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# Current Status of Financing and Reimbursement of Trastuzumab (Herceptin®) for Adjuvant and Advanced Therapy of Breast Cancer in Germany

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**Key Words**

Breast cancer · Therapy, adjuvant and advanced · Cost management · Reimbursement · Off-label use · Cost-effectiveness · Trastuzumab · HER2/neu

**Summary**

Trastuzumab (Herceptin®) is a monoclonal antibody treatment option for breast cancer patients costing up to 5–10 times more than state-of-the-art chemotherapy. A significantly improved outcome for defined groups of patients who are HER2/neu-positive was previously shown for advanced/metastatic breast cancer and recently also for adjuvant therapy in several large phase III trials. However, financial limitations of any health system, even in wealthy nations such as Germany, can prevent optimal treatment. The German Social Security Code requires cost-effectiveness of all medical treatment. Financing of off-label pharmaceuticals is strictly limited by law. In contrast to advanced breast cancer for which trastuzumab is licensed, in the adjuvant setting it is restricted to off-label use and could result in a massive financial loss for the health care provider. So, indication and reimbursement for innovative therapies during the interim phase between clinical trials and official approval remain difficult. In this review, the current situation in Germany and the experience with financing and reimbursement of the costs of trastuzumab in the adjuvant and advanced setting as well as the search for financial solutions are described.

**Schlüsselwörter**

Mammakarzinom · Therapie, adjuvante und fortgeschrittene · Kostenmanagement · Kostenerstattung · Off-Label-Gebrauch · Wirtschaftlichkeit · Trastuzumab · HER2/neu

**Zusammenfassung**

Trastuzumab (Herceptin®) ist ein monoklonaler Antikörper als Behandlungsoption für Brustkrebspatientinnen mit Kosten bis zum 5–10 fachen einer State-of-the-Art-Chemotherapie. Ein signifikant verbessertes Ergebnis für bestimmte Patientengruppen, die HER2/neu-positiv sind, wurde bereits für das fortgeschrittene/metastasierte Mammakarzinom nachgewiesen sowie kürzlich auch in mehreren großen Phase-III-Studien für die adjuvante Anwendung. Allerdings können finanzielle Rahmenbedingungen in jedem Gesundheitssystem, sogar in wohlhabenden Nationen wie Deutschland, den optimalen Einsatz der Therapie einschränken. Das deutsche Sozialgesetzbuch fordert Wirtschaftlichkeit für alle medizinischen Behandlungen. Der Finanzierung von Off-Label-Medikamenten sind rechtlich enge Grenzen gesetzt. Im Gegensatz zum fortgeschrittenen Mammakarzinom, für das Trastuzumab zugelassen ist, ist das Medikament in der adjuvanten Behandlung immer noch auf den Off-Label-Gebrauch beschränkt und könnte zu massiven finanziellen Verlusten für den Leistungserbringer führen. So bleiben die Indikationsstellung und Kostenerstattung für innovative Therapien in der Zwischenphase von klinischen Studien bis zur offiziellen Zulassung schwierig. In dieser Übersicht wird der gegenwärtige Stand in Deutschland und die Erfahrungen mit der Finanzierung und Kostenerstattung von Trastuzumab für die adjuvante und metastasierte Anwendung in der Klinik und die Suche nach finanziellen Lösungen beschrieben.

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## Introduction

Therapy of breast cancer is usually based on surgery often followed by chemotherapy, radiotherapy and endocrine medication. Trastuzumab (Herceptin®, Hoffmann-La Roche, Grenzach-Whylen, Germany) is a rather new therapy option based on the development of specific humanized monoclonal antibodies against the HER2/neu receptor [1–3] which is also of independent prognostic value [4]. Patients with a DAKO score of HER2/neu 3+ or 2+ with additional fluorescence in situ hybridization (FISH) amplification performed by a validated method [5, 6] are considered to benefit from intravenous trastuzumab treatment. This was shown for advanced (metastatic) breast cancer [7] and led to an increase in survival both as monotherapy [8] and in combination with chemotherapy [9, 10]. According to the current product information for physicians (September 2005), trastuzumab is certified and approved for metastasized breast cancer as monotherapy or in combination with paclitaxel or docetaxel [11]. Since its approval, trastuzumab has also been recommended for the adjuvant setting [12] and is currently under investigation in 4 large phase III trials (NSABP B-31, BCIRG 006, NCCTG 9831 and HERA). The results of the FinHer study have just been published [13]. All recent publications [5, 6, 13] have shown similar remarkable results [14, 15]. Trastuzumab therapy has since been recommended by leading expert groups, such as the St. Gallen Consensus Statement 2005 [16], the German AGO guidelines [17] and the German S3 Breast Cancer Guidelines [18].

However, innovative therapy always comes at a price, and trastuzumab is exceeding the costs of standard state-of-the-art chemotherapy by up to 5–10 times (table 1). One the one hand, health insurance companies – despite publicly advertising almost unlimited care for all patients – are trying to limit the use of trastuzumab as far as possible to cut the excessive costs. Medical care providers, on the other hand, are under increasing economic pressure and can neither subsidize trastuzumab therapies nor foot the bill for such an expensive drug.

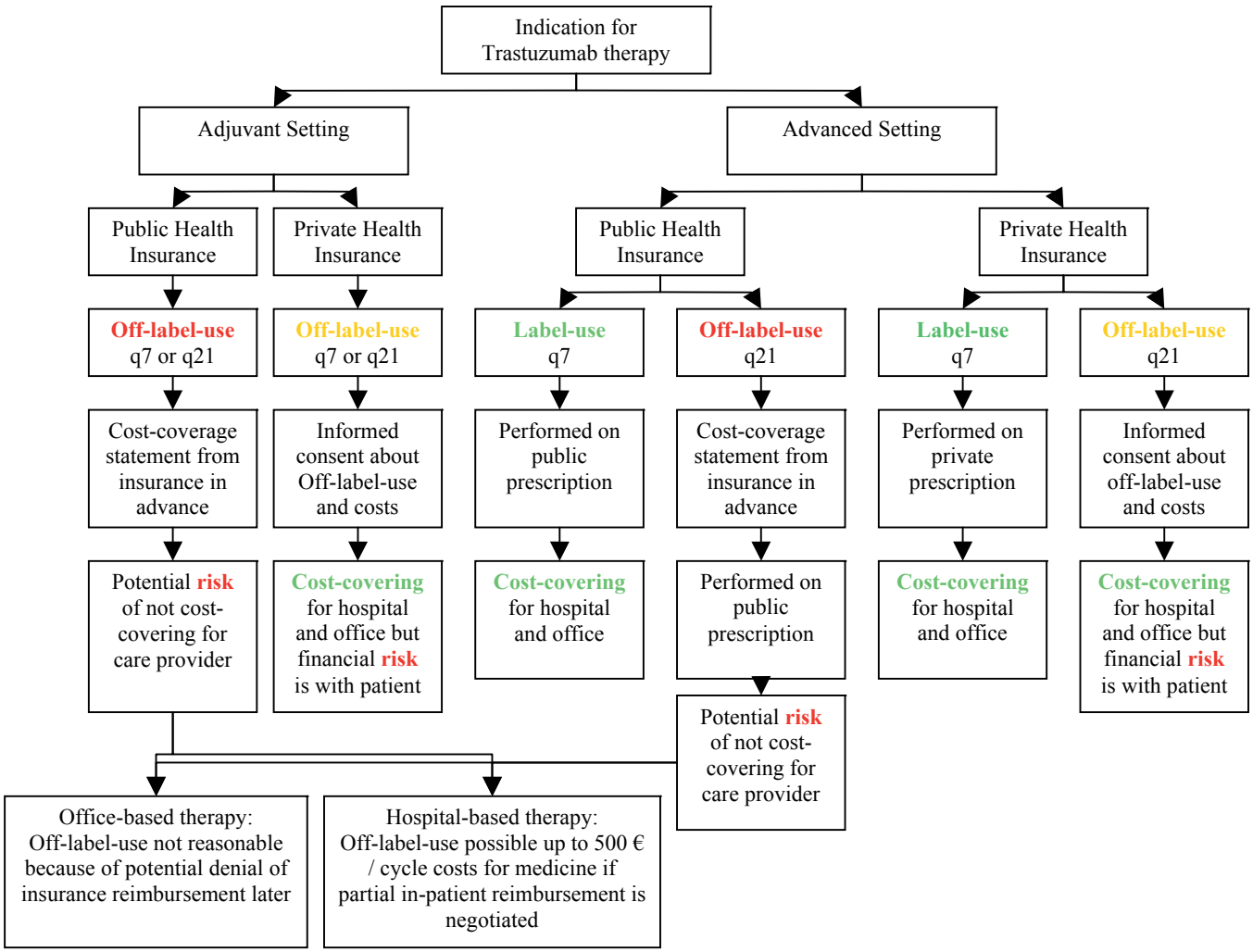


**Fig. 1.** 'Traffic light'. Decision-making flowchart on cost-effective trastuzumab therapy at the Gynecological Hospital of the Technical University Munich depending on several influential factors (1st January 2006). Red = financial risk or non-reimbursement of costs, yellow = financial risk for patient, green = reimbursement of costs for the health care provider.

**Table 1.** Comparison of pharmaceutical costs for different breast cancer therapies in Germany for a standard patient of 70 kg body weight and 1.8 $m^2$ body surface

| Therapy | Regimen | Costs[a], € |
|---|---|---|
| Antracycline | 6 × FEC 500/100/500 mg/$m^2$, q21 | 6,357.54 |
| Antracycline/taxane | 4 × EC 90/600 mg/$m^2$ + 4 × DOC 100 mg/$m^2$, q21 | 12,052.12 |
| Antibody | 18 × trastuzumab 6 mg/kg (initial dose 8 mg), q21 | 43,725.55 |

[a]All costs table 1–5: [19].

In the following, an overview of the current state of financing and reimbursement of the costs of trastuzumab in Germany is given, and related aspects are discussed.

## Actual Pharmaceutical Costs of Trastuzumab Therapy

Trastuzumab is usually given intravenously, either weekly (q7) or every 3 weeks (q21), as a triple dose. So far, only the q7 regimen for advanced (metastastic) breast cancer is licensed. The q21 regimen in the advanced setting as well as q7 and q21 in the adjuvant setting are restricted to off-label use (fig. 1). For the q7 regimen, the initial loading dose is 4 mg/kg, followed by 2 mg/kg. For q21, the initially dose is 8 mg/kg, followed by 6 mg/kg. Based on the available trial data, adjuvant therapy is currently limited to 1-year, whereas advanced therapy with trastuzumab is given (at least) until progression of disease. The actual pharmaceutical costs (all costs listed here are based on 'Große Deutsche Spezialitätentaxe/Lauer-Taxe', 1st January 2006 [19]) depend not only on the weight of the patient but also on the actual amount of trastuzumab used, because it is exclusively available in packages of 150 mg (table 2). Thus, pharmaceutical costs for a single-day treatment can range from € 795.01 for a 2-mg/kg dose for a 50-kg patient to € 4,770.06 for an initial 8-mg/kg dose for a 110-kg patient (table 3). The yearly costs for q21 administration vary considerably and may range from € 29,415.37 for a 50-kg patient to € 72,345.91 for a 110-kg patient (table 4). However, adjusting the treatment to the pharmaceutical costs could result in remarkable savings. Presuming that patient outcome is identical with trastuzumab q7 and q21, as suggested by comparable pharmacokinetics, public health insurance companies could save up to > € 25,000 (> 30%) per year of therapy if they agreed to off-label use q21 instead of the approved q7 use, even in the advanced setting – not to mention the increase in quality of life for the patient.

## Current Reimbursement of Trastuzumab Therapy in Germany

Reimbursement of costs of identical amounts of trastuzumab is not consistent throughout Germany but depends on a variety of factors, such as where the patient is insured, where the therapy is performed and which reimbursement mode is available to or used by the care provider. Depending on these factors, performing trastuzumab therapy can be either cost-covering for the institution or cause big financial losses which the institution has to cover with its own budget. Hence, this affects physicians' therapy decision [20] and requires an understanding of all financial aspects of performing oncological therapies [21] as well as active cost management, preferably by the oncological care provider [22, 23]. Since the pharmaceutical costs for a 1-year trastuzumab therapy alone equal a 1-year salary of a full-time physician, the financial risks of no or incomplete reimbursement of the costs need to be fully evaluated in advance.

Trastuzumab, like any other oncological therapy in Germany, can be administered either as outpatient treatment or in a hospital. For outpatient treatment, approved trastuzumab therapy is performed on a private or public prescription, and the physician receives a performance fee. The private and public health insurance companies pay completely for the pharmaceutical substance and the physician's fee. Hence, trastuzumab therapy can be carried out in a cost-covering manner. However, because off-label use of trastuzumab can lead to financial regress and demands to pay back all therapy costs to the health insurance, off-label use on an outpatient basis is preferably avoided by physicians. In case of doubt, the physician has to obtain advance confirmation (precertification) that all treatment costs will be met by the health insurance company (fig. 1).

Reimbursement of the costs of trastuzumab therapy in a hospital setting is more complex. Treatment can either be performed on an inpatient, partial inpatient or outpatient basis, but not all options are available in every German hospital. Outpatient therapy on a prescription basis with a performance fee similar to that of an independent physician is always available to privately insured patients. However, patients with public health insurance can only avail themselves of the service if one of the clinicians or the head of the department have a special license from the local self-administration. This license is only issued if no or insufficient amounts of oncological practices are locally available and/or the existing practices do not object to its issuing. The license can be revoked at any time. Trastuzumab therapy on an outpatient basis is always cost-covering for privately insured patients but not necessarily for public health insurance patients. If treatment costs are not fully covered for the hospital, patients are better send to a local oncologist for trastuzumab therapy. This is particularly important if a public health in-

surance company insists on outpatient hospital treatment based on the quarterly voucher of statutory health insurance payment with a flat rate value of only € 64.06 covering 3 months of medical service. This payment option does not make sense for the hospital, because it is by no means cost-covering. Hospitals also have to avoid outpatient off-label trastuzumab therapy since they face the same sanctions as independent physicians. Some hospitals have negotiated an option with insurance companies to perform trastuzumab therapy as partial inpatient treatment with a flat rate reimbursement or as a Diagnosis-Related Groups (DRG)-single day payment which amounts to about € 650 per day. This reimbursement option is not cost-covering because of the much higher pharmaceutical costs for trastuzumab. However, if an off-label trastuzumab therapy is performed, this is an option to cover at least a fraction (up to € 500) of the generally much higher pharmaceutical costs (fig. 1, table 3, 4).

The third option for hospitals is to administer trastuzumab as inpatient treatment. The problem here is that since 2004, it has been mandatory that any hospital stay is calculated and reimbursed according to the DRG system. This implies that all drugs given during a stationary hospital visit are covered by flat rate DRG reimbursement without taking excessively expensive drugs into account. However, for some pharmaceuticals given during an inpatient hospital therapy, an extra fee can be reimbursed if properly documented. For trastuzumab, such additional payment (Zusatzentgelt ZE 27) is defined. But in contrast to the meaning of the word, it is not given in addition to the DRG payment but merely shifted within the hospital's annual budget. To stay within the budget, inpatient trastuzumab therapy on the basis of additional payment will have to be compensated by reducing surgical procedures of the same value. Thus, this only makes sense for hospitals that do not fully use their allocated budget and/or procedures. However, the additional payment compensates only for part of the pharmaceutical costs, so a financial deficit of several hundred € Euro remains with the care provider for inpatient trastuzumab therapy (table 5). Hospitals that already exceed their budget should not administer trastuzumab on an inpatient basis, as it is not cost-effective. Moreover, the German Social Security Code (Sozialgesetzbuch, SGB V) requires that any medical treatment is performed as cost-effectively as possible: preferably as outpatient treatment or, if that is not possible, as partial inpatient treatment. Inpatient therapy should be the last instance. Thus, if according to SGB V §275, the Health Insurance Medical Service (Medizinischer Dienst der Krankenversicherung, MDK) later complains that there was no appropriate indication for inpatient trastuzumab therapy, the hospital is in danger of losing the entire reimbursement. Despite temporary uncertainty about financing of studies due to a Federal Social Court ruling in 2004 [24], to further support performance of and participation in clinical trials, trastuzumab treatment in studies is reimbursed analog to standard oncological treatment.

**Table 2.** Comparison of costs of q7 trastuzumab therapy 2 mg/kg depending on body weight

| Body weight, kg | Trastuzumab absolute, mg | Costs, € |
|---|---|---|
| 50 | 100 | 795.01 |
| 70 | 140 | 795.01 |
| 90 | 180 | 1,590.02[a] |
| 110 | 220 | 1,590.02[a] |

[a] Body weight of > 75 kg is the threshold for using another 150-mg trastuzumab package.

**Table 3.** Official pharmaceutical price (1st January 2006) for a single-day trastuzumab therapy depending on dose, weight and administration scheme

| Body weight, kg | Costs of q7 regimen, € | | Costs of q21 regimen, € | |
|---|---|---|---|---|
| | 2 mg | 4 mg (loading dose) | 6 mg | 8 mg (loading dose) |
| 50 | 795.01 | 1,590.02 | 1,590.02 | 2,385.03 |
| 70 | 795.01 | 1,590.02 | 2,385.03 | 3,180.04 |
| 90 | 1,590.02 | 2,385.03 | 3,180.04 | 3,975.05 |
| 110 | 1,590.02 | 2,385.03 | 3,975.05 | 4,770.06 |

Based on our experience with trastuzumab therapy and its reimbursement [21–23] in a university hospital, every single trastuzumab therapy should be pre-calculated regarding its cost-effectiveness for the hospital prior to being carried out. If an oncological therapy cannot be performed in a cost-covering way, trastuzumab patients should be send to a local physician, because there reimbursement of costs is guaranteed for as long as trastuzumab is not used off-label (fig 1). Keeping patients in hospital to perform a not cost-covering treatment will necessitate subsidization of the treatment by the clinic's own budget and possibly lead to cut backs, such as job losses.

## Mechanisms to Prevent Implementation of Expensive New Therapies in Germany

Every physician is required by German law [25] to perform any medical service economically. If 2 equal therapy options are available regarding outcome, physicians are obliged to use the cheaper therapy ('economic principle'). Medical care should be performed with the least possible use of resources ('minimal principle'). Due to the repeated yearly attempts by the German Ministry of Health to cut pharmaceutical costs, every independent physician as well as hospital doctors are affected in some way. The German Social Court (Bundessozialgericht, BSG) has issued a ruling [26] that any physician is legally obliged to treat all patients and perform any indicated therapy independent of payment for medical service and reimbursement of costs, even if there was to be no pay-

**Table 4.** Comparison of annual pharmaceutical costs (1st January 2006) of trastuzumab therapy: q7 vs. q21 and potential savings

| Body weight, kg | Costs of trastuzumab q7 (4→2 mg/kg), € | Costs of trastuzumab q21 (8→6 mg/kg), € | Difference q21 vs. q7, € (%) |
|---|---|---|---|
| 50 | 1 × 1,590.02 + 51 × 795.01 = 42,135.53 | 1 × 2,385.03 + 17 × 1,590.02 = 29,415.37 | –12,720.16 (–30.2%) |
| 70 | 1 × 1,590.02 + 51 × 795.01 = 42,135.53 | 1 × 3,180.04 + 17 × 2,385.03 = 43,725.55 € | +1,590.02 (+3.8%) |
| 90 | 1 × 2,385.03 + 51 × 1,590.02 = 83,476.05 | 1 × 3,975.05 + 17 × 3,180.04 = 58,035.73 € | –25,440.32 (–30.5%) |
| 110 | 1 × 2,385.03 + 51 × 1,590.02 = 83,476.05 | 1 × 4,770.06 + 17 × 3,975.05 = 72,345.91 | –11,130.14 (–13.3%) |

**Table 5.** Additional payments (Zusatzentgelt ZE 27, 1st January 2006) for hospital inpatient administration of trastuzumab; under-reimbursement is calculated by subtracting additional payment from official drug price (Lauer-Taxe, [19]) without any other source of reimbursement

| Additional payment code | OPS-301 procedure code | Dose absolute, mg | Additional payment, € | Under-reimbursement, € |
|---|---|---|---|---|
| ZE27.01 | 8–012.h0 | 100 – < 150 | 554.19 | –240.82 |
| ZE27.02 | 8–012.h1 | 150 – < 200 | 789.95 | –800.07 |
| ZE27.03 | 8–012.h2 | 200 – < 250 | 1,029.20 | –560.82 |
| ZE27.04 | 8–012.h3 | 250 – < 300 | 1,266.71 | –323.31 |
| ZE27.05 | 8–012.h4 | 300 – < 350 | 1,504.22 | –880.81 |
| ZE27.06 | 8–012.h5 | 350 – < 400 | 1,741.73 | –643.30 |
| ZE27.07 | 8–012.h6 | 400 – < 450 | 1,979.23 | –406.07 |
| ZE27.08 | 8–012.h7 | 450 – < 500 | 2,213.72 | –966.32 |
| ZE27.09 | 8–012.h8 | 500 – < 600 | 2,533.42 | –646.62 |
| ZE27.10 | 8–012.h9 | 600 – < 700 | 3,008.43 | –966.62 |
| ZE27.11 | 8–012.ha | 700 – < 800 | 3,483.45 | –491.60 or –811.59 |
| ZE27.12 | 8–012.hb | 800 – < 900 | 3,958.47 | –811.59 |
| ZE27.13 | 8–012.hc | 900 – < 1,000 | 4,433.48 | –1,131.59 |
| ZE27.14 | 8–012.hd | 1,000 – < 1,200 | 5,066.84 | –498.23 or –1,293.24 |
| ZE27.15 | 8–012.he | 1,200 – < 1,400 | 6,016.87 | –1,138.22 or –1,933.23 |
| ZE27.16 | 8–012.hf | 1,400 – < 1,600 | 6,966.90 | –983.20 or –1,778.21 |
| ZE27.17 | 8–012.hg | 1,600 or more | 7,916.93 | –828.18 or more |

ment at all. This is another reason for physicians to ensure reimbursement for expensive therapies in advance. Furthermore, the German DRG system is calculated retrospectively, and no extra payment for expensive pharmaceuticals exists if not negotiated in advance. Due to this retrospective calculation, new and expensive therapies are paid for by the indicating medical institution itself until they are used nationwide as a standard and are hopefully reimbursed after some years, provided they have been comprehensively documented.

## Off-Label Use and German Social Court Rulings

A key word in the verbal fight for or against reimbursement of the costs of expensive pharmaceutical treatment is 'off-label use'. The term means that a pharmaceutical substance is used in a way for which it has not been officially approved, e.g. different indication, pharmaceutical combination, dosage, age group, administration scheme, route of administration, etc. There is also a legal difference between off-label use of otherwise approved pharmaceuticals (in Germany) vs. not approved at all [27, 28]. In principle, the SGB V does not allow payment for off-label use by public health insurance companies. However, this principle does not imply that the substance cannot be successfully used or that the patient has no right to request and receive it. In a 2002 ruling [29], the BSG made it very clear that there are exemptions from this rule and that patients do have the right to receive off-label drugs in case of: i) severe and/or life threatening illness, ii) no available alternative treatment, iii) potential and/or evident treatment success (e.g. phase III trials).

Public health insurance companies often try to reject legitimate (from the patient's view) requests for trastuzumab treatment in the adjuvant setting because of its off-label use. From the point of view of the physicians trying to provide patients with maximum care, this is a rather weak and insufficient excuse by the public health insurance companies to avoid financial responsibility. However, there seems to be a double standard which appears to be based only on financial assumptions. The formerly widely used CMF (cyclophosphamide, methotrexate, 5-fluorouracil (5-FU)) chemotherapy regime for breast cancer has always been used off-label, because the component 5-FU was never approved for breast cancer. Since CMF is the least expensive chemotherapy regime available up to now, with extremely low costs of only € 10–20 per treatment, to our knowledge no public health insurance provider has ever complained about its off-label use. As a direct result of the 2002 BSG ruling, an expert commission was founded at the Federal

Institute for Pharmaceuticals and Medical Products (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) to solve the disputed off-label use conflict [30]. In addition, a still ongoing discussion was started [31] covering different points of view ranging from public health insurance companies [30], pharmaceutical industry [32], to federal administration [33] and legal aspects [34], which also stresses the necessity for off-label use of pharmaceuticals, especially in oncology [35].

## Refusal of Public Health Insurance Providers to Pay for Trastuzumab Therapy

Despite the public appearance of public health insurance companies as defenders of patient rights, they try to limit the reimbursement of the massive costs of adjuvant trastuzumab therapy (table 4). As a result, physicians carry the risk of not being reimbursed for the trastuzumab costs of an already performed therapy. Therefore, in contrast to approved trastuzumab therapy where reimbursement is not a problem, advance confirmation prior to treatment should be obtained from the patient's public health insurance provider that the costs of adjuvant trastuzumab will be covered. Our experience is that public health insurance companies react in multiple ways to this challenge. The outcome of a request for precertification for adjuvant trastuzumab therapy is not predictable and, from the patients' point of view, depends purely on chance and luck. Here are 5 examples: Deutsche Angestellten Krankenkasse (DAK) rejected such a request in 10/2005 stating that 'this off-label use can not be financed because no scientific phase III study has been published'. Barmer Krankenkasse rejected it in 8/2005 with a quotation from the SGB V that 'unnecessary or not cost-effective service cannot be financed' and recommends that the physician complies with the law and the physicians' self-administration regulations regarding pharmaceutical prescriptions. Techniker Krankenkasse (TK) rejected the request in 8/2005 with the explanation that 'only 3 instead of 4 cycles of EC-Doc (epirubicin/cyclophosphamide-docetaxel) had been administered before'. From a clinician's and a scientist's point of view, this is not logical, because the effect of trastuzumab is based on the fact that it interacts with overexpressed or amplified HER2/neu receptors and not on the number of administered chemotherapy cycles prior to trastuzumab therapy. MDK of Techniker Krankenkasse rejected another request in 1/2006 by applying additional administrative hurdles, e.g. that breast cancer is not a rare disease which can otherwise be investigated systematically for treatment options citing other sources [36]. Despite these examples of rejection of payment by public health insurance providers, one health insurance – Siemens Betriebskrankenkasse – has solved this problem with a remarkable approach [37]. They reply to advanced cost reimbursement requests by patients with a standard letter recognizing that physicians are uncertain about the reimbursement of adjuvant trastuzumab therapy and waive any potential future sanction payments against the trastuzumab-administering physician if the physician is convinced that his/her indication fulfils the BSG requirements for off-label use [29].

## Influence of MDK Reports

Lately, an increasing number of public health insurance companies seem to issue their decision regarding the reimbursement of costs for adjuvant trastuzumab based on reports issued by the MDK. The 47-page report of the MDK Nordrhein, available in its most recent version of 28th October 2005 [38], evaluates adjuvant trastuzumab. To avoid administrative hassle and later potential non-reimbursement of the costs of trastuzumab therapy by public health insurance companies, physicians increasingly pay attention to this report and, if in doubt, restrict their indication in anticipatory obedience, even if their patients might have potentially benefited from adjuvant off-label trastuzumab. This report targets the restriction of trastuzumab administration as far as possible. Therefore, many decisions are questionable from the oncologist's point of view [14].

## Social Court Rulings in Favor of Adjuvant Trastuzumab Therapy

Patients in Germany who are dissatisfied with rejection of reimbursement of adjuvant trastuzumab treatment costs by their public health insurance company have the right to go before a Social Court and request a restraining order against the company regarding reimbursement of costs. Although the judges' decisions [39, 40] are presently based on individual cases, the majority of decisions have been in favor of the patient. Since the publication of the HERA (Herceptin Adjuvant) trial results [5], all 3 requirements of the German Social Court [29] are fulfilled for adjuvant trastuzumab therapy. Thus, future rulings are likely to have a similar outcome.

## Private Health Insurance and Reimbursement of Trastuzumab Costs

In 2004, 16.5 million Germans, about 18–19% of the entire population, had partial or full private health insurance, 8.2 million of them with partial private insurance for hospital inpatient treatment and 8.3 million with full coverage for private in- and outpatient health care [41]. In contrast to a public health insurance where the contract partners are the insurance company and the health care provider, privately insured patients have a direct contract with the health care provider and have to pay any medical bill upfront before later being reim-

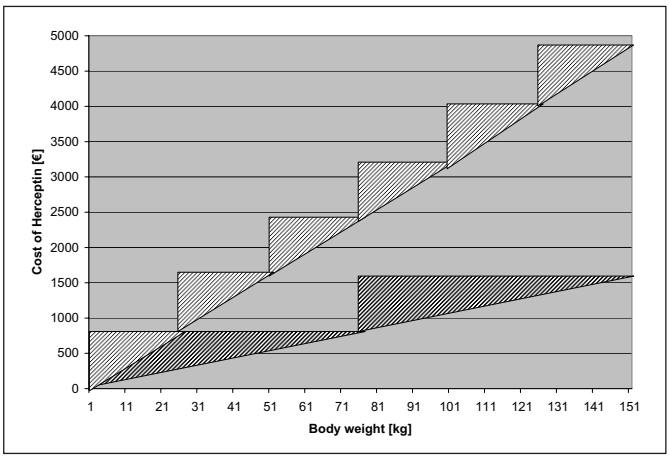


**Fig. 2.** Graphic quantification (marked areas) of wasted pharmaceutical substance due to availability of only 150-mg Herceptin packages (upper graph: q21 therapy with 6 mg/kg, lower graph: q7 therapy with 2 mg/kg).

bursed by their private health insurance company. Due to this fact, any patient with private health insurance can immediately receive approved as well as off-label trastuzumab therapy if indicated, after giving informed consent regarding the potential off-label use and high costs. To our knowledge, all of our patients with private health insurance have always been completely reimbursed for trastuzumab treatment in the adjuvant or the advanced setting.

## Projected Costs of Adjuvant Trastuzumab for the German Health System

In Germany, in the year 2000, 47,517 patients were newly diagnosed with breast cancer [42]. Up to 25% of all breast cancer patients have either a HER2/neu overexpression, DAKO score 3+ or a 2+ score plus positive FISH test showing gene amplification [43] and are therefore eligible for trastuzumab therapy. At estimated pharmaceutical costs of on average € 50,000 for a 1-year therapy (table 4), which is similar to the costs in the UK [44], the financial burden on the German health system will reach about 594 million Euro/year after nationwide implementation of this therapy. These costs are newly generated without any potential savings for the health system and represent a financial quantum leap even for the relatively wealthy German society and health care system. The pharmaceutical budget of the German public health insurance (Gesetzliche Krankenversicherung, GKV) in 2005 was estimated at 24.6 billion Euro, which is a dramatic increase of 17.2% within 1 year [45]. Based on the 2004 pharmaceutical costs, adjuvant trastuzumab therapy alone would account for a yearly increase of up to 2.4% in the pharmaceutical budget. This is in contrast to the increasing economic pressure on the German health system to decrease costs instead of increase them. Plans by the German Government and the self-administration authority for physicians (Kassenärztliche Bundesvereinigung, KBV) to limit the pharmaceutical cost increase for 2006 via contracts to only 4.8%, imply further forced price reductions by the pharmaceutical industry or limited access to drug prescriptions in 2006 [46]. These are helpless attempts to limit spending for pharmaceuticals without too obviously rationing medical care in the public eye, and they are likely to fail again. An option on the pharmaceutical company side to reduce costs would be to provide trastuzumab in different package sizes adjustable to actual body weight, rather than only in a 150-mg package [38] which leads to a remarkable and costly waste (fig. 2). For a trastuzumab dose of 2 mg per kg, one package is sufficient for a person weighing up to 75 kg, but pharmaceutical costs are doubled instantly if this weight is marginally exceeded as another 150 mg trastuzumab package has to be opened (table 2).

## Physicians' Role in Implementing Adjuvant Herceptin Off-Label Therapy

The physicians' role in rapid implementation of trastuzumab off-label use is unique and can not be underestimated. But despite the remarkable results published recently, there is also skepticism among physicians [47] that the benefits of Herceptin could be overestimated by enthusiastic researchers [15, 48] and that long-term results are missing and setbacks such as cardiotoxicity [49] or an increase in brain metastasis [50] might occur in Herceptin patients. The controversy continues [51–54]. Furthermore, researchers involved in large trials are often key opinion leaders giving scientific talks paid by pharmaceutical companies. By presenting dramatic results, they fuel the hopes of patients and satisfy the media as well as the pockets of pharmaceutical companies. The subsequent rise in demand by physicians pushing the widespread off-label use of Herceptin adjuvant may be for good ethical reasons and in the best interest of their patients. At the same time, however, it puts an increased financial pressure on any public health system, even in wealthy countries, if a conclusive scientific discussion, comprehensive medical evaluation with publication of study and final decision about financing this therapy have not yet been completed. Herceptin has so created an avalanche of costs for health insurance providers before data for drug approval had even been submitted by the pharmaceutical company [47].

## Perspective

For physicians willing to prescribe and administer trastuzumab in the adjuvant setting based on the available phase III trial results and the consecutive national and international guidelines, the transition period between off-label and approved use during the next few months will be difficult. Final

approval for use of trastuzumab in adjuvant breast cancer therapy and the reimbursement-relevant change from off-label to approved use is expected in Germany in the second half of 2006, since Hoffman-La Roche have officially submitted all files for regulatory approval on 16th February 2006. We encourage colleagues not to give up their negotiations with public health insurance providers in order to convince them of the necessity of payment for trastuzumab-eligible patients according to German social court rulings and patient needs. Therefore, we supply such patients with detailed information and prepared application forms for adjuvant cost compensation for the health insurance companies.

However, in the long run, the entire German society has to decide how to deal with innovative and expensive pharmaceuticals and also if the German society is willing to pay about € 720,000 for the prevention of a single breast cancer recurrence using trastuzumab [38]. So far, the decision to introduce and apply new therapies and innovative pharmaceuticals is mainly based on the results of large clinical trials and not on costs or cost-effectiveness. Thus, if a new substance or regimen proves in adequately designed studies to benefit patients, e.g. by prolonging overall survival or time to progression or by improving quality of life, ethical pressure is put on oncologists to use it in every eligible patient as soon as possible [55]. So far, even excessive costs did not matter. However, with up to several hundreds of novel targeted therapeutics, such as antibody-based products, in the pipeline of pharmaceutical companies worldwide, costs might soon exceed even health experts' estimates and expectations. The current situation for physicians who prescribe and administer innovative and expensive drugs such as trastuzumab while risking non-reimbursement or pay-back claims for therapy costs by the health insurance, is absurd. Physicians should not be punished if legitimate therapy costs are not being paid for [56]. Maybe, instead of yet another attempt to negotiate price reductions with the pharmaceutical industry or a fixed yearly pharmaceutical budget with the KBV, the German society should decide about potential financial limitations of the treatment for an illness. And finally, access to expensive drugs and rationing of their use can and should be done only after a comprehensive public discussion and final consensus by the entire society and not secretly by underpaying or non-reimbursing physicians for their medical service and pharmaceutical expenses.

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