0375)	n. s.	de Boer, 2011 [28]
NSABP-B34	3 323	all stages	65%	clodronate 1 600 mg/d over 5 years	101 m	0.91 (p = 0.27)	0.84 (p = 0.13)	Paterson, 2011 [32]
Powles	1 069	all stages	?	clodronate 1 600 mg/d over 2 years	88 m	0.77 (p = 0.127)	0.77 (p = 0.047)	Powles, 2002 [44]
Diel	302	DTC in KM	40%	clodronate 1 600 mg/d over 2 years	103 m	0.98 (p = 0.222)	0.83 (p = 0.049)	Diel, 2008 [43]
Sarto	296	nodal positive	90%	clodronate 1 600 mg/d over 2 years	98 m	n. s.	n. s.	

attracted increasing attention not only through clinical trials but also through the plethora of preclinical and clinical reports.

An update of the ABCSG-12 trial [39] has examined the use of zoledronate (4 mg, q6m over 3 years) in premenopausal patients (n = 1803) with hormone receptor-positive tumours who received an adjuvant endocrine therapy consisting of GnRH analogues plus tamoxifen or anastrozole [40]. The median follow-up time now amounts to 84 months. The DFS is still better in the zoledronate arm as compared to the control arm (HR 0.72 [0.56–0.94]; p = 0.014). In particular, nodal-positive patients and those over 40 years of age have profited. The effect was apparent both in the group treated with anastrozole and the group treated with tamoxifen. In the meantime, interestingly, a significant improvement of overall survival in favour of the zoledronate-treated group has been observed (HR 0.63; 95% CI: 0.40–0.99; p = 0.049), which again was predominantly due to patients over 40 years of age. At these doses no severe side effects were seen (jaw bone necrosis, nephrotoxicity).

The ZOFAST trial investigated the protective effect of zoledronate (4 mg, q6m, over 5 years) on the bone density of postmenopausal patients and secondarily also recorded recurrences and overall survival (n = 1065) [41]. After a median follow-up of 60 months an improved bone density was still seen in the a priori treated group in comparison with the group treated according to indications. The DFS was also better in the a priori treated group (HR 0.66; p = 0.0375), this was due above all to the patients who had been in menopause for longer times.

However, it must again be emphasised here that, in the AZURE trial presented last year, an intensive adjuvant therapy with zoledronate over 5 years did not lead to an improved DFS in the entire group (n = 3360). A significant advantage was only apparent for the group of confirmed postmenopausal patients (n = 1100) [42].

Two studies on clodronate are already available and show that clodronate (1600 mg/d over 2 years) can improve the overall survival of primary breast cancer patients [43, 44]. The NSABP-B34 trial is a further study with the same objectives. Altogether 3323 primary breast cancer patients in all studies were treated with 1600 mg clodronate per day or placebo for 3 years [45]. After 8.4 years follow-up there were no differences in DFS (HR 0.91; 95%

CI: 0.78–1.07; p = 0.27) or OS (0.84; 95% CI: 0.67–1.05; p = 0.13). Older patients benefited more but this was only with regard to recurrence-free survival and bone metastasis-free survival. As a limitation it must be stated that the compliance in both groups was very poor (ca. 60% after 2 years). It is not known whether the patients in the placebo group received zoledronate “secretly” on the basis of the published ABCSG-12 and ZOFAST trials.

In the framework of the GAIN trial ibandronate was combined with epirubicin, paclitaxel and cyclophosphamide under the hypothesis that a bisphosphonate could further improve the treatment success in primary breast cancer. However, there were no significant differences referred to disease-free survival and overall survival in patients with or without ibandronate [46]. In analogy to the NSABP-B34 trial, older patients appear to benefit more from ibandronate than younger ones although here also there was no significant difference.

Final analysis of the ADEBAR trial

Currently it needs to be clarified whether or not patients with more than 3 affected lymph nodes will benefit from the additional administration of taxane in the framework of their adjuvant therapy. Furthermore, more evidence is needed concerning the optimal time course of taxane therapy, either simultaneous with or in sequence after the anthracycline therapy. Janni et al. presented the final data analysis of the German multicentre ADEBAR phase III trial. Patients with primary breast cancer and more than 3 diseased lymph nodes received either a purely anthracycline-containing chemotherapy according to the Canadian FEC120 scheme (6 cycles with epirubicin 60 mg/m² d1 + d8, 5-FU 500 mg/m² d1 + 8, C75 mg/m² d1–14, q4w) or a sequential anthracycline-/taxane-containing chemotherapy EC-D (4 cycles of epirubicin 90 mg/m² and cyclophosphamide 600 mg/m² q21 followed by 4 cycles of doxorubicin 100 mg/m² q21). No differences were seen with regard to recurrence-free and overall survival. However, patients under the sequential anthracycline-/taxane-containing therapy exhibited markedly less haematological toxicity, terminated the therapy more rarely (3.7 vs. 8.0%) and required less antibiotics (10.4 vs. 19.7%) and growth factors in the form of G-CSF (39.2 vs. 61.4%) [47].

An anthracycline-/taxane-containing therapy is equally effective as an adequately dosed anthracycline-containing chemotherapy (epirubicin dosed at 120 mg/m²!). However this is associated with significantly less haematological toxicities. There are as yet no comparative data available regarding long-term toxicity (e.g., second malignancy, cardiotoxicity). However, these would also show a tendency in favour of the sequential anthracycline-/taxane-containing therapy.

Effect of darbepoetin- α on the efficacy of a chemotherapy

Darbepoetin- α is currently employed to avoid a chemotherapy-associated anaemia. Even so, it has often been reported that the use of factors stimulating haematopoiesis may have a negative effect of the prognosis of breast cancer patients. Even when the differences in the PREPARE trial, in which patients undergoing neoadjuvant chemotherapy were randomised for a therapy with darbepoetin, were not significant with regard to disease-free survival, the poorer prognosis in the darbepoetin arm was at least suggestive. In the framework of the WSG-ARA trial the influence of darbepoetin- α was evaluated in a high-risk collective. The patients received either chemotherapy with 6 $\times$ T₇₅ A₅₀ C₅₀₀ q3w or 6 $\times$ F₅₀₀ E₁₀₀ C₅₀₀ q3w. The administration of darbepoetin- α was randomised (ARA+/ARA-). In the ARA+ group the use of darbepoetin- α was initiated at an Hb of 13 mg/dL and continued until an Hb of 14 mg/dL or maximally to the conclusion of the adjuvant radiotherapy. Altogether 1234 patients were included. Both event-free survival (ARA+/ARA-: 89.2 vs. 87.6%) and overall survival (95.4 vs. 95.1%) were not influenced by the administration of darbepoetin- α after a median follow-up of 40 months [50]. The administration of darbepoetin- α to avoid a chemotherapy-induced anaemia seems to be validated based on data of the WSG-ARA trial. However, the data cannot be transferred to the neoadjuvant situation. In the course of the neoadjuvant PREPARE trial, a negative effect of darbepoetin- α on the recurrence-free survival of patients treated with darbepoetin- α was observed [48,49].

Lapatinib in adjuvant use – the TEACH trial

In the meantime all HER2-positive patients with breast cancer undergoing adjuvant chemotherapy routinely receive trastuzumab for 1 year. The adjuvant utility of lapatinib is still unclear and is, among others, being evaluated in the framework of the randomised, multicentre, placebo-controlled TEACH trial. The first survival data have now been presented by Paul Goss [51]. In the TEACH trial, HER2-positive primary breast cancer patients who, e.g., due to the registration status had not received trastuzumab initially, were enrolled. Chemotherapy could have been carried out many years previously. Altogether, 3147 patients were randomised. The median follow-up amounted to 4 years. Although the risk of recurrence could be reduced by 17% with the adjuvant administration of lapatinib, lapatinib did not have any statistically significant effect of the recurrence-free and overall survivals [51]. However, in the subgroup analysis a significant benefit could be demonstrated for hormone receptor-negative patients as well as for patients who had received lapatinib within one year after the diagnosis had been made. This was also true for patients whose HER2 status was determined centrally. The most frequent side effects of adjuvant lapatinib therapy were diarrhoea (61%) and skin rashes (59%). Adjuvant therapy with lapatinib may be an important alternative in cases with a contraindication to trastuzumab. In particular,

those patients who received lapatinib early in the disease course profit markedly from this therapy even though it cannot match the efficacy of trastuzumab. The sole or combined use of lapatinib and trastuzumab in an adjuvant setting is also being studied in the ALTTO trial (www.clinicaltrials.gov/ct/show/NCT00490139). First survival data are expected in 2013.

Treatment of Patients with Metastasis

New therapy schemes and new substances for the treatment of patients with breast cancer often find their way into clinical practice in the metastasis situation since phase II trials and registration studies most often involve these patients. In the past few years numerous new drugs have been developed with the idea that they can specifically block signalling pathways of relevance to the tumour. Mechanisms for the pathogenesis as well as mechanisms of therapy resistance are hereby taken into consideration. In some fields this has already led to the development of efficient drugs that will be approved shortly.

CLEOPATRA – double HER2 blockade

The anti-HER2 antibody pertuzumab will surely open new possibilities for HER2-positive, metastatic breast cancer. In contrast to trastuzumab, it binds to the dimerisation domain of HER2 and thus hinders the heterodimerisation of HER2 with other members of the HER family. Trastuzumab and pertuzumab putatively have complementary mechanisms of action and can thus more effectively block HER2-dependent signalling cascades.

In the “Cleopatra” trial (Clinical Evaluation Of Pertuzumab And TRastuzumab), performed in this context, the combination of pertuzumab with trastuzumab and docetaxel in the first-line therapy for HER2-positive breast cancer significantly lengthened the progression-free survival of the patients in comparison to monotherapies with trastuzumab and docetaxel [52]. The progression-free survival for patients in the test arm amounted to 18.5 months compared with 12.4 months in patients in the placebo arm (HR 0.62; 95% CI: 0.51–0.75; $p < 0.0001$) (► Fig. 4). This effect was consistently seen in all subgroups. In addition, the data show a survival advantage in the arm with pertuzumab treatment (HR 0.64; 95% CI: 0.47–0.88; $p = 0.0053$). However, HR did not reach the limiting value predefined in the trial protocol (HR ≤ 0.603 ; $p \leq 0.0012$). The final analysis of overall survival is expected for 2013. Pertuzumab did not exhibit any additional cardiac side effects.

Another drug that blocks parts of the HER2 signalling pathway is the tyrosine kinase inhibitor neratinib. Neratinib is an oral, irreversible pan-HER inhibitor that blocks the tyrosine kinase function of HER1 = EGFR, HER2 and HER4. In the recently presented, randomised phase II trial neratinib (240 mg/day) was compared with the combination of lapatinib and capecitabine in the second- and third-line therapy for local, advanced or metastatic, HER-2/neu positive breast cancer [53]. The trial was aimed at non-inferiority. With a progression-free interval of 4.5 months, neratinib was clearly inferior to the combination of lapatinib and capecitabine (PFS of 6.8 months). It must be mentioned, however, that in spite of the clearly lower objective remission rate under neratinib (29%) in comparison to capecitabine/lapatinib (40%), neratinib must still be considered as an effective substance that, in this special trial, was possibly doomed to failure due to the lack of an appropriate chemotherapeutic combination

Fig. 4 CLEOPATRA trial – central, independent evaluation of the primary endpoint progression-free survival (PFS). Modified after Baselga et al. [52].

partner. In any case sufficient objective remissions were achieved.

The Avelar trial is a further study that has examined the administration of bevacizumab, as an anti-angiogenesis therapy together with docetaxel and trastuzumab in patients with HER2-positive, metastatic or locally recurrent breast cancer. 216 from a total of 424 patients in the trial received the three-fold combination as first-line therapy in an advanced situation. Through the addition of bevacizumab the progression-free survival was slightly extended by 2.9 months, albeit without reaching statistical significance. After a median follow-up of 26 months there was a reduction in the risk for progression or death of 28% [54]. The authors

consider the Avelar trial as further confirmation for the efficacy of an antiangiogenic therapy. However, a task for the future must be to define biomarkers that can predict a benefit through the administration of bevacizumab. For example, a subgroup analysis showed that patients with tumours that exhibit higher VEGF-A values will benefit more strongly from bevacizumab [54].

First results of EMILIA

The randomised phase III EMILIA study [55] that was recently presented during the ASCO-2012 congress is a further study that attempted to find an optimal therapy for metastasizing patients who had experienced a progression after therapy with trastuzumab and a taxane. The approved comparison arm contained the drugs lapatinib and capecitabine whereas the experimental arm contained the relatively new substance T-DM1, which is a conjugate of an anti-HER2 antibody and the cytotoxic compound DM1. Thus, this drug follows a new strategy, namely to “deliver” the cytotoxic substance directly to the HER2-positive cells. Progression-free survival amounted to 6.4 months in the arm with lapatinib and capecitabine compared with 9.6 months in the T-DM1 arm (HR 0.65; 95% CI: 0.549–0.771; p < 0.0001; ● Fig. 5). Also the difference with regard to overall survival was significantly better under therapy with T-DM1 (HR 0.621; 95% CI: 0.475–0.813; p = 0.0005). The most frequent side effects were thrombopenia and elevated liver enzymes [55]. The presentation of these study results suggests that this therapeutic concept may also prove valuable for targets other than HER2/neu.

Biomarkers PTEN and PIK3CA

Biomarkers are playing a more and more important role in the explanation of therapy resistance. Thus it is known that the mode of action of the two proteins PTEN und PIK3CA positioned downstream from HER2 appears to play a key role. Both the assignment of HER2-positive patients into prognostic groups as well as the resistance to an anti-HER2 therapy appear to be linked to the mode of action of these two proteins. Mutations in the gene PIK3CA under treatment with paclitaxel ± lapatinib have been investigated. In 30.1% of the cases a genetic change was found which was accompanied by a statistically poorer overall survival for the patients [56]. Similarly, the trend was apparent that just

Fig. 5 Progression-free survival in the EMILIA trial. Adapted after Blackwell et al. [55].

Fig. 6 SWOG S0226 trial – Evaluation of the primary endpoint progression-free survival. Adapted after Mehta et al. [62].

these HER2-positive patients profited from the administration of lapatinib by way of an improved progression-free survival. The therapy with lapatinib together with paclitaxel was in this study with 444 patients, additionally independent of the PTEN mutation, associated with an extended PFS but which only corresponded to an improved overall survival only in the group with loss of PTEN (12.4% of all patients).

Also in cases of hormone receptor-positive breast cancer advances have been reported recently. Already last year, an advantage of aromatase inhibitors for the treatment of postmenopausal breast cancer in the adjuvant situation in overall survival was shown for the first time through long-term studies [57]. The further development of antihormone therapy in the post-aromatase inhibitor era attempted to establish the oestrogen receptor antagonist fulvestrant in combination with aromatase inhibitors but this has proved to be difficult in several studies [58–61]. In the recently presented SWOG-S0226 trial which tested the combination of anastrozole and fulvestrant vs. anastrozole alone for metastatic breast cancer, surprisingly, significant differences were found both in progression-free survival (HR 0.8, 95% CI: 0.68–0.94; $p = 0.007$, **Fig. 6**) and, above all, also in overall survival (HR 0.81; 95% CI: 0.65–1.00; $p = 0.049$) [62]. This success was achieved almost exclusively in those patients who had not previously received tamoxifen. The clinical applicability of these results is thus mainly limited to patients in whom the hormone sensitivity of the tumour is newly discovered, perhaps in the course of a metastasis biopsy.

Final PFS analysis of the BOLERO-2 trial

As already mentioned, newly developed substances are aimed especially at those patients who are in situations in which their current therapy is insufficient or after a certain time loses its activity. An interesting molecule in this context is mTOR that exhibits a central role in many signalling pathways in both healthy cells and in cancer cells. Especially for those patients who no longer responded to an antihormone therapy in the adjuvant situation, this molecule appears to be of particular significance, thus a blockade of this mechanism could possibly lead to a renewed response to such a therapy or could overcome the resistance. The BOLERO-2 trial has investigated just this question in hormone re-

ceptor-positive, metastatic or very advanced breast cancer. It compared the administration of everolimus (RAD001), an mTOR inhibitor, in combination with the aromatase inhibitor exemestane vs. placebo and exemestane in patients who experienced a progression under therapy with anastrozole or letrozole. In the first interim analysis a significant advantage for the combination therapy was already seen [63]. The final analysis of progression-free survival after a subsequent median observation period of 18 months presented in the course of the ASCO 2012 Annual Meeting revealed a significant difference of 7.8 vs. 3.2 months (HR 0.45, 95% CI: 0.38–0.54; $p < 0.0001$) in the decentral radiological evaluation and of 11.0 vs. 4.1 months (HR 0.38, 95% CI: 0.31–0.48, $p < 0.001$) in the central pathological evaluation in favour of the therapy with everolimus and exemestane (**Fig. 7**) [64]. The advantage with respect to progression-free survival was consistent throughout all subgroups. Side effects occurred more frequently in the study arm but were well manageable through dose reductions or therapy interruptions. The trial results were so motivating that since June 2012 the phase III E trial “4EVER” is recruiting in Germany in order to investigate the mechanism of action of this therapy.

Pharmacoeconomics

The costs of health care are increasing exponentially worldwide. Accordingly, the costs per head and year in Germany rose from 2520 € in the year 1999 to 3210 € in the year 2008. The total expenditure of the German health-care system in 1999 amounted to 206.6 billion € and subsequently rose in 2008 to 263.2 billion € [65]. Outpatient facilities such as, for example, doctors' practices and apothecaries are of greatest relevance here with a proportion of 49.7% or 130.9 billion €. However, as inpatient or partial inpatient facilities, the highest costs fell to the German hospitals, above all individually viewed facilities of the German health-care system with a proportion of over 25% or 66.7 billion €. Taking the health-care costs into consideration differentiated according to the various types of care offered, there are especially 3 major cost factors: for physicians' services the expenditure in 2008 was 71.5 billion € (27.2%), for nursing and thera-

Fig. 7 BOLERO-2 trial – final, central evaluation of the primary endpoint progression-free survival (PFS) after 18 months median follow-up time. Adapted after Piccart et al. [64].

peutic services it was 61.9 billion € (23.5%) and for materials such as, for example, drugs and medical aids the total costs amounted to 73.0 billion € (27.7%).

The increase in health-care costs also affects oncology and thus also senology. The discussions of the past years have certainly led to acceptance of the fact that medical decisions involve more and more a further dimension – the financial aspect [66].

Health-care research and health-care economics could help to make trial results more comparable and thus better to evaluate and enable assessment of new innovative procedures from a further perspective. The essential questions of health-care economics are: how much is actually spent?, for what has the money been paid?, and how can the money perhaps be better spent?

On the topic of resource expenditure in the therapy for breast cancer up-to-date data from the USA are available. Among all the types of cancer, the largest proportion of resources is spent on breast cancer. Here, the costs are divided between the initial (primary therapy) and the subsequent phases (follow-up care) and then especially in the last year of life. For patients under the age of 65 years these were 27 700, 2200 und 94 300 \$ per year (≥ 65 years of age: 23 000, 2200 und 62 900) [67]. The costs of the initial phase are divided among the different therapies. Here surgery belongs rather to the more cost-favourable options (Table 3). Under this aspect it is hard to understand why the health insurances and their medical services view just the hospitalisation duration of surgical therapy so critically and disallow days of inpatient stays that are not justifiable from their point of view.

Current data on the costs for patients with breast cancer are also available from Europe. In a French study the costs of 437 chemotherapy cycles in adjuvant therapy situations were retrospectively analysed [68]. Here the average cost per cycle amounted to 1752 € and that for the entire chemotherapy to 13 593 €. However, the social perspective of therapy such as loss of working time must also be taken into account, thus the costs per patient amount to 15 740 €.

In therapy for the metastatic situation the costs of specialist treatment are even higher as will be clearly shown for the exam-

Table 3 Costs of the initial phase (2002, US \$) [76].

	Percent with maintenance of therapy form	Average costs for patient with therapy
Total	100%	21 000 \$
Operation	91%	5 700 \$
Chemotherapy	24%	12 800 \$
Radiotherapy	51%	4 500 \$
Further inpatient stays	23%	16 700 \$

ple of an HER2-positive patient with brain metastases [69]. When looking at the time-course, therapy costs of 19 402 € were incurred in months 1–6, of 17 379 € for months 7–12, of 15 337 € for months 13–18 and of 14 679 € for months 19–24. However, cost calculations for the various different therapeutic situations are rather rare, but do provide the basis for every health-care economic evaluation and should be further promoted specifically for each country.

That the costs for systemic therapy have increased markedly is clearly apparent when comparing the approval of new drugs (LIT ELKIN). Whereas tamoxifen on its market introduction had a price of 100 \$/month, the prices of newly approved substances are markedly higher, e.g. Nab-paclitaxel at over 7500 \$ per month. In addition more and more patients are receiving systemic therapy for ever longer periods of time.

Whereas currently in the USA 15 billion US \$/year are spent on therapy for breast cancer, an increase to almost 25 billion US \$ is calculated for the year 2020 – and this without taking inflation into account, which will of course increase the costs even more. Cost-benefit analyses that take the regained quality of life into consideration could help to assign the resources more appropriately and to plan expenditures. On the basis of quality-adjusted life years (QALYs) the subsequently achieved advantages of the various therapies could be made comparable with the necessary costs. At present in Germany there is no clear reference value for the acceptable costs of the gained quality adjusted life years. In

the USA a price of < 50 000 \$ per QALY is considered to be favourable. Whereas costs of over 100 000 \$ per QALY seem to be extremely high and demand an exact clinical justification, costs between 50 000 \$ and 100 000 \$ can be considered after assessment of the benefits.

The value of cost-benefit analyses can be clearly illustrated by means of examples. For instance, when ixabepilone is added to capecitabine in patients with anthracycline- and taxane-resistant breast cancer, additional costs of 21 000 \$ are incurred for 5 cycles. Thus, on consideration of the QALYs costs of 360 000 \$ per QALY arise [70] – in this case an evaluation of the cost-benefit analysis is clearly more transparent. Further examples are listed in **Table 4**. However, it is also clear that cost-benefit analyses may never be the sole basis for a decision, but should be taken as further sources of information to support the decision-making processes.

The increasing per head costs affect not only Germany – as mentioned above – but also above all the USA. Whereas in the USA the per head expenditure in the health-care system amounted to 2814 \$ in the year in 1999, it is now 8047 \$. For the year 2019 costs of 13 387 \$ per head and year are expected [71]. However, the high costs do not also correspond with the achieved benefit – also in senology. An evaluation of the SEER/Medicare database with regard to breast cancer mortality and the therapy costs for 99 regions showed that a 5-year survival of 88% can be achieved at a cost of 17 315 \$. With costs of 26 808 \$ the 5-year survival rate was also 88%.

Solutions to limit costs are also being sought in the USA. One option is fixed costs (national coverage determination) which, however, also harbours risks, e.g., changes in prescription behaviour. Thus, after introduction of fixed costs in 2005 there was a massive decline in the consumption of docetaxel. This is also relevant for Germany, where fixed costs for drugs have been in existence for some years and are further demanded by the current drug prescription laws [Arzneimittelverordnungsgesetz (AMNOG)] of 1.1.2011.

Who then should be the decision maker concerning costs for the health-care system? When the society or the government make the decision the costs can be adapted to the available resources and distributed equally, but then the patients and physicians would have fewer options. When the patients would decide more options would be available but the administrative expenditure would be too high and the question would arise as to whether an information basis is available for the decision (Kaskett, SABCS, 2011). Leaving the decision to the cost-bearer would also be critical since then restrictions would have to be feared. For example, a recent report has investigated what factors influence the reconstruction rate after mastectomy [72]. On the basis of data from 109 992 women with invasive breast cancer and 14 710 women with DCIS between 2000 and 2010 a dramatic difference was seen with regard to the insurance situation. For patients with private insurance the reconstruction rate was significantly higher with an OR of 2.98 (95% CI: 2.61–3.49), for patients with statutory insurance the reconstruction rate was only marginally higher than that for patients with no health insurance (Medicare 1.58 [95% CI: 1.37–1.82]; Medicaid [95% CI: 1.01–1.37]).

Physicians themselves could make the decision but in this case a strong ethical component would soon arise, especially when the patients could not afford expensive treatment. A questionnaire among American oncologists as to who should decide on the assignment of resources showed that 60% voted for physicians, 57% for independent non-profit-making organisations, 37% for the

Table 4 QALYs in the therapy for breast cancer (2010, US \$) [66].

Intervention	Incremental cost-efficiency ratio (ICER)
BRCA-1/2-test (age ≥ 35; family case history)	5 400 \$/QALY
Raloxifen to reduce risk (age 55)	22 000 \$/QALY
Letrozole vs. anastrozole (postmenopausal, HR+)	26 000 \$/QALY
Lapatinib plus capecitabine vs. capecitabine	170 000 \$/QALY
Yearly screening by MRI vs. mammography (BRCA1)	210 000 \$/QALY
Bevacizumab plus paclitaxel vs. paclitaxel	280 000 \$/QALY
Partial breast irradiation vs. whole breast irradiation (stage I, ER+, postmenopausal)	730 000 \$/QALY
Digital mammography screening vs. film (age ≥ 40)	930 000 \$/QALY

patients, 21% for the government, and 6% for the cost-bearers [73]. It is thus apparent that the question of the ideal decision-making apparatus is by far from the answered. Even so 80% agreed that data on cost-benefit analyses are necessary – health-care economics is gaining in importance.

A special aspect of health-care economics in senology is the possible influence of individualised or, respectively, targeted therapies. On the one hand increased costs are possible as a result of more extensive testing, new cost-intensive therapies and increased complexity while, on the other hand, costs may also be reduced by the avoidance of excessive therapy and the achievement of better cure rates.

In the context of individualised therapy, the economic influence of Oncotype DX® has been the focus of several studies. On the basis of data of the NSABP-B-14 and B-20 validation trials, one study examined the cost-efficacy of Oncotype DX® in Ireland [74]. Here the respective test costs (3180 €), the costs for the chemotherapeutics (1002 €), administration and monitoring of the chemotherapy (1646 €), the cost for side effects (756 €) and costs of supportive and preventive measures (3561 €) as well as the costs for recurrences (35 160 €) were taken into consideration. Through the use of Oncotype DX® 0.12 QALYs were gained. Altogether, the calculated costs per QALY were 9642 €. With a probability of 74.2% the sensitivity analysis showed that the ICER amounted to less than 20 000 €/QALY. Meta-analyses on this topic are also available. One such report investigated 9 published cost-efficiency analyses of Oncotype DX® [75]. The meta-analyses revealed a median cost-efficiency ratio of 27 000 \$/QALY, which the authors considered to represent a cost-efficient option.

It is apparent that cost-benefit analyses can help to weigh the advantages and disadvantages of not only novel, innovative diagnostic but also therapeutic measures against each other and to provide clarity.

Conflict of Interest

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Affiliations

- ¹ Klinik für Gynäkologie und Geburtshilfe, Marienhospital Bottrop, Bottrop
- ² Medizinische Klinik und Poliklinik II, Campus Charité Mitte, Berlin
- ³ Frauenklinik, Universitätsklinikum Erlangen, Erlangen
- ⁴ Department of Gynecology and Obstetrics, University Hospital Aachen
- ⁵ Frauenklinik, Universitätsklinikum Heidelberg, Heidelberg
- ⁶ Department of Gynecology and Obstetrics, University Hospital Erlangen, Erlangen
- ⁷ Department of Obstetrics and Gynecology, University Tübingen, Tübingen
- ⁸ Frauenklinik, Klinikum der Heinrich-Heine-Universität Düsseldorf, Düsseldorf
- ⁹ Klinik für Senologie, Kliniken Essen-Mitte, Essen

References

- 1 Fasching PA, Fehm T, Janni W et al. Breast cancer therapy – a state of the art review. *Geburtsh Frauenheilk* 2010; 70: 875–886, DOI: 10.1055/s-0030-1250437
- 2 Kummel S, Kolberg HC, Luftner D et al. Breast cancer 2011 – new aspects. *Geburtsh Frauenheilk* 2011; 71: 939–953, DOI: 10.1055/s-0031-1280313
- 3 Fisher B, Anderson S, Bryant J et al. Twenty-year follow-up of a randomized trial comparing breast-conserving surgery with radical mastectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002; 347: 1233–1241, DOI: 10.1056/NEJMoa022152
- 4 Veronesi U, Cascinelli N, Mariani L et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002; 347: 1227–1232, DOI: 10.1056/NEJMoa020989
- 5 Bani HA, Fasching PA, Lux MM et al. Lymphedema in breast cancer survivors: assessment and information provision in a specialized breast unit. *Patient education and counseling* 2007; 66: 311–318, DOI: 10.1016/j.pec.2007.01.004
- 6 Veronesi U, Paganelli G, Viale G et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med* 2003; 349: 546–553, DOI: 10.1056/NEJMoa012782
- 7 Kühn T. Mammakarzinom. Stellenwert des axillären Stagings. *Gynäkologe* 2011; 44: 999–1004
- 8 Galimberti V, Cole BF, Zurrada S et al. Update of International Breast Cancer Study Group trial 23-01 to compare axillary dissection versus no axillary dissection in patients with clinically node negative breast cancer and micrometastases in the sentinel node. *Cancer Res* 2011; 71: 102 s
- 9 Moebus V, Jackisch C, Lueck HJ et al. Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel, and cyclophosphamide compared with conventionally scheduled chemotherapy in high-risk primary breast cancer: mature results of an AGO phase III study. *J Clin Oncol* 2010; 28: 2874–2880, DOI: 10.1200/JCO.2009.24.7643
- 10 Engel J, Lebeau A, Sauer H et al. Are we wasting our time with the sentinel technique? Fifteen reasons to stop axilla dissection. *Breast* 2006; 15: 452–455, DOI: 10.1016/j.breast.2005.05.009
- 11 Giuliano AE, Hunt KK, Ballman KV et al. Axillary dissection vs. no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA* 2011; 305: 569–575, DOI: 10.1001/jama.2011.90
- 12 Krag DN, Anderson SJ, Julian TB et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol* 2010; 11: 927–933, DOI: 10.1016/S1470-2045(10)70207-2
- 13 Arbeitsgemeinschaft für Gynäkologische Onkologie e.V. AGO Guidelines. www.ago-online.org; last access: 2012
- 14 Veronesi U, Orecchia R, Luini A et al. Intraoperative radiotherapy during breast conserving surgery: a study on 1,822 cases treated with electrons. *Breast Cancer Res Treat* 2010; 124: 141–151, DOI: 10.1007/s10549-010-1115-5
- 15 Vaidya JS, Baum M, Tobias JS et al. Long-term results of targeted intraoperative radiotherapy (Targit) boost during breast-conserving surgery. *Int J Radiat Oncol, Biol, Phys* 2011; 81: 1091–1097, DOI: 10.1016/j.ijrobp.2010.07.1996
- 16 Smith GL, Xu Y, Buchholz TA et al. Partial breast brachytherapy is associated with inferior effectiveness and increased toxicity compared with whole breast irradiation in older patients. *Cancer Res* 2011; 71: 99 s
- 17 Cutuli B, Cohen-Solal-le Nir C, de Lafontan B et al. Breast-conserving therapy for ductal carcinoma in situ of the breast: the French Cancer Centers' experience. *Int J Radiat Oncol, Biol, Phys* 2002; 53: 868–879
- 18 Clarke M, Collins R, Darby S et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; 366: 2087–2106, DOI: 10.1016/S0140-6736(05)67887-7
- 19 Bijker N, Meijnen P, Peterse JL et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853 – a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. *J Clin Oncol* 2006; 24: 3381–3387, DOI: 10.1200/JCO.2006.06.1366
- 20 Hughes LL, Wang M, Page DL et al. Local excision alone without irradiation for ductal carcinoma in situ of the breast: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2009; 27: 5319–5324, DOI: 10.1200/JCO.2009.21.8560
- 21 Solin LJ, Gray R, Baehner FL et al. A quantitative multigene RT-PCR assay for predicting recurrence risk after surgical excision alone without irradiation for ductal carcinoma in situ (DCIS): a prospective validation study of the DCIS score from ECOG E5194. *Cancer Res* 2011; 71: 108 s
- 22 Untch M, von Minckwitz G. Neoadjuvant treatment of breast cancer. *Breast Care (Basel)* 2011; 6: 417, DOI: 10.1159/000335444
- 23 von Minckwitz G, Eidtmann H, Rezai M et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. *N Engl J Med* 2012; 366: 299–309, DOI: 10.1056/NEJMoa1111065
- 24 Untch M, Loibl S, Bischoff J et al. Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG 44): a randomised phase 3 trial. *Lancet Oncol* 2012; 13: 135–144, DOI: 10.1016/S1470-2045(11)70397-7
- 25 Untch M, Fasching PA, Konecny GE et al. Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. *J Clin Oncol* 2011; 29: 3351–3357, DOI: 10.1200/JCO.2010.31.4930
- 26 von Minckwitz G, Untch M, Nuesch E et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. *Breast cancer research and treatment* 2011; 125: 145–156, DOI: 10.1007/s10549-010-1228-x
- 27 von Minckwitz G, Untch M, Blohmer JU et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol* 2012; DOI: 10.1200/JCO.2011.38.8595
- 28 Gianni L, Bianchini G, Kiermaier A et al. Neoadjuvant pertuzumab and trastuzumab: biomarker analyses of a 4-arm randomized phase II study (NeoSphere) in patients with HER2-positive breast cancer. *Cancer Res* 2011; 71: 109 s–110 s
- 29 Gianni L, Pienkowski T, Im YH et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012; 13: 25–32, DOI: 10.1016/S1470-2045(11)70336-9
- 30 Schneeweiss A, Chia S, Hickish T et al. Neoadjuvant pertuzumab and trastuzumab concurrent or sequential with an anthracycline-containing or concurrent with an anthracycline-free standard regimen: A randomized phase II study (TRYPHAENA). *Cancer Res* 2011; 71: 112 s–113 s
- 31 Fasching PA, Heusinger K, Haeberle L et al. Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment. *BMC cancer* 2011; 11: 486, DOI: 10.1186/1471-2407-11-486
- 32 Liedtke C, Mazouni C, Hess KR et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. *J Clin Oncol* 2008; 26: 1275–1281, DOI: 10.1200/JCO.2007.14.4147
- 33 Loibl S, von Minckwitz G, Blohmer JU et al. pCR as a surrogate in HER2-positive patients treated with trastuzumab. *Cancer Res* 2011; 71: 111 s
- 34 Cheang MCU, Prat A, Fan C et al. PAM50 HER2-enriched subtype enriches for tumor response to neoadjuvant anthracyclines/taxane and trastuzumab/taxane containing regimens in HER2-positive breast cancer. *Cancer Res* 2011; 71: 110 s
- 35 von Minckwitz G, Kümmel S, Vogel P et al. Neoadjuvant vinorelbine–capecitabine versus docetaxel–doxorubicin–cyclophosphamide in early nonresponsive breast cancer: phase III randomized GeparTrio trial. *J Natl Cancer Inst* 2008; 100: 542–551

- 36 Goldhirsch A, Wood WC, Coates AS *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: 1736–1747, DOI: 10.1093/annonc/mdr304
- 37 von Minckwitz G, Eidtmann H, Loibl S *et al.* Integrating bevacizumab, everolimus, and lapatinib into current neoadjuvant chemotherapy regimen for primary breast cancer. Safety results of the GeparQuinto trial. *Ann Oncol* 2011; 22: 301–306, DOI: 10.1093/annonc/mdq350
- 38 Huober J, Hanusch C, Fasching PA *et al.* Neoadjuvant chemotherapy of paclitaxel with or without Rad001: results of the non-responder part of the GEPARQUINTO study (GBG 44). *Cancer Res* 2011; 71: 105 s
- 39 Gnant M, Mlineritsch B, Schippinger W *et al.* Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med* 2009; 360: 679–691, DOI: 10.1056/NEJMoa0806285
- 40 Gnant M, Mlineritsch B, Luschin-Ebengreuth G *et al.* Long-term follow-up in ABCSG-12: significantly improved overall survival with adjuvant zoledronic acid in postmenopausal patients with endocrine-receptor-positive early breast cancer. *Cancer Res* 2011; 71: 95 s–96 s
- 41 de Boer R, Bundred N, Eidtmann H *et al.* Long-term survival outcomes among postmenopausal women with hormone receptor-positive early breast cancer receiving adjuvant letrozole and zoledronic acid: 5-year follow-up of ZO-FAST. *Cancer Res* 2011; 71: 96 s
- 42 Coleman RE, Marshall H, Cameron D *et al.* Breast-cancer adjuvant therapy with zoledronic acid. *N Engl J Med* 2011; 365: 1396–1405, DOI: 10.1056/NEJMoa1105195
- 43 Diel IJ, Jaschke A, Solomayer EF *et al.* Adjuvant oral clodronate improves the overall survival of primary breast cancer patients with micrometastases to the bone marrow: a long-term follow-up. *Ann Oncol* 2008; 19: 2007–2011, DOI: 10.1093/annonc/mdn429
- 44 Powles T, Paterson S, Kanis JA *et al.* Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer. *J Clin Oncol* 2002; 20: 3219–3224
- 45 Paterson AHG, Anderson SJ, Lembersky BC *et al.* NSABP protocol B-34: a clinical trial comparing adjuvant clodronate vs. placebo in early stage breast cancer patients receiving systemic chemotherapy and/or tamoxifen or no therapy – final analysis. *Cancer Res* 2011; 71: 100 s
- 46 Moebus V, Thomssen C, Harbeck N *et al.* Gain (German Adjuvant Intergroup Node Positive) study: a phase-III multicenter trial to compare dose dense, dose intense ETC (iddETC) vs. EC-TX and Ibandronate vs. observation in patients with node-positive primary breast cancer – 1st interim efficacy analysis. *Cancer Res* 2011; 71: 6 s
- 47 Janni WJ, Harbeck N, Sommer H *et al.* Sequential treatment with epirubicin/cyclophosphamide, followed by docetaxel vs. FEC120 in the adjuvant treatment of breast cancer patients with extensive lymph node involvement: final survival analysis of the German ADEBAR phase III study. *Cancer Res* 2011; 71: 140 s
- 48 Untch M, Fasching PA, Konecny GE *et al.* PREPARE trial: a randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel and CMF versus a standard-dosed epirubicin/cyclophosphamide followed by paclitaxel ± darbepoetin alfa in primary breast cancer – results at the time of surgery. *Ann Oncol* 2011; 22: 1988–1998, DOI: 10.1093/annonc/mdq709
- 49 Untch M, von Minckwitz G, Konecny GE *et al.* PREPARE trial: a randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel, and CMF versus a standard-dosed epirubicin/cyclophosphamide followed by paclitaxel with or without darbepoetin alfa in primary breast cancer – outcome on prognosis. *Ann Oncol* 2011; 22: 1999–2006, DOI: 10.1093/annonc/mdq713
- 50 Nitz U, Gluz O, Oberhoff C *et al.* Adjuvant chemotherapy with or without darbepoetin alpha in node-positive breast cancer: survival and quality of life analysis from the prospective randomized WSG ARA plus trial. *Cancer Res* 2011; 71: 143 s
- 51 Goss P, Smith I, O'Shaughnessy J *et al.* Results of a randomized, double-blind, multicenter, placebo-controlled study of adjuvant lapatinib in women with early-stage ErbB2-overexpressing breast cancer. *Cancer Res* 2011; 71: 109 s
- 52 Baselga J, Cortes J, Kim SB *et al.* Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012; 366: 109–119, DOI: 10.1056/NEJMoa1113216
- 53 Saura C, Garcia-Saenz JA, Xu B *et al.* Safety and efficacy of neratinib in combination with capecitabine in patients with ErbB2-positive breast cancer. *Cancer Res* 2011; 71: 225 s
- 54 Gianni L, Romieu G, Lichinitser M *et al.* First results of AVEREL, a randomized phase III trial to evaluate bevacizumab (BEV) in combination with trastuzumab (H) + docetaxel (DOC) as first-line therapy for HER2-positive locally recurrent/metastatic breast cancer (LR/mBC). *Cancer Res* 2011; 71: 109 s
- 55 Blackwell KL, Miles D, Gianni L *et al.* Primary results from EMILIA, a phase III study of trastuzumab emtansine (T-DM1) versus capecitabine (X) and lapatinib (L) in HER2-positive locally advanced or metastatic breast cancer (MBC) previously treated with trastuzumab (T) and a taxane. *J Clin Oncol* 2012; 30 (suppl; abstr 512)
- 56 Xu B, Guan ZZ, Shen ZZ *et al.* Association of PTEN loss and PIK3CA mutations on outcome in HER2+ metastatic breast cancer patients treated with first-line lapatinib plus paclitaxel or paclitaxel alone. *Cancer Res* 2011; 71: 103 s–104 s
- 57 Colleoni M, Giobbie-Hurder A, Regan MM *et al.* Analyses adjusting for selective crossover show improved overall survival with adjuvant letrozole compared with tamoxifen in the BIG 1-98 study. *J Clin Oncol* 2011; 29: 1117–1124, DOI: 10.1200/JCO.2010.31.6455
- 58 Paridaens RJ, Dirix LY, Beex LV *et al.*; The European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women. *J Clin Oncol* 2008; 26: 4883–4890, DOI: 10.1200/JCO.2007.14.4659
- 59 Mouridsen H, Gershonovich M, Sun Y *et al.* Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol* 2003; 21: 2101–2109, DOI: 10.1200/JCO.2003.04.194
- 60 Nabholz JM, Bonnetterre J, Buzdar A *et al.* Anastrozole (Arimidex) versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: survival analysis and updated safety results. *Eur J Cancer* 2003; 39: 1684–1689
- 61 Bergh J, Jonsson PE, Lidbrink EK *et al.* FACT: an open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. *J Clin Oncol* 2012; DOI: 10.1200/JCO.2011.38.1095
- 62 Mehta RS, Barlow WE, Albain KS *et al.* A Phase III randomized trial of anastrozole versus anastrozole and fulvestrant as first-line therapy for postmenopausal women with metastatic breast cancer: SWOG S0226. *Cancer Res* 2011; 71: 95 s
- 63 Baselga J, Campone M, Piccart M *et al.* Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2012; 366: 520–529, DOI: 10.1056/NEJMoa1109653
- 64 Piccart-Gebhart MJ, Noguchi S, Pritchard KI *et al.* Everolimus for postmenopausal women with advanced breast cancer: Updated results of the BOLERO-2 phase III trial. *J Clin Oncol* 2012; 30 (suppl; abstr 559)
- 65 Statistisches Bundesamt. Gesundheit – Ausgaben (Lange Reihe) – Fachserie 12, Reihe 7.1.2 – 1995 bis 2012. Erschienen am 5.4.2012. Artikelnummer: 2120712107004
- 66 Lux MP, Fasching PA, Loehberg CR *et al.* Health services research and health economy – quality care training in gynaecology, with focus on gynaecological oncology. *Geburtsh Frauenheilk* 2011; 71: 1046–1055, DOI: 10.1055/s-0031-1280435
- 67 Mariotto AB, Yabroff KR, Shao Y *et al.* Projections of the cost of cancer care in the United States: 2010–2020. *J Natl Cancer Inst* 2011; 103: 117–128, DOI: 10.1093/jnci/djq495
- 68 Chereau E, Vataire AL, Laas E *et al.* Economic analysis of chemotherapy costs for adjuvant therapy in breast cancer in France. *Cancer Res* 2011; 71: 214 s–215 s
- 69 Baffert S, Cottu PH, Kirova Y *et al.* Burden of brain metastases in HER2-positive breast cancer: healthcare use and costs from a French observational retrospective multicenter study. *Cancer Res* 2011; 71: 212 s–213 s
- 70 Reed SD, Li Y, Anstrom KJ *et al.* Cost effectiveness of ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. *J Clin Oncol* 2009; 27: 2185–2191
- 71 Centers for Medicare & Medicaid Services, Office of the Actuary. Updated national health expenditure projections 2009–2019. <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/downloads/proj2009pdf>; last access: September 2011

- 72 *Hershman DL, Neugut AI, Richards CA et al.* Influence of hospital factors, physician factors and type of health insurance on receipt of immediate postmastectomy reconstruction in young women with breast cancer. *Cancer Res* 2011; 71: 114 s–115 s
- 73 *Neumann PJ, Palmer JA, Nadler E et al.* Cancer therapy costs influence treatment: a national survey of oncologists. *Health Affairs* 2010; 29: 196–202
- 74 *Lacey L, Chien R, Hornberger J.* Cost-utility of the 21-gene breast cancer assay (Oncotype DX®) in the Irish healthcare setting. *Cancer Res* 2011; 71: 213 s
- 75 *Pronzato P, Plun-Favreau J.* Is the 21-gene breast cancer test (Oncotype DX®) cost-effective? *Cancer Res* 2011; 71: 213 s–214 s
- 76 *Warren JL, Yabroff KR, Meekins A et al.* Evaluation of trends in the cost of initial cancer treatment. *J Natl Cancer Inst* 2008; 100: 888–897
- 77 *von Minckwitz G, Blohmer JU, Costa SD et al.* Neoadjuvant chemotherapy adapted by interim response improves overall survival of primary breast cancer patients – results of the GeparTrio trial. *Cancer Res* 2011; 71: 103 s

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