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ORIGINAL ARTICLE

Trastuzumab use in breast cancer patients in the six Health Care Regions in Sweden

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Abstract

Background. Approximately 14% of Early Breast Cancers, EBCs, and 25% of Metastatic BCs, MBCs, are HER2 positive. There is an effective treatment (trastuzumab) for both EBC (9% increased absolute disease free survival at five years) and MBC (five to nine months' prolonged overall survival). Patients with BC are treated within each of the six different Health Care Regions (HCRs) in Sweden. This aim of this project was to study the introduction and usage of trastuzumab in BC in the six HCRs in Sweden. *Materials and methods.* We used official sales data and cancer statistics in the model, and HER2 positive proportions of 25% (prevalent population in year 2000; first year of trastuzumab sales) and 14% and treatment times of 38 weeks and 52 weeks for MBC and EBC, respectively, based on clinical trial data. We used years 2000–2004 for the MBC analyses. In year 2005 data on trastuzumab in EBC were presented, and approval came in year 2006. We studied years 2006–2008 for the use in both EBC and MBC. *Results.* The percentage trastuzumab treated MBC patients for the entire period in the different HCRs (quarter 4 2000 to end 2004) was: North 57%, Stockholm 48%, South East 40%, South 17%, Uppsala 52%, West 34%. The Sweden average was 40%. The percentage treated patients (MBC and EBC), years 2006–2008 in the different HCRs was: North 68%, Stockholm 75%, South East 43%, South 44%, Uppsala 74%, West 43%. The Sweden average was 59%. *Conclusion.* The differences in usage of trastuzumab may be explained by variable interpretations of the clinical data and applications in clinical practice, budget issues and differences in coordination, experience and training.

In Sweden the incidence in beast cancer (BC) was around 5000 patients in 1990 and around 7000 patients in 2007. The number of deaths in Sweden due to BC has been stable since 1990, at around 1 500 per year. The relative reduction in mortality (20–30%), and the increased 10-year survival rate from 65% in 1996 (reflecting treatment in the mid 1980s) to 78.8% in 2007 (reflecting treatment in the 1990s) is related to the introduction of adjuvant treatments and screening programs in the 1980–1990s. Improved survival after eight to ten years of mammography screening, i.e. after the mid 1990s, would then indicate other factors [1]. During this time period the main change, in disease management, has been the introduction of new medical treatments, and wider use of existing treatments, often in combinations [2].

HER2 (Human Epidermal Growth Factor Receptor 2) positive BC is a subgroup constituting of approximately 14% of all EBCs and approximately 25% of all MBCs [3–6]. A diagnostic test (IHC, Immunohistochemistry or FISH, Fluoroscence *in situ* hybridisation) of the tumour cells is required to define HER2 status, and there is an effective treatment available, trastuzumab.

Trastuzumab is a monoclonal antibody, binding to HER2 of the cell, blocking HER2 signalling. In HER2 positive MBC, response rates are 50–61% in combination with chemotherapy with prolonged TTP, Time to Progression, and OS, Overall Survival [7,8]. Trastuzumab was approved for MBC in the EU quarter 3, year 2000, and was available on a named patient basis in Sweden already from December 1998 (after approval of the Swedish Medical Product Agency).

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Data on trastuzumab treatment post surgery, in EBC, were presented in 2005 and the drug was approved in 2006 for this indication, after a uniquely short process at EMEA of only two months. This rapid process reflected the impressive effects by trastuzumab, recorded in the randomised adjuvant studies [9–10]. The three year results showed 12% absolute overall survival benefit for trastuzumab treatment. The hazard ratio for death after 60 months follow-up was 0.63 for the trastuzumab treated group compared to controls, and the absolute disease free survival gain at five years was 9% [11]. The Swedish recommendations on HER2 testing and trastuzumab treatment, for MBC, were published in November 2002 and the guidelines on treatment for HER2 positive EBC were published in July 2005 [12].

The state organ, National Board for Health and Welfare, outlines overall aims for the health care sector in Sweden and one important goal of the Swedish health care system is to offer patients same treatments, irrespective of residential location. Sweden has a Beveridgean Health Care system, which means that it is funded through taxes and services are mainly provided by publicly owned hospitals. The Swedish health care system is organised in six Health Care Regions (HCRs). These HCRs are further subdivided into 22 county councils, which are politically ruled and economically independent, with taxation rights and budget accountability.

Trastuzumab treatment should only be offered to patients with HER2 receptor overexpression, or HER2 gene amplification. Since the start, there has been national quality assurance programmes for HER2 testing [3]. Accordingly, the group of patients with HER2 alterations is well defined and it is appropriate to make comparisons on testing and treatment between the HCRs.

In this report we present the uptake and usage of trastuzumab, in the six Swedish HCRs.

The purpose of the study was to:

1. Present variations in use of trastuzumab between HCRs in Sweden, for MBC and EBC.
2. Compare actual use of trastuzumab with the total number of patients that potentially would benefit from treatment (actual versus optimal use).
3. Discuss possible explanations for any differences between HCRs, including medical factors as well as other factors.

Materials and methods

We use sales data, received from the Retail Drug Supplier in Sweden. All drug supplies are distributed through this system, and sales are therefore easy to follow and reflect 100% of usage.

Cancer statistics and death statistics (i.e. cause of death breast cancer) were received from the National Board of Health and Welfare [13] and for general statistics; Statistics Sweden was used [14]. Data on treatment recommendations by the Swedish Breast Cancer Group was retrieved from their web site [12].

In Sweden, cancer care is organised in the following six HCRs: Stockholm-, Uppsala-, South East-, South-, West- and North- HCR. The population in each of the HCRs is (approximately in 1000 inh): Stockholm 2 000, Uppsala 1 900, South East 900, South 1 700, West 1 700 and North 900 [14].

There is a difference in the proportion of HER2 positive patients in EBC and in MBC. This is probably due to the fact that HER2 is a predictor of poor prognosis. Accordingly, a higher proportion of HER2 positive MBC patients should be expected.

The early studies show that 18–30% of BC patients have HER2 positive disease. Our own database of over 600 BC patients shows that 27% of MBC patients have HER2 positive disease. We use 25% HER2 positive MBC patients in the calculations, to reflect data previously reported and our data [4].

In EBC, an average of 14% of the patients in Sweden has HER2 positive disease [3]. This means that around 1 000 EBC patients would potentially be eligible for trastuzumab treatment each year. Not all patients are offered treatment with trastuzumab, due to, e.g. clinical stage (tumour size < 1 cm and/or no indication for adjuvant chemotherapy), or co morbidities. These factors are not taken into consideration in the calculations as this should not differ between HCRs. MBC use is included in the estimates from 2006 to 2008 (25% HER2 positive MBC patients). We also report year 2008 separately, as this is the latest year with full year sales data and this year is two years after the adjuvant introduction. As it is not possible to separate actual EBC use from actual MBC use during 2006–2008, we report the use in units and combine the use of EBC and MBC (both actual use and expected use).

To define the target population for trastuzumab use in MBC, we use mortality data (actual number of cases) from the six HCRs for the years 2000–2004. We also report year 2004 separately, as this is the last year with MBC use only. Median survival in HER2 positive MBC in more than one year [7,8]. There were – of course – patients with HER2 positive MBC before trastuzumab was approved in 2000, and therefore we include data for 1999 for a prevalent MBC population in need of treatment year 2000.

We used a treatment time of 38 weeks, in MBC, in the calculations, based on the median treatment

time in the pivotal study in MBC by Slamon in 2001 (mean treatment time was not available) [7]. In EBC the intended treatment time was 52 weeks and only 8.6% stopped treatment earlier (e.g. progression, side effects) [9], and thus, in EBC treatment time is set at 52 weeks.

In the estimates we analysed trastuzumab use in MBC from quarter 4 2000 through to the end of 2004, and for EBC and MBC use from 2006 through to the end of 2008.

The dose is set at 2 mg per kg per week per patient, according to the label. The average patient should receive 140 mg trastuzumab per week (based on weight of approximately 70 kg). One unit of trastuzumab contains 150 mg of active substance. Thus, the calculations are based on one unit of trastuzumab per patient per week.

Data on HER2 testing and percentage tested EBC patients, years 2005–2007, was reported on questionnaires sent out to the pathology departments by the Swedish HER2 analysis group. [3, and pers. comm.].

This study was approved by the Ethics Committee at the Karolinska Institutet, Stockholm, Sweden

Results

Metastatic breast cancer

The BC mortality rates have been relatively stable during the period and the relative differences between HCRs are small. The largest average difference is 12% over ten years time (Uppsala HCR lowest and South HCR highest). In Sweden the mortality rates in BC were 1494 in 1997 and 1477 in 2007.

Sales per 100000 inhabitants were at the same level in year 2000 in the HCRs, but soon thereafter sales started to differ. In 2004 there is a 2.5 fold difference between the HCR with the highest (North HCR) and the lowest (South HCR) sales of trastuzumab (Figure 1). We also investigated sales data, related to mortality in the HCRs, and the differences were similar, as when population related.

The difference between the total number of HER2 positive MBC patients and the actual number of treated patients varies over time and between HCRs. According to our estimates, there were approximately 190 HER2 positive MBC patients (prevalent group) in Sweden in 4/2000 (the time when trastuzumab was first available, outside of the named patient basis program). Based on our model, around 11% received trastuzumab treatment year 2000. For the following years the percentage treated patients was 19% (2001), 33% (2002), 47% (2003) and 73% (2004), respectively. The proportion trastuzumab treated patients in each HCR for the entire period (4/2000 to end 2004) is shown in Figure 2. In 2004, the actual use in HER2 positive MBC patients was: Stockholm HCR 100%, Uppsala HCR 104%, North HCR 114%, South East HCR 52%, South HCR 35% and West HCR 53%. The percentage score over 100% in the North and Uppsala HCRs may indicate longer treatment periods than used is the estimates (38 weeks), as well as treatment beyond disease progression.

Adjuvant treatment

Sales increased markedly in 2005–2006 (Figure 1). The increase is likely based on the adjuvant data presented this year (12% increased disease free survival in EBC) [10–12] and the adjuvant treatment recommendations by the Swedish Breast Cancer Group, made public mid 2005 [12].

The total number of units used, versus optimal number of units used, years 2006–2008 is presented in Figure 3. The estimates include MBC patients (25% HER2 positive patients, 38 weeks of treatment) and EBC (14% HER2 positive patients, 52 weeks of treatment). The actual use in year 2008 was 84% for North HCR, 82% for Stockholm HCR, 54% for South East HCR, and 49% for South HCR, 75% for Uppsala HCR, 54% for the West HCR. The Sweden average this year was 66%.

When we analyse the sales in relation to incidence, we see similar variations as during the first years.

The estimated number of HER2 positive EBC patients is around 1000 per year. Based on this, at least 52000 vials should be used each year (52 weeks treatment and one vial/week/patient), reflecting a sale of approx. SEK 3.1 million/100000 inhabitants. In 2006, the sales in the Stockholm and Uppsala HCRs passed SEK 3.0 million/100000 females, and this was more than twice the sales in the South East and West HCRs (Figure 1).

HER2 testing

The number of HER2 tests performed during the period varied markedly between the HCRs. In 2000, the number of tests reported was few in all HCRs. The proportion HER2 tested patients in the HCRs for years 2005–2007 is shown in Table I.

Discussion

This study shows that the use of trastuzumab was low during the first year after approval, with large variations between HCRs over the first four years, even if results from the pivotal clinical studies show trastuzumab treatment benefit [7–11]. After adjuvant introduction the use remained variable between the HCRs.

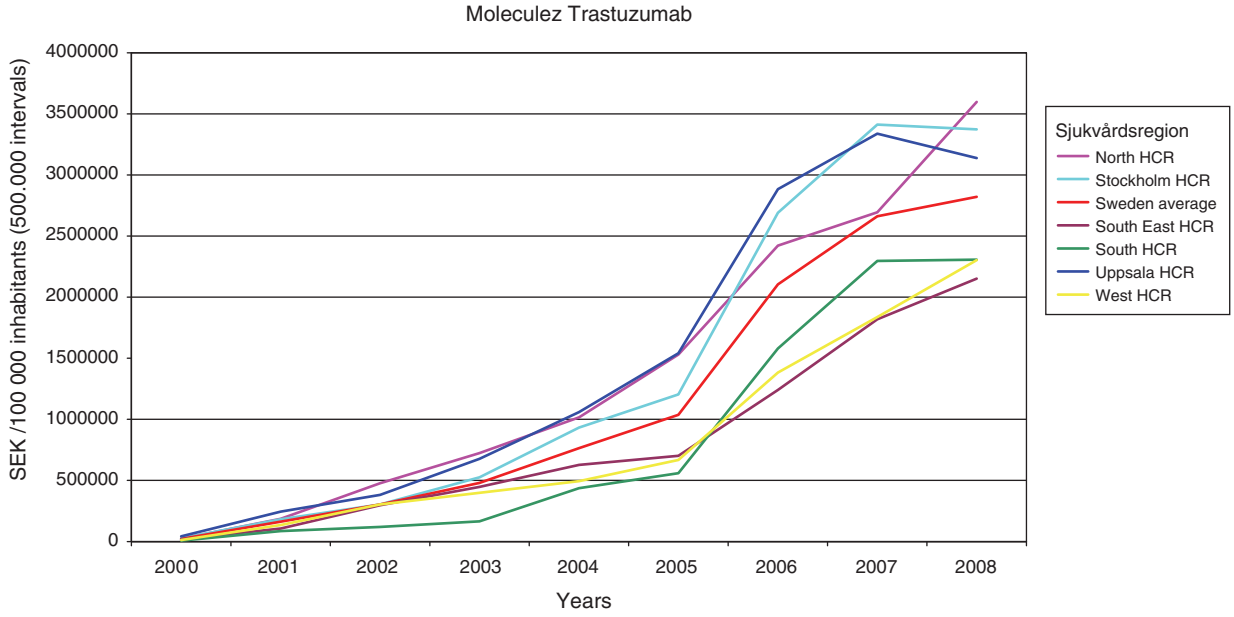

Figure 1. Sales of trastuzumab (per 100 000 inhabitants) in the six HCRs in Sweden from quarter 4 2000–2008.

The Swedish Breast Cancer Group Recommendation, on HER2 testing and trastuzumab use in MBC, was introduced in 2002. In 2004, according to our model, 73% (varying from 35–114%) of all patients in Sweden with HER2 positive MBC, received trastuzumab treatment. Also after the introduction of trastuzumab in EBC, there are large differences between HCRs, even eight years after introduction.

The numbers of patients with HER2 positive disease vary between 18–30% in different reports [3–6]. The early data included analyses of tumours from patients with different prognosis, as well as from MBC patients. More recent data from Sweden show that 14% HER2 positive EBC patients is more correct (in a screening population) [3]. There are small differences between HCRs (North HCR 11.4% and West HCR 14.6%) in reported number of HER2 positive EBC patients in 2007. There are also differences in the numbers of HER2 tested EBC patients (Table I). One could expect that patients with less aggressive, smaller tumours would not be HER2 tested, and thus, the proportion of HER2 positive EBC patients is higher if fewer patients are tested, as indicated by the difference between the North and West HCRs. The differences in number of HER2 tested EBC patients may therefore reflect variable definitions of target population, although the same proportion of patients should be eligible for treatment, as tumour biology is expected to be similar among BC patients in all HCRs. Differences in HER2 analysis results should not be expected, as the pathology departments in the HCRs are included in the Swedish quality control system and results for IHC are reported to have a "good correlation", with kappa-values of 0.67 for 2005 and of 0.77 for 2006, and results for FISH to have a "very good correlation" with kappa-values of 0.92 in 2005 and of 0.96 in 2006 [3].

There may be differences in treatment length in MBC, as the early reports did not show that trastuzumab treatment length was related to survival in MBC patients. In the pivotal clinical studies, in MBC, the median treatment time is only given (36–40 weeks, with a range of 1–171 weeks) [7]. For patients in our database, the mean treatment time was 29 weeks, with a similar range of 2–132 weeks. There are now available data showing that trastuzumab given beyond progression will significantly prolong survival [15]. Even if these data are new, some HCRs may have continued to treat with trastuzumab beyond progression, substituting the cytotoxic agent, while others more likely stopped therapy after progression after first line treatment, as there was – at the time – no evidence for continued therapy with trastuzumab.

All adjuvant studies include one year treatment, except for the Finnher study, in which patients were treated for nine weeks (concomitantly with chemotherapy). The benefits with this short treatment were reduced with time [16,17]. The regulatory approved treatment time, is also one year. To our knowledge this short treatment duration is not used in Sweden outside the ongoing SOLD study (inclusion in Sweden stared March 2008),

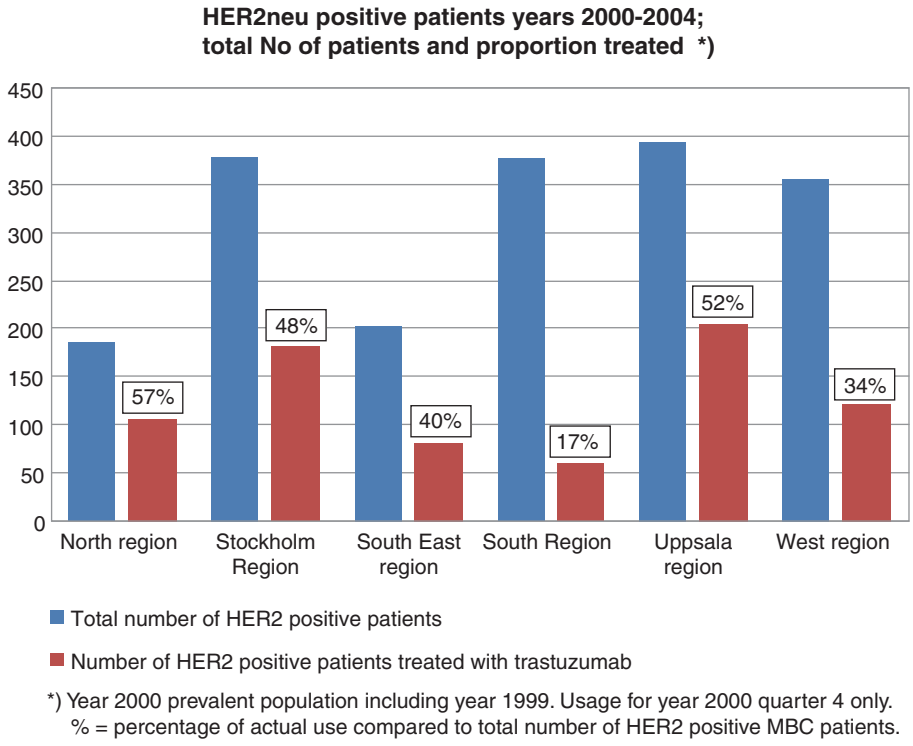

Figure 2. Usage of trastuzumab in MBC patients years 2000–2004, in the six HCRs in Sweden, at 25% HER2 positive MBC patients and 38 weeks treatment time.

with around 100 patients included (March 2010), and thereof some 75% of the patients in the Uppsala-Örebro region. For EBC the difference in trastuzumab use between the HCRs, is unlikely explained by different trastuzumab treatment duration.

More recent data indicate that also patients with small, node negative HER2 positive tumours may benefit from adjuvant trastuzumab treatment [18,19], even if the standard today is not to offer these patients any trastuzumab. These data indicate possible differences in defining the target EBC population, as patients with HER2 positive disease, but with tumours less than 1 cm, may have been offered treatment in some HCRs.

The use within clinical studies would not be captured in the sales data. Clinical trial experience could also potentially influence the number of later treated patients. If clinicians have previous experience at introduction, this may have a positive effect on clinical usage. The number of patients in Sweden included in the clinical studies in MBC was few (below 50). In the adjuvant studies the included numbers from Sweden were also few. The majority of the patients were included in the Stockholm and Uppsala HCRs, and only single patients were included in other HCRs (communication from Hoffman La Roche).

Clinical studies with lapatinib could also have included HER2 positive BC patients, reducing the number of trastuzumab treated patients. The lapatinib registration study ALTO was not approved by the Medical Products Agency in Sweden, although the NEOALTO was approved (neoadjuvant treatment, few patients included in Sweden). Later studies with lapatinib from 2007 and onwards, included at maximum 40 MBC patients in several HCRs (pers. comm. by GSK).

We have also previously reported data on the first 48 patients who received trastuzumab therapy on a named patient basis in Sweden between December 1998 and April 2000 [20]. In short, the clinical experience with trastuzumab use in Sweden has largely been based on use outside of clinical trials, and after approval.

As there is an increased cardiac risk with trastuzumab treatment, the perception of the risk may differ between HCRs. Data show that CHF occur in 0.38–3.3% of trastuzumab treated EBC patients; risk also related to concurrent treatments. The number of patients at cardiac risk is also related to previous treatment, preexisting cardiac conditions and age [21]. These factors could affect trastuzumab use, especially in EBC (curative intent), although the reduction in target patient population should be the same in all HCRs, as there is no indication of major

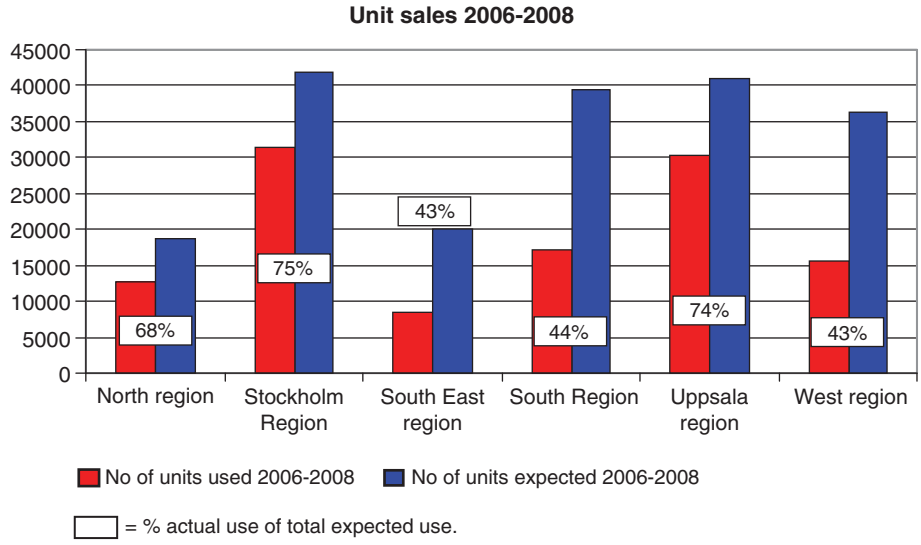

Figure 3. Unit usage of trastuzumab years 2006–2008, in the six HCRs in Sweden, at 14% HER2 positive EBC patients and 52 weeks treatment time and 25% HER2 positive MBC patients and 38 weeks treatment time.

differences in cardiac risk factors between the HCRs (although there are some differences in age distribution between HCRs).

The cost of trastuzumab treatment is added to other treatment costs, as it was first in class for treatment of HER2 positive BC. The budget consequences for each clinic may result in reluctance in prescribing trastuzumab. The priorities and budget constraints may differ between the HCRs. This may have a general impact on the usage of cancer drugs. Although BC therapy is very drug intense, it is important to point out that only about 1/3 of the total cost of disease management relates to direct costs and 2/3 relates to indirect costs, like loss of work capacity, sick leave and mortality [22]. Treatment should also be put in a wider perspective, as there are many factors influencing the total burden of disease (hospitalisation, other drug costs, sick leave, etc.). Understanding the full benefit of any new treatment is an important goal, and health economic studies are important in terms of outcome of BC. There are health economic data showing that HER2 testing and treatment with trastuzumab in Sweden is cost-effective, in both MBC and EBC [23,24]. In the MBC study there were two factors that were sensitive to change in the utility results (cost per Quality Adjusted Life Year, QALY): mortality and test characteristics, and not trastuzumab treatment [24].

Table I. Proportion (%) of patients reported to be HER2 tested in the six HCRs.

	Year		
HCR	2005 *)	2006	2007 *)
Stockholm	78	85	98
Uppsala	79	92	94
South East	78	91	93
South	78	87	84
West	62	90	94
North	100	100	100

*) Personal communication by the Swedish HER2 analysis group. Data not included in reference [4].

One way forward could be to manage these small patient populations at a limited number of hospitals, guided by the most recent guidelines. There should be similar systems for priorities and budget allocations in all HCRs. Furthermore, it is critical that the benefit-risk balances are evaluated when drugs are used in clinical practice. The balance may differ from the clinical studies, as these mainly include patients at lower age, without co-morbidities, etc. Accordingly, it is important to run non interventional and follow-up studies after introduction; such a National initiative has now also been taken on in Sweden.

The conclusion of this study is that the introduction and usage of trastuzumab differs markedly between HCR in Sweden. There are several possible explanatory factors to this:

1. There are variable interpretations of the clinical data, resulting in different target population.
2. There are local budget issues, affecting the use.
3. There are differences in coordination, experience and training in the management of HER2 positive BC patients, resulting in different applications in clinical practice.

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