Effectiveness of expensive drugs frequently used in daily practice in the treatment of breast cancer in the Netherlands.

A review of effectiveness of trastuzumab in advanced breast cancer, and of docetaxel and paclitaxel in the treatment of early and advanced breast cancer

Maastricht, November 11, 2010

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1. Introduction

Annually, breast cancer is diagnosed in more than 12.000 patients in the Netherlands. Although prognosis in the early disease setting has significantly improved during the last two decades, breast cancer is still the major cause of death among women with the age of 40-60 years. More and more it is recognized that breast cancer is not one disease but a constellation of many different diseases. Currently, the main distinction between patient groups is based on the HER2 and ER status. These predictive tumor characteristics help to determine the best treatment for early and advanced breast cancer. Although advanced breast cancer still remains incurable, it is highly sensitive to systemic therapy and more and more therapeutic options for advanced breast cancer are available. However, these therapeutic drugs are frequently associated with high costs. For example, in 2005 a total of €23 million was spent on drugs used in the treatment of breast cancer in the Netherlands.[1] These drugs are considered to have a significant budgetary impact on the health care system. Therefore, some drugs, including trastuzumab and taxanes, are allowed for provisional reimbursement. One of the requirements for expensive drugs to allow for reimbursement, is registration of the drug with the Dutch Medicines Evaluation Board (CBG-MEB) or the European Medicines Agency (EMA). The Dutch Health Care Insurance Board (CVZ) advises the Dutch Government on reimbursement of these expensive drugs. Trastuzumab and taxanes are listed on the Dutch policy of expensive hospital medicines and therefore, the drugs are reimbursed for the registered indications and only for 80% of the costs. The registered indications of trastuzumab and taxanes, the drugs of interest for this review, are discussed here and presented in appendix A and B. To decide on the continuation of the reimbursement of these expensive medicines, information on the cost-effectiveness in daily practice in the Netherlands is essential.

Trastuzumab is a monoclonal antibody directed against the extracellular part of human epidermal growth factor receptor (HER2), which is amplified in 15 to 20% of breast cancers. In the Netherlands, trastuzumab is indicated for the treatment of HER2 positive metastatic breast cancer as monotherapy for patients who have received at least two palliative chemotherapy regimens, including an anthracycline and a taxane, unless patients are unsuitable for this treatment. Furthermore, trastuzumab is indicated in combination with docetaxel or paclitaxel as first-line metastatic treatment for

patients in whom an anthracycline is not suitable. In 2006 the indication was expended to include adjuvant treatment in patients with HER2 positive early breast cancer, and in 2007 trastuzumab was registered in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive and HER2 positive metastatic breast cancer. The scope of this review is the use of trastuzumab in advanced breast cancer with all indications registered before the year 2006. Therefore, the latter two indications will not be reviewed.

The taxanes, docetaxel and paclitaxel, are one of the most active chemotherapeutic drugs. Paclitaxel was discovered in 1971 as part of a National Cancer Institute programme to discover natural compounds with antineoplastic activity. Paclitaxel is isolated from the bark of the Pacific yew tree, whereas docetaxel is synthesized from extracts of the needles of the European yew tree.[2]
In the Netherlands, taxanes as single-agent are indicated for the treatment of metastatic breast cancer as second and further line monotherapy, after failure of anthracycline or alkylating therapy. Docetaxel in combination with capecitabine is also registered for this indication. Furthermore, taxanes are in combination with doxorubicin indicated as first-line metastatic breast cancer treatment, as well as in combination with trastuzumab for HER2 positive metastatic breast cancer treatment. Paclitaxel in combination with gemcitabine is registered as first-line treatment for locally recurrent or metastatic breast cancer after failure of anthracycline therapy. As from 2005, taxanes were also registered in adjuvant setting, for docetaxel in combination with doxorubicin and cyclophosphamide and for paclitaxel when administered sequentially to an anthracycline and cyclophosphamide regimen. The registration of paclitaxel in combination with bevacizumab is not reviewed, since this indication was registered after 2006 and is beyond the scope of this review.

This aim of this review is to provide up-to-date information on therapeutic value, cost-effectiveness and experience and daily use in the Netherlands of trastuzumab in advanced breast cancer and the taxanes, docetaxel and paclitaxel, in early and advanced breast cancer. This not only offers an overview of the effectiveness of these drugs, as well as an insight into areas of interest for future research.

2. Methods

2.a. Search strategy

A detailed search strategy, consisting of numerous MeSH heading and text word combinations, for example “breast cancer”, “chemotherapy”, “trastuzumab”, “taxanes”, “docetaxel” and “paclitaxel”, was used to search the PubMed database. Publications of clinical phase III trials between 1995 and 2010 in the English language were included. In addition, we reviewed the references of the relevant papers. Abstracts of the annual meetings of the American Society of Clinical Oncology (ASCO) and of the San Antonio Breast Cancer Symposium (SABCS) were searched for relevant trials. Furthermore, the references of the Cochrane reviews on taxane-containing regimens for metastatic and early breast cancer were examined[3,4], as well as the references of the reviews of Piccart *et al.*[5] and of De Laurentiis *et al.*[6] The reports from the EMA and the FDA on the drugs of interest were searched by hand to include trials and data on safety and adverse events.

2.b. Comparative treatment

As stated earlier, we focused on trastuzumab in advanced breast cancer, with all licensed indications from registration until the year 2006, and on taxanes in advanced and early breast cancer, again with only licensed indications from registration until the year 2006. From our extensive search, only randomized phase III trials with trastuzumab and the taxanes, docetaxel and paclitaxel, used within its licensed indications, as well as comparator regimens which are considered as standard of care, were eligible. With on exception, we included one phase II trial, since that trial is considered one of the pivotal registration trials of trastuzumab in combination with docetaxel in advanced breast cancer.[7] Consequently, we excluded trials that used first generation chemotherapy schemes, other combinations with no licensed indication, as well as trials using pegylated doxorubicin or nab-paclitaxel.

2.c. Data and statistical methods

Data on the outcomes of interest: response rate in metastatic breast cancer, progression-free survival in metastatic breast cancer and disease-free survival in early breast cancer and overall survival in both early and advanced breast cancer, were extracted from the studies. For many studies with regard to trials on taxanes in early

breast cancer, overall survival data were not available due to immature follow-up. Also, trials were not consistent in the way they defined the progression-free survival. Some trials only provided data on time to progression or time to treatment failure. For the outcome response rate, odds ratio is the most appropriate statistic, whereas with progression-free survival, disease-free survival and overall survival hazard ratios are used. We extracted the odds ratios and hazard ratios and their 95% confidence intervals directly from the studies when possible. If not provided, it was obtained using the available summary statistic, by the method described by Tierney *et al.*[8] However, some trials did not report sufficient data to extract odds ratios or hazard ratios for the outcomes of interest. These trials were therefore not included in the pooled analysis.

We performed a pooled analysis using the Review Manager software (RevMan 5) provided by the Cochrane Collaboration. We used the fixed effect model, based on observed minus expected number of events and the variance of each trial. Chi squared test was used to test for heterogeneity over all trials included in the pooled analyses. Due to the limited number of trials in each pooled analysis, no sensitivity analysis could be performed when significant heterogeneity occurred among the trials. A pooled analysis was only performed when there was more than one study available in the researched area. Furthermore, only fully published reports were entered in the pooled analysis, with the exception of a few abstracts with sufficient data on outcomes measures.

3. Trastuzumab in advanced breast cancer

3.a. Efficacy

Trastuzumab monotherapy

Trastuzumab is registered as single-agent after at least two palliative chemotherapy regimens, including an anthracycline and taxane unless patients are unsuitable for this chemotherapeutic agents. No phase III trials are available on trastuzumab monotherapy, which means that trastuzumab monotherapy could not be compared directly with chemotherapy or supportive care. The registration of trastuzumab as a single-agent in the treatment of metastatic breast cancer was based on two phase II trials. A large trial of 222 heavily pre-treated HER2 positive metastatic breast cancer patients demonstrated an overall response rate of 15%.[9] Trastuzumab as single-agent in the first-line treatment of metastatic breast cancer proved to be effective in a trial of Vogel *et al.*[10], with an overall response rate of 26%.
Since then, no other trials regarding trastuzumab monotherapy were published.

First-line trastuzumab in combination with taxanes

The efficacy of single-agent trastuzumab led to a large phase III trial to determine the efficacy of adding trastuzumab to first-line chemotherapy, compared with chemotherapy alone.[11] In this well-designed randomized trial, a total of 469 patients with progressive HER2 positive metastatic breast cancer, with no previous chemotherapy for metastatic disease, were enrolled. A group of 235 patients received chemotherapy alone and a group of 234 patients received chemotherapy in combination with trastuzumab. The regimen of chemotherapy was based on prior adjuvant systemic treatment for breast cancer. Patients without prior anthracycline treatment received an anthracycline (doxorubicin or epirubicin) with cyclophosphamide and patients with prior anthracycline treatment received paclitaxel. This trial demonstrated an improvement of progression-free and overall survival with the addition of trastuzumab to first-line chemotherapy in metastatic breast cancer. Compared with the group with chemotherapy alone, the median progression-free survival was significantly improved when trastuzumab was added to either type of chemotherapy, respectively 4.6 versus 7.4 months ($P < 0.001$) (table 1). This improvement was significant in both subgroups with different types of chemotherapy.

In the group where trastuzumab was added to an anthracycline and cyclophosphamide, the median progression-free survival was 7.8 months, compared with 6.1 months in the group given only an anthracycline and cyclophosphamide. Compared with the paclitaxel monotherapy group, the median progression-free survival improved from 3.0 to 6.9 months in the group where trastuzumab was added to paclitaxel. The median overall survival was significantly improved with the addition of trastuzumab to any type of chemotherapy from 20.3 to 25.1 months (hazard ratio of 0.8; 95% confidence interval (CI) 0.64 to 1.00).
A randomized phase II study of Marty *et al.*[7] confirmed the therapeutic efficacy of trastuzumab in combination with a taxane as first-line treatment of advanced breast cancer. In this trial, a total of 186 patients were randomly assigned to receive 3-weekly docetaxel or 3-weekly docetaxel combined with weekly trastuzumab until disease progression. The addition of trastuzumab to docetaxel showed an improved efficacy in terms of response rate, progression-free survival and overall survival (median progression-free survival 11.7 versus 6.1 months and median overall survival 31.2 versus 22.7 months, Table 1).

By combining the results of these two trials a significant improvement in progression-free survival is seen for the addition of trastuzumab to first-line chemotherapy, at a hazard ratio of 0.51 (95% CI 0.42 to 0.61; no significant heterogeneity: chi squared = 0.03, df = 1, P = 0.86) as well as an improvement in overall survival, at a hazard ratio of 0.77 (95% CI 0.64 to 0.92), as shown in figure 1. These two trials led to the registration of trastuzumab in combination with a taxane as first-line metastatic therapy in advanced breast cancer.

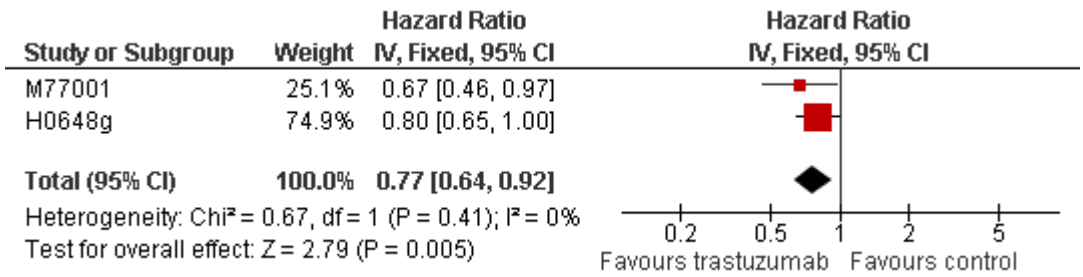


Figure 1: hazard ratio of overall survival of trastuzumab combined with first-line chemotherapy versus first-line chemotherapy alone.

Further, of note, in both trials patients who were progressive after chemotherapy alone were given the option to cross-over to receive trastuzumab. In the H0648g trial two thirds of patients assigned to chemotherapy alone crossed over to receive trastuzumab at disease progression.[11] In the M77001 trial[7], a total of 53 patients (57%) crossed over, which improved their median overall survival to 30.1 months when receiving trastuzumab after docetaxel. Median overall survival was 16.6 months for the patients who received docetaxel only.

These results suggest that the survival benefit is actually larger than what is seen in the intention-to-treat analysis, because a large group of patients crossed-over from chemotherapy alone to the effective trastuzumab-taxane regimen. Furthermore, the overall survival rates of the group that initially treated with the combination of trastuzumab and docetaxel compared with the overall survival rates of patients treated with docetaxel and sequential treatment suggests that earlier treatment with trastuzumab may be important, although confounding factors such as patient selection may have played a role.[7]

Sequential versus concurrent trastuzumab – taxane

With established efficacy of addition of trastuzumab to first-line chemotherapy, two trials (one only provided as abstract) investigated the efficacy of a sequential versus a concurrent trastuzumab-docetaxel approach (Table 1).[12,13] In the Japanese trial, also known as the JO17360 trial[12], the sequential arm consisted of trastuzumab followed by trastuzumab in combination with docetaxel at disease progression, whereas in the Dutch trial, also known as the HERTAX trial[13], patients progressive on trastuzumab were subsequently treated with docetaxel monotherapy (trastuzumab discontinued). The Japanese trial administered docetaxel at a dose of 60 mg/m^2, whereas the Dutch trial used a dose of 100 mg/m^2. In the Japanese trial the median progression-free survival was 14.6 months for the upfront concurrent arm versus 3.7 months for trastuzumab monotherapy (hazard ratio of 4.24; 95% CI 2.48 to 7.24) and versus 12.4 months for trastuzumab followed by trastuzumab/docetaxel (hazard ratio of 1.35; 95% CI 0.79 to 2.30, not significant). In the Dutch trial median progression-free survival was 9.4 months for the upfront combination arm versus 3.9 months after trastuzumab monotherapy (hazard ratio of 2.47; 95% CI 1.56 to 3.92) and versus 10.8 months (hazard ratio of 1.21; 95% CI 0.76 to 1.94, not significant) for trastuzumab followed by docetaxel.

Figure 2 shows the hazard ratios of progression-free survival of both trials of the sequential arm (trastuzumab followed by trastuzumab/docetaxel in the JO17360 trial and trastuzumab followed by docetaxel in the HERTAX trial) versus the concurrent arm. In the pooled analysis, the sequential approach resulted in a trend for reduced progression-free survival, at a hazard ratio of 1.27 (95% CI 0.89 to 1.80) compared with the concurrent approach. Moreover, the tumor load in patients twice having had tumor progression (in the sequential arm) may in fact be larger at the time of the second progression than the tumor load in patients once having had tumor progression (in the concurrent arm).

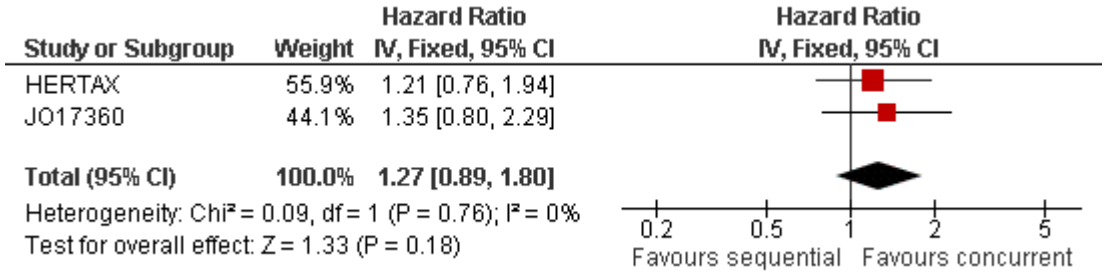


Figure 2: hazard ratio of progression-free survival of sequential arm versus concurrent trastzumab-docetaxel arm.

Compared with the upfront concurrent treatment, the sequential treatment of trastuzumab followed by docetaxel resulted in a significantly decreased overall survival in the Japanese trial (median survival not yet reached, hazard ratio of 2.72; 95% CI 1.03 to 7.18), and in a trend for worse survival in the Dutch trial (median, 30.5 versus 20.2 months, hazard ratio of 1.45; 95% CI 0.87 to 2.41). Figure 3 demonstrates the hazard ratios of the sequential treatment versus the concurrent treatment of trastuzumab and docetaxel. In the pooled analysis, the concurrent upfront treatment with trastuzumab and docetaxel resulted in a significantly improved overall survival (hazard ratio of 1.66; 95% CI 1.05 to 2.60).

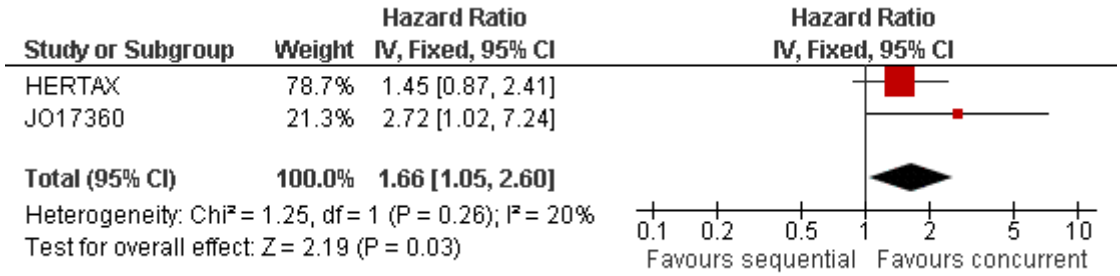


Figure 3: hazard ratio of overall survival of sequential arm versus concurrent trastuzumab-docetaxel arm.

This result suggest that an early start with docetaxel, in addition to trastuzumab, results in an improved outcome of patients with HER2 positive breast cancer who are considered candidates for chemotherapy.[12]

Trastuzumab beyond progression

Several randomized clinical trials were designed to address the place of trastuzumab as second-line (continued) treatment of advanced breast cancer. Unfortunately, most of these trials closed due to lack of accrual, which is most likely based on the prevision of oncologists and patients of a superiority of continuing trastuzumab, as well as based on results of phase II and III trials assessing the efficacy of lapatinib after disease progression with trastuzumab.

The results of one randomized clinical trial, with premature closure due to slow accrual, showed a significant improvement of overall response rate when trastuzumab was continued and combined with capecitabine as second-line treatment, compared with capecitabine monotherapy.[14] A total of 156 patients with progressive metastatic breast cancer under first-line trastuzumab based therapy was enrolled. One group of 78 patients received capecitabine monotherapy (2500 mg/m² day 1-14) and the other group of 78 patients received the same dose of capecitabine combined with three-weekly trastuzumab (6 mg/kg). The response rate was 48% in the capecitabine-plus-trastuzumab group compared with 27% in the capecitabine monotherapy group, statistically significant with an odds ratio of 2.5 (P = 0.0115) (table 1). The time to progression and duration of response were also significantly longer in the trastuzumab-plus-capecitabine group, with a trend to improved median overall survival (25.5 versus 20.4 months, hazard ratio of 0.76; 95% CI, 0.48 to 1.22).

So, even though trastuzumab is not formally registered for continuation beyond progression, based on this randomized trial[14]*, in addition to results from various preclinical and retrospective analyses, evidence suggest that trastuzumab beyond progression is an effective strategy.*

Table 1. Treatment effects of trastuzumab in advanced breast cancer

Author	Study	Regimens	N	Response rate in %				Median PFS in months				Median OS in months			
				Exp	Con	OR	95% CI	Exp	Con	HR	95% CI	Exp	Con	HR	95% CI
		First-line trastuzumab with chemotherapy													
Marty	M77001	Tras+ D100 vs D100	186	61	34	3.01	1.66-5.48	11.7	6.1	0.49	0.34-0.71	31.2	22.7	0.67	0.46-0.97
Slamon	H0648g	Tras + AC or P vs AC or P	469	50	32	2.18	1.50-3.18	7.4	4.6	0.51	0.41-0.63	25.1	20.3	0.80	0.64-1.00
		Sequential versus concurrent													
Inoue	JO17360	Tras* →Tras + D60† vs Tras + D60	107	47	68	0.41	0.19-0.89	3.7* 12.4†	14.6	4.24* 1.35†	2.48-7.24 0.79-2.30			2.72†	1.03-7.18
Bontenbal (abstract)	HERTAX	Tras* → D100† vs Tras + D100	99	50	73	0.36	0.16-0.83	3.9* 10.8†	9.4	2.47* 1.21†	1.56-3.92 0.76-1.94	20.2†	30.5	1.45†	0.87-2.41
		Trastuzumab beyond progression													
v. Minckwitz	GBG 26/ BIG 03-05	Tras + C vs C	156	48	27	2.5	1.23-4.94	8.2	5.6	0.69	0.48-0.97	25.5	20.4	0.76	0.48-1.22

** Result based on the trastuzumab monotherapy group*

† Results based on sequential treatment group of trastuzumab monotherapy, followed by (trastuzumab combined with) docetaxel during disease progression

Abbreviations: AC=anthracycline and cyclophosphamide, C=capecitabine, CI=confidence interval, Con=control arm, D=Docetaxel, Exp=experimental arm, HR=hazard ratio, N=number, OR=odds ratio, OS=overall survival, P =paclitaxel, PFS= progression-free survival, Tras= trastuzumab

3.b. Safety

Adverse events

The most common adverse events are infusion-related side effects, such as fever and chills, which is most frequent during first infusion and becomes less frequent after subsequent infusions.[15] In two of the pivotal trials, more than 10% of all patients receiving trastuzumab experienced symptoms attributable to trastuzumab, which included abdominal pain, asthenia, nausea and vomiting, headaches, myalgia and rash.[9,10] The majority of adverse events was mild to moderate and frequency or severity of adverse events was independent of used trastuzumab dose, suggesting an allergic origin of these symptoms.

In post marketing reports, serious and fatal infusion reactions have been reported infrequently.[16] These severe reactions, which include bronchospasm, anaphylaxis, angioedema, hypoxia, and severe hypotension, were usually reported during or immediately following the initial infusion. However, the onset and clinical course were variable, including progressive worsening, initial improvement followed by clinical deterioration, or delayed post-infusion events with rapid clinical deterioration. For fatal events, death occurred within hours to days following a serious infusion reaction. As taxanes may also lead to allergic reactions, in the studies taxanes and trastuzumab were not delivered at one day, but on subsequent days.

With the addition of trastuzumab to docetaxel, more grade 3 and 4 adverse events, typical to docetaxel, were seen compared with docetaxel monotherapy. The rate of grade 3 adverse events was 67% in the combination group, compared with 55% in the docetaxel monotherapy group.[7] The rates for grade 4 adverse events were 34% in the combination group and 23% in the docetaxel monotherapy group. These adverse events include non-hematologic adverse events, with asthenia being most frequently reported, as well as hematologic adverse events. The incidence of grade 3/4 neutropenia was 32% in the combination group, compared with 22% in the docetaxel monotherapy group.[12] This resulted in an incidence of 23% febrile neutropenia or neutropenic sepsis in the combination group. In the trial of Slamon *et al.*[11] the incidence of infections, not specified according to severity, was 47% in the trastuzumab combined with chemotherapy group and 29% in those treated with chemotherapy alone. Trastuzumab is associated with cardiac dysfunction. A retrospective analysis of all cases of cardiac dysfunction was performed in the large phase III trial of Slamon *et al.*[11] Compared with treatment with anthracycline and

cyclophosphamide, the risk of cardiac dysfunction was significantly increased with concurrent treatment of trastuzumab, anthracycline and cyclophosphamide, with an incidence of respectively 8% versus 27%. In the group were trastuzumab was added to paclitaxel, the incidence of cardiac dysfunction was 13%, compared with 1% in the paclitaxel monotherapy group. Of note, these patients received anthracycline-containing treatment in the adjuvant treatment of breast cancer.
The trial of Marty *et al.*[7] measured cardiac function as left ventricle ejection fraction (LVEF) during trastuzumab treatment, which showed an (asymptomatic) decrease of LVEF of 15 or more points in 17% of patients receiving trastuzumab combined with docetaxel and in 8% of patients receiving docetaxel monotherapy. Two patients experienced symptomatic congestive heart failure, both received docetaxel in combination with trastuzumab, but also prior adjuvant anthracycline treatment. In the Japanese phase III trial[12], no case of congestive heart failure was reported, even though it is not described how this was measured. The LVEF was measured frequently and only two patients developed a decrease in LVEF of 20 points or more (4% of all patients in the monotherapy trastuzumab group, including patients who received combination therapy after progression).
It is concluded that trastuzumab has few side effects. Allergic reactions are seldom, but may be severe, even leading to death. Like other monoclonal antibodies, trastuzumab aggravates chemotherapy-related side effects. Grade 3/4 cardiac toxicity is an important other side effect occurring in 2% of patients, though generally reversible.[17] According to current evidence, trastuzumab should not be combined with other cardiotoxic drugs, such as anthracyclines. It is recommended to carefully monitor cardiac function during trastuzumab treatment.

3.c. Quality of life

In a safety and effectiveness analysis of a phase II study by Vogel *et al.*[10], 41% of all patients completed a quality of life questionnaire at baseline and 12 weeks of trastuzumab treatment. Quality of life was unchanged during trastuzumab treatment, except for responders, who seemed to experience a slight improvement in quality of life. The trial of Slamon *et al.*[11] reported effects on quality of life during trastuzumab treatment of 400 patients. These patients either received trastuzumab and chemotherapy or chemotherapy alone. The addition of trastuzumab led to a significant improvement of global quality of life ($P = <0.05$).

3.d. Applicability

Trastuzumab is indicated in patients with breast cancer, whose tumors have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay. The addition of trastuzumab to chemotherapy in tumors not having HER2 overexpression or gene amplification showed no benefit, as demonstrated by the CALGB 9480 trial.[18] Patients with HER2 positive metastatic breast cancer (FISH+ or IHC3+) all received trastuzumab. The other group of patients with HER2 negative tumors (a total of 226 patients) were randomly assigned to receive either a taxane alone or a taxane in combination with trastuzumab. This trial did not demonstrate any improvement of adding trastuzumab in HER2 negative patients, in terms of response rate (38% versus 32%; odds ratio of 1.35; 95% CI, 0.78 to 2.34), progression-free survival (median, 7 months versus 6 months, P = 0.28) or overall survival. No pharmacokinetic studies were performed with regards to disposition of trastuzumab in elderly patients, or patients with hepatic or renal impairment. However based on the extensive experience with the administration, it is considered safe to administer trastuzumab without dose reduction in these cases.[19]

3.e. Dosage and administration

Trastuzumab should be administered intravenously and is recently reviewed by the Dutch Health Care Insurance Board for outpatient treatment.[20] They indicated that trastuzumab is effective and safe to be administered in an extramural setting, however this indication was considered as having no additional value by the Dutch profession of medical oncologists and was therefore not registered.

As defined in appendix A, trastuzumab is registered as monotherapy during second and further lines of therapy, and in combination with taxane chemotherapy in first-line treatment of advanced breast cancer. In 2006, trastuzumab was approved for the adjuvant breast cancer setting, and recently, trastuzumab was also approved in combination with hormonal treatment in the advanced disease setting (beyond the scope of this report). For these indications several schedules of trastuzumab administration are available. For a weekly schedule, the recommended loading dose is 4 mg/kg body weight, followed by a weekly dose of 2 mg/kg. For a 3-weekly schedule, the initial loading dose is 8 mg/kg body weight, followed by a 3-weekly dose of 6 mg/kg.[15]

In the registration trials where trastuzumab was administered in combination with a taxane, the first dose of the used taxane was administered the day following the first dose of trastuzumab and immediately after the subsequent dose of trastuzumab if the preceding dose of trastuzumab was well tolerated. In daily practice, even with first dose of trastuzumab, the taxane is generally administered on the same day. When trastuzumab is combined with hormonal therapy, no specific restrictions on timing of trastuzumab and hormonal therapy are applicable. Furthermore, no limitation of number of cycles of trastuzumab is applied. Trastuzumab in advanced breast cancer should be administered until disease progression, as is opposite to trastuzumab in adjuvant setting, where trastuzumab is administered for one year.

3.f. Cost effectiveness

As previously described in the chapter on efficacy, the addition of trastuzumab in HER2 positive patients has a therapeutic value with no major difference in quality of life. Therefore, to determine the effectiveness of trastuzumab in the advanced setting, the use of a cost-effectiveness analysis is appropriate. A recent review on cost-effectiveness of trastuzumab and chemotherapy in advanced breast cancer was published by Blank *et al.*[21] In this review, four cost-effective analyses on trastuzumab were included. All cost-effectiveness analyses focused on trastuzumab as first-line therapy. The authors concluded that the incremental cost-effectiveness ratio (ICER) is higher for trastuzumab, than it is for chemotherapeutic agents in advanced breast cancer. However, the ICER varies to a large extend between the different cost-effectiveness analyses. The included studies in the aforementioned review are described in detail below (table 2).

The first cost-effectiveness analysis was reported by Norum *et al.*[22] This model-based cost-effectiveness analysis was conducted from a Norwegian health care perspective. The life-years gained (LYG) were based on data of the phase III trial of Slamon *et al.*[11] and the phase II trial of Marty *et al.*[7] In these trials adding trastuzumab to first-line chemotherapy was compared with chemotherapy alone, in which chemotherapy consisted of a taxane (either docetaxel or paclitaxel) or anthracycline and cyclophosphamide combination. The health care costs included in the analysis were drug costs of trastuzumab, HER2 testing costs of all included patients (based on the assumption that one positive test is found in every four patients tested with IHC), costs of hospitalization and outpatient clinic costs. The costs of chemotherapeutic

agents were assumed to be similar in both groups and were therefore not implemented in the model. Neither included were indirect costs (traveling costs and productivity loss), based on the assumption that there were no significant differences between the two comparative treatment groups. A 5% discount rate was applied for future benefits and costs, but as all included costs occurred within the first year of treatment, the discount rate of 5% effectively was only applied to the benefits. No clear description of the economic model used was provided. The survival gain with the addition of trastuzumab was calculated to range between 3.7 and 8.4 months, depending on which trial was used . The total additional costs per patient treated with trastuzumab was €44 196, mainly due to the cost of trastuzumab itself (89% of total costs) and prolonged outpatient treatment (8% of total cost). As a result, the discounted ICER ranged between €69 212 and €162 417, depending on the used survival gain. A multivariate sensitivity analysis was conducted, evaluating several factors. Two of them proved to have a significant influence on base-case results, namely the cost of trastuzumab and improvement in survival time. The overall conclusion of the authors was that trastuzumab in the treatment of advanced breast cancer is not cost-effective, based on a cut-off at €46 000 per life-year gained.

The second cost-effectiveness analysis was based on an after-and-before-study of 47 HER2 positive metastatic breast cancer patients, conducted in a single hospital in Marseille, France.[23] In this study, the first 19 patients did not yet receive trastuzumab (their treatment consisted of taxane- and/or anthracycline-based chemotherapy) and the following 28 patients received trastuzumab as single-agent or in combination with a taxane. In this analysis only direct hospital cost were included. The costs of HER2 testing were omitted from the analysis. The costs of chemotherapy were similar in trastuzumab and non trastuzumab group, however costs of growth factors were significantly higher in the trastuzumab group. The economic model used for the assessment was not defined in the report.

The median overall survival was 37.0 months in the trastuzumab group, compared with 19.0 months in the non-trastuzumab group ($P < 0.001$). The total costs per patient treated with trastuzumab were €39 607, as compared to €12 795 for patients not treated with trastuzumab. The difference was largely due to the costs of trastuzumab itself (43% of total costs). This led to an ICER of €17 800 per life-year gained. A bivariate sensitivity analysis on trastuzumab unit costs and hospitalization unit costs showed that the ICER ranged between €8 000 and €20 000. The

bootstrapped 95% confidence interval of the ICER ranged from €20 964 to €34 020 per life-year gained.

Third, Poncet *et al.*[24] published a cost-effectiveness analysis based on a prospective comparison of 2 groups of patients with HER2 positive metastatic breast cancer with a total of 45 patients. One group was treated with 3-weekly paclitaxel and 3-weekly trastuzumab, the other group was treated with any schedule of chemotherapy without trastuzumab. The study was conducted in 10 centers (4 trastuzumab prescribing centers and 6 control centers) in France. Only hospital costs were included (chemotherapy, trastuzumab, immunohistochemical tumor analysis, pretreatment tumor assessment, response evaluation, and hospital stay). The 1-year overall survival rate was 85% in the trastuzumab combined with paclitaxel group, compared with 47% in the comparative treatment group. The incremental costs with the treatment of trastuzumab and paclitaxel were € 21 980. This led to an ICER of €15 370 per life-year gained, which the authors considered cost-effective. Sensitivity analyses were not performed.

Finally, the cost-effectiveness analysis of Garrison *et al.*[25] described a dynamic life-cycle model in which adjuvant and metastatic treatment with trastuzumab was evaluated. The model was based on the forecasted volume of trastuzumab use over the product life cycle (in this model the life cycle is a period from 1998-2016), with the incorporation of the cost-effectiveness of trastuzumab in adjuvant and metastatic breast cancer treatment. They based this analysis on an earlier model by Garrison *et al*.[26] The effectiveness data were based on the trial of Slamon *et al.*[11] in which patients received first-line chemotherapy (either a taxane or anthracycline and cyclophosphamide combination) with or without the addition of trastuzumab. The cost and survival data were taken from a study by Hornberger *et al*.[27] In contrast with the aforementioned analyses, this study used quality-adjusted life years (QALYS) instead of life-years gained. The quality weights (utilities) were taken from Elkin *et al.*[28] An annual discount rate of 3% was used for costs and benefits. The incremental costs with the addition of trastuzumab were €34 248 ($US 47 728). Only direct and non-direct medical costs were evaluated. The estimated incremental QALY was 0.56. This led to an ICER of €61 478 ($US 85 676) of trastuzumab in metastatic breast cancer. However, the goal of this report was to establish the economic value of trastuzumab over the product life cycle, which can vary over different indications. Therefore, the volume of trastuzumab use over the aforementioned period was incorporated. The

volume was projected to be three times lower in metastatic breast cancer than in the adjuvant setting, leading to 161 000 patients with advanced breast cancer treated with trastuzumab during the period in the United States. The overall life-cycle ICER (including use of trastuzumab in both the metastatic and adjuvant setting) was € 25 538 ($US 35 590), which was considered as cost-effective by the authors.
In addition to the studies included in the review, the study by Elkin *et al.*[28] may be of relevance. The authors conducted a model-based cost-effectiveness analysis in which alternative test–treat strategies were examined, whereby patients were tested with IHC only, IHC with FISH confirmation under various circumstances, or FISH alone. The decision model was clearly described. Transition probabilities were derived from the study by Slamon *et al.*[11] Costs included drug costs, other breast cancer related health care costs (based on Medicare reimbursements) and travel and time costs. Costs were expressed in 2002 US dollars. QALYs were used as an outcome, and quality weights (utilities) were based on a study by Brown & Hutton.[29] Costs and QALYs were discounted by 3% annually. Compared with no testing and treatment with chemotherapy alone, trastuzumab after a HercepTest with FISH confirmation of 2+ and 3+ results had an ICER of €89 638 (US$125 000) per QALY gained. Sensitivity analyses showed similar results.

However, all presented cost-effectiveness analyses are conducted from a foreign health care perspective. It would be of relevance to determine whether these foreign cost-efficacy analyses could be transferred to the Dutch setting.
For the use of trastuzumab in adjuvant setting, Essers *et al.*[30] obtained a Dutch estimate of the cost-effectiveness based on a model-based cost-effectiveness analysis performed from the UK health care perspective. In order to do so, they established the transferability of the used UK cost-effectiveness analysis to the Dutch setting by applying several checklists. The authors concluded that overall the structure of the model used in the UK setting was transferable to the Dutch setting, although some of the model inputs, such as price level, utilities, resource use and productivity loss, needed adaptation to the Dutch setting. However, the authors identified a lack of Dutch data on the economic consequences of breast cancer.
In order to fully evaluate the relevance of the foreign cost-efficacy analyses for the Dutch setting, further Dutch date on economic consequences of breast cancer are essential. Therefore, data on real-life efficacy, costs and utilities need to be examined.

Furthermore, in order to adapt foreign model-based cost-effectiveness studies to the Dutch setting, the used models and methods need to be transparent, which is lacking in some of the described cost-effectiveness analyses.
In conclusion, the ICER of trastuzumab in the advanced setting varies widely between the different studies. Moreover, due to different comparators, methods, and study objectives the results are difficult to combine and adapt to the Dutch setting. In the Netherlands €80 000 per QALY gained has been referred to as a cut-off point of cost-effectiveness.[31] *With that in mind, the results of three of the five described foreign studies indicate that trastuzumab in the advanced setting is a cost-effective strategy. It can be concluded that trastuzumab is an expensive drug in the treatment of metastatic breast cancer, that might be considered cost-effective.*

Cost-effectiveness of the continuation of trastuzumab beyond progression is a new area of research. A recent cost-utility analysis was published on trastuzumab beyond progression.[32] In this analysis a Markov-model was used. The efficacy data were obtained from the study of von Minckwitz *et al.*[14], in which patients with metastatic breast cancer who progressed on trastuzumab either received capecitabine monotherapy or capecitabine with the continuation of trastuzumab. Only direct medical costs were considered in this analysis. The incremental costs associated with continuation of trastuzumab range from €27 502 to €41 456 (depending on patients body surface area and weight). The outcome of this study was ICER expressed as cost per quality adjusted life year gained. With an incremental QALY of 0.35 per patient, the ICER was €98 329 per QALY. A univariate sensitivity analysis revealed that time from progression to death had the most influence on the ICER. The authors concluded that the base-case ICER of continuation of trastuzumab beyond progression was higher than what is generally considered as cost-effective, although they also stated that the additional cost falls within the value ranges found for established regimens in the treatment of metastatic breast cancer.
Based on this single cost-effectiveness analysis on trastuzumab beyond progression, this treatment strategy is not considered cost-effective.

Table 2. Cost-effectiveness of trastuzumab in advanced breast cancer treatment

Author	Country	Costs			Effect			ICER
		Total costs trastuzumab	Total costs comparator	Incremental costs	Total effect trastuzumab	Total effect Comparator	Incremental effect	per LYG or QALY
Norum	Norway			44 196			0.3-0.7 y	69 212-162 417 per LYG
Perez-Ellis	France	39 607	12 795	26 812	3.08 y	1.58 y	1.50 y	17 800 per LYG
Poncet	France	33 271	11 291	21 980	2.4 y	0.97 y	1.43 y	15 370 per LYG
Garrison	U.S.	62 797	28 633	34 164	1.26 y	0.70 y	0.56 y	25 538 per QALY
Matter-Waldstra	Switzerland			33 980			0.35 QALY	98 329 per QALY

Of note, all costs are shown in Euros (€1 = US$1.40 and US$1 = €0.72 and €1 = £0.88 and £1 = €1.14)
Abbreviations: ICER=incremental cost-effectiveness ratio, LYG=life year gained, U.S.=United States of America, QALY=quality adjusted life year, y=year

4. *Taxanes in early and advanced breast cancer*

4.a. Efficacy of taxanes in advanced breast cancer

Single-agent taxanes (compared with single-agent anthracycline)

The registration of single-agent docetaxel was based on a large randomized trial of Chan *et al*.[33] (TAX 303 trial) in which a total of 326 patients, who failed on alkylating therapy, received either 3-weekly docetaxel (D) 100 mg/m² or adriamycine (A) 75 mg/m². Compared with adriamycine, 3-weekly docetaxel was superior with respect to response rate. Although progression-free survival was longer in the docetaxel arm (median, 6.0 versus 4.8 months), this was statistically not significantly different (table 3). There was no significant difference in overall survival after a median follow-up of 23 months. Of note, after adjusting for cross-over (26% of patients in the adriamycine arm received taxanes and 28% of patients in the docetaxel group received anthracycline therapy after progression) the difference remained not significant.

The results of two other phase III trials of single-agent taxane versus single-agent anthracycline were published (table 3).[34,35] In the EORTC 10923 trial of Paridaens *et al.*[35], 331 patients with no previous chemotherapy for advanced breast cancer, were randomized to receive either 3-weekly paclitaxel (P) 200 mg/m² or adriamycine 75 mg/m². Cross-over was seen in 55% of patients in the paclitaxel group and in 47% of patients who initially received adriamycine.

The North-American trial of Sledge *et al.*[34] (ECOG E1193) is a three-arm trial in which a total of 739 patients were randomized to receive single-agent paclitaxel (3-weekly 175 mg/m²), single-agent adriamycine (3-weekly 60 mg/m²) or the combination of both (adriamycine 50 mg/m² and paclitaxel 150 mg/m² with granulocyte-colony stimulating factor). In this trial, cross-over was seen between the two single-agent arms. Compared with the accepted single-agent adriamycine dose of 75 mg/m² every 3 weeks, 3-weekly paclitaxel was inferior with respect to response rate and progression-free survival.[35] Compared with a lower dose adriamycine of 60 mg/m² every 3 weeks, 3-weekly paclitaxel showed similar efficacy in terms of response rate, progression-free survival and overall survival.[34]

In the most recent Cochrane review[3], it was concluded that, based on these three trials (TAX 303, EORTC 10923 and ECOG E1193), there was no evidence of a difference in median overall survival in favor of either drug, taxane or anthracycline, with a

hazard ratio of 1.00 (95% CI 0.88 to1.15; P = 0.94; no significant heterogeneity: heterogeneity chi squared = 1.50; df = 2; P = 0.47). There was also no evidence of a difference in time to progression (hazard ratio of 1.10; 95% CI 0.97 to 1.26, P = 0.12), though this analysis was with significant heterogeneity. In contrast, Piccart *et al.*[5] concluded in their review that single-agent taxane is less effective than single-agent anthracycline as first line treatment, based on the EORTC study 10923.

However, in both reviews the taxane schedule was not taken into account. More recent studies, that compared 3-weekly with weekly taxane schedules as first- and second line treatment in advanced breast cancer, showed a differential impact of schedule on therapeutic efficacy. As presented in table 3, the three studies that compared 3-weekly docetaxel with weekly docetaxel showed a slightly better efficacy of 3-weekly docetaxel, in terms of response rate in two of three studies that used docetaxel as predominately first-line treatment,[36,37] and in terms of overall survival in one study, that used docetaxel as second-line treatment after failure of anthracycline-based therapy. [38] The opposite was seen for paclitaxel. Compared with 3-weekly paclitaxel, two phase III trials using paclitaxel as first and second-line treatment for advanced breast cancer showed that weekly paclitaxel favorably affected the therapeutic efficacy, with respect to response rate in both studies, and with respect to progression-free survival in one study, although without significant differences in overall survival.[18,39]

There is only one trial that directly compared the two taxanes, paclitaxel and docetaxel.[40] A total of 449 patients with advanced breast cancer, progressing on anthracycline therapy, were randomized to receive 3-weekly docetaxel 100 mg/m² or 3-weekly paclitaxel 175 mg/m². Response rate was higher in the docetaxel group, although the difference was not significant (31 versus 25%, odds ratio of 1.41; 95% CI 0.93 to 2.13). Also progression-free and overall survival were significantly prolonged in the docetaxel group (table 3).

In conclusion, 3-weekly single-agent docetaxel is preferred over a weekly schedule, showing to be at least as effective compared to single-agent adriamycine. In contrast, paclitaxel is best delivered in a weekly schedule. This is in line with the observed superiority of 3-weekly docetaxel compared with 3-weekly paclitaxel,[40] and in line with the observed higher response rates of 3-weekly docetaxel and observed lower response rates of 3-weekly paclitaxel compared with 3-weekly adriamycine at a dose

of 75 mg/m^2.[33,35] *And also in line with the observed equivalent efficacy of 3-weekly paclitaxel and 3-weekly adriamycine at a dose of 60 mg/m^2.*[34]

Aside from schedule, the used dose of single-agent taxanes varies between the randomized trials. The optimal dose of weekly paclitaxel is 80-100 mg/m², with 90 mg/m² commonly used in trials.[41,42,43] For docetaxel 100 mg/m² seems to be the most effective dose, as was the subject of a large randomized trial of 529 patients in which 3-weekly single-agent docetaxel at a dose of 60, 75 or 100 mg/m² was administered.[44] In light of the aforementioned considerations, regarding the use of different dosages and schedules in the three single-agent taxane studies, it seems not possible to combine the results of these studies.[33,34,35] Indeed, when testing this, we observed significant heterogeneity between studies with respect to response rate and progression-free survival. (figure 4A and 4B). In line with the results of the review of Ghersi *et al.*[3], we found no evidence of a difference in median overall survival between single-agent taxanes and single-agent anthracyclines (figure 4C).

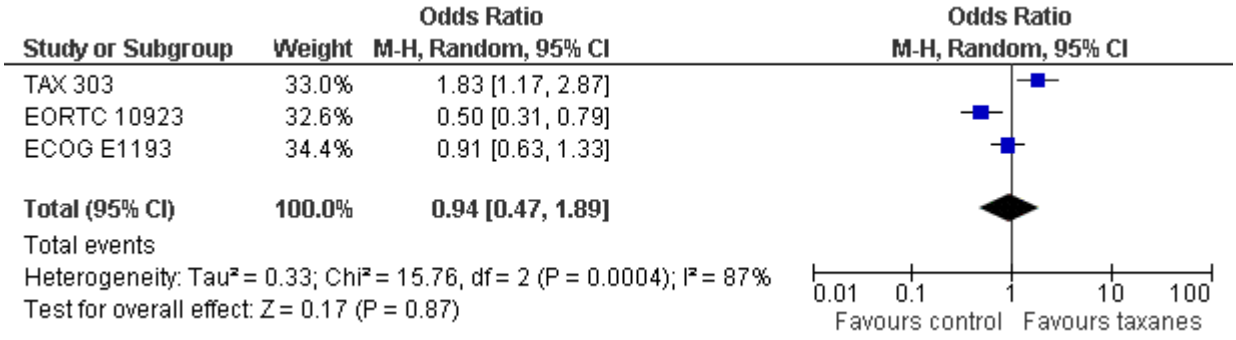


Figure 4A : odds ratio of response in single-agent taxanes versus single-agent anthracyclines

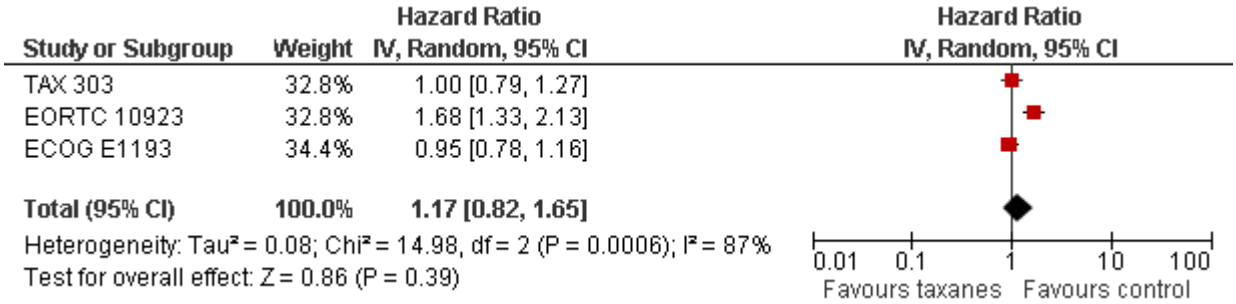


Figure 4B: hazard ratio of progression-free survival of single-agent taxanes versus single-agent anthracyclines

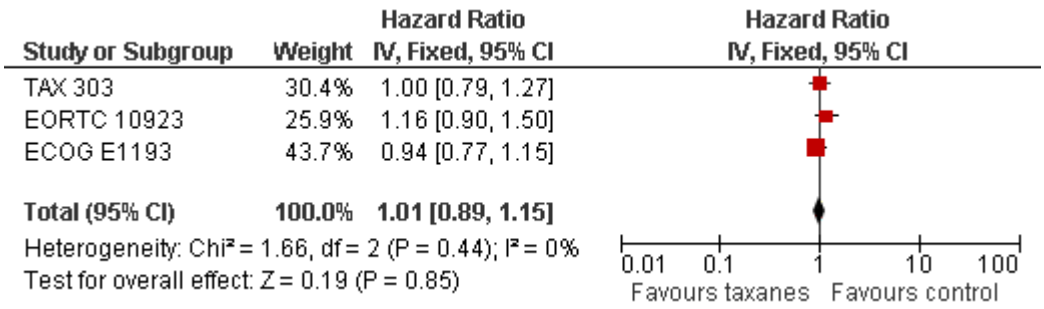


Figure 4C: hazard ratio of overall survival of single-agent taxanes versus single-agent anthracyclines

Based on the single-agent taxane studies[33-35] in combination with results from studies on taxane-schedule, we conclude that optimally delivered single-agent taxanes seem to be at least as effective as optimally delivered single-agent anthracyclines in first and second line treatment of advanced breast cancer.

Table 3. Treatment effects of single-agent taxanes, docetaxel or paclitaxel, in advanced breast cancer in first and second line																
Author	**Study**	**Regimen**	**N**	**Median FU**	**Response rate in %**				**Median PFS in months**				**Median OS in months**			
				months	**Exp**	**Con**	**OR**	**95% CI**	**Exp**	**Con**	**HR**	**95% CI**	**Exp**	**Con**	**HR**	**95% CI**
Single agent taxanes studies																
		T vs A														
Chan	Tax 303	D 100 vs A 75	326	23	48	33	1.80	1.10 - 2.90	6.0	4.8	1.00	0.80 - 1.30	15.0	14.0	1.00	0.80 - 1.30
Paridaens	EORTC 10923	P 200 vs A 75	331		25	41	0.50	0.31-0.81	3.9	7.5	1.69	1.33-2.13	15.6	18.3	1.16	0.90-1.49
Sledge	ECOG E1193	P 175 vs A 60	453		34	36	0.91	0.62-1.34	6.3	6.0	0.95	0.77-1.16	22.5	19.1	0.95	0.77-1.16
		D vs P														
Jones	Tax 311	D 100 vs P 175	449	61	32	25	1.41	0.93-2.13	5.7	3.6	0.61	0.50-0.75	15.4	12.7	0.71	0.58-0.87
Schedule taxanes																
		Wkl vs 3-wkl														
Rivera	US	D wkl vs D 3wkl	125	15	20	36	0.46	0.45-1.00	5.5	5.7	1.16	0.79-1.69	18.6	18.3	1.25	0.76-1.96
Stemmler (abstract)	D2	D wkl vs D 3wkl	102		27	50		P = 0.08	5.4	6.3		P = 0.91	22.7	15.8		P = 0.24
Willemse (abstract)	Tax 613	D wkl vs D 3wkl	162	15	28	29	0.95	0.46-1.95	3.1	3.8		P = 0.015	7.8	9.8		P = 0.035
Seidman	CALGB 9840	P wkl vs P 3wkl	735		42	29	1.75	1.28 - 2.37	9	5	0.70	0.62-0.82	24	12	0.78	0.65 - 0.94
Verril (abstract)	Anglo- Celtic IV	P wkl vs P 3wkl	569		43	27		P = 0.002	5.5	5.1	0.92	P = 0.06				

Abbreviations: A=adriamycine, CI=confidence interval, Con =control arm, D= docetaxel, Exp=experimental arm, FU=follow-up, HR = hazard ratio N=number, OR=odds ratio, OS =overall survival , P= paclitaxel, PFS=progression-free survival, T=taxane, wkl=weekly, 3-wkl=3-weekly

Taxanes in and versus anthracycline combination regimens

After determining the efficacy of single-agent taxanes, the combination with anthracyclines was evaluated. Several anthracycline-taxane combination regimens were subject to randomized trials.

Piccart *et al.*[5] stated in their review that first-line anthracycline-taxane combinations seem slightly better than anthracycline-based regimens with regard to tumor response (57 versus 46%, odds ratio = 0.63; $P < 0.001$) and progression-free survival (median, 7.7 versus 6.9 months, hazard ratio of 0.92; $P = 0.031$), but not with regard to overall survival.

In the Cochrane review[3], it was concluded that, based on all taxane containing regimens including first and second-line trials, there is a benefit in overall survival in favor of taxanes (hazard ratio of 0.92; 95% CI 0.86 to 1.00), with no statistically significant heterogeneity across all trials. The benefit was also seen with respect to progression-free survival, at a hazard ratio of 0.92 (95% CI 0.85 to 0.99), but this analysis was with significant heterogeneity. However, some of the included trials used chemotherapy regimens which could be considered as suboptimal nowadays, such as mitomycin and vinblastin. When excluding those regimens, which means that the non-taxane containing comparative regimens were largely limited to anthracycline-containing regimen, the superiority of taxane-containing regimens over nontaxane-containing regimens with respect to overall survival was not seen.

These analyses of available randomized trials are, however, hampered by the lack of correction for use of different comparator regimens and of currently considered suboptimal dosages or schedules of the cytotoxic drugs. For instance, all studies assessing the anthracycline-paclitaxel efficacy used a 3-weekly paclitaxel schedule, whereas, as discussed before, 3-weekly paclitaxel is now considered as a suboptimal taxane schedule. For that reason, we discuss the studies assessing docetaxel and paclitaxel efficacy per comparator regimen and per taxane drug used.

There is one phase III trial that addressed the efficacy of adding a taxane to a single-agent anthracycline.[34] This North American three-arm trial, described in the previous section, compared 3-weekly adriamycine (60 mg/m²) to the combination of 3-weekly paclitaxel (150 mg/m²) and adriamycine (50 mg/m²). Compared with single-agent anthracycline, the addition of paclitaxel to adriamycine is superior with respect to

response rate and progression-free survival, but not with respect to overall survival (table 4).

There are five phase III trials that report on the comparison between an anthracycline-taxane combination regimen (AT) and an anthracycline-cyclophosphamide (AC) combination regimen, two of them using docetaxel and three of them using paclitaxel as taxane (table 4).[45,46,47,48,49]

The TAX 306 study[45] led to the registration of the AT-regimen for the treatment of advanced breast cancer. In this trial, a total of 429 patients received either AT (3-weekly adriamycine 50 mg/m² and docetaxel 75 mg/m²) or AC (3-weekly adriamycine 60 mg/m² and cyclophosphamide 600 mg/m²). Compared with AC, the AT-regimen proved to be superior in terms of response rate (59 versus 47%, odds ratio of 1.68; 95% CI 1.15 to 2.46) and progression-free survival (median, 8.6 versus 7.4 months, hazard ratio of 0.76; 95% CI 0.60 to 0.94) and at least equal in terms of overall survival. Of relevance, a high cross-over to docetaxel in the AC group was seen, potentially affecting overall survival rates. The other trial using docetaxel, compared 3-weekly epirubicin (90 mg/m²) and cyclophosphamide (600 mg/m²) with 3-weekly epirubicin (lower dose of 75 mg/m²) and docetaxel (75 mg/m²).[46] A total of 240 patients were randomized, with an imbalance in treatment arms (125 versus 111); cross-over not being described. This trial showed no difference in efficacy between anthracycline-taxane combination and anthracycline-cyclophosphamide combination in terms of response rate, progression-free survival and overall survival. As no sufficient data on progression-free and overall survival were reported to calculate confidence intervals, these data were not used in our pooled analysis.

Of the three trials using paclitaxel, one trial showed superiority of paclitaxel in combination with an anthracycline. In this UK NCRI AB01 trial, Langley *et al.*[47], randomized 705 patients to receive either AT (3-weekly epirubicin 75 mg/m² and paclitaxel 200 mg/m²) or AC (epirubicin 75 mg/m² and cyclophosphamide 600 mg/m²). Compared with AC, the AT combination significantly improved response rate (65 versus 55%, odds ratio of 1.49; 95% CI 1.11 to 2.02), but was equally effective in terms of progression-free survival (median, 7.0 versus 7.1 months, hazard ratio of 1.07, 95% CI 0.92 to 1.24) and overall survival (median, 13 versus 14 months, hazard ratio of 1.02; 95% CI 0.87 to 1.19). The other two trials using paclitaxel showed comparable efficacy of AT compared with AC[48,49] One of these trials, an

AGO-trial, only reported preliminary results.[48] However, the review of Piccart *et al.*[5] reported on response rate, progression-free survival and overall survival. They provided median survival times and hazard ratios based upon individual patient data collected from the trial. Therefore, the presented data in table 4 from the AGO-trial, are the hazard ratios we abstracted from the review of Piccart *et al.*[5] The other trial, also known as EORTC 10961 trial[49], randomized 271 patients to an AT combination (3-weekly adriamycine 60 mg/m² and paclitaxel 175 mg/m²) or to the AC combination (3-weekly adriamycine 75 mg/m² and cyclophosphamide 600 mg/m²). A dose escalation of paclitaxel to 200 mg/m² and cyclophosphamide to 750 mg/m² was planned after cycle 2, if no grade 3 or 4 neutropenia occurred in the first cycle. This dose escalation was only possible in 17% of AT and 20% of AC patients. No superiority of AT was seen in terms of response rate, progression-free survival and overall survival.

In our pooled analysis, excluding the study with insufficient data on confidence intervals, the odds ratio of response to AT versus AC is 1.51 (95% CI, 1.26 to 1.81), the hazard ratio of progression-free survival is 0.95 (95% CI, 0.86 to 1.04) and the hazard ratio of overall survival is 1.03 (95% CI, 0.93 to 1.14), with no significant heterogeneity in all analyses, as shown in figure 5A, 5B and 5C.

In conclusion, AT (with either docetaxel and paclitaxel) seems to be at least as effective as AC in the first line treatment of advanced breast cancer.

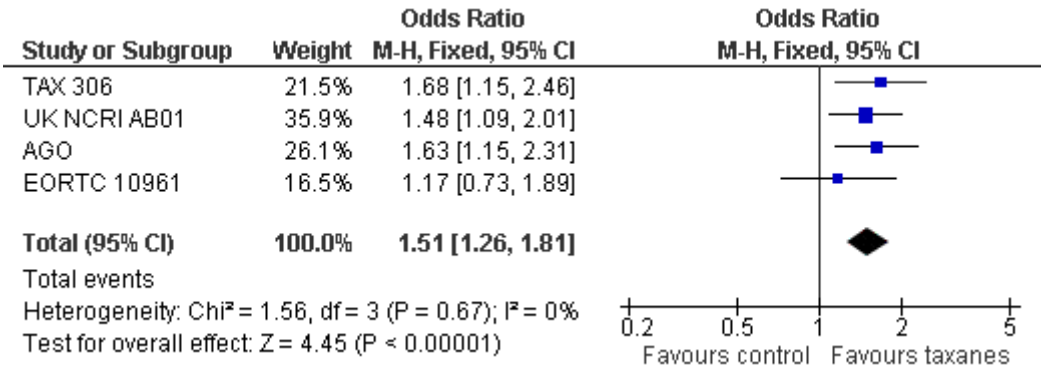


Figure 5A: odds ratio of response in AT versus AC

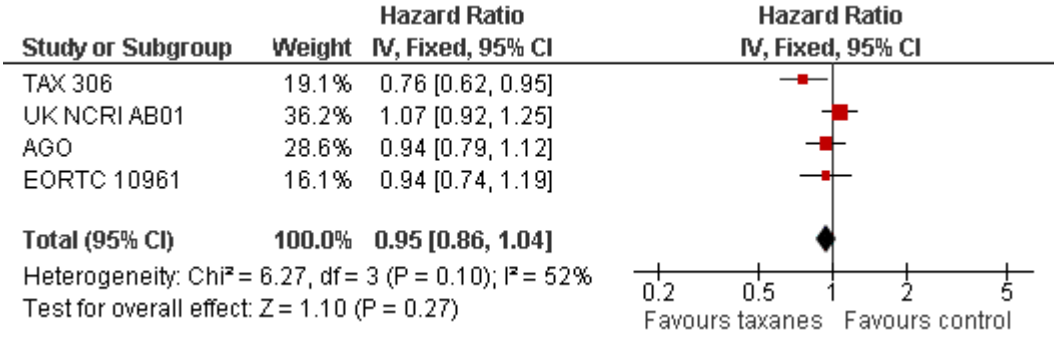


Figure 5B: hazard ratio of progression-free survival in AT versus AC

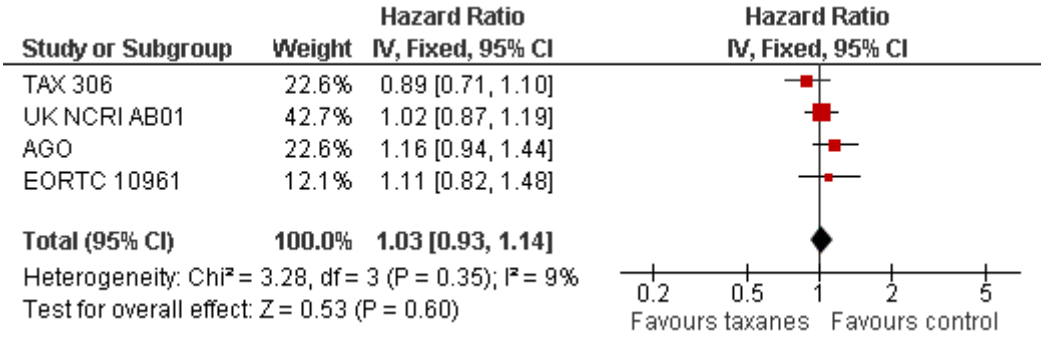


Figure 5C: hazard ratio of overall survival in AT versus AC

Based on two trials, the anthracycline-taxane combination (AT) is superior to 5-fluorouracil-adriamycine-cyclophosphamide (FAC) with respect to response rate, progression-free and overall survival[50,51]. The first trial of Bontenbal *et al.*[50] randomized 216 patients to receive either AT (adriamycine 50 mg/m2 and docetaxel 75 mg/m²) or FAC (adriamycine 50 mg/m², cyclophosphamide 500 mg/m² and 5-fluorouracil 500 mg/m²). Due to slow accrual, the trial was stopped prematurely. Even so, AT was superior with respect to all efficacy endpoints (table 4). This result was confirmed in a multi-center trial of 267 patients, receiving either the same schedule of FAC or adriamycine 50 mg/m² in combination with 3-weekly paclitaxel 220 mg/m².[51]

Compared with FAC, the AT regimen proved to be superior in terms of response rate, progression-free survival and overall survival. The duration of this treatment effect was confirmed in a long-term analysis with a follow-up of 69 months.
Although only two studies addressed the comparison of AT versus FAC, the superiority of AT to the triplet combination of FAC is in our pooled analysis significant in terms of response rate (odds ratio of 1.91; 95% CI 1.32 to 2.76), progression-free survival (hazard ratio of 0.72; 95% CI 0.60 to 0.87) and overall survival (hazard ratio of 0.69; 95% CI 0.56 to 0.85) (see figure 6A, 6B and 6C).

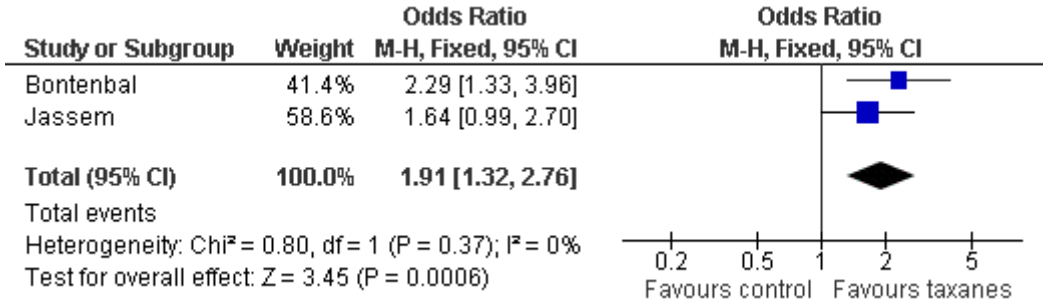


Figure 6A: odds ratio of response in AT versus FAC

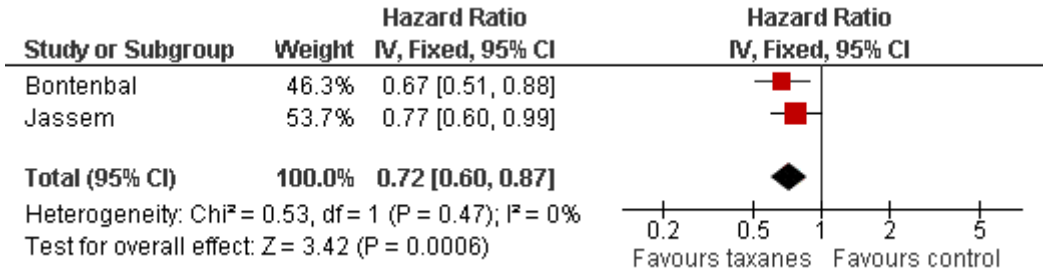


Figure 6B: hazard ratio of progression-free survival in AT versus FAC

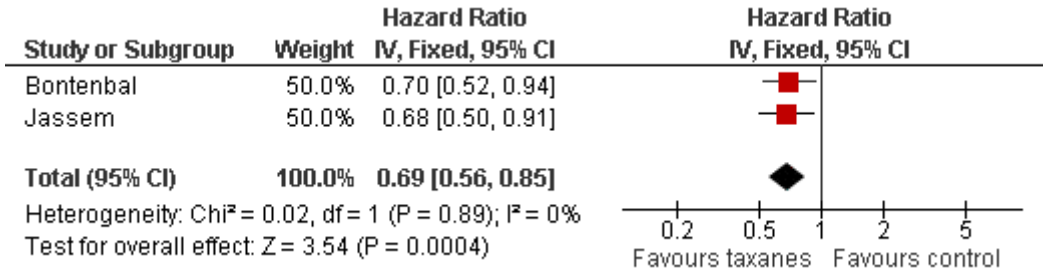


Figure 6C: hazard ratio of overall survival in AT versus FAC

Of note for the comparisons of AT versus AC or FAC: in AC, A is given as 60mg/m^2 adriamycine or 75-90 mg/m^2 epi-adriamycine in all but one study, whereas in FAC, A is given as 50 mg/m^2 adriamycine. In AC, C is given as 600 mg/m^2 cyclophosphamide, whereas in FAC, C is given as 500 mg/m^2 cyclophosphamide.

The lower AC doses in FAC triplets compared with the doses in AC doublets may explain the inferior results of FAC versus AT, as opposed to the only minimally inferior results of AC versus AT. A few trials have compared AC versus FAC, with indeed no advantage for addition of 5-fluorouracil to anthracycline-cyclophosphamide.[52]

In one trial with preliminary results only, the triplet taxane-anthracycline-cyclophosphamide combination (TAC) was superior compared with FAC for response rate, but not for progression-free or overall survival (table 4).[53] No studies have reported on the comparison of AT versus TAC.

In our pooled analysis combining all trials in which an anthracycline-taxane is compared with AC or FAC, the superiority of the anthracycline-taxane combination is significant in terms of response rate (figure 7A: odds ratio of 1.58; 95% CI 1.34 to 1.86), and in terms of progression-free survival (figure 7B: hazard ratio of 0.87; 95% CI 0.75 to 1.00), although the latter with significant heterogeneity. Moreover, a trend for improved overall survival (hazard ratio of 0.92; 95% CI 0.78 to 1.09) was seen, but with significant heterogeneity (see figure 7C).

When analyzing the docetaxel and paclitaxel studies separately, heterogeneity disappears in the analysis of progression-free survival. Heterogeneity in the analysis of overall survival is due to the trial of Jassem *et al.*[51], which is the only trial that used paclitaxel to demonstrate an advantage for the anthracycline-taxane combination (of note, it is also the only trial comparing doublet to triplet combination in the paclitaxel subgroup).

The anthracycline-docetaxel regimen shows improved efficacy in the pooled analysis compared with (F)AC for response rate (odds ratio of 1.86; 95% CI, 1.36 to 2.54), progression-free survival (hazard ratio of 0.73; 95% CI, 0.61 to 0.86) and overall survival (hazard ratio of 0.80; 95% CI, 0.64 to 1.01), whereas the anthracycline-paclitaxel regimen is superior with respect to response rate, but comparably effective with regard to progression-free and overall survival. However, it is stressed again that this latter result is obtained with paclitaxel delivered at an inferior 3-weekly schedule.

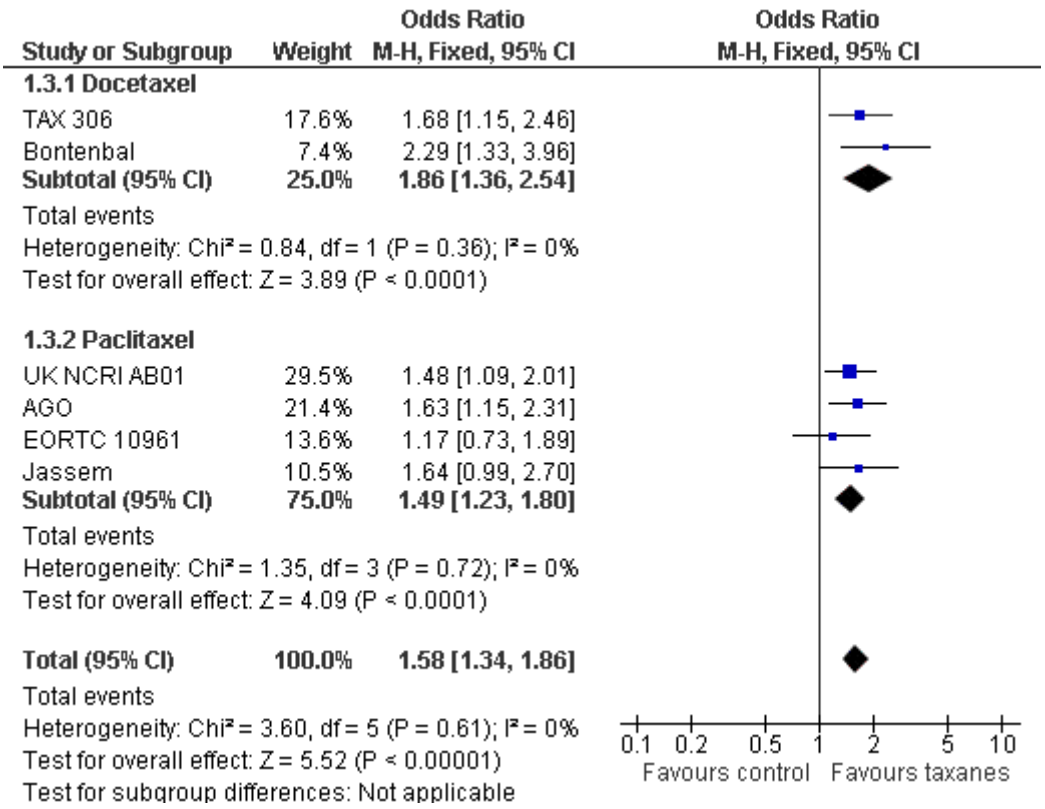


Figure 7A: odds ratio of response for anthracycline-taxane combinations versus all anthracycline combination regimens. Subgroups are based on the type of taxane used.

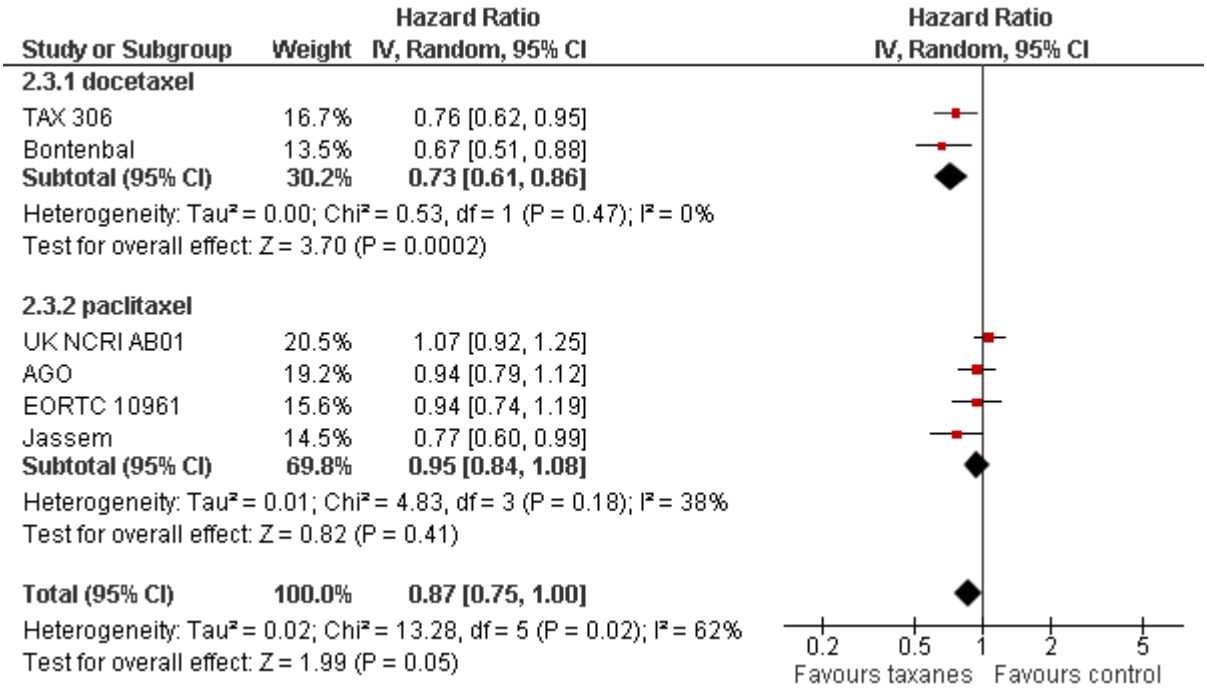


Figure 7B: hazard ratio of progression-free survival for anthracycline-taxane combination versus all anthracycline combination regimens. Subgroups are based on the type of taxane used.

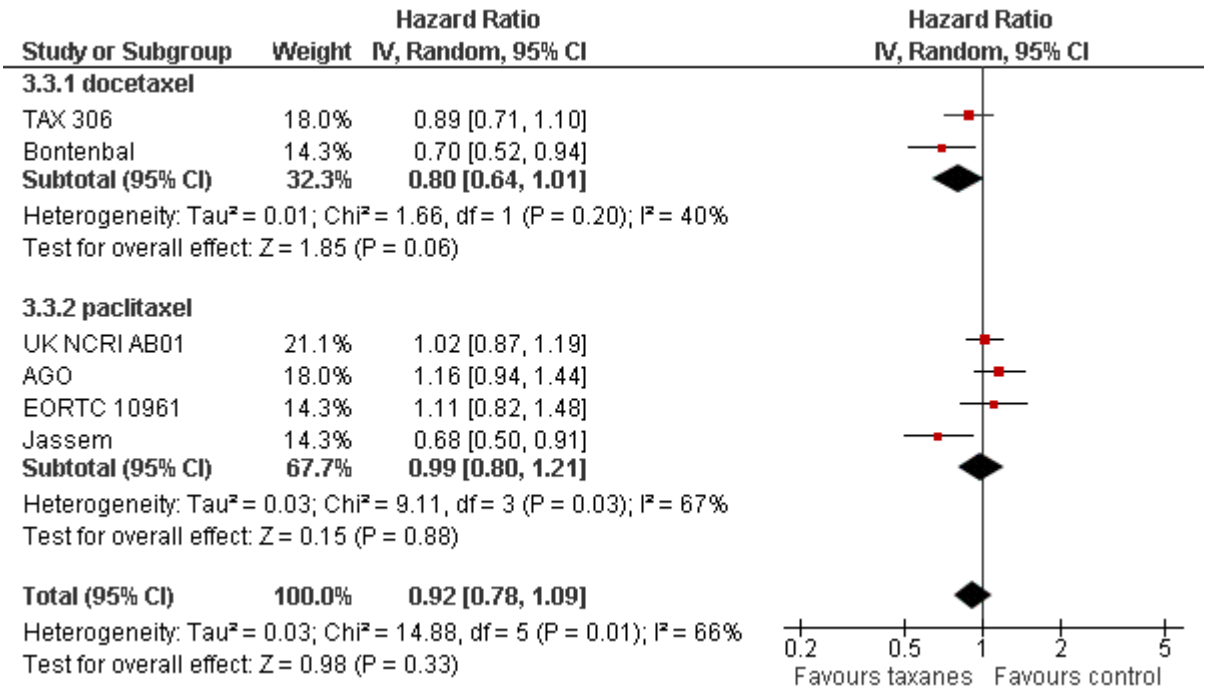


Figure 7C: hazard ratio of overall survival for anthracycline-taxane combinations versus all anthracycline combination regimens. Subgroups are based on the type of taxane used.

In conclusion, based on these studies, anthracycline-docetaxel combinations are superior compared with (F)AC in the first-line treatment of advanced breast cancer, whereas 3-weekly anthracycline-paclitaxel combinations have comparable efficacy as other anthracycline-containing regimens (i.e. (F)AC). The anthracycline-docetaxel combination as first-line metastatic breast cancer treatment is registered in Europe, however the FDA does not mention this specific regimen in their approval report of docetaxel or doxorubicin (see appendix B).

In one small phase III study, with quality of life as primary endpoint, 210 patients were included.[54] They were randomized to receive adriamycine-docetaxel (AD) or adriamycine-paclitaxel (AP), with no significant difference in efficacy for the taxane doses and schedules used (3-weekly docetaxel 75m/mg^2 or 3-weekly paclitaxel 175 mg/m^2 in combination with adriamycine 50 mg/m^2).

Table 4. Treatment effects of anthracycline-taxane combinations in advanced breast cancer in first line																
Author	**Study**	**Regimen**	**N**	**Median FU**	**Response Rate in %**				**Median PFS in months**				**Median OS in months**			
				months	**Exp**	**Con**	**OR**	**95% CI**	**Exp**	**Con**	**HR**	**95% CI**	**Exp**	**Con**	**HR**	**95% CI**
Combination regimens																
		AT vs A														
Sledge	ECOG E1193	AP 50/150 vs A 60	454	NA	47	36	1.56	1.07 - 2.28	8.2	6.0	0.78	0.63 - 0.96	22.4	19.1	1.00	0.81 - 1.20
		AT vs AC or ET vs EC														
Nabholtz	Tax 306	AD 50/75 vs AC 60/600	429	49	59	47	1.68	1.15 - 2.46	8.6	7.4	0.76	0.60 – 0.94	22.5	21.7	0.89	0.72 - 1.09
Blohmer	German	ED 75/75 vs EC 90/600	240	24	47	42	1.22	0.73 - 2.04	10.3	10.1	0.98	P = 0.38	30.0	19.9	0.66	P = 0.21
Langley	UK NCR I ABO1	EP 75/200 vs EC 75/600	705	NA	65	55	1.49	1.11 - 2.02	7.0	7.1	1.07	0.92 - 1.24	13.0	14.0	1.02	0.87 - 1.19
Lück (abstract)	AGO	EP 60/175 vs EC 60/600	516	NA	51	39	1.64	1.16 - 2.33	9.2	7.4	0.94	0.78 - 1.13	19.1	22.1	1.16	0.94 - 1.43
Biganzoli	EORTC 10961	AP 60/175 vs AC 60/600	275	29	58	54	1.17	0.73 - 1.89	6.0	6.0	0.94	0.74 - 1.20	20.6	20.5	1.11	0.83 - 1.49
		AT vs FAC														
Bontenbal	Dutch	AD 50/75 vs FAC 500/50/500	216	27	58	37	2.29	1.33 - 3.96	8.0	6.6	0.67	0.51 - 0.88	22.6	16.2	0.70	0.52 - 0.94
Jassem	CCEI Pac BCSG	AP 50/220 vs FAC 500/50/500	267	69	66	53	1.64	0.99 - 2.70	8.1	6.2	0.77	0.58 – 1.01	23.3	18.3	0.69	0.51 - 0.93
		DAC vs FAC														
Mackey (abstract)	Tax 307	DAC75/50/500 vs FAC500/50/500	484	NA	50	41	1.44	1.01 - 2.07	7.6	7.2	0.96	0.79 - 1.16	20.6	22.0	0.96	0.78 - 1.19
		AD vs AP														
Cassier	ERASME 3	AD 50/75 vs AP 50/175	210	50	39.6	41.8		P = 0.774	8.7	8.0		P = 0.977	21.4	27.3		P = 0.081

Abbreviations: A =adriamycine, C=cyclophosphamide, CI=confidence interval, Con=control arm, D=docetaxel, E=epirubicin, Exp=experimental arm, F=5-fluorouracil, FU=follow-up, HR=hazard ratio, N=number, OR=odds ratio, OS=overall survival , P=paclitaxel, PFS=progression- free survival, T=taxane

Taxanes in and versus non-anthracycline combination regimens

Taxanes are also registered in combination with capecitabine, as second line treatment for advanced breast cancer. This registration was based on the only available randomized trial of O'Shaughnessy *et al.* in which docetaxel (75 mg/m² every 3 weeks) in combination with capecitabine (1250 mg/m² twice daily for 14 days) was compared with single-agent docetaxel (100 mg/m² every 3 weeks).[55] All patients were previously treated with anthracyclines. Of relevance, a high number of patients received post-study chemotherapy (27% of patients in the single-agent docetaxel arm received capecitabine after progression). The addition of capecitabine to docetaxel led to a significant improvement in response rate, progression-free survival and overall survival (table 5).

Several trials investigated the substitution of an anthracycline by capecitabine in a taxane combination, two trials using docetaxel and one trial using paclitaxel.
In a trial of Mavroudis *et al.*[56], a total of 307 patients were treated with either docetaxel 75 mg/m² every 3 weeks and capecitabine 950 mg/m² twice daily for 14 days (lower dose then used in the study of O'Shaughnessy) or 3-weekly docetaxel and epirubicin (both 75 mg/m²) as first line treatment of advance breast cancer. In this trial, 18% of patients with epirubicin and docetaxel received post-study capecitabine. No significant difference was seen for all efficacy end points (table 5).
From the preliminary results of the small ERASME 4 trial[57], with the same design as the trial of Mavroudis *et al.*[56], a significant improvement in progression-free survival was seen, but not for overall survival, with the capecitabine instead of anthracycline.
The results of a trial investigating a taxane-capecitabine combination compared with anthracycline-taxane combination using paclitaxel is only available as a abstract.[58] In this AGO-trial, known as MAMMA 3 trial, 340 patients were randomized to receive 3-weekly paclitaxel 175 mg/m² and epirubicin 60 mg/m² or 3-weekly paclitaxel with capecitabine (1000 mg/m² twice daily for 14 days). After 25 months follow-up no significant differences were seen with respect to response rate, progression-free and overall survival.
From these trials it can be concluded that addition of capecitabine to single-agent docetaxel improves efficacy, whereas capecitabine instead of epirubicin is equally effective if used in combination with a taxane.

Paclitaxel in combination with gemcitabine is also registered for the treatment of advanced breast cancer, after local recurrence or metastatic disease when anthracycline therapy has failed. This registration is based on the trial of Albain *et al.*[59], where a total of 529 patients were randomized to receive 3-weekly paclitaxel (175 mg/m^2) in combination with gemcitabine (on days 1 and 8 every 21 days 1250 mg/m^2) or single-agent paclitaxel (3-weekly 175 mg/m^2). Baseline characteristics were well balanced between the two groups, with all patients receiving prior adjuvant anthracycline treatment. Response rate was significantly improved with gemcitabine-paclitaxel, compared with single-agent paclitaxel (41.4% versus 26.2%, odds ratio of 1.98; 95% CI 1.37 to 2.86). Progression-free survival and overall survival were both significantly improved in the gemcitabine-paclitaxel arm compared with single-agent paclitaxel. Of note, again paclitaxel is used in an inferior 3-weekly schedule as discussed previously. The median time to progression was 6.1 months in the gemcitabine-paclitaxel arm versus 4.0 in the single-agent paclitaxel arm (hazard ratio of 0.70; 95% CI, 0.59 to 0.85). The median overall survival was 18.6 months in the paclitaxel-gemcitabine arm, compared with 15.8 months in the single-agent paclitaxel arm (hazard ratio of 0.82; 95% CI, 0.67 to 1.00) (table 5).

No other phase III trials were fully published on the registered combination of gemcitabine and paclitaxel.

Based on the one phase III study[59] gemcitabine-paclitaxel doublet is an effective therapeutic regimen in metastatic breast cancer. However, the doublet gemcitabine-paclitaxel is compared with 3-weekly single-agent paclitaxel, which is a suboptimal schedule of paclitaxel. For that reason, it would be of importance to evaluate the efficacy of gemcitabine-paclitaxel compared with weekly paclitaxel.

Table 5. Treatment effects of taxanes and non-anthracycline combination in advanced breast cancer																
Author	**Study**	**Regimen**	**N**	**Median FU**	**Response rate in %**				**Median PFS in months**				**Median OS in months**			
				months	**Exp**	**Con**	**OR**	**95% CI**	**Exp**	**Con**	**HR**	**95% CI**	**Exp**	**Con**	**HR**	**95% CI**
Combination regimens																
		Adding Cap to D														
O'Shaughnessy	SO14999	CapD 1250/75 vs D 100	511	23	42.0	30.0	1.68	1.17 – 2.43	6.1	4.2	0.65	0.55-0.78	14.5	11.5	0.78	0.63-0.95
		Substitution of A or E by Cap														
Mavroudis	HORG	CapD 950/75 vs ED 75/75	286	42	53	52	1.06	0.66 – 1.71	11.0	10.6	0.93	0.73 – 1.25	35.7	37.6	1.06	0.75 – 1.50
Bachelot (abstract)	ERASME 4	CapD 1000/75 vs ED 75/75	68	42	64	48	1.90	0.64 – 5.69	12.4	6.8		P = 0.004	37.0	27.0		P = 0.49
Lück (abstract)	MAMMA-3	CapP 1000/175 vs EP 60/175	340	25	47	42	1.23	0.79 – 1.91	10.4	9.2	1.01	0.79 – 1.30	22.0	26.1	1.03	0.74 – 1.42
		Adding Gem to P														
Albain	MOSG	GemP vs P	529	36	41	26	1.98	1.37 – 2.86	6.1	4.0	0.70	0.59 – 0.85	18.6	15.8	0.82	0.67 – 1.00

Abbreviations: A=adriamycine, Cap=capecitabine, CI=confidence interval, Con=control arm, D=docetaxel, E=epirubicin, Exp=experimental arm, FU=follow-up, Gem=gemcitabine, HR=hazard ratio, N=number, OR=odds ratio, OS=overall survival , P=paclitaxel, PFS =progression- free survival

Taxanes as combination or sequential therapy

The question remains whether sequential therapy of single-agents is as effective as combined therapy.

In the previously mentioned North-American study, patients were either treated with single agent 3-weekly adriamycine (60 mg/m²), single-agent 3-weekly paclitaxel (175 mg/m^2) or with the combination of 3-weekly paclitaxel (150 mg/m²) and adriamycine (50 mg/m²) (table 3 and 4).[34] In the combination arm, a reduced dose per drug was used. Compared with single-agent anthracycline and compared with single-agent paclitaxel, the combination treatment was superior in terms of response rate and progression-free survival, but not in terms of overall survival. Cross-over was recommended for patients treated with single-agents at progression of disease. However, only 57% of patients actually crossed over to the other regimen, of whom on average 21% had a response to the second-line regimen (table 6).

In contrast, in a phase III trial of Conte *et al.*[60] no significant difference was found in response rate between sequential regimen of epirubicin followed by paclitaxel, compared with a combined regimen of epirubicin and paclitaxel (table 6).

One phase III trial of Soto *et al*.[61] published preliminary results regarding combination or sequential use of docetaxel and capecitabine. In this trial, 277 patients received either capecitabine (dose of 825 mg/m² twice daily for 14 days) in combination with a taxane (docetaxel 75 mg/m² every 3 weeks or paclitaxel 175 mg/m² every 3 weeks), or capecitabine monotherapy (1250 mg/m² twice daily for 14 days) followed by any of the aforementioned taxanes on progression. Compared with single-agent capecitabine, the response rate of the combined therapy of capecitabine with a taxane (docetaxel or paclitaxel) was significantly better. The progression-free survival and overall survival were not different for sequential versus combined regimens, suggesting that in long-term efficacy sequential therapy can be an appropriate option. Of the 91 patients receiving capecitabine monotherapy, actually 64% received sequential taxanes. The remaining 36% was still on capecitabine monotherapy, or had complete response, or was rapidly progressing with no further therapy.

In conclusion, doublet combination in advanced breast cancer therapy results in more responses compared to either single-agents[34], but not in improved overall survival if cross-over was allowed.[60]

Table 6. Treatment effects of sequential versus concurrent taxane-combinations in advanced breast cancer																
Author	**Study**	**Regimen**	**N**	**Median FU**	**Response Rate in %**				**Median PFS in months**				**Median OS in months**			
				months	**Exp**	**Con**	**OR**	**95% CI**	**Exp**	**Con**	**HR**	**95% CI**	**Exp**	**Con**	**HR**	**95% CI**
Combination regimens																
		Single-agent vs combination														
Sledge	ECOG E1193	A 60 vs AP 50/150	454		36	47	0.64	0.44 - 0.93	6.0	8.2	1.28	1.04 – 1.59	19.1	22.4	1.00	0.83 – 1.23
		Sequential vs combination														
Soto (abstract)	MOSG	Cap 1250 → D100 or P175 vs CapD 825/75	182	16	46*	74	0.31	0.16 – 0.57	8.4†	8.1		NS	31.5†	28.6		NS
Soto (abstract)	MOSG	Cap 1250 → D100 or P175 vs CapP 825/175	186	16	46*	65	0.46	0.26 – 0.84	8.4†	6.7		NS	31.5†	33.1		NS
Conte	GONO	E → P vs EP	198	NA	53	62	0.97	0.55 – 1.70	10.8	11		NS	26	20		NS

** response rate after single-agent capecitabine*

† survival rate after sequential treatment of capecitabine monotherapy, followed by taxane on disease progression

Abbreviations: A=adriamycine, Cap = capecitabine, CI=confidence interval, Con=control arm, D=docetaxel, E=epirubicin, Exp=experimental arm, FU=follow-up, Gem=gemcitabine, HR=hazard ratio, N=number, NS=not significant, OR=odds ratio, OS=overall survival , P=paclitaxel, PFS=progression- free survival

4.b. Efficacy of taxanes in early breast cancer

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has assessed the 10-year and 15-year effects of various systematic adjuvant therapies on breast cancer recurrence and survival.[62] Many trials involved CMF and anthracycline-based combinations. Compared with CMF, allocation to anthracycline-based poly-chemotherapy further reduced the annual breast cancer death rate by about 38% for women younger than 50 years of age and by about 20% for women of 50 to 69 years of age, largely irrespective of the use of tamoxifen and of estrogen receptor status, nodal status, or other tumor characteristics.

The motivation to use taxanes as adjuvant therapy derived initially from their lack of cross resistance with anthracyclines both preclinical and in human trials.[5] There is still some doubt on whether all taxane regimens improve survival over a non-taxane regimen. In fact, various strategies have been tested: addition of taxanes to anthracyclines, a sequential use of taxanes following anthracyclines or a concurrent approach in which one drug, e.g. cyclophosphamide, is substituted for a taxane. In this present systematic review we provide the available evidence with regard to efficacy, safety and effectiveness of taxane-based chemotherapy in the adjuvant setting.

Different taxane schedules

There was already a suggestion that weekly paclitaxel and 3-weekly docetaxel were more effective than 3-weekly paclitaxel in patients with metastatic breast cancer.[33,34] The ECOG 1199 trial was designed to examine this in the adjuvant setting.[41] Patients received four cycles of adriamycine and cyclophosphamide followed by either paclitaxel 175 mg/m^2 (q3w), paclitaxel 80 mg/m^2 (q1w), docetaxel 100 mg/m^2 (q3w) or docetaxel 35 mg/m^2 (q1w). This trial confirmed the results seen in the advanced disease setting: both 3-weekly docetaxel and weekly paclitaxel were superior as compared with 3-weekly paclitaxel (table 7), hazard ratio of disease-free survival respectively 0.81 (95% CI 0.66 to 1.00) and 0.79 (95% CI 0.64 to 0.97).

Table 7. Treatment effects of single-agent taxanes, docetaxel or paclitaxel, in early breast cancer

Author	Study	Comparison	N	No of cycles		5-years DFS				5-years OS			
				Exp	Con	% Exp	% Con	HR	95% CI	% Exp	% Con	HR	95% CI
		D vs P and D and P (after AC)											
Sparano	ECOG,SWOG,CALGB	wkl D35 vs 3wkl P175	2483	12	4	78	77	0.92	0.75-1.12	86	87	0.98	0.76-1.25
Sparano	ECOG,SWOG,CALGB	3wkl D100 vs 3wkl P175	2489	4	4	81	77	0.81	0.66-1.00	87	87	0.88	0.68-1.14
Sparano	ECOG,SWOG,CALGB	wkl P80 vs 3wkl P175	2484	12	4	82	77	0.79	0.64-0.97	90	87	0.76	0.58-0.98

Abbrevations: A=doxorubicin, CI=confidential interval, C=cyclophosphamide, Con=control arm, D=docetaxel, DFS= disease free survival, Exp=experimental arm, HR=hazard ratio, OS=overall survival, P=paclitaxel.

Chemotherapy regimens with versus without taxanes

In total 21 trials in the adjuvant breast cancer setting were included, comparing chemotherapy schemes with and without taxanes (table 8). We were able to calculate pooled hazard ratios for 20 trials, with regard to disease-free survival (figure 8A). The pooled analyses showed a hazard ratio for disease-free survival of 0.86 (95% CI 0.82 to 0.90) in favour of adding a taxane. Moreover, a significant difference in favour of taxanes was seen in overall survival (hazard ratio 0.85, 95% CI 0.79 to 0.91) (figure 8B). This is in line with a Cochrane meta-analysis[4], that reported the relative risks for disease-free and overall survival to be 0.81 (95% CI 0.77 to 0.86) and 0.81 (95% CI 0.75 to 0.88), respectively, in favor of the taxane containing treatment group, and results seen in other meta-analyses.[63,6]

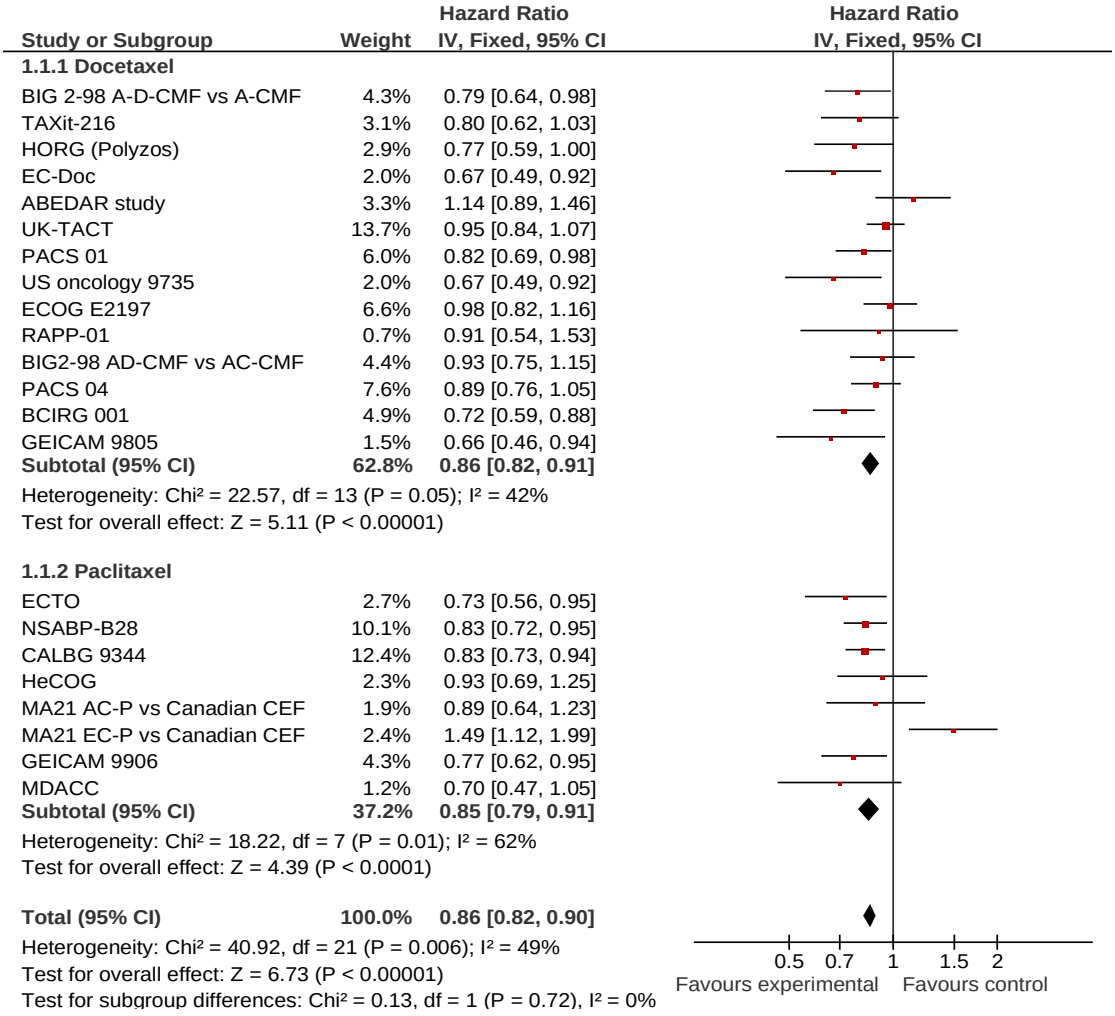


Figure 8A: hazard ratio of disease-free survival in chemotherapy regimens with versus without taxane. Subgroups are based on the type of taxane used.

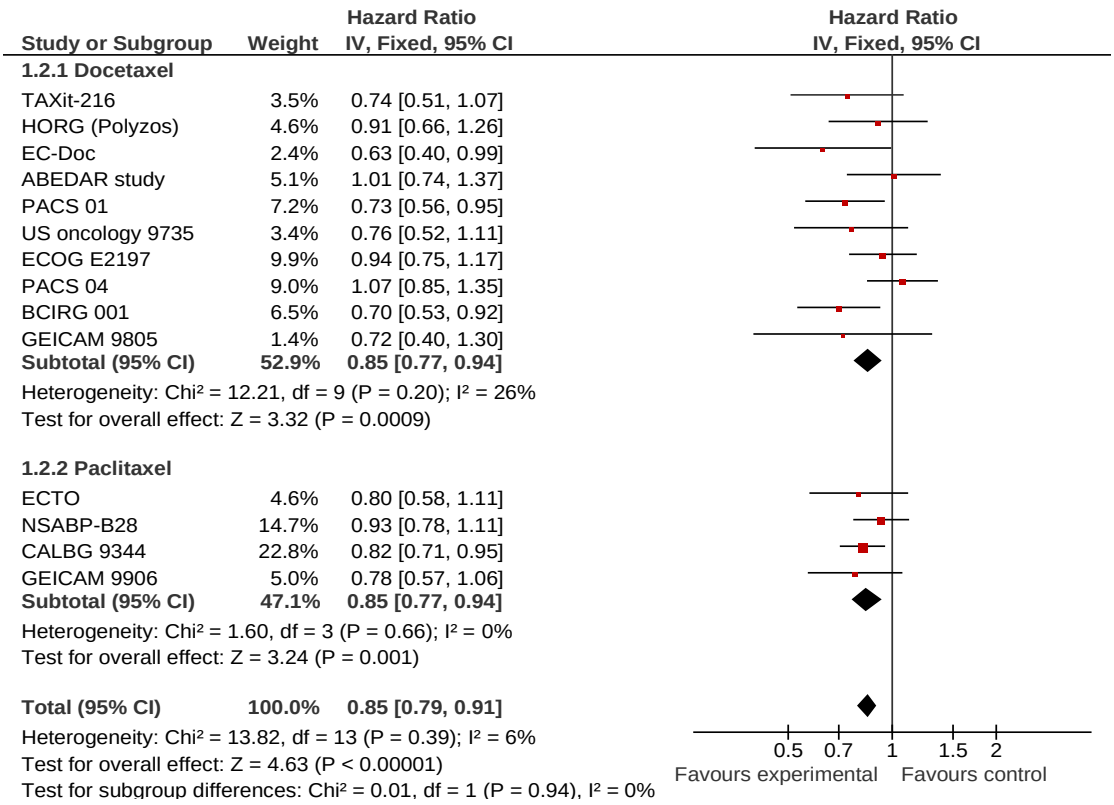


Figure 8B: hazard ratio of overall survival in chemotherapy regimens with versus without taxane. Subgroups are based on the type of taxane used.

However, from the 21 included trials, some data were only available as abstracts. Therefore, we also performed a pooled analysis of published data only, with no difference in outcome of disease-free and overall survival. The survival benefit with taxanes remained, with a hazard ratio of 0.85 (95% CI 0.81 to 0.90) for disease-free survival and of 0.83 (95% CI 0.77 to 0.90) for overall survival (data not further shown).

Next, we categorized the studies by the way the taxanes were used: added concurrently to anthracyclines, used in sequence to anthracyclines, or substituting one or more other cytotoxic drugs.

Addition: taxanes added to an anthracycline

Taxanes added concurrently: AT→CMF vs A→CMF

In the ECTO trial a taxane was added concurrently to an anthracycline, followed by CMF.[64] In total, 904 patients either received four cycles of monotherapy adriamycine 75 mg/m^2 followed by four cycles of classical CMF or four cycles of adriamycine 60

mg/m^2 in combination with paclitaxel 200 mg/m^2, followed by four cycles of CMF. Patients treated with the taxane combination chemotherapy had an improved 5-year disease-free survival (hazard ratio 0.73; 95% CI 0.57 to 0.97), and a trend for improved overall survival (hazard ratio 0.80; 95% CI 0.56 to 1.07).

Taxanes added in sequence: A(C)→ T versus A(C)

In five studies a taxane was given in sequence: either following an anthracycline (A→T vs A) or following a combination of an anthracycline and cyclophosphamide (AC→T vs AC), and next followed by CMF in three studies.[65,66, 67,68, 69] In the BIG 2-98 trial[65], three cycles of docetaxel in sequence to adriamycine, and followed by CMF, resulted in an improved 5-year disease-free survival when compared with the non-taxane control group (hazard ratio of 0.79; 95% CI 0.64 to 0.98). Overall survival data are not yet available. The TAXit-216 study[66] with a more or less similar design, showed that with four additional docetaxel cycles, 5-year disease-free survival was improved (hazard ratio of 0.80; 95% CI 0.62 to 1.03), and after adjustment for predefined factors in a hazard ratio of 0.78 (95% CI 0.61 to 1.00), of borderline significance. At 5 years follow-up no difference in overall survival was seen. In both the NSABP-B28 trial[67] and the CALGB 9344 trial[68], more than 3000 women with node-positive breast cancer were treated with four cycles of AC or four cycles of AC followed by four cycles of 3-weekly paclitaxel at doses of 225 mg/m^2 and 175 mg/m^2, respectively (AC-P). Comparable results were seen, with a significant improvement in 5-year disease-free survival in favor of paclitaxel at a hazard ratio of 0.83 in both trials. Five-year overall survival was not significantly improved in the NSABP-B28 study (hazard ratio 0.93; 95% CI 0.78 to 1.12), but significantly improved in the CALGB 9344 study (hazard ratio 0.82; 95% CI 0.71 to 0.95). In the CALGB trial patients had a higher number of tumor positive nodes. In the smaller HeCOG study[69], including only 595 patients, 3-weekly paclitaxel (250 mg/m^2) did not significantly improve disease-free or overall survival (hazard ratio 0.93; 95% CI 0.69 to 1.24). The overall hazard ratio of disease-free survival in these five studies is 0.83 (95% CI 0.77 to 0.90) in favor of the taxane containing arm (Figure 9).

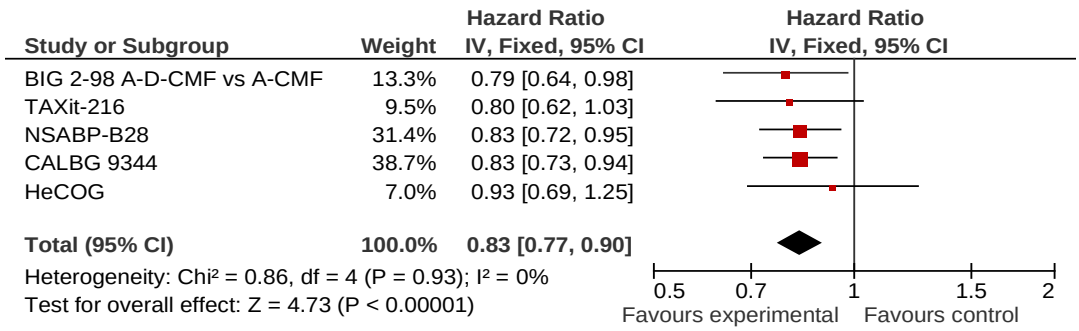


Figure 9: hazard ratio of disease-free survival in A(C)→T versus A(C)

In conclusion, addition of taxanes to anthracycline containing regimens, either concurrently or sequentially, improves disease-free survival in early breast cancer.

<u>Taxanes in sequence, added to/partly substituting anthracyclines versus FEC/FAC or CEF</u>

Taxanes in sequence: AC→T or T→AC versus FEC

Two studies compared sequential docetaxel following or preceding an epirubicin/cyclophosphamide combination (EC→D or D→EC) with that of FEC triplet.[70,71] Both studies demonstrated an improvement in disease-free survival for the taxane group with a hazard ratio of 0.77 (95% CI 0.59 to 0.99) and of 0.67 (95% CI 0.48 to 0.90), respectively. The pooled hazard ratio for disease-free survival is 0.73 (95% CI 0.60 to 0.89) (figure 10). The larger study reported by Nitz *et al.*[71], including 1837 patients, showed also a significant improvement in overall survival (hazard ratio 0.67; 95% CI 0.48 to 0.90).

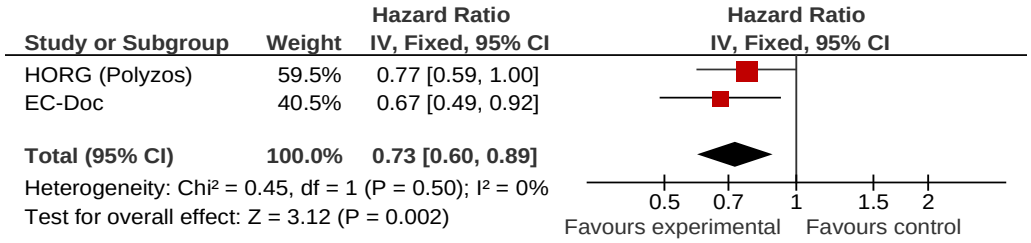


Figure 10: hazard ratio of disease-free survival in AC→T or T→AC versus FEC

Taxanes in sequence: FEC/FAC→T versus FEC/FAC

Four studies compared a taxane in sequence with 5-fluorouracil, anthracycline and cyclophosphamide with six or eight cycles 5-fluorouracil, anthracycline and cyclophosphamide.[72,73,74,75] The UK-TACT trial[72] compared four cycles of FEC followed by four cycles of docetaxel with eight cycles of FEC. The UK-TACT did not

show an advantage in disease-free survival with the sequential administration of docetaxel (hazard ratio 0.95; 95% CI 0.85 to 1.08). The PACS-01 study[73] used the same regimen but with a different dose of FEC and in each arm six cycles were given instead of eight. The results of the taxane group were better than in the control group for both disease-free and overall survival (hazard ratio disease-free survival 0.82; 95% CI 0.69 to 0.99, and hazard ratio overall survival 0.73; 95% CI 0.56 to 0.94). The GEICAM 9906[74] compared four cycles of FEC followed by eight cycles of weekly paclitaxel with six cycles of FEC. A disease-free survival advantage in favor of paclitaxel was observed (hazard ratio 0.77, 95% CI 0.62 to 0.95). In addition, a trend for improved overall survival was observed (hazard ratio 0.78; 95% CI 0.57-1.06). The MDACC trial[75] is a sequential anthracycline-taxane trial in which four cycles of three-weekly paclitaxel was given before four cycles of FAC, and compared with eight cycles of FAC. No differences in disease-free survival was seen. In the forest plot of these four studies, also including the MDACC study with the 3-weekly inferior paclitaxel schedule, the hazard ratio for 5-year disease-free survival was 0.87 (95% CI 0.80-0.95) in favor of the taxane arm (Figure 11). Analyzing the docetaxel and paclitaxel studies separately the hazard ratio is respectively 0.91 (95% CI 0.82 to 1.00) and 0.75 (95% CI 0.62 to 0.91).

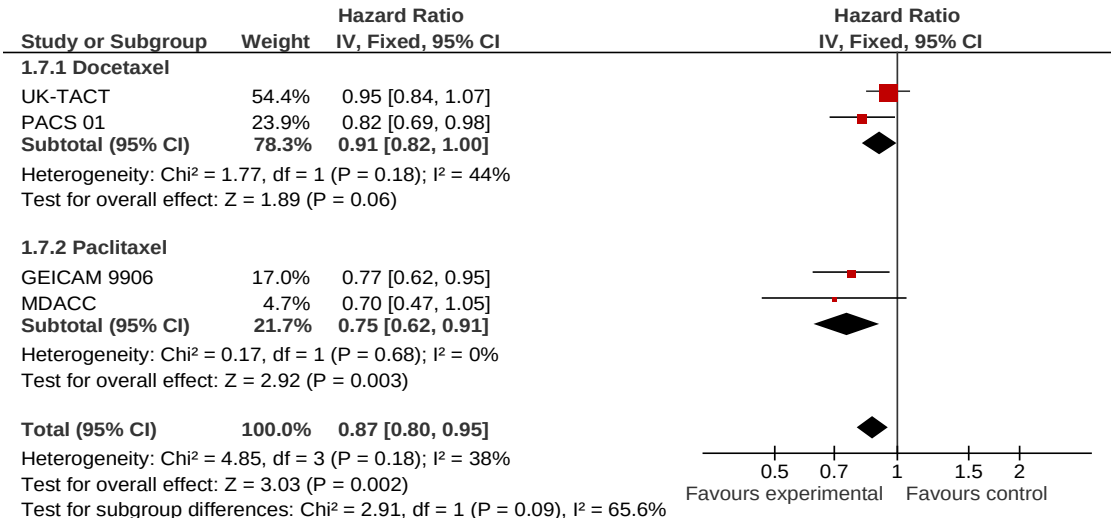


Figure 11: hazard ratio of disease-free survival in F(A/E)C→T versus F(A/E)C. Subgroups are based on the type of taxane used

Taxanes in sequence: AC→T versus Canadian CEF

Two studies compared a sequential anthracycline-taxane regimen with a dose-intensive anthracycline-containing poly-chemotherapy.[76,77] In the German ADEBAR

study[76], a sequential epirubicin/cyclophosphamide-docetaxel chemotherapy regimen was compared to Canadian CEF, with no significant difference in disease-free or overall survival between the two treatment arms. In the MA21 study[77], two or three-weekly anthracyclines in combination with cyclophosphamide (AC) and followed by 3 cycles of paclitaxel was compared with the standard arm, consisting of Canadian CEF. The AC-P arm (comparison A) with 3-weekly paclitaxel was significantly inferior to Canadian CEF in terms of disease-free survival (hazard ratio 1.49; 95% 1.12 to 1.99). The dose-dense epirubicin arm, with 3-weekly paclitaxel (comparison B) was not significantly different from Canadian CEF, in terms of disease-free survival (hazard ratio 0.89; 0.64 to 1.22). In the forest plot of these two studies, there was a trend for improved 5-year disease-free survival for Canadian CEF (hazard ratio 1.17; 95% CI 0.99 to 1.37) (figure 12).

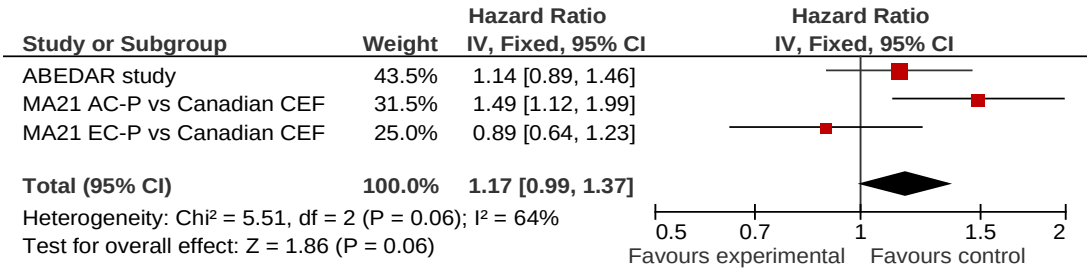


Figure 12: hazard ratio of disease-free survival in AC→T versus Canadian CEF

When excluding the studies in which the dose-intensified triplet Canadian CEF was used as comparator, sequential use of taxanes after or before an anthracycline-containing regimen resulted in an improved disease-free survival at a hazard ratio of 0.84 (95% CI 0.79 to 0.98) (figure 13A).

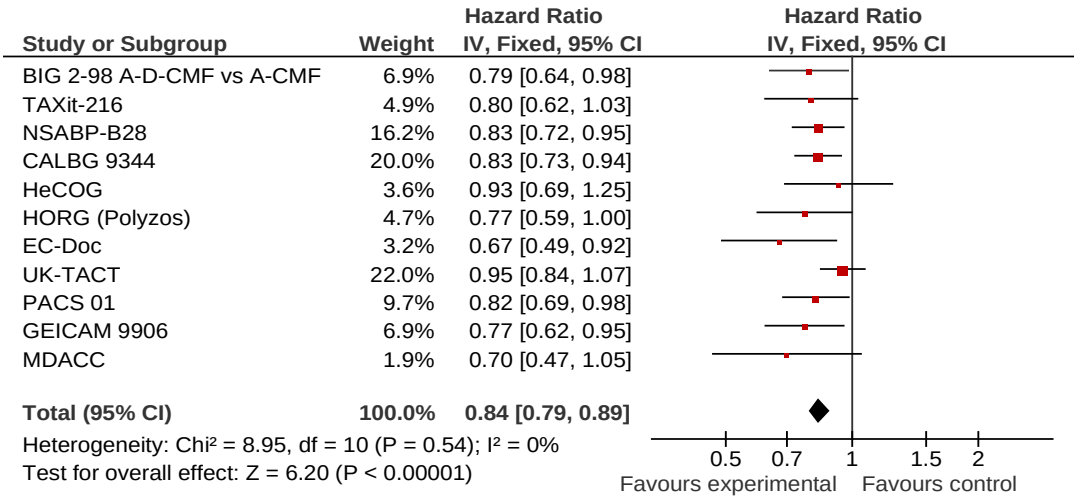


Figure 13A: hazard ratio of disease-free survival of sequential use of taxanes before or after an anthracycline regimen versus non sequential therapy

Pooled analysis from the studies in which data from overall survival was available, showed also a significant improved overall survival with a hazard ratio of 0.82 (95% CI 0.75-0.90) (figure 13B)

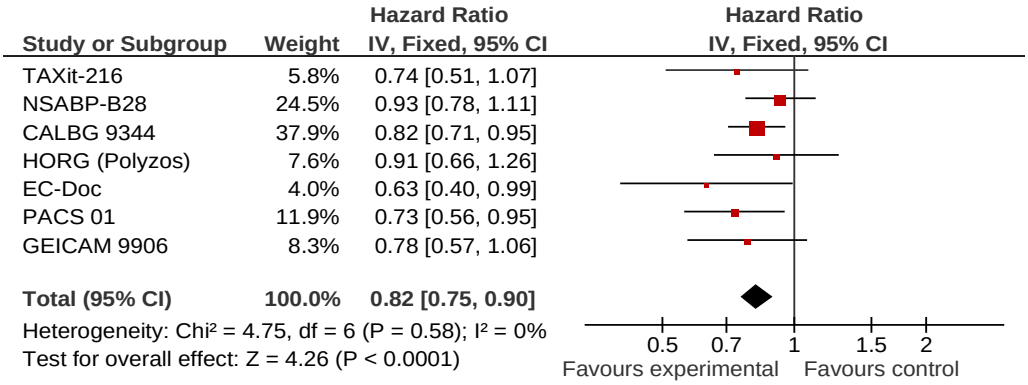


Figure 13B: hazard ratio of overall survival of sequential use of taxanes before or after an anthracycline regimen versus non sequential therapy

Next, we excluded the studies in which taxanes were added without substitution. We observed that taxanes in sequence of triplet therapy, in part replacing the triplet, also improves efficacy compared to the triplet alone: for disease-free survival at a hazard ratio of 0.85 (95% CI 0.78 to 0.92) and for overall survival at a hazard ratio of 0.77 (95% CI 0.66-0.90) (figure 13C and 13D).

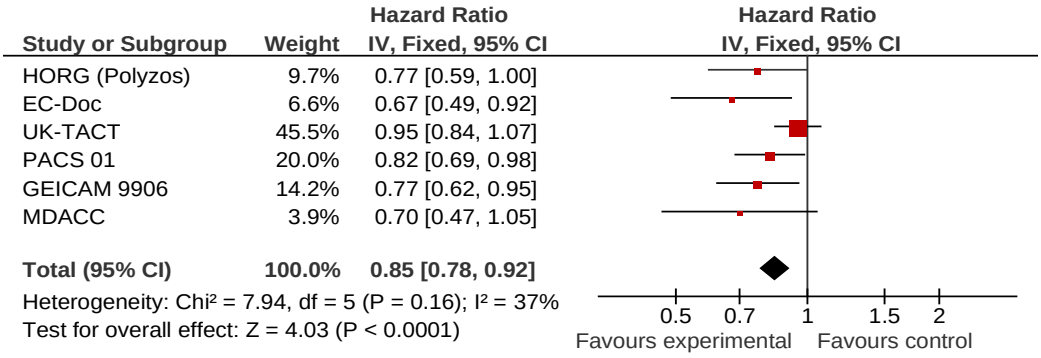


Figure 13C: hazard ratio of disease-free survival of sequential use of taxanes before or after an anthracycline regimen versus concurrent non-taxane therapy

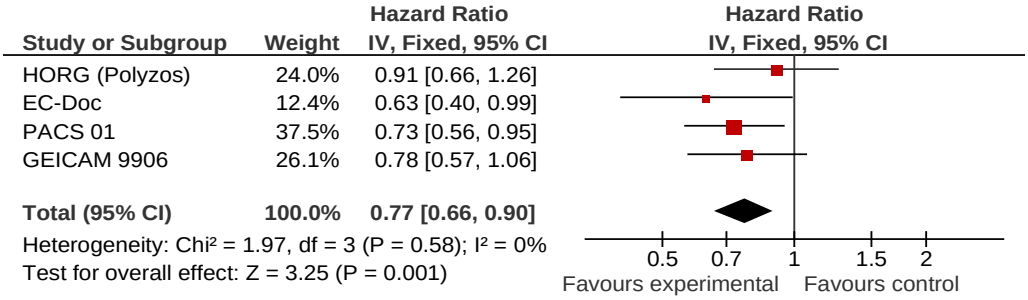


Figure 13D: hazard ratio of overall survival of sequential use of taxanes before or after an anthracycline regimen versus concurrent non-taxane therapy

We conclude that sequential use of (F)AC and taxanes for on average eight cycles is superior to four cycles of AC and also superior to six (eight) cycles of FAC or FEC, and if optimally dosed probably equivalent to Canadian CEF. Canadian CEF is an intensified anthracycline regimen: it is active, but associated with a worse toxicity profile compared to taxanes.

Taxanes instead of other cytotoxic drugs: substitution

Substitution: TC versus AC

In a US Oncology study, patients were either treated with four cycles of a non-anthracycline containing regimen of docetaxel combined with cyclophosphamide (TC) or four cycles of adriamycine and cyclophosphamide (AC).[78] The taxane containing regimen resulted in a significant improvement of 5-year disease-free survival (hazard ratio 0.67; 95% CI 0.50 to 0.94). Overall survival was non-significantly improved at 5 years follow-up, and significantly improved at 7 years of follow (hazard ratio 0.69; 95% CI 0.50 to 0.97).

Substitution: AT versus AC

Cyclophosphamide was replaced by docetaxel in three phase III studies, in combination with adriamycine: AT versus AC.[79,80,65] None of the three trials showed superiority for the docetaxel-adriamycine combination regimen. In the pooled analysis of these three studies, the hazard ratio for 5-year disease-free survival was 0.96 (95% CI 0.84 to 1.09) (Figure 14).

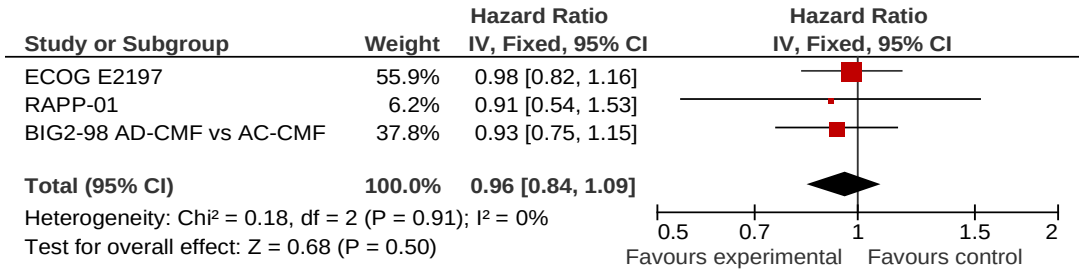


Figure 14 : hazard ratio of disease-free survival in AT vs AC

Substitution: AT versus FEC

Two studies compared a concurrent regimen of anthracyclines and taxane (respectively four and six cycles) with six cycles of FEC.[81,82] No difference in

disease-free and overall survival was observed between the two treatment arms. The hazard ratio is only given in the study of Roché *et al*.[81], so no pooled analysis could be made.

Substitution: TAC versus FAC

In two studies docetaxel was given instead of 5-fluorouracil, in combination with adriamycine and cyclophosphamide, that is, TAC versus FAC.[83, 84]

Compared with FAC, TAC resulted in a 28% relative improvement in disease-free survival and a 30% relative improvement of overall survival, in lymph node positive patients (BCIRG 001[83]). The outcome did not seem to be driven by number of positive nodes, or by hormone receptor or HER2-status. A relative improvement in disease-free survival (34%) and in overall survival (28%) was also seen in the GEICAM 9805 study[84] in lymph node negative patients. The overall hazard ratio of disease-free survival in these two studies is 0.70 (95% CI 0.59-0.84) in favor of the taxane containing arm (Figure 15).

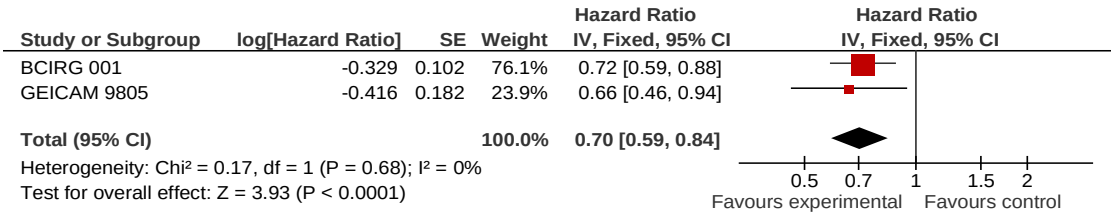


Figure 15: hazard ratio of disease-free survival in TAC vs FAC

It is concluded that taxane combination regimens are superior to conventionally dosed anthracycline-regimens, if used in combination with cyclophosphamide (i.e., TC or TAC). Of note, a randomized trial is currently running, comparing the efficacy of TC versus TAC [Clinicaltrials.gov: NCT 00493870]. Obviously, an effective non-anthracycline containing regimen would be very attractive considering long term toxicities of anthracyclines.

Table 8. Treatment effects of anthracycline-taxane combinations in early breast cancer

Author	Study	Comparison	*N*	No of cycles		5-years DFS				5-years OS			
				Exp	Con	% Exp	% Con	HR	95% CI	% Exp	% Con	HR	95% CI
		AT vs A											
Gianni	ECTO	AP60/200-CMF vs A75-CMF	904	4+4	4+4	76	69	0.73	0.57-0.97	85	85	0.80	0.56-1.07
		A(C)->T vs A(C) or E->T vs E											
Francis	BIG 2-98 comparison A	A75-D100-CMF vs A75-CMF	1441	3+3+3	4+3	78	73	0.79	0.64-0.98				
Bianco#	TAXit- 216	E 120-D100-CMF vs E120–CMF	972	4+4+4	4+4	74	67	0.78	0.61-1.00			0.74	0.51-1.07
Mamounas	NSABP-B28	AC60/600-P225 vs AC60/600	3060	4+4	4	76	72	0.83	0.72-0.95	85	85	0.93	0.78-1.12
Henderson	CALGB 9344	$AC_{(60,75,90)}$/600-P175 vs AC $_{(60,75,90)}$/600	3121	4+4	4	70	65	0.83	0.73-0.94	80	77	0.82	0.71-0.95
Fountzilas	HeCOG	E110-P250-CMF vs E110-CMF	595	3+3+3	4+4	70	68	0.93	0.69-1.24	80	77		
		T-> EC or EC->T vs FEC											
Polyzos	T->EC vs FEC	D100-EC 75/700 vs FEC 700/75/700	756	4+4	6	73	67	0.77	0.59 - 0.99	84	81	0.91	0.66 - 1.26
Nitz#	EC-Doc	EC 90/600-D100 vs FEC 500/100/500	1837	4+4	6	90	86	0.67	0.48-0.90	95	93	0.63	0.40-0.98
		FEC-T vs FEC or T-FAC vs FAC											
Ellis	UK-TACT	FEC-D100 vs FEC 600/60/600 or E-CMF	4162	4+4	8	76	74	0.95	0.85-1.08				
Roché	PACS 01	FEC-D100 vs FEC 500/100/500	1999	3+3	6	78	73	0.82	0.69-0.99	91	87	0.73	0.56 - 0.94
Martin	GEICAM 9906	FEC-P100 vs FEC 600/90/600	1248	4+8wkl	6	79	72	0.77	0.62-0.95	90	87	0.78	0.57 - 1.06
Buzdar	MDACC	P250-FAC vs FAC1000/50/500	524	4+4	8	86	83	0.70	0.47-1.06				
		EC->T or AC->T vs Can CEF($Q4_w$)											
Janni#	The German ADEBAR study	EC 90/600-D100 vs Canadian CEF	1502	4+4	6			1.14	0.89-1.45			1.01	0.74-1.37
Burnell	MA21 comparison A	AC60/600-P175 vs Canadian CEF	1403	4+4	6	85	90	1.49	1.12-1.99				
Burnell	MA21 comparison B	EC120/830Q2wk-P175 vs Canadian CEF	1402	6+4	6	90	90	0.89	0.64-1.22				
		TC vs AC											
Jones	US Onc 9735	DC 75/600 vs AC 60/600	1016	4	4	86	80	0.67	0.50-0.94	90	87	0.76	0.52-1.1
		AT vs AC											
Goldstein	ECOG E2197	AD 60/60 vs AC 60/600	2882	4	4	85	85	0.98	0.82-1.16	92	91	0.94	0.76-1.18
Brain#	RAPP-01	AD 50/75 vs AC 60/600	627	4	4	91	91	0.91	0.54-1.52				
Francis	BIG 2-98 comparison B	AD-CMF 50/75 vs AC 60/600-CMF	1446	4+3	4+3	74	72	0.93	0.75-1.14				
		ET vs FEC											
Roche#	PACS04	ED 75/75 vs FEC 500/100/500	3010	6	6	82	80	0.89	0.76-1.05	90	90	1.07	0.85-1.35
Mastro#	Gono MIG5	EP 90/175 vs FEC 600/60/600	1055	4	6	70	71	NS		88	89	NS	
		TAC vs FAC											
Martin	BCIRG 001	DAC 75/50/500 vs FAC 500/50/500	1491	6	6	75	68	0.72	0.59-0.88	87	81	0.70	0.53-0.91
Martin#	GEICAM 9805	DAC 75/50/500 vs FAC 500/50/500	1059	6	6	91	86	0.66	0.46-0.94	97	95	0.72	0.40-1.30

Abbrevations: A=doxorubicin, CI=confidential interval, Con=control arm, C=cyclophosphamide, D=docetaxel, DFS= disease free survival, E=epirubicin, Exp=experimental arm, F=5-fluorouracil, HR=hazard ratio, M=methotrexate, OS=overall survival, P=paclitaxel, T=taxane, #=abstract

Sequential versus concurrent use of taxanes

A (C)→ T versus AT

In two studies docetaxel was given in sequence to adriamycine (and CMF) or in sequence to a combination of adriamycine and cyclophosphamide, and compared with adriamycine-docetaxel.[65,85] In the BIG 2-98 trial[65], three cycles adriamycine followed by three cycles docetaxel (A-D, followed by CMF) resulted in an improved disease-free survival compared with four cycles of concurrent adriamycine-docetaxel (AD, followed by CMF) arm (hazard ratio 0.83; 95% CI 0.69 to 1.00). The NSABP-B30 trial[85] compared four cycles of adriamycine-cyclophosphamide (AC) followed by four cycles of docetaxel (D) with four cycles of concurrent adriamycine and docetaxel (AD). Sequential AC→D improved disease-free survival as compared with AD (hazard ratio 0.80; P = 0.70 to 0.91). Also a significant improvement in overall survival was reported (hazard ratio 0.83; 0.70 to 0.98). In the pooled analysis, we combined these two trials and found a significant improvement of disease-free survival with a hazard ratio of 0.81 (95% CI 0.73 to 0.90) with the sequential arm.

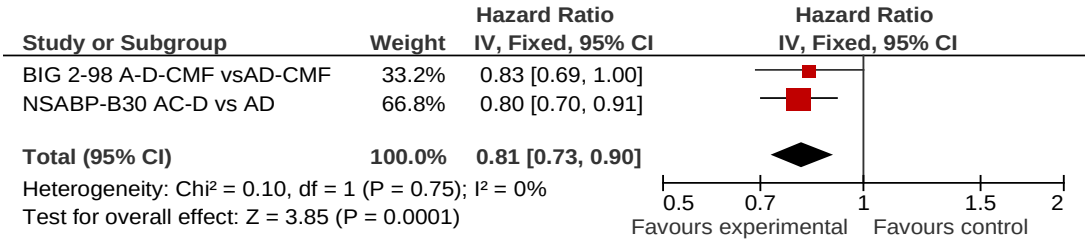


Figure 16: hazard ratio of disease-free survival in A(C) → T versus AD

We conclude that A(C)→ D is more effective than AD. The higher efficacy of the sequential arm may be due to a higher number of chemotherapy cycles, use of full dosed single agents per cycle (with comparable cumulative dose in the BIG 2—98 trial[65]) or due to use of cyclophosphamide (in the NSABP-B30 trial[85]).

AC→ T versus TAC

In two studies docetaxel was either given in sequence following a combination of adriamycine and cyclophosphamide (AC-T) or given concurrently with adriamycine and cyclophosphamide (TAC) (table 9).[85,86]

In the NSABP-B30 trial[85], AC→D was compared with four cycles of TAC. Patients treated with sequential chemotherapy had an improvement of 5-year disease-free survival (hazard ratio 0.83, 95% CI 0.73 to 0.95) and a trend for improved overall survival (hazard ratio 0.86; 95%

0.72 to 1.02). The BCIRG 005 study used the same sequential regimen, but compared this with six instead of four cycles of TAC chemotherapy.[86] No difference in disease-free survival was seen (hazard ratio 1.00; 95% CI 0.86 to 1.16).

We conclude that sequential use of AC → T for a total of eight cycles is equivalent to six cycles of TAC, but superior to four cycles of TAC We hypothesize that with a sequential regimen with a lower cumulative dose and dose-intensity comparable efficacy can be achieved than with a triplet combination.

Table 9. Treatment effects of sequential versus concurrent anthracycline-taxane combinations in early breast cancer

Author	Study	Comparison	*N*	No of cycles		5-years DFS				5-years OS			
				Exp	Con	% Exp	% Con	HR	95% CI	% Exp	% Con	HR	95% CI
		A(C)-T vs AT or TAC											
Francis	BIG 2-98 comparison C	A75-D100-CMF vs AD 50/75-CMF	1919	3+3+3	4+3	78	74	0.83	0.69-1.00				
Swain	NSABP-B30 comp A	AC60/600-D100 vs AD 50/75	3506	4+4	4	74	69	0.80	0.70-0.91	83	79	0.83	0.70-0.98
Swain	NSABP-B30 comp B	AC60/600-D100 vs DAC 75/50/500	3511	4+4	4	74	69	0.83	0.73-0.95	83	79	0.86	0.72-1.02
Eiermann#	BCIRG 005	AC 60/600-D100vs DAC 75/50/500	3298	4+4	6	79	79	1.00	0.86-1.16				

Abbrevations: A=doxorubicin, CI=confidential interval, Con=control arm, C=cyclophosphamide, D=docetaxel, DFS= disease free survival, Exp=experimental arm, HR=hazard ratio, M=methotrexate, OS=overall survival, T=taxanes, #=abstract

4.c. Safety

Two Cochrane reviews reported on taxane toxicity, one in adjuvant setting, the other in advanced breast cancer setting, showing that regimens containing a taxane were associated with significantly more neutropenia and neurotoxicity, but less nausea and vomiting compared with anthracycline-containing regimens.[3,4]

The different types of combinations in which the taxanes are used are of influence on toxicity. The taxane toxicity profile seems to differ between docetaxel and paclitaxel. In the trial that compared single-agent docetaxel with single-agent paclitaxel in metastatic breast cancer, the incidence of all grade 3-4 adverse events was significantly higher in the docetaxel group (55.4 versus 23.0%).[40] Overall neutropenia an febrile neutropenia was more seen in the docetaxel group, although thrombocytopenia and anemia were similar in both groups. The incidence of grade 3/4 neurotoxicity was 2% in both groups after four cycles, although the incidence of overall neurotoxicity was greater in the docetaxel group. Because of the higher rate of adverse events in the docetaxel group, the discontinuation rate was higher as well, even though the number of administered cycles in the docetaxel group was also higher.

With docetaxel added to capecitabine more patients experienced gastrointestinal toxicity and more hand-foot syndrome, contrary to more neutropenic fever and arthralgia in the single-agent docetaxel group.[55] This toxicities could be managed by dose reductions without affecting efficacy.

With the addition of gemcitabine to paclitaxel, the rate of hematologic toxicities raised, mainly due to neutropenia which also resulted in more febrile neutropenia.[59] Neurotoxicity occurred at similar rates in both groups.

Cassier *et al.*[54] reported a different toxicity profile for the docetaxel-anthracycline combination than for the paclitaxel-anthracycline combination. Overall hematological adverse events grade 3-4 were most common in both treatment arms, but more pronounced in the docetaxel group than in the paclitaxel group (febrile neutropenia 48.6% in docetaxel group versus 21.4% in paclitaxel group, $P < 0.000001$). The EMA reports on an incidence of 17% febrile neutropenia with docetaxel.[87] However no granulocyte-colony stimulating factor was administered in almost all trials, whereas nowadays primary G-CSF prophylaxis is recommended in anthracycline-docetaxel combination regimens.[88] On the other hand, significant more grade 3/4 neurotoxicity

is seen with paclitaxel, compared with docetaxel; in the study reported by Cassier *et al*.[54] this was 6.8% with paclitaxel versus 0.9% with docetaxel (P = 0.03).
In the adjuvant setting, the combination of docetaxel with cyclophosphamide and doxorubicin (TAC) led to significantly more non-hematologic and hematologic adverse events compared with FAC. Of relevance, when administering taxanes in adjuvant setting, is the knowledge of long-term toxicity. As reported by the EMA, alopecia remains in 3.2% of patients treated with TAC versus 1.4% with FAC. Furthermore, more patients experience ongoing fluid retention and neurotoxicity compared with patients treated with FAC. The occurrence of secondary leukemia after docetaxel is under review. As until now, 3 patients treated with FAC and 1 patients treated with FAC developed acute leukemia.
Not only the choice of combination chemotherapy, but also dose, schedule and number of cycles play a role in toxicity of the combinations used.
The neurotoxicity of paclitaxel is associated with the type of schedule used. In the CALGB 9840 trial neuropathy grade 3 was more common with a weekly schedule (24% versus 12%; P = 0.0003).[18] In the trial of Rivera *et al.*,[36] there was a statistically significant difference in toxicity rate, with a higher incidence in the 3-weekly docetaxel group compared with the weekly docetaxel group (88.1 versus 55.9%).
With regard to the dose-cumulative toxicities, fluid retention was commonly seen in the docetaxel group (59.7%), despite pre-medication with dexamethasone.[33]
Another dose-cumulative toxicity with the combination of paclitaxel and an anthracycline is cardiac toxicity. In the trial of Sedge *et al.*[34] the same incidence of cardiac dysfunction was seen in the doxorubicin monotherapy group compared with the paclitaxel-doxorubicin group. In several trials, the combination of paclitaxel with doxorubicin reported high rates of congestive heart failure (up to 21%), although Biganzoli *et al.*[89] showed that this combination could be administered safely up to a cumulative dose of doxorubicin of 360 mg/m². In adjuvant setting, the Cochrane review of Ferguson *et al.*[4], pooled data of several studies comparing taxane-containing regimens with non-taxane containing regimens. No difference was found in the risk of developing cardiac toxicity between taxane-containing regimens and non taxane-containing regimens, with an odds ratio of 0.90 (95% CI, 0.53 to 1.55).
In conclusion, febrile neutropenia is an important side effect of the taxanes, more common with docetaxel than paclitaxel and more common with the combination of doxorubicin and docetaxel. Neurotoxicity is a frequent side-effect of paclitaxel.

However, most of these toxicities are reversible and manageable and compared with anthracycline-containing regimens taxanes are a safe and well tolerated treatment option.

4.d. Quality of life

None of the studies investigating quality of life, reported a significant difference between the taxane-containing and nontaxane-containing regimens in advanced breast cancer treatment. Several trials in adjuvant setting evaluated the effect of taxane containing therapy on quality of life. Data of the BCIRG001[83], TACT[72] and GEICAM 9805[90] indicate that taxane based regimens have greater negative effect on quality of life during therapy compared with the anthracycline based comparing arms. These differences in quality of life resolve, however, at the end of the chemotherapy period. The HeCOG trial[69] reported no difference in quality of life between the two treatment arms at the beginning and at the end of chemotherapy. Because of the variety of questionnaires used to determine quality of life, as well as risk of bias due to different rates of completion of the questionnaires (some studies reported difference in completion rates, with patients in poorer health not completing the questionnaires), both Cochrane reviews did not report on pooled data of quality of life.[3,4] Furthermore, most studies used suboptimal taxane schedules as described previously which could have an effect on quality of life as evaluated by the patients as well. In the one study where docetaxel and paclitaxel combination regimens with an anthracycline were compared, no difference in quality of life was observed.[54]

4.e. Applicability

Taxanes are indicated in combination or as single-agent in the treatment of early and advanced breast cancer (appendix B). For early breast cancer, taxanes are indicated for node-positive breast cancer only. A lot of studies tried to identify the patients most likely in need of adjuvant chemotherapy based on risk estimation and those most likely to benefit from it (prediction).[91] Investigators have focused on molecular markers and gene expression in tumor tissues to identify optimal therapy selection. In the adjuvant setting, the interaction between HER2 status and benefit from taxanes was evaluated by Hayes *et al.*[92] in a subset of 1322 women who were treated on CALBG 9344. They observed a significant interaction between the expression or amplification of HER2 and the benefit of adjuvant paclitaxel in patients with node-

positive breast cancer who received four cycles of doxorubicin plus cyclophosphamide, regardless of ER status, while there was no evidence of benefit in the subgroup with ER-positive, HER2-negative tumors.

The investigators of the UK-TACT trial[72] combined trials of taxane based versus anthracycline based adjuvant chemotherapy that reported combined ER/HER2 subgroup analysis. They also concluded that the benefit of docetaxel was most apparent in patients whose tumors were ER negative and HER2 positive. No benefit was seen in the ER-positive and HER2 negative group.

In the meta-analysis of Laurentiis *et al.*[6] a pooled analysis was made for different subgroups. The investigators showed that taxanes significantly reduced the risk of recurrence irrespective of ER status (ER positive versus ER negative), nodal status (N1 to 3 versus N4+), and age/menopausal status ($\leq$ 50 years/premenopausal versus 50 years/postmenopausal), and that the magnitude of the relative benefit was approximately constant across such subgroups of patients. Therefore they recommended that age, menopausal status, and ER status should not be used in clinical practice to identify patients who may not benefit from a taxane-based regimen. In this meta-analysis of de Laurentiis *et al.*[6], only two studies reported disease-free survival data according to HER2 expression. Nonetheless, no interaction between HER2 status and taxane administration in terms of reduction of risk of recurrence was seen. Further, the authors showed no difference of benefit with regard to nodal status (N1 to 3 versus N4+). With regard to the high risk node negative breast cancer patients, there is one study (GEICAM 9805) to justify the use of taxanes as adjuvant treatment for this group of patients.[84]

We conclude that evidence so far is conflicting, and patient selection for taxane therapy based on biological tumor characteristics is not yet possible.

4.f. Dosage and administration

Taxanes are administered intravenously, in concordance with most other used chemotherapeutic agents in the treatment of advanced breast cancer. With the use of pre-medication, in the form of dexamethasone, the incidence of hypersensitivity reactions and fluid retention is reduced. Dose adjustments of docetaxel and paclitaxel should be made following an episode of febrile neutropenia, as well as for patients with hepatic impairment.[87]

As discussed earlier, the dosage and schedule of taxanes is associated with therapeutic efficacy and toxicity profiles. The recommended dosage and schedule of docetaxel is 3-weekly administration of 100 mg/m² docetaxel monotherapy. With docetaxel being added to doxorubicin or capecitabine, the administered dose should be 75 mg/m². In adjuvant setting docetaxel should be administered in a dose of 75 mg/m^2, one hour after administration of doxorubicin and cyclophosphamide. [Sanofi Aventis, Taxotere® summary of product characteristics]. For paclitaxel, which is the only of the taxanes available as generic drug, the studied dose of monotherapy is 175-220 mg/m^2 in a 3-weekly schedule, and a dose of 80-100 mg/m^2 in a weekly schedule [Bristol-Meyers Squibb Ltd, Taxol® summary of product characteristics]. However, the advised schedule and dose by the FDA, EMA and Dutch CBG is only that of a 3-weekly paclitaxel schedule with a dose of 175 mg/m^2 when administered as monotherapy, in combination with trastuzumab, and in adjuvant setting when administered sequential to anthracycline and cyclophosphamide. When used in combination with doxorubicin, the registered paclitaxel dose is 220 mg/m^2 to be administered 24 hours after the doxorubicin. However, the 3-weekly dose is presently considered as inferior. So, if paclitaxel is used a weekly regimen is recommended. As seen in the clinical trials, in adjuvant setting a limited number of taxane cycles are used, whereas in advanced breast cancer treatment taxanes can be applied until disease progression or unacceptable toxicity.

4.g. Cost effectiveness

Taxanes in advanced breast cancer treatment

In 2000, in the United Kingdom a health technology assessment report was published on the efficacy of taxanes in the treatment of advanced breast cancer.[93] There were 6 studies included in the review, which were all cost-utility analyses published from 1996 - 1999. The incremental cost-effectiveness ratios varied from €2 278 to €2 783 (£1 990 - £2 431). The major problem with these studies was that they are based on mainly phase II trials, or trials with no direct comparison between docetaxel and paclitaxel.

A recent review on the cost-effectiveness on cytotoxic therapy in the treatment of advanced breast cancer was published by Blank *et al*.[21] In this review 3 cost-effectiveness analyses on the use of taxanes in advanced breast cancer treatment were

included. These economic evaluations were all considered cost-effective by their authors. However, the review illustrated large differences in the quality of the included reports, mainly due to lack of transparency on how the economic model was built.

The first included cost-utility analysis was published by Maniadakis *et al.*[94] This analysis was conducted alongside a phase III trial comparing carboplatin and paclitaxel versus weekly paclitaxel or 3-weekly docetaxel and gemcitabine. In this trial a total of 416 women with advanced breast cancer were randomly assigned to receive one of these three treatment regimens as first-line treatment. The cost-utility analysis was conducted from the perspective of the Greek national health service. A discount rate of 3.5% was used for benefits and costs. Uncertainty was addressed using bootstrapping.

The highest overall survival was seen in the patients treated with weekly paclitaxel. The incremental survival time of weekly paclitaxel compared with 3-weekly paclitaxel and carboplatin is 0.9 years and compared with 3-weekly docetaxel and gemcitabine 1.18 years. The total costs per patient in each group varied from € 19 343 in the 3-weekly docetaxel and gemcitabine group, to € 20 498 in the 3-weekly paclitaxel and carboplatin group and € 20 578 in the weekly paclitaxel treatment group. This led to an ICER of weekly paclitaxel versus 3-weekly docetaxel and gemcitabine of €3 596 per QALY gained. Weekly paclitaxel is more effective and less costly than paclitaxel and carboplatin. A cost-effectiveness acceptability curve showed that the probability that weekly paclitaxel is cost-effective was high, also for relatively low (<€ 12 000) cut off points for the maximum willingness to pay for a QALY. This led to the conclusion that weekly paclitaxel is a cost-effective treatment option.

Vu *et al.*[95] compared the cost-effectiveness of 3-weekly docetaxel versus 3-weekly paclitaxel as second-line treatment for advanced breast cancer. They based their report on survival data from a provincial cancer registry in Canada. This study was also conducted from a healthcare system perspective. No discount rate was applied, because, as stated by the authors, the treatment lasted less than one year. No description of the economic model used was supplied. The administration of 3-weekly docetaxel led to an improved overall survival, compared with 3-weekly paclitaxel, with an incremental survival time of 0.2 years. The incremental costs of docetaxel versus paclitaxel were €4 601 (CA$ 6 497). This was due to the higher costs of

docetaxel itself. This led to an ICER of €21 485 (CA$30 377) per life-year gained for docetaxel compared with paclitaxel. In the sensitivity analyses the ICERs ranged from €10 029 (CDN$13 972) to €65 842 (CDN$91 724) per LYG when varying median overall survival, and from dominant to €129 212 (CDN$1 80 005) when varying costs.

One of the limitations of the study of Vu *et al.*[78] is that the most effective docetaxel schedule is compared to a less effective paclitaxel schedule, as discussed in the chapter on efficacy of taxanes. In the cost-effectiveness analysis of Benedict *et al.*[96] the more effective weekly paclitaxel schedule was used. This study based their analysis of the randomized controlled trial of Jones *et al.*[40] in which 3-weekly docetaxel with 3-weekly paclitaxel was compared. Additionally, they incorporated the analysis of 3-weekly docetaxel versus weekly paclitaxel, based on the abstract of the Anglo-Celtic IV study by Verril *et al.*[39] This cost-utility analysis used a Markov model and adopted the perspective of the National Health Service in the United Kingdom. An annual 3.5% discount rate for future costs and outcomes was used.

The incremental survival time with 3-weekly docetaxel compared with 3-weekly paclitaxel was 0.53 life years (0.33 QALYs) and compared with weekly paclitaxel 0.47 life years (0.29 QALYs). The discounted total cost per treatment regimen per patient were €19 803 (£17 321) for the 3-weekly docetaxel regiment compared with €15 207 (£13 301) in the paclitaxel weekly regimen and €18 262 (£15 973) in the 3-weekly paclitaxel regiment. This leads to ICERs of €13 756 (£12 032) per QALY for docetaxel versus 3-weekly paclitaxel and €5 240 (£4 583) per QALY for docetaxel versus weekly paclitaxel.

The latter ICER was surrounded with very wide confidence intervals, due to a lack of significant difference in the clinical outcomes. The ICERs were sensitive to the hazard ratios for PFS and OS between the comparators, the drug cost of initial treatment, and the treatment costs after progression. A probabilistic sensitivity analysis was undertaken to simultaneously assess the impact of uncertainty around the model-parameters on the results. Comparing all treatments, at a willingness to pay of £20000 per QALY gained, the probability of docetaxel being the most cost-effective treatment was around 70%.

In conclusion, the ICER of the used taxanes varied with a wide range from dominance to €21 485 per QALY (table 10). However, there is substantial variation between the

separate cost-efficacy analyses and the treatment regimens are not all registered combinations. Furthermore, due to a lack of Dutch data on cost-effectiveness of taxanes, it is difficult to transfer the foreign model-based cost-effectiveness analyses to the Dutch setting.

Table 10. Cost-efficacy of taxanes in advanced breast cancer									
Author	**Regimen**	**Country**	**Costs**			**Effect**			**ICER**
	Taxanes vs comparator		**Total costs taxanes**	**Total costs comparator**	**Incremental costs**	**Total effect Taxanes**	**Total effect Comparator**	**Incremental effect**	**Per LYG or QALY**
Benedict	D3w vs P3w	United Kingdom	19 803	15 207	4596	1.18 QALY	0.85 QALY	0.33 QALY	13 756 per QALY
Benedict	D3w vs P1w	United Kingdom	19 803	18 262	1541	1.18 QALY	0.89 QALY	0.29 QALY	5 240 per QALY
Vu	D3w vs P3w	Canada	6 686	2 085	4 601	0.91 y	0.69 y	0.22 y	21 485 per LYG
Manidiakis	Pw vs P+Carbo	Greece	20 578	20 498	80	3.42 y	2.49 y	0.92 y	Dominance
Manidiakis	Pw vs P+Gem	Greece	20 578	19 343	1 235	3.42 y	2.24 y	1.18 y	3 596 per QALY

Of note, all costs are shown in Euros (€1 = CA$1.41 and CA$1 = €0.71 and €1 = £0.87 and £1 = €1.14)

Abbreviations: Carbo=carboplatin, D=docetaxel, ICER=incremental cost-effectiveness ratio, LYG=life year gained, P=paclitaxel, QALY=quality adjusted life year, w=weekly, 3-w=3-weekly, y=year

Taxanes in adjuvant breast cancer treatment

In adjuvant breast cancer, the cost-effectiveness of taxanes was evaluated in 2007 by Ward *et al.*[97] An extensive literature search did not reveal any cost-effectiveness analyses at that time, therefore a new economic model was developed to assess the cost-effectiveness of paclitaxel and docetaxel in the adjuvant setting. The description of the used model is extensive and clear. At the time of the analysis, no complete data of trials comparing taxanes within its licensed indication, with the comparative standard of care in the UK (non-taxane, anthracycline-containing chemotherapy regimens) were available. Therefore, the best available data was used, including all trials with full results published and using the taxanes within its licensed indications. That led to use of data from 3 trials:

BCIRG 001[83]: adjuvant administration of six cycles of docetaxel in combination with cyclophosphamide and adriamycine (TAC) compared to six cycles of 5-fluorouracil in combination with cyclophosphamide and adriamycine (FAC);

NSABP-B28[67] and CALGB 9344[68]: both comparing four cycles of AC followed by four cycles of paclitaxel with four cycles of anthracycline-cyclophosphamide.

The maximum length of follow-up of these trials was 69 months. The cost-effectiveness analysis was conducted from a health care perspective. Both costs and QALYs were discounted with a rate of 3.5%. The costs of the treatment regimens were calculated, using several well defined assumptions. In the base case analysis, based on the BCIRG 001 trial, the incremental costs of TAC versus FAC were €7 904 (£6 961). The cost difference was mainly due to the costs of docetaxel itself and higher costs of adverse events with docetaxel. In the total costs, secondary prophylaxis with G-CSF was included. The incremental quality adjusted life years gained were 0.56 with the administration of TAC instead of FAC. This led to an ICER of €14 102 (£12 418) per QALY gained (see table 11). Based on the two trials using paclitaxel, the incremental costs of that regimen were €5 044 (£4 442, based on the CALGB 9344 trial) and € 6 687 (£5 899, based on the NSABP B28 trial), again mainly due to costs of paclitaxel itself.

In the CALGB 9344 trial and the NSABP B28 trial, the incremental QALYs were 0.11 and 0.14, respectively. This led to an ICER of €44 665 (£39 332, based on the CALG 9344 trial) and €48 799 (£ 42 672, based on NSABP B28 trial) per QALY (see table 11). A univariate sensitivity analysis was performed. This showed an ICER of docetaxel and paclitaxel below €17 269 (£15 000), when assuming that the benefits of

taxanes continued for 10 years instead of the 5 years used in the base case scenario. However, none of these comparative regimens (i.e. four cycles of AC) were standard of care in the United Kingdom. The conclusion of this study, as made by the authors was that the cost-effectiveness of the taxanes compared with standard comparative treatment is uncertain and unproven, because of the lack of direct comparison between taxanes regimens and standard regimens. For that reason an indirect comparison was made to compare the taxanes with FEC50-100. However, this comparison was highly uncertain due to the heterogeneity across the trials.

After 2007, several cost-effectiveness analyses were published[98,99,100,101] However, these cost-effectiveness analyses all assessed docetaxel in adjuvant treatment of breast cancer, and no new data on the cost-effectiveness of paclitaxel were reported. Four cost-effectiveness analyses are based on data from the BCIRG 001 trial (TAC versus FAC). The first study is a model-based cost-effectiveness analysis by Wolowacz *et al.*[98] The study was performed from the perspective of the national health service in the United Kingdom, and had a time horizon of 10 years. In contrast with the BCIRG 001 trial, in this analysis the costs of primary G-CSF prophylaxis were included. TAC was associated with a gain of 0.32 QALY compared to FAC. The incremental costs associated with TAC were €6 540 (£5 759). This led to an ICER of €20 654 (£18 188). A sensitivity analysis was performed, in which the time horizon was found to have the greatest impact on the cost-effectiveness, with an ICER of €11 150 (£9 685) when all expected costs and benefits over a patients' life time (time horizon of 40 years) were accounted for. The authors conclude that TAC is a cost-effective regimen, even with primary G-CSF prophylaxis.

The second study was a Canadian model-based cost-effectiveness analysis from a health care perspective.[99] The time horizon of this study was 10 years. The ICER in this study was €13 013 (CA$18 500) per QALY gained. Based on a probabilistic sensitivity analysis it was calculated that the probability that TAC was cost-effective as compared to FAC was 70% for CA$50 000/QALY (€35 000), which is used as a cut-off point in Canada for determining cost-effectiveness.

The third-model based cost-effectiveness analysis of FAC versus TAC based on the data of the BCIRG 001 trial was a Korean study that adopted both a health care and patient perspective.[100] The latter, because in Korea patients pay 30-40% of the hospital fees. The study used a Markov model with a lifetime time horizon. A

discount rate of 5% was applied. The ICER of TAC versus FAC was €7 277 per QALY gained. A sensitivity analysis showed that the percentage of patients receiving prophylactic G-CSF was the most influential factor, with an ICER of €9 926 per QALY when 100% received primary G-CSF prophylaxis. Fourth, a Spanish model-based cost-effectiveness analysis was performed on the data of the BCIRG 001 trial.[101] The analysis used a Markov model and adopted a health care perspective. The time horizon was lifetime, and the discount rate 3%. The costs of primary G-CSF prophylaxis in all patients were included. The ICER of TAC versus FAC was €2 631 per QALY gained, which the authors considered as cost-effective, employing a cut-off at €30 000.

Based on these cost-effectiveness analyses, compared to FAC, TAC is considered a cost-effective treatment regimen with ICER ranging between €2 631 - €20 654. Differences are mainly due to different utility weights used per health states in the different economic models.

Two cost-effectiveness analyses used the PACS 01 study[73] to asses the cost-effectiveness of docetaxel in the adjuvant treatment of breast cancer. In the PACS 001 study patients were treated with 6 cycles of fluorouracil, epirubicin and cyclophosphamide (FEC100) or with 3 cycles of FEC100 followed by 3 cycles of docetaxel (FEC-D).

The first cost-effectiveness analysis was reported from a Canadian health care system perspective. A Markov model with a time horizon of 10 years was used. An annual discount rate of 3% was applied to costs and benefits. The ICER of FEC-D versus FEC100 was €10 278 (CA$14 612) per QALY gained, which was considered as cost-effective in Canada.[102] The second cost-effectiveness analysis based on the same trial was performed from a French hospital perspective. No clear description of the model was provided and the time horizon was only 5 years. The reported ICER of FEC-D versus FEC100 was €9 665 per QALY, with the sensitivity analysis showing that the cost of docetaxel itself was the most influential.[103]

Based on these 2 reports, compared to FEC100, FEC-D can be considered a cost-effective treatment option in early breast cancer treatment.

Again with a lack of Dutch data, no conclusions can be made on cost-effectiveness of taxanes in adjuvant setting in the Netherlands.

Table 11. Cost-effectiveness of taxanes in adjuvant breast cancer

Author	Regimen	Country	Costs			Effect			ICER
	Taxane vs comparator		Total costs taxanes	Total costs comparator	Incremental costs	Total effect Taxanes	Total effect Comparator	Incremental effect	Per LYG or QALY
Ward	TAC vs FAC	United Kingdom	26 902	18 998	7 904	8.36 QALY	7.80 QALY	0.56 QALY	14 102 per QALY
Wolowacz	TAC vs FAC	United Kingdom	17 700	11 161	6 540	5.52 QALY	5.20 QALY	0.32 QALY	20 654 per QALY
Au	TAC vs FAC	Canada			4 080			0.31 QALY	13 013 per QALY
Lee	TAC vs FAC	Korea			6 113			0.80 QALY	7 277 per QALY
Martín-Jiménez	TAC vs FAC	Spain	14 611	11 586	3025	14.95 QALY	13.80 QALY	1.15 QALY	2 631 per QALY
Ward	AC-P vs AC	United Kingdom	24 199-24 230	17 512-19 187	5 044- 6687	8.35 - 9.05 QALY	8.24 - 8.91 QALY	0.11 - 0.14 QALY	44 665 - 48 799 per QALY
Younis	FEC-D vs FEC100	Canada	8 380	5 887	2 493			0.16 QALY	10 278 per QALY
Marino	FEC-D vs FEC100	France	12 969	9 725	3 244	5.9 QALY	5.7 QALY	0.2 QALY	9 665 per QALY

Of note, all costs are shown in Euros (€1 = CA$1.42 and CA$1 = €0.70 and €1 = £0.88 and £1 = €1.14)

Abbreviations: A=adriamycine, C=cyclophosphamide, D=docetaxel, E=epirubicin, F=5-fluorouracil, ICER=incremental cost-efficacy ratio, LYG=life year gained, P=paclitaxel, QALY=quality adjusted life year, T=taxane

5. Experience and daily use in the Netherlands

Trastuzumab

In Europe, trastuzumab was officially registered for the treatment of advanced breast cancer in 2000. Since then, more than 450 000 patients have been treated with trastuzumab worldwide, which led to a broad experience with the administration of trastuzumab. In the Netherlands, an estimated 3250 patients are diagnosed with metastatic breast cancer each year. Between 15-20% of all breast cancer patients are estimated to have HER2 positive disease, and are therefore potential candidates for trastuzumab therapy.

The daily use of trastuzumab in the Netherlands was a question of research. Concerns were expressed by the Dutch Confederation of Cancer Patients (NFK) and the Dutch Breast Cancer Association (BVN) regarding possible undertreatment of patients with an indication for the treatment with trastuzumab, as well as other drugs listed on the Dutch policy of expensive hospital medicines, based on the numbers and current guidelines (see appendix A). Therefore, a Dutch retrospective cohort study was performed to assess the real world use of trastuzumab in the Netherlands.[104] In this report a cohort of 610 metastatic breast cancer patients from 7 hospitals from June 2008 until December 2009 was studied. A total of 103 of these patients had proven HER2 positive disease (17%). All patients with proven HER2 positive metastatic breast cancer with an indication for treatment with trastuzumab, according to the Dutch NABON guideline, actually had received trastuzumab.

In 20% of patients with metastatic breast cancer the HER2 status was unknown, which is in concordance with 17% unknown HER2 status of metastatic breast cancer patients in a retrospective study performed in the Netherlands, also known as the MYSIGHT-study.[105] However, that percentage is more than expected based on the evaluation of the Dutch guidelines in 2007, where only 7% had an unknown HER2 status.[106]

The MYSIGHT-study was performed to retrospectively assess the use of different systemic treatment options in the treatment of advanced breast cancer in the years 2003-2010. A total of 434 patients with advanced breast cancer from 18 hospitals was included. In a subgroup analysis of HER2 positive metastatic breast cancer patients (total of 133 patients), 42% received trastzumab in combination with a taxane as first-line treatment for their metastatic disease. Of note, as second-line treatment

trastuzumab in combination with a taxane was used in 34% of HER2 positive metastatic breast cancer patients.

As stated earlier in the chapter on cost-effectiveness on trastuzumab, this drug is associated with high costs. Even though no Dutch cost-effectiveness analysis on the use of trastuzumab in advanced breast cancer is available, it is of relevance to know the costs involved with trastuzumab in the Netherlands.

An estimated 3250 patients are diagnosed with metastatic breast cancer each year in the Netherlands and between 15-20% of these patients all breast cancer patients are estimated to have HER2 positive disease. This leads to a total of 488 to 650 patients (15% to 20% x 3250) with advanced HER2 positive breast cancer each year. As seen in the MYSIGHT study[105] a total of 43% of patients with advanced disease are treated with chemotherapy and/or targeted therapy. That indicates that between 210 and 280 patients are treated with trastuzumab each year. The NVMO (acronym for the Dutch Society of Medical Oncologists) has published an estimate of costs of new drugs in 2004. They also found an estimate of 280 patients with HER2 positive metastatic breast cancer treated with trastuzumab each year.

For the costs associated with the administration of trastuzumab, we used the data from the Dutch cost-effectiveness analysis on trastuzumab in the adjuvant setting.[30] The authors also provided costs of trastuzumab in metastatic breast cancer. This is a total of €29 826 for the drug itself and €3 906 for the administration. The total costs associated with trastuzumab in advanced breast cancer would be around €9.44 million. However, this figure does not include costs of testing for HER2, costs associated with toxicity and costs. The Foundation for Pharmaceutical Statistics (SFK, stichting farmaceutische kerngetallen) published a report on total costs of expensive medicines in the Netherlands in 2007. The total costs associated with trastuzumab, including the adjuvant en advanced setting, were €59.3 million.

In conclusion, the results show that trastuzumab in advanced breast cancer is used according to the Dutch NABON guideline and according to committee BOM ('Beoordeling Oncologische Middelen') recommendations. Based on the studied patients and hospitals, there is no under use of this expensive medicine in daily practice.

Taxanes

The taxanes, docetaxel and paclitaxel, are also listed on the Dutch policy of expensive hospital medicines. The use of taxanes is reviewed in the adjuvant setting as well as in the treatment of advanced breast cancer. Since the introduction of taxanes in the early nineties, many patients have been treated with taxanes. Therefore, it is safe to say that there is an extensive experience with administration of taxanes, as single-agent as well as in combination regimens.

In an evaluation of the previous Dutch national guideline from 2005, which is based on a cohort of the Dutch National Cancer Registration, a total of 16% of all patients treated with neo-adjuvant chemotherapy received taxane-based chemotherapy and 24% of all patients treated with adjuvant chemotherapy received taxane-based chemotherapy.[106] Type of regimens were not further specified.

In 2008, the guidelines were updated, and more patients were recommended to be given taxane containing chemotherapy. No formal evaluation of the implementation of this updated guideline has been undertaken yet.

However, based on questions asked in the field, the impression is that taxanes are used in patients with HER2 positive tumors, irrespective of nodal status, and in patients with node positive disease, irrespective of HER2 status. Although, taxanes are also increasingly used in node-negative HER2 negative disease. Taxane containing regimens that are most frequently used are FEC followed by single-agent docetaxel, AC followed by weekly single-agent paclitaxel or 3-weekly docetaxel, and TAC.

The MYSIGHT-study[105], as previously discussed, included 434 patients with advanced breast cancer from 18 general hospitals in the Netherlands, between the years 2003 and 2010. Almost all patients (96%) received systemic treatment for their metastatic disease. Of these patients, 43% was treated with chemotherapy and/or targeted therapy, 52% with chemotherapy and endocrine therapy and 5% received only endocrine therapy for their metastatic disease in all lines of therapy. However, in this study they focused on specific lines of chemotherapy, so a selection bias may partly account for these figures. As first-line chemotherapy for metastatic disease, 75% received combination chemotherapy (n = 312) and 25% received single-agent chemotherapy (n = 103). As first-line combination therapy, most patients received an anthracycline-based regimen (44%), and 24% received a taxane based combination

regimen, only 7% received an anthracycline-taxane combination as first-line treatment.

A quarter of all patients received a single-agent as first-line treatment, with docetaxel being the most frequently used single-agent in first-line metastatic treatment.

For second- and further lines of treatment, the used regimens became more varied, but with single-agent taxanes being most frequently used as second-line treatment for advanced breast cancer.

The total costs associated with taxanes in the treatment of early and advanced breast cancer is again of relevance to determine efficacy of the taxanes. But, as seen with trastuzumab, no cost-effectiveness analysis of the Dutch setting on docetaxel or paclitaxel is available. Therefore, we estimated total costs of patients treated with taxanes. As for taxanes in metastatic breast cancer, a total of 3250 patients are diagnosed with metastatic breast cancer each year. Around 60% of these patients are eligible for chemotherapeutic treatment which leads to 1950 patients. As seen in the retrospective cohort study, 75% of patients receiving first-line chemotherapy for their advanced disease receive combination chemotherapy (1463 patients) en 25% of patients receiving first-line chemotherapy for their advanced disease receive single-agent therapy.[105] From the same study it was known that from patients receiving first-line combination chemotherapy, 24% received taxane-based chemotherapy and 7% received anthracycline and taxane combination therapy. From the patients treated with single-agent therapy, the majority is treated with single-agent taxanes. That leads towards an estimate of 940 patients (24% x 1463 and 7% x 1463 and 25% of 1950) receiving taxanes for their advanced breast cancer per year. We estimated that these patients are treated with an average of 4 cycles of taxanes which results in an estimate of costs of 4 x €13 348 for docetaxel (estimated patients with body surface area of 1.6 m^2, receiving 3-weekly docetaxel with a dose of 100mg/m^2) and 4 x €416 for paclitaxel (estimated patient with body surface area of 1.6m^2, receiving weekly-paclitaxel with a dose of 80 mg/m^2). Total costs associated with taxanes in advanced breast cancer would then by between €1.56 million (using only paclitaxel) and €50.2 million (using only docetaxel). For adjuvant setting, the NVMO (acronym for the Dutch Society of Medical Oncologists) estimated the costs of taxanes in adjuvant setting to be around €2.27 million (based on 1200 patients treated with TAC each year). However, these are data from 2004 and as we know the use of taxanes in

adjuvant setting has increased which also leads to higher costs of taxanes in adjuvant setting.

Of course, this is a rough estimates since there are no real-life data on costs, utilities and resource use associated with taxanes available on the Dutch setting. The Foundation for Pharmaceutical Statistics (SFK, stichting farmaceutische kerngetallen) reported on total costs associated with docetaxel (adjuvant and advanced setting) being €26.2 million and of paclitaxel being €6.2 million.
In conclusion, this retrospective study showed that taxanes have an important place in the treatment of advanced breast cancer, as monotherapy or in combination with anthracyclines or trastuzumab. A total of 71% of all patients treated with chemotherapy for advanced breast cancer, received a taxane, an anthracycline or a combination of both.

Experience of pharmacists with use of trastuzumab and taxanes in breast cancer treatment

In the previously mentioned Dutch retrospective cohort study on use of expensive drugs in the Netherlands, several medical specialists, patients and managers were interviewed to determine whether costs of drugs influenced their day to day decision making.[104] The overall perspective for patients and their treating medical specialists was, that the treatment of patients with a drug listed on the Dutch policy of expensive hospital medicines was based on data on efficacy and guideline recommendations, as opposed to costs of the drug itself. However, for hospitals and thereby pharmacists, costs of these expensive drugs are known to have an important budgetary impact, which may become increasingly relevant with the introduction of new expensive drugs into clinical practice in the near future. Currently, the expensive drugs listed on the policy are reimbursed to hospitals for 80% and only for their licensed indications. Because the costs of the remaining 20% still can become a financial problem for health care institutions, we explored the options to restrain these costs. The costs of trastuzumab for all indications (including adjuvant setting) in 2008 were nearly €60 million, for docetaxel €32 million and for paclitaxel only €5 million. With paclitaxel becoming available as generic drug, the costs decreased rapidly. Consequently, the costs of trastuzumab and docetaxel will decrease when patents on Herceptin® and Taxotere® will expire. Today, due to only a small amount of different doses of vials

being available, the waste of expensive drugs can be an important factor in the total costs of the drug. Calculations from pharmacists of the Maastricht University Medical Centre indicated that a 11% decrease in costs could be initiated with restraining the waste of trastuzumab by implementing 100 mg and 50 mg vials next to the only available vial of 150 mg. With the total costs of trastuzumab being €60 million, a 11% decrease in costs could save up to €6 million per year.

Place in guidelines

An important contributor to use of trastuzumab and taxanes in daily practice is the place that these drugs have in the national and international treatment guidelines. Therefore, we examined the statements on the use of these drugs in our national guideline, the guideline of the National Breast cancer Organisation of the Netherlands (NABON) from 2008 [www.oncoline.nl], and in the following international guidelines: European Society for Medical Oncology (ESMO) [www.esmo.org], National Comprehensive Cancer Network from the United States (NCCN) [www.nccn.org], National Institute for Health and Clinical Excellence from the United Kingdom (NICE) [www.nice.org.uk], the Canadian Cancer care Ontario (CCO) [www.cancercare.on.ca] and the St. Gallen recommendations[107], to compare with the registered indications of the drugs.

Concerning trastuzumab in advanced breast cancer, all guidelines recommend the use of trastuzumab only in patients with HER2 positive disease. The NABON and CCO did not make a recommendation about the use of trastuzumab monotherapy, although this is a licensed indication. All guidelines advised to use trastuzumab in combination with a taxane as first-line treatment of advanced breast cancer. NICE recommends the use of paclitaxel as the taxane of choice in combination with trastuzumab, because no data on cost-effectiveness of docetaxel in combination with trastuzumab are available. The different recommendations concerning continuation of trastuzumab beyond progression had no uniformity. The 2008 NABON guideline does not provide a statement on the use of trastuzumab beyond progression. However, the Dutch Committee of the evaluation of new drugs in Oncology (cieBOM) stated that there is a therapeutic value of continuation of trastuzumab beyond progression [www.nvmo.eu]. The ESMO guidelines and the NCCN guidelines advise to continue trastuzumab beyond progression, whereas the CCO guideline and NICE guideline advise to stop at disease progression. The NICE guideline gives on exception on that

statement, namely with disease progression only in the central nervous system, trastuzumab should be continued.
In conclusion, most guidelines advise on the use of trastuzumab in advanced disease according to the registered indications. However, the NICE guideline recommends the use of trastuzumab in combination with paclitaxel, rather than docetaxel, whereas both taxanes are registered for this indication. Furthermore, trastuzumab beyond progression is advised in several guidelines, even though this is no licensed indication.

Taxanes are somewhat a matter of debate between the different guidelines. The 2008 NABON guideline states that taxanes and anthracyclines are both very active drugs in the treatment of advanced breast cancer. When using taxanes, docetaxel is advised to administer in a 3-weekly schedule, whereas paclitaxel is recommended to administer in a weekly schedule. The latter is in line with the findings of our review, however not completely in line with the schedule named in the summary of product characteristics, as part of the registration. The ESMO states that the only standard of care with level 1 evidence is the use of a taxane-based regimen as first-line therapy in anthracycline pre-treated patients with metastatic breast cancer. The NICE is the only guideline to provide a recommendation of first- and subsequent lines of treatment when patients are not suitable for anthracycline therapy. First-line therapy should be single-agent docetaxel, followed by single-agent capecitabine or single-agent vinorelbine. The NCCN guidelines differentiate between preferential therapeutic regimens versus other therapeutic regimens, with no subdivision in the preferential regimens. The taxanes in all licensed indications are in the list of preferential therapeutic regimens.

In adjuvant treatment of breast cancer, taxanes are advised according to their licensed indications in the NABON and CCO guidelines. The optimal duration of the treatment is not known. However, at least four cycles (12-16 weeks) should be administered, generally aiming for six to eight cycles (18-24 weeks), in particular for patients with a higher risk of recurrence (e.g. node-positive disease). The NICE recommends the use of docetaxel as taxane, based on the same reason as in advanced breast cancer. The NCCN again only provides preferential chemotherapeutic regimens, with all licensed indications as preferred option.

In the St. Gallen recommendations on the systemic therapy of early breast cancer it is recommended that anti-HER2 treatment is given in combination (sequence or concurrent) with chemotherapy in patients with HER2 positive disease. However, the authors also state that there is too limited evidence to recommend anti-HER2 therapy for all node-negative, HER2 positive tumors, < 1 cm in size. St. Gallen Consensus also recognised two clear situations to prescribe chemotherapy. First, for patients with triple negative disease, most patients are at sufficient risk to justify this treatment. Secondly chemotherapy is given with or preceding trastuzumab for patients with HER2 positive breast cancer. There was no agreement about the definition of standard chemotherapy in the group of patients with ER-positive and HER2 negative disease, it is variable according to risk. Anthracycline-taxane combinations, as well as dose-dense doxorubicin and cyclophosphamide followed by paclitaxel were viewed as standard therapies in adjuvant setting.

In conclusion, the recommendations for use of taxanes in breast cancer is more in contrast between countries than the recommendations on trastuzumab. However, with less definite statements, use of taxanes is open to all licensed indications and leaves room for patients' and professionals' view.

6. Discussion

Trastuzumab

Trastuzumab is an active drug in patients with advanced HER2 positive breast cancer. As monotherapy it results in response rates varying from 15 to 26% in heavily pretreated patients. As first-line treatment in combination with chemotherapy, it leads to a significant improvement in overall survival of about 5 to 8 months (hazard ratio of 0.77), even though a substantial number of patients in the control group of studies had crossed over to receive trastuzumab. There are not only arguments to initiate trastuzumab as early as possible in the disease course, but there are also arguments to initiate chemotherapy as early as possible, in stead of choosing for a sequential approach, to obtain the best survival (if patients are candidates for chemotherapy, e.g. because of rapidly progressive visceral disease). Formally, trastuzumab is not registered for continued use beyond progression. However, a recent study showed a trend for survival benefit of about 5 months with continued use of trastuzumab after first-line treatment at the time of disease progression, with similar hazard ratios for response, progression-free survival and overall survival as seen with trastuzumab in first-line. Of relevance, this is the only clinical trial available on this topic, with premature closure (recruiting only 32% of planned patients).

It is concluded that trastuzumab has few side effects. Allergic reactions are seldom, but may be severe, even leading to death. Like other monoclonal antibodies, trastuzumab aggravates chemotherapy-related side effects. Grade 3/4 cardiac toxicity is an important other side effect occurring in 2% of patients, though generally reversible. According to current evidence, trastuzumab should not be combined with other cardiotoxic drugs, such as anthracyclines. It is recommended to carefully monitor cardiac function during trastuzumab treatment.

Apart from few side effect, trastuzumab combined with chemotherapy improves quality of life compared with chemotherapy alone. Of relevance when measuring quality of life in terminally ill patients, it is known that when patients deteriorate, less data on quality of life of these patients is available.

Trastuzumab should be administered intravenously, which previously constrained to intramural use, however it was recently reviewed, by the Dutch Committee of Health Insurance, to be safe for extramural use provided a strict protocol is used.[20]

Trastuzumab in advanced breast cancer treatment meets most of the requirements of the PASQUIL algorithm, used in the Netherlands for the evaluation of drugs.[108] However, this effective drug with few side-effects is associated with high costs. The various incremental cost-effectiveness ratios varied largely from €16 000 to € 162 000. These analyses are based on studies in which survival gains may be underestimated due to large cross-over, and therefore the estimated ICER may be higher than the 'real life' costs of trastuzumab in advanced breast cancer. Furthermore, it is difficult to interpret these different outcomes, due to lack of uniform ways to calculate cost-effectiveness. Different assumptions and utility weights are used and data from studies needs to be extrapolated because of limited time-period of clinical trials.

An interesting challenge is the cost-effectiveness of the use of trastuzumab beyond progression. Even though it is not registered and there is only one trial to report on efficacy, continuation of trastuzumab beyond progression is common practice and several guidelines recommend this treatment strategy. There is only one cost-effectiveness analysis on this topic, which concluded that this strategy is not cost-effective.[32] However, the ICER is based on data from the only clinical trial from von Minckwitz *et al.*[14] And it is not known if the patients included in that trial, are representative of the population of HER2 positive breast cancer patients who progressed on trastuzumab. That question comes to mind, when comparing the progression-free survival in the control arm (i.e. capecitabine monotherapy after progression on trastuzumab and chemotherapy) with the progression-free survival rates seen in the trials of Slamon *et al.*[11] and Marty *et al.*[7] They reported similar progression-free survival rates in the control arm of their trials, which were patients treated with chemotherapy as first-line treatment without trastuzumab. This could implicate that the observed significant improvement on survival with trastuzumab beyond progression in real life is actually lower, leading to an even higher ICER. On the other hand, with trastuzumab beyond progression during several lines of therapy, the ICER of the chemotherapy regimens combined with trastzumab will decrease, due to an increase of efficacy.

Even so, the Netherlands have not stated a threshold to determine the cost-effectiveness of drugs, as is provided by the NICE in the United Kingdom. The council of public health care and cure has named a limit of €80 000 per QALY as a

financial limit for cost-effectiveness[31], but this is not used as a cut-off to decide on reimbursement.

However, with more expensive drugs being introduced, it is inevitable to make choices on reimbursement. With respect to costs associated with trastuzumab, the main influential factor on costs is the drug itself. Ideally, the manufacturing costs should be lowered to decrease the ICER. And with increasing survival gains, the ICER will also decrease. Future research should be aiming at defining a subgroup of HER2 positive breast cancer patients who will benefit the most from treatment with trastuzumab.

In order to determine whether trastuzumab, a proven effective therapeutic treatment option in advanced breast cancer, is a cost-effective one, data on 'real life' costs should become available.

Not only 'real life' costs are important to review the effectiveness of a drug, also 'real life' efficacy is essential. Clinical trials are limited to shorter time-periods and there is a selection bias in included patients compared with patients receiving trastuzumab in daily practice. The use of trastuzumab in daily practice also gives insight into the influence on the course of disease. A striking observation based on 'real life' observations, is that of a higher incidence of brain metastases in patients with HER2 positive metastatic breast cancer.[109,110]

In conclusion, trastuzumab is a very effective drug in the treatment of advanced breast cancer, with improvement in overall survival rates even with high cross-over between the treatment arms. And importantly, trastuzumab has few side effects compared with chemotherapy. Our results our concordant with the earlier evaluations of trastuzumab by the Dutch health care insurance board.[20]

Even though costs associated with trastuzumab are high, the majority of the cost-effectiveness analyses provided ICERs that would fall below the cut-off of €80 000. Trastuzumab beyond progression seems an effective strategy. However, in the only one available cost-effectiveness analysis it would not be considered a cost-effective strategy. Further research with regard to subgroups of HER2 positive breast cancer patients with most benefit of this costly therapy is, therefore, needed.

Taxanes

In our review, we included 17 randomized trials that have assessed the role of taxanes in the advanced breast cancer setting, and 21 trials in the adjuvant setting. Overall, use of taxanes in the advanced setting resulted in improved response rates, frequently in improved progression-free survival and infrequently in improved overall survival. In the adjuvant setting, taxanes resulted overall in improved disease-free and overall survival at a hazard ratio of 0.86 (95% CI 0.82 to 0.90) and 0.85 (95% CI 0.79 to 0.91), respectively.

Only one (adjuvant) paclitaxel study used weekly paclitaxel[74], the others used 3-weekly paclitaxel. This is highly unfortunate, because 3-weekly paclitaxel is nowadays considered to be an inferior schedule for paclitaxel. In contrast, all docetaxel studies were performed with 3-weekly docetaxel, which is the most optimal docetaxel schedule.

In the majority of advanced breast cancer studies, taxanes were used instead of other cytotoxic drugs (substitution of adriamycine, cyclophosphamide and/or 5-fluorouracil). In early breast cancer studies, taxanes were either added to an anthracycline concurrently or in sequence, or substituting another cytotoxic drug.

As comparators, both in the early and in the adjuvant setting, anthracycline as single agent, or in combination with cyclophosphamide (doublet) or in combination with 5-fluorouracil and cyclophosphamide (triplet) were used.

In order to better understand which taxane-containing regimens are truly beneficial, we categorized most studies per type of taxane (docetaxel or paclitaxel), per strategy (concurrent or sequential addition, or substitution), and per comparator (single-agent anthracycline, anthracycline-cyclophosphamide, or 5-flourouracil-anthracycline-cyclophosphamide or equivalent regimen).

Taxanes, administered as optimally dosed single-agents (docetaxel 100 mg/m^2) in advanced breast cancer, are at least as effective as single-agent standard-dosed anthracyclines (75 mg/m^2), considering the improved response rate.[33] The higher efficacy of docetaxel compared with standard-dosed anthracyclines is confirmed in the adjuvant setting, where Jones *et al.*[78] proved that docetaxel-cyclophosphamide resulted in an overall survival benefit after 7 years of follow-up, as compared with

anthracycline-cyclophosphamide. The development of a non-anthracycline regimen is attractive, also in patients not having a contra-indication for anthracyclines, because anthracyclines are associated with cardiac toxicity and leukemia, that may occur even many years after treatment. Therefore, it would be of relevance to know whether taxane-cyclophosphamide is as effective as TAC, provided the number of cycles administered is sufficient. Data from the trial comparing six cycles of TC versus six cycles of TAC are awaited. In the Netherlands, taxane-cyclophosphamide (TC) is used if there is a contra-indication for anthracyclines, for instance because of prior use of anthracyclines for another primary breast tumor.

It is important to realize that where docetaxel, when substituting adriamycine, improved overall survival in the adjuvant setting, it did not do so in the advanced disease setting. Apparently, cross-over between treatment arms in metastatic trials masks survival effects, which was also seen in the ECOG E1193 study.[34] This is extremely important to account for when interpreting the available data in the advanced setting. Studies should preferable correct for cross-over, and thus collect treatment information after end of study treatment. Or, effects on response rates and progression-free survival may in future be used as a surrogate for overall survival effects, in line with FDA approval for progression-free survival as a surrogate endpoint in advanced colorectal cancer studies.

Anthracycline-taxane doublets seem to be at least as effective compared to the anthracycline-cyclophosphamide combination regimens in the advanced setting (hazard ratio of overall survival of 1.03, not significant; though with an improved response rate). However, when excluding the studies using inferior 3-weekly paclitaxel schedule, it is shown that anthracycline-docetaxel is slightly more effective than anthracycline-cyclophosphamide. Remarkably, the anthracycline-taxane combination leads to a significant improvement of overall survival in the advanced disease setting of about 5 to 6 months, when compared with the triplet 5-fluorouracil-adriamycine-cyclophosphamide (FAC) (hazard ratio of 0.70, 95% CI), whereas the anthracycline-taxane combination does not lead to an improvement of overall survival when compared with the doublet AC. This differential effect may be due to the fact that the dose of the separate drugs in FAC triplet regimen is lower than in doublet therapy, in order to reduce toxicity. This suggests that triplets, given at reduced doses

per drug, may actually be less effective than adequately dosed doublets. Indeed, studies in the adjuvant setting confirm the comparable efficacy of anthracycline-docetaxel doublet and anthracycline-cyclophosphamide doublet. Moreover, studies in the adjuvant setting show that once the control arm FEC is delivered at increased dose (compared with FAC schedules that were used in advanced disease; note: A60 is equivalent to E90 or A50 is equivalent to E75), anthracycline-docetaxel is not superior to FEC.[73,82]

The anthracycline-docetaxel combination as first-line metastatic breast cancer is registered in Europe, but not by the FDA. Considering costs and toxicities there is, however, in our opinion, generally no reason to substitute cyclophosphamide by a taxane in advanced and adjuvant setting, in the established AC combination. It is concluded that cyclophosphamide is also an active drug in breast cancer.

Several studies evaluated whether replacing 5-fluorouracil by docetaxel in the triplet FAC would impact efficacy. Compared with FAC in the advanced disease setting, TAC showed higher response rates, although with equivalent progression-free and overall survival rates. But, again, this lack of impact on survival in advanced breast cancer is possibly due to cross-over to taxanes in further lines of treatment. Indeed, in early breast cancer TAC significantly improved disease-free survival at a hazard ratio of 0.70 (95% CI 0.59 to 0.84) compared with FAC. Based on the TAC versus FAC studies it may be concluded that TAC has superior efficacy. Since 'AC' in TAC and in FAC was delivered at the same doses, it can be concluded that docetaxel 75 mg/m^2 is superior to 5-fluorouracil 500 mg/m^2, at least in the TAC combination.

In early breast cancer, many studies focused on assessing the impact of taxanes when delivered in sequence to anthracyclines and/or cyclophosphamide with or without 5-flourouracil. When comparing the sequential regimen of 3-weekly AC-paclitaxel with Canadian CEF, the Canadian CEF showed superior efficacy. When comparing with dose-dense EC followed by 3-weekly paclitaxel, Canadian CEF showed comparable efficacy, and also comparable effectiveness to EC-docetaxel. In other words, an intensified anthracycline regimen is equally effective as an optimally delivered sequential AC – taxane regimen. However, an intensified anthracycline regimen, like Canadian CEF, is associated with increased risks for long term toxicities, like

cardiotoxicity and leukemia. For that reason, most physicians prefer a taxane containing regimen.

When excluding the studies in which the dose-intensified triplet Canadian CEF was used as comparator, sequential use of taxanes after or before an anthracycline-containing regimen resulted in an improved disease-free survival at a hazard ratio of 0.84 (0.79 to 0.98) and also in improved overall survival at a hazard ratio of 0.82 (95% 0.75-0.90). Apparently, a strategy in which an additional cytotoxic drug is added at full dose by giving it sequentially instead of replacing another cytotoxic drug with dose reductions of all drugs, is very effective. Apart from full-dose, the higher number of cycles could have contributed to the increased efficacy of sequential regimens. Indeed, sequentially adding a taxane to a single-agent anthracycline showed superiority compared with single-agent anthracycline in advanced and early breast cancer.[34,64] When adding an optimally dosed taxane sequentially to doublet therapy, again this showed superiority.[65,66] Even though one trial in early breast cancer[69] and one trial in advanced breast cancer[60] did not show an improvement of sequentially adding a taxane to doublet therapy, that may be due to the fact that the sequentially added taxane was not optimally dosed (both inferior 3-weekly paclitaxel schedules). The addition of an optimally dosed taxane in sequence of triplet therapy, in part replacing the triplet, also improves efficacy compared to the triplet alone: for disease-free survival at a hazard ratio of 0.85 (95% CI 0.78 to 0.92) and for overall survival at a hazard ratio of 0.77 (95% CI 0.66-0.90).

No studies were found that examined TAC versus AC in advanced or early breast cancer. We hypothesised that AC → T in fact could even be better than a taxane based triplet (TAC). That is based on the results that AC → T is better than the doublet AC and because we showed that optimal dosed cytotoxic drugs are essential for efficacy, what is based on the indirect observation that AC (optimally dosed doublet) is even better that FAC. That suggests that triplets, given at reduced doses per drug, may actually be less effective than adequately dosed doublets. Recently, study results were presented on the direct comparison of AC-T and TAC in early breast cancer[65,85,86] These studies compared adriamycine with or without cyclophosphamide and followed by docetaxel versus triplet docetaxel-adriamycine-cyclophosphamide or doublet adriamycine-docetaxel. Sequential treatment seemed to be slightly superior in terms

of disease-free survival in three of four studies. However, in three studies the comparator consisted of only four cycles whereas the experimental arm consisted of six or eight cycles. In the study where the comparator arm was continued for six cycles, no differences in disease-free survival rates were seen compared to sequential treatment. So, although there is a trend for improved outcome for a sequential approach, this may also be due to differences in treatment duration. Further research on this issue is certainly needed.
From the point of view that triplets cannot be optimally dosed, one might prefer doublets, e.g. two doublets in sequence as was done in a Finnish trial.

Most important side effect associated with taxanes are neutropenia and associated febrile neutropenia, which is more common with docetaxel than with paclitaxel. However, in most trials in advanced breast cancer, no primary G-CSF prophylaxis was used, which is now considered standard of care with several taxane-schedules. Furthermore, allergic reactions and fluid retention are seen with the administration of taxanes, but manageable with pre-medication in the form of corticosteroids. Neurotoxicity is more common with weekly paclitaxel than with docetaxel.
There seems to be no difference in quality of life with taxane compared with non-taxane chemotherapy, at the end of treatment. Both taxanes should be administered intravenously, as is the case for all comparator regimens.

Again, costs of treatment with taxanes are a relevant matter to determine effectiveness of treatment with taxanes. Based on the cost-effectiveness analyses on taxanes in early and advanced breast cancer, we can conclude that taxanes are a cost-effective strategy. The additional costs associated with taxanes are mainly based on costs of G-CSF prophylaxes and costs of the drug itself. However, some of these analyses used comparative regimens that are not licensed registrations and can not be considered as standard of care. Furthermore, as it is seen with the cost-effectiveness analyses of trastuzumab, it is difficult to combine the various ICERs on taxanes in advanced breast cancer.

In summary, we conclude that the use of docetaxel and paclitaxel in early and advanced breast cancer is effective provided the optimal dose and schedule is given. An important lesson to learn is that whereas taxanes did not improve overall survival in advanced breast cancer studies, taxanes did so in the adjuvant studies. Cross-over to the experimental drug seems to explain this finding, and thorough appreciation of this observation is of pivotal importance in drug development and approval procedures.

The available data at the moment cannot support a claim for any single regimen, although it is concluded that incorporation of cyclophosphamide in a taxane containing regimen may also be of relevance.

An intensified anthracycline regimen is equally effective as an optimally delivered taxane regimen, but at the cost of more long term toxicity and for that reason not to be recommended.

There is a suggestion that a sequential approach in early breast cancer may be a preferred strategy, but more data are awaited for before robust recommendations on this issue can be made.

Because taxanes can be considered cost-effective, the effectiveness of taxanes in breast cancer treatment is not a question of research. As with trastuzumab, further research with respect to identifying subgroups who benefit the most, needs to be done, as well as identifying what schedule of taxanes is most beneficial.

7. Future research

There are still several aspects on the use of trastuzumab that remain unclear. An important question regards the use of trastuzumab beyond progression. With scarce evidence on efficacy as presented in this review and very high costs associated with this treatment strategy, the need for evidence of this strategy is urgent. As stated earlier, the need for 'real life' costs and efficacy are needed to determine the effectiveness of trastuzumab in daily practice.

We become increasingly aware that the biological variables amongst breast cancer patients are different, which urges the need to better define a subgroup of patients who will benefit from trastuzumab and taxanes in treatment of early and advanced breast cancer. The future should focus on defining these subgroups, based on translational oncology, instead of treating patients empirically with subsequent lines of chemotherapy that are tested in trials with selected patients and may not be representative of the patients in real life.

In the future, a possible approach could be, that in the first years after implementation of a new drug physicians are encouraged to collect frozen tissue of metastatic sites for translational research, for instance by giving a 'bonus'. Institutes like ZonMw could stimulate researchers to apply for grants using these tissues for translational research, offset against efficacy in daily practice. Also the pharmaceutical company could contribute to such a programme (perhaps even not only on a voluntary basis?). But, of course, this is a complete change in paradigm, and would therefore take some time before implemented. But, in our view certainly worthwhile to consider.

Further, the need to establish whether sequential therapy produces the same efficacy as combined therapy is important. We found that in advanced breast cancer doublet therapy with anthracycline-taxanes are more or less equally active as the doublet anthracycline-cyclophosphamide, but more effective than triplet therapy with FAC, implying that the lower dose of chemotherapeutic agents used in the triplet combination therapy may decrease efficacy of these agents. Similarly, in the early breast cancer setting sequential use of taxanes seems also to have a favorable efficacy and toxicity profile. Further research on schedules is considered important to improve therapeutic range of available drugs.

All these questions are leading to new and ongoing clinical trials, whose results are awaited. When searching the register of clinicaltrials.gov, we found 137 open clinical

trials associated with trastuzumab in breast cancer. These trials include new treatment strategies in adjuvant treatment as well as trastuzumab combined and or compared with new anti-HER2 therapies. Also searching for open trials with the taxanes reveals hundreds of different trials in breast cancer treatment.

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Appendices

A. Registered indications of trastuzumab in the treatment of breast cancer

Registration Europe **(EMA)**	Registration U.S. **(FDA)**	Registration trial
as monotherapy for the treatment of patients who have received at least two chemotherapy regimens for their HER2 positive metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments (2000).	as monotherapy for treatment of patients with HER2 positive metastatic breast cancer and who have received one or more chemotherapy regimens for their metastatic disease (1998).	H0649g, Vogel
-	-	
in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their HER2 positive metastatic disease and for whom an anthracycline is not suitable (2000).	in combination with paclitaxel is indicated for treatment of patients with HER2 positive metastatic breast cancer and who have not received chemotherapy for their metastatic disease (1998).	H0648g
in combination with docetaxel for the treatment of those patients with HER2 positive metastatic breast cancer, who have not received chemotherapy for their metastatic disease (2004).	not registered	M77001
for the treatment of patients with HER2 positive early breast cancer following surgery, chemotherapy (neo-adjuvant or adjuvant) and radiotherapy (if applicable) (2006).	for the adjuvant treatment of HER2 positive, node positive or node negative (ER/PR negative or with one high risk feature) breast cancer: -As part of the treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel (2006). -As part of the treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel (2008). -In combination with docetaxel and carboplatin (2008). -As single-agent following multi-modality anthracycline based therapy (2008).	HERA-trial, joint analysis of NSABP B31 and NCCTG N9831, BCIRG 006
in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive, HER2 positive metastatic breast cancer, not previously treated with trastuzumab (2007).	not registered	TANDEM-trial

B. Registered indications of taxanes in the treatment of breast cancer

Registration Europe **(EMA)**	Registration U.S. **(FDA)**	Registration trial
for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic therapy. Previous chemotherapy should have included an anthracycline or an alkylating agent: - paclitaxel monotherapy (1994) -docetaxel monotherapy (1995)	for treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease -paclitaxel monotherapy (1997) -docetaxel monotherapy (1996)	TAX 303, EORTC 10923
Docetaxel and paclitaxel in combination with doxorubicin for the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition (2000)	not registered	E1193, TAX 306
for the treatment of those patients with HER2 positive metastatic breast cancer, who have not received chemotherapy for and for whom an anthracycline is not suitable: -paclitaxel in combination with trastuzumab (2000) -docetaxel in combination with trastuzumab (2004).	for the treatment of patients with HER2 positive metastatic breast cancer who have not received chemotherapy for their metastatic disease: -paclitaxel in combination with trastuzumab (1998)	H06499, M77001
Docetaxel in combination with capecitabine for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline (2003).	Docetaxel in combination with capecitabine for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline (2001).	O'Shaughnessy
Paclitaxel, in combination with gemcitabine is indicated for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neo-adjuvant chemotherapy. Prior chemotherapy should have included an anthracycline (2004)	Paclitaxel, in combination with gemcitabine is indicated for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neo-adjuvant chemotherapy. Prior chemotherapy should have included an anthracycline (2004)	Albain
Docetaxel in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node- positive breast cancer (2005)	Docetaxel in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node- positive breast cancer (2004)	BCIRG 001/TAX316
paclitaxel is indicated for the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy (2005)	paclitaxel is indicated for the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy (1999)	CALGB 9344

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Training / Education (including graduation)

1976-1982:	Secondary school at Gymnasium-B, St. Michiel Scholengemeenschap in Geleen, The Netherlands. Final examination June 1982: cum laude.
1982-1989:	Medical study at Radboud University Nijmegen, The Netherlands
1983:	Propedeuse examination, Radboud University Nijmegen, cum laude.
1986:	Master of Science in medicine, Radboud University Nijmegen, cum laude.
1989:	M.D. examination, Radboud University Nijmegen, cum laude.
1989-1993:	Resident internal medicine at Jeroen Bosch Ziekenhuis (Groot Ziekengasthuis), 's Hertogenbosch, The Netherlands (head: Dr. J.L.J. Janssen, thereafter Dr. J.Th.M. Burghouts)
1993-1996:	Resident internal medicine at the Radboud University Nijmegen (head: Prof. Dr. J. van der Meer)
2/1996:	Registration as specialist in internal medicine (re-registration till February 2011)
1996-1997:	Fellow Medical Oncology, department of Medical Oncology, Radboud University Nijmegen, The Netherlands (head: Prof. Dr. D.J.Th. Wagener)
7/1997:	Registration as medical oncologist
10/2002:	PhD. Thesis: Dose and dose-intensity of chemotherapy, studies in small cell lung cancer. Promotores: Prof. Dr. D.J.Th. Wagener, medical oncologist, Radboud University Nijmegen, prof. Dr. P.E. Postmus, pulmonologist VUmc Amsterdam; co-promotor: Dr. J.Th.M. Burghouts, medical oncologist, Jeroen Bosch Hospital, 's

Hertogenbosch, the Netherlands.

Management course

2003-2004: Radboud Course Integrated Management (RLIM, 550 hrs in 15 months, Management certificate: 8 October 2004), Nijmegen, the Netherlands

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Professional appointments

Employment history and functions
Licenses and certifications

3/1997-1/9/2006	Staff member at the Dept. Medical Oncology of Radboud University Nijmegen Medical Centre, Nijmegen, Head Prof. dr. DJTh Wagener till September 2000. Head prof. dr. PHM De Mulder since September 2000
3/2003-1/9/2006	Senior Chef de Clinique department Medical Oncology RUNmc, Nijmegen
1/8/2005-1/9/2006	Associate professor on systemic treatment of breast cancer, RUN, Nijmegen, the Netherlands
1/9/2006-present:	Professor Medical Oncology and Head Division Medical Oncology at dept. Internal Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands
1/1/2008-present	Chair multidisciplinary Oncology Committee Maastricht UMC

Awards:

- Tjan-Heijnen VCG et al. For the EORTC Lung Cancer Group. Reduction of chemotherapy-induced febrile leucopenia by prophylactic use of ciprofloxacin and roxithromycin in small cell lung cancer patients: An EORTC double-blind placebo-controlled phase III study. Ann Oncol 12: 1359- 1368, 2001 (Awarded for the *Annals of Oncology Prize* for Phase III studies)
- Thesis of PhD student mrs. dr. P. Manders: awarded as the best NVMO (Netherlands Society of Medical Oncology) thesis of 2004
- Thesis of PhD student mrs. dr. A. Timmer-Bonte: awarded as the best NVMO thesis of 2008 (October 2008) and also awarded by the Vera Bonta Prize (16th January 2009)
- Thesis of PhD student mrs. dr. C. vanDeurzen: awarded as the best NVMO thesis of 2009
- November 2009: elected for 'Best Doctors' Netherlands in the field of Breast Cancer

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Main research themes

Professor dr. Vivianne Tjan-Heijnen (46 years) is head of the division Medical Oncology at the Maastricht University Medical Centre, Maastricht, the Netherlands. Since April 2008 she is the chair of the National Breast Cancer Organization of the Netherlands (NABON), and active member of the Dutch Breast Cancer Research Group (BOOG). The NABON updates the national breast cancer guidelines every other year. Further, she is chair of the committee BOM (committee for the Assessment of Oncological Drugs), a working party of the Netherlands Society of Medical Oncology (NVMO). This committee advises the medical oncologist in the field regarding implementation of new oncological drugs.
Her research focuses on breast cancer and more specifically on health economic issues, guideline development and implementation, and prognostic and predictive studies. She has obtained various grants for large projects on health economic issues: EORTC 08923; OG-99053; VAZ DO-01122; VAZ DO 2001/2/5; ZonMw 945-06-509, ZonMw 80-82310-98-08006 and ZonMw 80-82500-98-9056. In total, about 3 million euro's from competetive funding have been received as principal project leader. Five studies have recently successfully been closed and final analyses are completed or underway. The EORTC 08923, OG-99053 and ZonMw 80-82310-98-08006 concern studies on cost-effectiveness of antibiotics and G-CSF prophylaxis. In the VAZ-DO 2001-2/05 project a device - instrument was developed for the modelling assessment of the generic effect (medical, economical, quality of life) of follow-up in cancer patients treated with curative intention. The VAZ DO-01122 concerned the role of completion axillary lymph node dissection after the sentinel lymph node (SN) procedure. The ZonMw 945-06-509 concerned the impact of micro metastasis and isolated tumour cells, detected by the SN procedure, on use of adjuvant systemic therapy and on survival. Recently, the main results from the ZonMw MIRROR study were published in the N Engl J Med (de Boer et al, NEJM 13th August 2009). Two recent systematic reviews on micro metastases were both published in the high-ranking Journal of the National Cancer Institute. In 2008 and 2009 two (ZonMw) registry studies were initiated regarding the cost-effectiveness of bevacizumab and adjuvant trastzumab in breast cancer. From about 3,500 patients all diagnostic tests and delivered therapies will be colleced. Currently, 15 PhD students are supervised on breast cancer projects.

List of selected publications

1. Tjan-Heijnen VCG, Postmus PE, Ardizzoni A, Manegold C, Burghouts J, van Meerbeeck J, Gans S, Mollers M, Buchholz E, Biesma B, Legrand C, Debruyne C, Giaccone G, for the European Organisation for Research and Treatment of Cancer – Lung Cancer Group. Reduction of chemotherapy-induced febrile leucopenia by prophylactic use of ciprofloxacin and roxithromycin in small cell lung cancer patients: An EORTC double-blind placebo-controlled phase III study. Ann Oncol 12: 1359-1368, 2001 (Awarded for the *Annals of Oncology Prize* for Phase III studies) (IF 4,935)
2. Ardizzoni A, Tjan-Heijnen VCG, Postmus PE, Buchholz E, Biesma B, Karnicka-Mlodkowska H, Dziadziuszko R, Burghouts J, van Meerbeck JP, Gans S, Legrand C, Debruyne Ch, Giaccone G,

Maneogold C for the EORTC-LCG. Standard versus intensified chemotherapy with G-CSF support in small cell lung cancer patients: A prospective EORTC LCG phase III trial (08923). J Clin Oncol 20: 3947-3955, 2002 (IF 17,157)

3. Tjan-Heijnen VCG, Caleo S, Postmus PE, Ardizzoni A, Burghouts JThM, Buccholz E, Biesma B, Giaccone G, Gorlia T, Crot R, Debruyne Ch, Manegold Ch, for the European Organisation for Reasearch and Treatment of Cancer – Lung Cancer Group and Health Economics Unit. Economic evaluation of antibiotic prophylaxis in small cell lung cancer patients receiving chemotherapy: An EORTC double-blind placebo-controlled phase III study. Ann Oncol 14: 248-257, 2003 (IF 4,935)
4. Kievit W, Bolster MJ, Adang EMM, van der Wilt GJ, Bult P, Thunnissen FBJM, Meijer J, Strobbe LJA, Klinkenbijl JHG, Wobbes Th, Adang EMM, Beex LVAM, Tjan-Heijnen VCG. The cost-effectiveness of new guidelines for adjuvant systemic therapy for patients with primary breast cancer. Ann Oncol, 16:1874-1881, 2005 (IF 4,935)
5. Timmer-Bonte JN, de Boo ThM, Smit HJ, Biesma B, Wilschut FA, Cheragwandi SA, Termeer A, Hensing CA, Akkermans J, Bootsma GP, Tjan-Heijnen VCG. Prevention of chemotherapy-induced febrile neutropenia by prophylactic antibiotics plus or minus granulocyte-colony stimulating factor: a Dutch randomized phase III study. J Clin Oncol, 23: 7974-7984, 2005 (IF 17,157)
6. Timmer-Bonte JNH, Adang EMM, Smit HJM, Biesma B, Wilschut FA, Bootsma GP, de Boo Th, Tjan-Heijnen VCG. Cost-effectiveness of adding granulocyte-colony stimulating factor to primary prophylaxis with antibiotics in patients with small cell lung cancer. J Clin Oncol 24: 2991-7, 2006 (IF 17,157)
7. Aapro MS, Cameron DA, Pettengell R, Bohlius J, Crawford J, Ellis M, Kearney N, Lyman GH, Tjan-Heijnen VC, Walewski J, Weber DC, Zielinski; the EORTC G-CSF Guidelines Taskforce. EORTC Guidelines for the use of Granulocyte Colony-Stimulating Factor in Adult Patients with Chemotherapy-Induced Febrile Neutropenia. Eur J Cancer, 42: 2433-53, 2006 (IF 4,475)
8. Bolster MJ, Bult P, Thunnissen FBJM, Schapers RFM, Meijer JWR, Strobbe LJA, van Berlo CLH, Klinkenbijl JHG, Peer PGM, Wobbes Th, Tjan-Heijnen VCG. Differences in sentinel lymph node pathology protocols lead to differences in surgical strategy in breast cancer patients. Ann Surg Oncol 13:1466-73, 2006 (IF 3,898)
9. Timmer-Bonte JNH, Adang EMM, Termeer E, de Boo Th, Severens, H Tjan-Heijnen VCG. Modeling cost-effectiveness of secondary prophylaxis with antibiotics and G-CSF in patients with small cell lung cancer. J Clin Onc 2008: 26: 290-296, 2008 (IF 17,157)
10. Ho VKY, van der Heiden-van der Loo M, Rutgers, EJTh, van Diest PJ, Hobbelink MCG, Tjan-Heijnen VCG, Dirx MJM, Reedijk AM, van Dijck JAAM, Janssen-Heijnen MLG, Schaapveld M, Peeters PHM. Implementation of Sentinel Node Biopsy in Breast Cancer in The Netherlands. Eur J Cancer, 44: 683-691, 2008 (IF 4,454)
11. van Deurzen CHM, de Boer M, van der Wall E, Bult P, Tjan-Heijnen VCG, van Diest P. Frequency of non-sentinel lymph node metastases in breast cancer patients with isolated tumor cells in the sentinel node: a systematic review. J Natl Cancer Instit 100(22):1574-80, 2008 (IF 14,933)
12. de Boer M, van Deurzen CH, van Dijck JA, Borm GF, van Diest PJ, Adang EM, Nortier JW, Rutgers EJ, Seynaeve C, Menke-Pluymers MB, Bult P, Tjan-Heijnen VC. Micrometastases or isolated tumor cells and the outcome of breast cancer. New Engl J Med;361, 653-663, 2009 (IF 50.02)
13. Bolster MJ, Bult P, Wauters CA, Strobbe LJ, Peer PG, Wobbes T, Tjan-Heijnen VC. More tumor-affected lymph nodes because of the sentinel lymph node procedure but no stage migration, because the 2002 TNM classifies small tumor deposits as pathologic N0 breast cancer. Cancer 115:5589-95, 2009 (IF 5,238)
14. Ruiterkamp J, Voogd AC, Bosscha K, Tjan-Heijnen VCG, Ernst MF. Impact of breast surgery on survival in patients with distant metastases at initial presentation. Breast Cancer Res Treatm 120:9-16, 2010. (IF 5,684)
15. de Boer M, van Dijck JAAM, Bult P, Borm GF, Tjan-Heijnen VCG. Breast cancer prognosis and occult lymph node metastases, isolated tumor cells, and micrometastases. J Natl Cancer Inst 102:410-425, 2010 (IF 14,933)

Conflict of interest: research grants from Sanofi Aventis en Roche.

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Main research interests

Manuela Joore, PhD, is associate professor at the Maastricht University Medical Centre's department of 'Clinical Epidemiology and Medical Technology Assessment' as well as honorary lecturer at Maastricht University's department of 'Health Organization Policy and Economics'. In addition, she is a member of the committee 'Expensive Medicines and Orphan Drugs' of the Netherlands Organization of Health Research and Development (ZONMw), and of the committee 'Proton therapy' (advisory board for the reimbursement of proton therapy) of the Dutch Health Care Insurance Board (CVZ). She is course leader of the module 'Cost-effectiveness modelling methods' in the Master of Philosophy in Health Sciences Research of Maastricht University. Furthermore, she is advisor to the Maastricht Radiation Oncology Clinic. Manuela holds a Ph.D. in Economics and a M.Sc. in health sciences / epidemiology, both from Maastricht University, the Netherlands.

Manuela's research focus is on health economic evaluation. She has over 10 years of experience in conducting both trial-based and model-based economic evaluations, most of which have been funded by the "Health Care Efficiency Research Programme" of ZonMw, covering several clinical areas such as Oncology, Cardiology, Radiology, Urology and Audiology. In 2007, 2008 and twice in 2009 she was awarded methodological research grants by the Dutch Organization for Health Research and Development. This methodological research focuses on the measurement of the outcomes of health care and conducting economic evaluations. Besides this she received research grants from several pharmaceutical companies, the Dutch Hearing Council, and ZONMw. Currently, she is the co-supervisor of 8 PhD students. She has authored over 40 peer-reviewed journal articles, with publications in *Value in Health, Pharmacoeconomics, the Annals of Internal Medicine, Thorax, Medical Care* and *Cancer Treatment Review*.

Working experience

Associate Professor (2010 - present)	Department of Clinical Epidemiology and Medical Technology Assessment, University Hospital Maastricht
Senior researcher (2005 – 2010)	Department of Clinical Epidemiology and Medical Technology Assessment, University Hospital Maastricht
Lecturer (honorary position) (2005 - present)	Department of Health, Organisation, Policy and Economics, Maastricht University
Post-doc Researcher (2002 - 2005)	Department of Clinical Epidemiology and Medical Technology Assessment, University Hospital Maastricht
Junior Researcher (1998 - 2002)	Department of Clinical Epidemiology and Medical Technology Assessment, University Hospital Maastricht
Junior Researcher (1996 - 1998)	Department of Urology, University Hospital Maastricht

Education

Ph.D. in Economics (2002)	*Maastricht University* Chair: Prof. Hans Peters PhD, Department of Quantitative Economics, Maastricht University
Epidemiologist (2000)	*Maastricht University*
M.Sc. in Health Sciences (1996)	*Maastricht University* Major 1: Health Policy, Economics and Management Major 2: Epidemiology Chair: Prof. Reiner Leidl PhD, Department of Health Economics, Maastricht University

Relevant publications and teaching experience to the review of trastuzumab in early breast cancer

Selected publications

- Retèl VP, Joore MA, Knauer M, Linn SC, Hauptman M, van Harten WH. Cost-effectiveness of the 70-gene prognosis signature for node-negative breast cancer patients. European Journal of Cancer 2010. (Impact factor 4.475)
- Essers, B, Seferina S, Tjan-Heijnen V, Oron U, Pompen M, Novak A, Severens J, Joore M. Transferability of model-based economic evaluations: the case of trastuzumab for the adjuvant treatment of HER2-positive early breast cancer in the Netherlands. Value in Health 2010 15 January. (Impact factor: 3.009)
- Grutters JPC, Kessels AGH, Pijls-Johannesma M, De Ruysscher D, Joore MA / Lambin Ph. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for stage I to III non-small cell lung cancer: a meta-analysis. Radiotherapy and Oncology 2009. doi:10.1016/j.radonc.2009.08.003 (Impact factor 3.990)
- Retel V, Rutgers E, Joore M, van Harten W. Establishing of cost-effectiveness of genetic targeting of cancer therapies. European Journal of Hospital Pharmacy. 2008; 6: 52-54.
- Willems D.C.M., Joore M.A., Hendriks H., Wouters E.M., Severens J.L. Costs and cost-effectiveness of self-management in asthmatics based on peak-flow monitoring interventions: a literature review. International Journal of Technology Assessment in Health Care 2006 Fall;22(4):436-42. (Impact factor: 1.439)

Adri Voogd

Surname: Voogd
First names: Adrianus Cornelis
Date of birth: 4 mei 1968
Place of birth: The Hague
Gender: man
Nationality: Dutch

EDUCATION:

- Gymnasium ß, R.K. Scholengemeenschap 'Serviam' in Sittard, The Netherlands (graduated in 1986).

- Health Sciences (currently Biomedical Health Sciences) with a specialization in epidemiology, Medical Faculty, Catholic University Nijmegen, The Netherlands (graduated in 1991).

- PhD thesis, entitled: “Breast-conserving treatment of operable mammary cancer: evaluation of patient selection and treatment outcome”. Promotores: prof. dr. J.A. van Dongen (professor of surgical oncology) and prof. dr. G.M.M. Bartelink (professor of experimental radiotherapy). Co-promotor: dr. J.W.W. Coebergh. PhD obtained at the Medical Faculty of the University of Amsterdam on June 30, 1998 in Amsterdam, The Netherlands.

EMPLOYMENT:

March 2002 – now: Department of Epidemiology, Maastricht University, Maastricht, The Netherlands.

Position:
Assistant professor of Clinical Epidemiology, Faculty of Health, Medicine and Life Sciences.

December 1992 – March 2002: Comprehensive Cancer Centre South, Eindhoven Cancer Registry, Eindhoven, The Netherlands.

Positions:
- *Junior researcher (December 1992 – January 1998)*
- *Senior researcher quality of (oncological) care (January 1998- March 2002).*

MEMBERSHIPS AND BOARDS:

- Member of the Dutch Epidemiology Society (1992 - now)
- Member of Dutch Working Group (NABON) for the development of guidelines for breast cancer screening, diagnosis and treatment (January 2002 - now);
- Member of the Medical Ethics Committee Atrium and Orbis Medical Centre, Heerlen-Sittard, The Netherlands- Zuyd (January 2003 - now)
- Member of the Editorial Board of the European Journal of Cancer (September 2005 - now)
- Member of the Working Group on Biomarkers of the Dutch Breast Cancer Research Group (BOOG) (January 2009 - now)

SELECTION OF PUBLICATIONS

Voogd AC, van Tienhoven G, Peterse JL, Crommelin MA, Rutgers EJTh, van de Velde CJH, van Geel AN, Rodrigus PTR, Jobsen JJ, von Meyenfeldt MF, Coebergh JWW for the Dutch Study Group on Local Recurrence after Breast Conservation. Local recurrence after breast conservation therapy for early stage breast carcinoma. Detection, treatment and outcome in 266 patients. *Cancer* 1999; 85:437-46.

Voogd AC, Peterse JL, Crommelin MA, Rutgers EJTh, Elkhuizen PHM, van Geel AN, Hoekstra CJM, van Pel R, van de Vijver MJ, Coebergh JWW and the Dutch Study Group on Local Recurrence after Breast Conservation. Histologic determinants for different types of local recurrence after breast-conserving therapy of invasive breast cancer. *Eur J Cancer* 1999; 35:1828-37.

van Dongen JA, Voogd AC, Fentiman IS, Legrand C, Sylvester RJ, Tong D, van der Schueren E, Helle PA, van Zijl K, Bartelink H. Long-term results of a randomised trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst* 2000; 92:1143-50.

Voogd AC, Coebergh JWW, Repelaer van Driel OJ, Roumen RMH, van Beek MWPM, Vreugdenhil A, Crommelin MA. The risk of nodal metastases in breast cancer patients with clinically negative lymph nodes: a population-based analysis. Breast Cancer Res Treat *2000; 62:63-9.*

de Boer R, Hillen HFP, Roumen RMH, Rutten HJT, van der Sangen MJC, Voogd AC. Detection, treatment and outcome of axillary recurrence after axillary clearance for invasive breast cancer. *Br J Surg* 2001; 88:118-22.

Voogd AC, Nielsen M, Peterse HL, Blichert-Toft M, Bartelink H, Overgaard M, van Tienhoven G, Andersen KW, Sylvester R, van Dongen JA, on behalf of the Danish Breast Cancer Co-operative Group and the Breast Cancer Co-operative Group of the European Organisation for Research and Treatment of Cancer. Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer:

pooled results of two large European randomised trials. *J Clin Oncol* 2001; 19:1688-97.

Baaten G, Voogd AC, Wagstaff J. A systematic review of the relation between interleukin-2 schedule and outcome in patients with metastatic renal cell cancer. *Eur J Cancer* 2004; 40:1127-44.

van der Leest M, Evers L, van der Sangen MJ, Poortmans PM, van de Poll-Franse LV, Vulto AJ, Nieuwenhuijzen GA, Brenninkmeijer SJ, Creemers GJ, Voogd AC. The safety of breast-conserving therapy in patients with breast cancer aged </=40 years.*Cancer* 2007; 109:1957-64.

Louwman WJ, Voogd AC, van Dijck JA, Nieuwenhuijzen GA, Ribot J, Pruijt JF, Coebergh JW. On the rising trends of incidence and prognosis for breast cancer patients diagnosed 1975-2004: a long-term population-based study in southeastern Netherlands. Cancer Causes Control 2008;19:97-106.

Ruiterkamp J, Voogd AC, Bosscha K, Tjan-Heijnen VC, Ernst MF. Impact of breast surgery on survival in patients with distant metastases at initial presentation: a systematic review of the literature. Breast Cancer Res Treat 2010;120:9-16. Review.

Other publications can be found in PubMed under “Voogd AC”[au]

Conflict of interest: participating in ZonMw study, co-sponsored by Roche

Curriculum Vitae

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Education

1998 - 2003	Medical School, Maastricht University Medical Centre, Maastricht, the Netherlands. Graduation 2003.
1994 - 1999	Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands. Graduation 1999.

Relevant work experience

As of oct 2009	Medical oncologist Dept. Internal Medicine/div. Medical Oncology, Maastricht University Medical Centre, Maastricht, the Netherlands.
2007 – 2009	Resident Internal Medicine, fellow medical oncology, Maastricht University Medical Centre, Maastricht, the Netherlands.
2003 - 2007	Resident Internal Medicine, Catharina-hospital, Eindhoven, the Netherlands

Research experience

2007 – present	PhD project: Sequential versus upfront intensified neoadjuvant chemotherapy in patients with large resectable or locally advanced breast cancer, the INTENS study. Supervisor: Prof. V.C.G. Tjan-Heijnen, MD, PhD. Maastricht University Medical Centre, Maastricht, the Netherlands.

Publications

CHM van Deurzen, BEPJ Vriens, VCG Tjan-Heijnen, E van der Wall, M Albregts, R van Hilligersberg, EM Monninkhof and PJ van Diest. Accuracy of sentinel node biopsy after neoadjuvant chemotherapy in breast cancer patients: A systematic review. Eur J Cancer 2009 Dec;45(18):3124-30.

Conflict of Interest

Unrestricted grant for INTENS study from Sanofi Aventis

Curriculum Vitae

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Education

1997-2003	Secondary school at van Maerlant Lyceum, Eindhoven, the Netherlands
2003 - 2009	Medical School, Maastricht University Medical Centre, Maastricht, the Netherlands. Graduation 2009.

Relevant work experience

2010-present	junior researcher at Maastricht University Medical Centre, Maastricht, the Netherlands in collaboration with Maxima Medisch Centrum, Eindhoven, the Netherlands
2009-2010	Resident Internal Medicine, Maxima Medisch Centrum, Veldhoven, the Netherlands

Research experience

2010 – present	PhD project: Better understanding of patterns of disease course in metastatic breast cancer, in relation to received therapy. Promotor: Prof. V.C.G. Tjan-Heijnen, MD, PhD. Maastricht University Medical Centre, Maastricht, the Netherlands.

Conflict of Interest

participating in ZonMw study, co-sponsored by Roche