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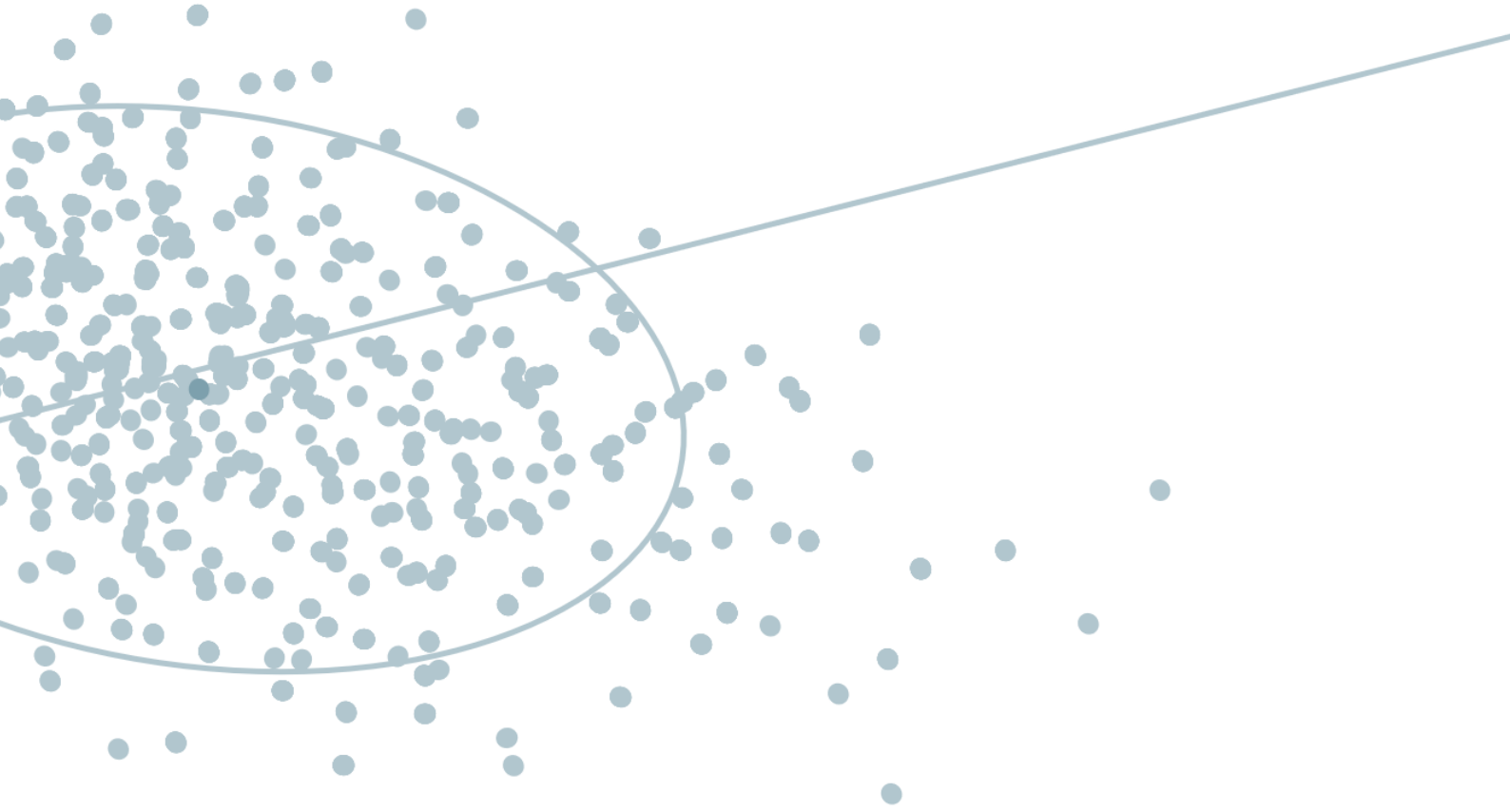
Health Technology Assessment (HTA)

**HTA Report**

# Treatment duration of trastuzumab in HER2-positive early breast cancer

16. May 2024



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| Title | Treatment duration of trastuzumab in HER2-positive early breast cancer |
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| Technology | Trastuzumab duration |
| Type of Technology | Pharmaceuticals |
| Date | 16.05.2024 |

**Conflict of Interest:**

The authors declare no conflict of interest.

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Cover image: Simplified representation of a fictional probabilistic sensitivity analysis on a cost-effectiveness plane with the diagonal willingness-to-pay line.

## Executive Summary

### *Background*

Breast cancer is the most common cancer in Swiss women. About 15-20% of women with breast cancers have an overexpression of the human epidermal growth factor receptor 2 (HER2), which is associated with uncontrolled cell growth. Inhibition of HER2 receptors can be the focus of targeted treatment. In Switzerland, the HER2-targeted pharmaceuticals trastuzumab and pertuzumab are approved for the treatment of HER2-positive early breast cancer, either starting before surgery (neoadjuvant) or after surgery (adjuvant). The present health technology assessment (HTA) addresses the question whether a reduced treatment duration of 6 months or less of trastuzumab or trastuzumab combined with pertuzumab is non-inferior in terms of clinical efficacy and has the potential of reducing adverse effects (AEs) and treatment costs compared with a treatment duration of 12 months.

### *Methods*

For the assessment of clinical efficacy and safety, a systematic review was conducted. Eligible studies were randomised controlled trials (RCTs) that compared a treatment duration of 6 months or less (≤6 months) of trastuzumab or trastuzumab combined with pertuzumab with a treatment duration of 12 months in HER2-positive early breast cancer. Non-inferiority meta-analyses were conducted for the outcomes of overall survival (OS) and disease-free survival (DFS). Furthermore, meta-analyses were conducted for AEs, and data was summarised narratively regarding the direction and size of any observed effects if pooling was not possible. The risk of bias was assessed based on the Cochrane risk of bias 2 tool. The certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, and summary statements were formulated according to GRADE guidance.

The economic assessment consisted of a systematic review of existing health economic evidence, the development of a *de novo* Markov model-based cost-effectiveness analysis and a budget impact analysis for Switzerland.

To address ethical, legal, social, and organisational issues relating to the different treatment durations, an exploratory literature search was conducted. The main issues identified were reported descriptively.

### *Results*

In the systematic review related to the clinical efficacy and safety, 6 RCTs with 11,603 women between 21 and 86 years of age – PHARE, E2198, HORG, Short-HER, SOLD, and PERSEPHONE – were included. The evaluated reduced durations for trastuzumab treatment were 6 months (3 RCTs), 12 weeks (1 RCT), and 9 weeks (2 RCTs). All RCTs evaluated trastuzumab treatment in the adjuvant setting. No RCTs were identified for different treatment durations for trastuzumab

and pertuzumab in combination. The primary findings of the assessment of clinical efficacy and safety were the following:

**Overall survival (OS)**: Considering a non-inferiority margin of HR 1.543 (corresponding to a 3% absolute difference for an assumed 5-year OS of 94.2%), OS with 6 months or less of trastuzumab treatment is likely non-inferior to 12 months of trastuzumab treatment (HR 1.13, 95% CI 0.99 to 1.28, p<0.0001 for non-inferiority, $I^2$ = 0%, 6 RCTs, 11,603 participants, moderate certainty of evidence).

**Disease-free survival (DFS)**: Considering a non-inferiority margin of HR 1.266 (corresponding to a 3% absolute difference for an assumed 5-year DFS of 87.7%), the evidence is inconclusive (i.e., inferiority cannot fully be ruled out) whether DFS with 6 months or less of trastuzumab treatment is non-inferior to 12 months of trastuzumab treatment (HR 1.14, 95% CI 0.98 to 1.32, p=0.22 for non-inferiority, $I^2$ = 37%, 6 RCTs, 11,603 participants, low certainty of evidence).

**Health-related quality of life (HRQoL)**: HRQoL with 6 months or less of trastuzumab treatment may be similar or higher compared with 12 months of trastuzumab treatment, but the evidence is very uncertain (1 RCT, 4,088 participants, very low certainty of evidence).

**Congestive heart failure**: The risk is likely lower with ≤6 vs. 12 months of trastuzumab treatment (RR 0.65, 95% CI 0.42 to 1.00, p=0.051, $I^2$ = 0%, 3 RCTs, 5,788 participants, moderate certainty of evidence).

**Left-ventricular ejection fraction (LVEF) <50% and LVEF decrease >10%**: The risk is likely lower with ≤6 vs. 12 months of trastuzumab treatment (RR 0.76, 95% CI 0.63 to 0.92, p=0.004, $I^2$ = 0%, 3 RCTs, 7,532 participants, moderate certainty of evidence).

**Any severe (grade ≥3) AE**: The risk may be lower with ≤6 vs. 12 months of trastuzumab treatment (RR 0.89, 95% CI 0.72 to 1.09, p=0.25, $I^2$ = 88%, 2 RCTs, 6,007 participants, low certainty of evidence).

**Trastuzumab discontinuation due to any AE**: The risk is likely lower with ≤6 vs. 12 months of trastuzumab treatment (RR 0.37, 95% CI 0.27 to 0.50, p<0.0001, $I^2$ = 61%, 3 RCTs, 6,807 participants, moderate certainty of evidence).

The findings of the assessment of clinical efficacy and safety for the comparison of 6 months compared with 12 months of trastuzumab treatment were overall similar to the results presented for the comparison of ≤6 months vs. 12 months of trastuzumab treatment, except that the evidence regarding congestive heart failure was considered very uncertain.

**All cost-effectiveness studies** identified in the systematic review reported that ≤6 months of trastuzumab treatment is less expensive than 12 months of treatment. The effects on quality-adjusted life-years (QALYs) were discordant, with 5 studies suggesting that ≤6 months of

trastuzumab led to more QALY gained, and 2 studies concluding that ≤6 months of trastuzumab led to less QALY gained than 12 months of trastuzumab.

The ***de novo* cost-effectiveness analysis** conducted for Switzerland suggested that 6 months of trastuzumab treatment resulted in lower costs (CHF -15,047 per patient) compared to 12 months of treatment. At the same time, 6 months of trastuzumab treatment led to a total decrease of 0.62 QALY per patient. Consequently, an incremental cost-effectiveness ratio (ICER) of CHF 24,242 saved per QALY lost was estimated. The results were in the lower-left quadrant of the cost-effectiveness plane. In this situation, low ICERs indicate that the amount of money saved per QALY lost is rather small. The probabilistic sensitivity analysis suggested that the results were highly uncertain: while most (57%) of the ICER results still indicated that 6 months led to lower costs but also to a decrease in QALYs (i.e., lower-left quadrant of the cost-effectiveness plane), a considerable proportion (43%) of the ICER results indicated that 6 months led to lower costs and to an increase in QALYs compared to 12 months trastuzumab (i.e., lower-right quadrant)

The **budget impact** analysis suggested that switching from 12 months to 6 months of trastuzumab treatment would lead to a decrease in total costs ranging between CHF 13.6 million in 2024 and CHF 14.1 million in 2028.

Regarding **ethical, legal, social and organisational issues (ELSO)**, there is very little literature in relation to the specific question of reducing the duration of cancer treatment. Application of the principles of biomedical ethics in a normative analysis reveals that shortening the course of trastuzumab is largely compatible with the principles of beneficence, nonmaleficence, and justice. No serious ELSO issues were found in the literature. A few ethical issues emerging from the analysis concern uncertainties with respect to non-inferiority in DFS, potential harms to a subset of patients, informing patients about these potential harms, and respecting patient's autonomy with regard to treatment choice.

***Conclusion***

OS with 6 months or less of trastuzumab treatment is likely non-inferior to 12 months of treatment, whereas the evidence for non-inferiority is inconclusive for DFS. While the evidence is very uncertain regarding HRQoL, the risk of cardiac AEs and trastuzumab discontinuation due to any AE is likely lower and the risk of any severe (grade ≥3) AEs may be lower with ≤6 months of treatment. The economic base case analysis suggested, that 6 months compared to 12 months of trastuzumab treatment leads to lower costs but also to a decrease in QALYs. However, the probabilistic sensitivity analyses revealed that results were highly uncertain (i.e., 6 months of treatment may also lead to an increase in QALYs). Due to a lack of evidence, the comparison of 6 months or less of adjuvant combination treatment with trastuzumab and pertuzumab compared to 12 months of combination treatment could not be assessed in this HTA.

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# Abbreviations and acronyms

| | |
|---|---|
| ADCC | Antibody-Dependent Cellular Cytotoxicity |
| AdViSHE | Assessment of the Validation Status of Health-Economic decision model |
| AE | Adverse Effect |
| AJCC | American Joint Commission on Cancer |
| CBA | Cost-Benefit Analysis |
| CENTRAL | Cochrane Central Register of Controlled Trials |
| CHEERS | Consolidated Health Economic Evaluation Reporting Standards |
| CHF | Swiss Francs |
| CI | Confidence Interval |
| cm | Centimeter |
| CrI | Credible Interval |
| CUA | Cost-Utility Analysis |
| DFS | Disease Free Survival |
| EBPI | Epidemiology, Biostatistics and Prevention Institute |
| ECOG | Eastern Cooperative Oncology Group |
| ECPM | Institute of Pharmaceutical Medicine |
| EMA | European Medicines Agency |
| ELSO | Ethical, Legal, Social and Organisational Issues |
| EQ-VAS | EuroQol Visual Analog Scale |
| ESMO | European Society for Medical Oncology |
| EUnetHTA | European Network for Health Technology Assessment |
| FDA | Food and Drug Administration |
| FOPH | Federal Office of Public Health |
| FSO | Federal Statistical Office |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| HER2 | Human Epidermal growth factor Receptor 2 |
| HORG | Hellenic Oncology Research Group |
| HR | Hazard Ratio |
| HRQoL | Health-Related Quality of Life |
| HTA | Health Technology Assessment |
| ICER | Incremental Cost-Effectiveness Ratio |
| INAHTA | International Network of Agencies for Health Technology Assessment |
| IQR | Inter-Quartile Range |
| ITT | Intention-To-Treat |
| kg | Kilogram |
| LVEF | Left-Ventricular Ejection Fraction |

| | |
|---|---|
| MD | Mean Difference |
| MeSH | Medical Subject Headings |
| mg | Milligram |
| NB | Nota Bene (= mark well) |
| NHSEED | National Health Service Economic Evaluation Database |
| NICE | National Institute for Health and Care Excellence |
| NKRS | National Agency for Cancer Registration |
| OS | Overall Survival |
| OR | Odds Ratio |
| PHARE | Protocol for Herceptin as Adjuvant therapy with Reduced Exposure |
| PICO | Population, Intervention, Comparator, Outcome |
| PP | Per-Protocol |
| PRISMA-P | Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols |
| QALY | Quality-Adjusted Life-Years |
| RCT | Randomised Controlled Trial |
| RoB | Risk of Bias |
| RR | Risk Ratio |
| SE | Standard Error |
| SMD | Standardised Mean Difference |
| SBCDB | Swiss Breast Center DataBase |
| SoF | Summary of Findings |
| TNM | Tumour-Node-Metastasis |
| UICC | Union for International Cancer Control |
| UK | United Kingdom |
| USA | United States of America |
| vs. | Versus |
| WHO | World Health Organisation |

## Objective of the HTA report

The objective of a health technology assessment (HTA) is to generate a focused assessment of various aspects of a health technology. The analytic methods applied to assess the value of using a health technology, their execution and the results are described. The analytical process is comparative, systematic, transparent and involves multiple stakeholders. The domains covered in a HTA report include clinical efficacy and safety, costs, cost-effectiveness and budget impact, ethical, legal, social and organisational issues. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.

# 1. Policy question and context

Each health technology assessment (HTA) topic entails a policy and a research question. In healthcare, a policy question is a request to regulate a reimbursement policy and is aimed at securing financing of health technologies. Such a request, related to a particular health technology, typically addresses an existing controversy around a technology. This HTA report addresses the following policy question brought forward by the applicant:

“Is ≤6 months non-inferior to 12 months adjuvant trastuzumab treatment in patients with HER2-positive early breast cancer?”

Trastuzumab is a treatment for human epidermal growth factor receptor 2 (HER2)-positive breast cancer approved by Swissmedic since 1999 in the metastatic setting.[1 2] Since 2006, treatment with trastuzumab is also approved for patients with early breast cancer until disease recurrence or for a total of 12 months, whichever occurs first. Trastuzumab has been approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) as an adjuvant therapy (2006) and by the EMA as a neoadjuvant therapy (2011) for patients with HER2-positive early breast cancer.[1 3] For HER2-positive early breast cancer, trastuzumab has been approved by Swissmedic in adjuvant and neoadjuvant treatment settings. The costs of trastuzumab are covered by the Swiss mandatory health insurance. In early breast cancer with high risk of recurrence, trastuzumab is also approved in combination with pertuzumab (another HER2-directed pharmaceutical).[2] In these patients, confirmation by the health insurance is a prerequisite for cost coverage of pertuzumab.

The aim of this HTA report is to evaluate available data on the question whether a reduced treatment duration of 6 months or less of trastuzumab or trastuzumab combined with pertuzumab is non-inferior in terms of clinical efficacy and has the potential of reducing adverse effects (AEs) and treatment costs, compared with a treatment duration of 12 months, in patients with HER2-positive early breast cancer. The findings of this assessment will support decision making regarding cost coverage by the mandatory health insurance in Switzerland.

# 2. Medical background

**Disease epidemiology**

Breast cancer is the most common type of cancer in Swiss women. Between 2013 and 2017 there was an average of 6,200 new cases per year. During the same period, breast cancer resulted in approximately 1,400 deaths per year.[3] A woman's risk of developing breast cancer and dying from breast cancer in her lifetime is 11.6% and 2.4%, respectively. More than 80% of the affected women survive for more than 5 years after diagnosis.[3]

**Disease aetiology**

One major driver of aggressive tumour development and metastasis in women with breast cancer is overexpression of the HER2 protein.[4] The HER2 protein is a protein that promotes breast cancer cell growth and high levels of HER2 protein are found in up to 15-20% of women with breast cancer.[5–9] According to the National Agency for Cancer Registration (NKRS, https://nkrs.ch), between 2018 and 2020, 13.2% of the diagnosed breast cancers were HER2-positive.

**Disease symptoms, diagnosis, and treatment options**

The most frequent symptoms of breast cancer are a new lump in the breast or armpit, nipple abnormalities (rash, redness, change in appearance, discharge of fluid), changes in breast size, colour, or shape, and breast pain.[10–12] However, some people do not have any clinical signs or symptoms at all before the cancer is diagnosed by imaging.[10–12]

The diagnostic process usually consists of physical examination, imaging (e.g., mammography, ultrasound, and magnetic resonance imaging in selected patients), and pathological examination of biopsies. The identified breast cancer is usually characterised according to the Tumour-Node-Metastasis (TNM) classification on cancer staging, jointly developed by the American Joint Commission on Cancer (AJCC) and the Union for International Cancer Control (UICC), and cancer biology.[13] The TNM system classifies cancers according to tumour size and location (T0, T1, T2, T3, T4), the lymph node status (N0, N1, N2, N3), and the presence of distant metastases (M0, M1). The TNM system can be used to classify breast cancer in stages (IA, IIA, IIB, IIIA, IIIB, IIIC, IV).[14] Clinicians often refer to stage I and stage IIA cancer as “early stage” and to stage IIB and stage III cancer as “locally advanced”. However, some clinical studies define patients up to stage IIIA as patients with early breast cancer,[15 16] while others do not provide a definition for early breast cancer in terms of stages (they presumably gather all the stages which are not metastatic).[17–20] Other information included in the diagnosis is oestrogen receptor and progesterone receptor status, HER2 status and the histological grade as a measure of cancer cell differentiation and proliferation.[21 22]

Treatment options for patients with HER2-positive breast cancer include surgery, HER2-directed therapy (further described in section 3), chemotherapy, endocrine therapy, and radiation therapy.[23] The combination of treatments, and the order in which they are applied, varies depending on a patient’s specific situation. Chemotherapy may be administered after surgery (adjuvant chemotherapy) or before surgery (neoadjuvant chemotherapy) with the goal of shrinking the tumour or stopping the spread of cancer. Surgery may include mastectomy or breast conserving surgery, axillary surgery, and removal of affected lymph nodes.[24]

# 3. Technology

## 3.1 Technology description

Trastuzumab is a recombinant DNA-derived humanised monoclonal antibody that binds to the HER2 protein, inhibiting cancer cell growth and division, and mediating antibody-dependent cellular cytotoxicity (ADCC).[25–27] In patients with HER2-positive early breast cancer, trastuzumab in combination with chemotherapy has been shown to be significantly more effective than chemotherapy alone.[28 29] For example, Moja et al. reported that trastuzumab-containing treatment regimens compared to chemotherapy alone have a hazard ratio (HR) of 0.66 for overall survival (OS, 95% confidence interval (CI) 0.57 to 0.77, p<0.00001) and a HR of 0.60 for disease-free survival (DFS, 95% CI 0.50 to 0.71, p<0.00001), respectively.[28]

Similarly, in another meta-analysis of individual data, the relative risk of breast cancer recurrence and death from breast cancer in patients treated with trastuzumab plus chemotherapy vs. chemotherapy alone were estimated to be 0.66 (95% CI 0.62 to 0.71; p<0.0001) and 0.67 (95% CI 0.61 to 0.73; p<0.0001), respectively.[29] The absolute 10-year recurrence risk was reduced by 9.0% and 10-year breast cancer mortality was reduced by 6.4%.[29]

**Dosage, administration, treatment duration, and indications**

Depending on the treatment scheme, patients are treated either weekly or every 3 weeks, with loading doses for the first cycle of either 4 mg/kg body weight or 8 mg/kg body weight, respectively, and a maintenance dose of either 2 mg/kg body weight or 6 mg/kg body weight, respectively. Most trastuzumab-containing drugs are administered through intravenous infusion, in concomitance with chemotherapy. Herceptin subkutan® is the only available subcutaneous formulation and is used during monotherapy administration (after acceptance by the health insurance). Treatment duration in HER2-positive early breast cancer patients is approved until disease recurrence or for a total of 12 months in Switzerland.[30] Swissmedic has approved trastuzumab for adult patients with HER2-positive early breast cancer as follows:[30]

- following surgery, chemotherapy (neoadjuvant or adjuvant), and radiotherapy (if applicable);
- following adjuvant chemotherapy with doxorubicin and cyclophosphamide in combination with paclitaxel or docetaxel;
- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin;
- in combination with neoadjuvant chemotherapy followed by adjuvant trastuzumab in locally advanced disease or tumours with a diameter > 2 cm, which are at higher risk of recurrence.

The main goal of the neoadjuvant treatment in HER2-positive breast cancer is to assess the tumour response to treatment and then adapt the adjuvant treatment accordingly.

In patients with HER2-positive early breast cancer with high recurrence risk, trastuzumab is also approved in combination with pertuzumab as adjuvant or neoadjuvant treatment for a total treatment duration of 12 months. Pertuzumab is approved in combination with trastuzumab (prescribed as a separate drug [Perjeta®] or as a fixed-dose subcutaneous combination [Phesgo®]).[30]

Trastuzumab is also approved for metastatic HER2-positive breast cancer, HER2-positive gastric cancer, and HER2-positive gastro-oesophageal carcinoma, which are not part of the current HTA report.

The reason why in the adjuvant treatment setting, 12 months of trastuzumab is considered the standard treatment is based upon the registration trial HERA for Herceptin® (the first trastuzumab-containing HER2-targeted drug for breast cancer) in 2005.[31 32] In this trial 24 months treatment was compared to 12 months treatment. The HERA trial demonstrated that extending trastuzumab to 24 months was not significantly different than treatment over 12 months in terms of DFS (HR 0.99, 95% CI 0.85 to 1.14, p=0.86), but increased grade 3 and 4 side effects (20.4% vs. 16.3%).[31 32] The results of the HERA trial as well as other RCTs comparing chemotherapy alone vs. chemotherapy combined with 12 months of trastuzumab (NCCTG trial N9831, NSABP trial B-31, and BCIRG 006 trial) led to the expert conclusion that 12 months treatment should become standard. Since then, efforts to de-escalate treatment have been ongoing to decrease side effects particularly cardiotoxicity, but also costs associated with treatment.

**Contraindications**

Trastuzumab (Herceptin®) should not be used to treat people with HER2-negative breast cancer. Furthermore, Herceptin® is contraindicated in patients with known hypersensitivity to trastuzumab, Chinese hamster ovary cell protein or any of the excipients of the medicinal product. Herceptin® and anthracyclines should not be administered concomitantly in adjuvant treatment. In neoadjuvant treatment, concomitant administration of trastuzumab and anthracyclines should be used with caution and only in chemotherapy-naïve patients.[33]

## 3.2 Alternative technologies

In HER2-positive breast cancer treatment, there are other pharmaceuticals than trastuzumab that can be used to target the HER2-receptor. However, none of these pharmaceuticals qualify as true treatment alternatives for the target population of this HTA, because they are not approved by Swissmedic in early HER2-positive breast cancer and/or are only approved when given combined with trastuzumab or subsequent to trastuzumab treatment (i.e., not as an alternative treatment). These include the monoclonal anti-HER2 antibodies margetuximab-cmkb and pertuzumab, the Pan-HER inhibitor neratinib, the signal transduction inhibitor lapatinib, and the tyrosine kinase inhibitor tucatinib.[34] Margetuximab-cmkb is not approved by Swissmedic. Neratinib is approved for the extended adjuvant treatment in early HER2-positive breast cancer less than 1 year after having completed adjuvant treatment with trastuzumab and chemotherapy. Lapatinitib is approved in

metastasised or advanced HER2-positive breast cancer after completed trastzumab treatment. Tucatinib is approved in combination with trastuzumab in metastasised or advanced HER2-positive breast cancer after completion of 2 or more different other anti-HER2 receptor therapies and treatment settings.[35]

## 3.3 Regulatory status / provider

Several trastuzumab-containing drugs are approved by Swissmedic for the targeted population of this HTA.[2] The first drug entering the Swiss market was Herceptin®, which was approved in 1999 by Swissmedic and entered the list of specialties (reimbursement list) held by the Federal Office of Public Health (FOPH) in 2002. Biosimilars to Herceptin® were approved after 2019 in the target population of this HTA (e.g., Herzuma®, Kanjinti®, Ogivri®, Trazimera®).[2] Herzuma®, Kanjinti®, Ogivri®, Trazimera® are biosimilars to Herceptin®. Costs for these biosimilars are covered by the mandatory health insurance if the drugs are used in the approved indications by Swissmedic. If trastuzumab is given in combination with the drug pertuzumab, either with pertuzumab as separate drug (Perjeta®) or as fixed-dose combination (Phesgo®), prior confirmation by the mandatory health insurance is a prerequisite for cost coverage.

Pertuzumab (Perjeta®) has been approved by Swissmedic in 2012 and is on the list of specialities since 2015 (temporary listing until 2024).[2]

# 4. Population, Intervention, Comparator, Outcome (PICO)

**PICO 1:**

| | |
|---|---|
| **P** | Adult patients with HER2-positive early (including locally advanced operable) breast cancer |
| **I** | Adjuvant or neoadjuvant trastuzumab treatment, ≤6 months treatment duration |
| **C** | Adjuvant or neoadjuvant trastuzumab treatment, 12 months treatment duration |
| **O** | - overall survival (OS)*<br>- disease free survival (DFS)[#]<br>- health-related quality of life (HRQoL) (measured through a validated scale)<br>- treatment-related adverse effects[†]: diarrhoea, rash, nausea, vomiting, fatigue<br>- serious treatment-related adverse effects[†]: cardiac toxicity (congestive heart failure, reduced left ventricular ejection fraction), bone loss/osteoporosis, vision/eye problems<br>- costs<br>- budget impact<br>- cost-effectiveness |

**PICO 2:**

| | |
|---|---|
| **P** | Adult patients with HER2-positive early (including locally advanced operable) breast cancer[§] |
| **I** | Adjuvant or neoadjuvant trastuzumab treatment combined with pertuzumab, ≤6 months treatment duration |
| **C** | Adjuvant or neoadjuvant trastuzumab treatment combined with pertuzumab, 12 months treatment duration |
| **O** | - overall survival (OS)*<br>- disease free survival (DFS)[#]<br>- health-related quality of life (HRQoL) (measured through a validated scale)<br>- treatment-related adverse effects[†]: diarrhoea, rash, nausea, vomiting, fatigue<br>- serious treatment-related adverse effects[†]: cardiac toxicity (congestive heart failure, reduced left ventricular ejection fraction), bone loss/osteoporosis, vision/eye problems<br>- costs<br>- budget impact<br>- cost-effectiveness |

* Overall survival was defined as the time time from randomisation, diagnostic biopsy, or start of treatment until death from any cause.

[#] Disease-free survival was defined as the time from randomisation, diagnostic biopsy, or start of treatment until first recurrence of invasive breast cancer (local, regional, or distant), contralateral breast cancer, any invasive second cancer, or death from any cause, whichever came first. In the field of oncology, progression-free survival (PFS) is often evaluated in clinical trials. However, this outcome is more likely to be used in a more advanced cancer setting or in incurable disease. This HTA focus on a potentially curative setting (early breast cancer) where women typically receive surgery plus (neo)adjuvant chemotherapy (potentially in combination with radiotherapy). The treatment goal is therefore being disease free, rather than avoiding progression (as in metastatic breast cancer, where PFS would be the relevant endpoint).

[†] Pre-determined safety (adverse effects) outcomes as defined in the protocol are shown in this table. Reporting was changed into 'cardiac adverse effects' and 'other adverse effects' in the HTA report and evaluated cardiac adverse effects outcomes were extended to incorporate all relevant evidence (see Section 6.1.1).

[§] Combination treatment with pertuzumab and trastuzumab is currently restricted in Switzerland to the adjuvant treatment of HER2-positive breast cancer patients with high risk of recurrence (i.e., lymph node-positive) and to the neoadjuvant therapy of HER2-positive breast cancer patients with locally advanced inflammatory breast cancer or with high risk of recurrence (i.e., tumour size >2 cm or lymph node-positive).

# 5. HTA research questions

For the evaluation of the technology the following research questions covering central HTA domains, as designated by the EUnetHTA Core Model (clinical efficacy, safety, costs, cost-effectiveness, budget impact, ethical, legal, social, and organisational aspects), are addressed:

1. Is adjuvant or neoadjuvant trastuzumab treatment (with or without pertuzumab) for ≤6 months compared to 12 months non-inferior in terms of clinical efficacy in women with early breast cancer?
2. Is adjuvant or neoadjuvant trastuzumab treatment (with or without pertuzumab) for ≤6 months compared to 12 months superior in terms of safety and quality of life in women with early breast cancer?
3. What are the estimated annual costs of trastuzumab treatment (with or without pertuzumab) in the specified population?
4. What is the budget impact of reducing treatment duration from 12 months to 6 months of trastuzumab?
5. Is 6 months treatment with adjuvant or neoadjuvant trastuzumab treatment (with or without pertuzumab) cost-effective compared to 12 months of treatment?
6. Are there ethical, legal, social or organisational issues related to the reduction of the treatment duration?

# 6. Efficacy and safety

***Summary statement efficacy and safety***

In the systematic review and meta-analysis of clinical efficacy and safety, a total of 6 RCTs with a total of 11,603 women comparing ≤6 months of trastuzumab treatment to 12 months of treatment (PICO 1) were included. All RCTs were judged to have 'some concerns' regarding risk of bias, mostly due to issues regarding deviations from intended interventions (OS, DFS), missing data (HRQoL), or measurement of the outcome (AEs). No RCTs were identified comparing ≤6 months vs. 12 months of trastuzumab and pertuzumab as a combination treatment (PICO 2).

Based on non-inferiority meta-analyses, shorter treatment with trastuzumab (6 months or less) is likely non-inferior compared to 12 months of trastuzumab treatment in terms of OS (moderate certainty of evidence), while the evidence for non-inferiority is inconclusive for DFS (low certainty of evidence). The evidence was very uncertain whether HRQoL was higher with ≤6 months vs.

12 months of treatment (very low certainty of evidence). Meanwhile, ≤6 months compared to 12 months of trastuzumab treatment likely reduces the risk of congestive heart failure (moderate certainty of evidence), having a left-ventricular ejection fraction (LVEF) <50% and a LVEF decrease >10% (moderate certainty of evidence), and trastuzumab discontinuation due to any AE (moderate certainty of evidence), and may reduce the risk of severe (grade ≥3) AE (low certainty of evidence). Analyses for the subgroup comparison of 6 months vs. 12 months of trastuzumab treatment resulted in overall similar findings.

## 6.1 Methodology efficacy and safety

The systematic literature review and meta-analysis related to the clinical efficacy and safety is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).[36]

### 6.1.1 Databases and search strategy

Systematic literature searches were conducted in MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and the International Network of Agencies for Health Technology Assessment (INAHTA) databases. The search was based on medical subject headings (MeSH) and keywords related to the concepts of “breast cancer”, “(neo)adjuvant chemotherapy”, “trastuzumab" and "pertuzumab", and "randomised controlled trial”. The search for studies on trastuzumab included a search concept for “treatment duration” (i.e., the comparison of interest), while the search for studies on pertuzumab did not in order to increase sensitivity. This was because the relative treatment duration for pertuzumab may be described less explicitly than for trastuzumab in studies involving the co-administration of pertuzumab and trastuzumab. The published sensitivity- and precision-maximizing search filter for RCTs by the Cochrane Collaboration was used, but search terms for "placebo" were excluded due to lack of applicability in the context of this HTA.[37] The search strategies are presented in Appendix 1. In addition, ClinicalTrials.gov and the World Health Organisation (WHO) Clinical Trials Registry were searched for records of further non-published, planned, or ongoing studies. All databases were searched from inception until 7 May 2023.[39–42]

Table 1 summarises the inclusion and exclusion criteria that were defined according to the Population, Intervention, Comparator and Outcome (PICO) criteria, as defined in the HTA protocol. Safety outcomes were prespecified as 'adverse effects' and 'serious adverse effects' in the protocol (see Table 1). Based on the specific importance of cardiac AE outcomes in the context of this HTA, the number and heterogeneity in definitions of cardiac AEs evaluated in RCTs, and to improve readability of the report, the reporting has been restructured into the categories of 'cardiac AEs' and 'other AEs'. The range of assessed cardiac AEs was extended to incorporate all relevant reported evidence. Last, safety outcomes were prioritised based on the feedback from 1 clinical expert (gynaecology) and the 4 most critical safety outcomes (congestive heart failure, left-ventricular

ejection fraction (LVEF) <50% and LVEF decrease >10%, any severe (grade ≥3) AE, and trastuzumab discontinuation due to any AE) were included in the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Summary of Findings (SoF) Tables (see Sections 6.1.3 and 6.2.6).

The titles and abstracts of all identified records were screened by 2 reviewers independently for potentially eligible studies using the inclusion and exclusion criteria presented in Table 1. Potentially eligible studies were then assessed in full-text for their eligibility, again independently by 2 reviewers. Any disagreement between reviewers was resolved through consensus or consultation with a third reviewer. The Rayyan (https://www.rayyan.ai/) software was used for the screening and study selection process. The screening and selection process is summarised in the Results (Section 6.2.1) using a PRISMA flow diagram.

**Table 1: Study inclusion and exclusion criteria for the assessment of clinical efficacy and safety.**

| Criterion | Inclusion | Exclusion |
|---|---|---|
| Publication period | No restriction | - |
| Publication status | Full text of publication available (published conference abstracts were considered eligible) | Full text of publication not available |
| Language | English, German, French, Italian | All other languages |
| Setting/Location | No restriction | - |
| Study design | RCT | Not RCT |
| Population | Females or males (≥18 years) with early breast cancer. | Females or males without breast cancer or with advanced breast cancer<br>Animal studies |
| Intervention | PICO 1: Adjuvant or neoadjuvant trastuzumab treatment, ≤6 months treatment duration.<br>PICO 2: Adjuvant or neoadjuvant trastuzumab treatment combined with pertuzumab, ≤6 months treatment duration | Other drugs for the treatment of early breast cancer |
| Comparator | PICO 1: Adjuvant or neoadjuvant trastuzumab treatment, 12 months treatment duration.<br>PICO 2: Adjuvant or neoadjuvant trastuzumab treatment combined with pertuzumab, 12 months treatment duration | Other drugs for the treatment of early breast cancer (except as co-treatments used equally in all relevant study arms)<br>No drug treatment / placebo |
| Outcomes | Overall survival<br>Disease free survival<br>Health-related quality of life<br>Adverse effects*: diarrhoea, rash, nausea, vomiting, fatigue<br>Serious adverse effects*: cardiac toxicity (congestive heart failure, left ventricular ejection fraction), bone loss/osteoporosis, vision/eye problems | - |

**Legend**: * Pre-determined safety (adverse effects) outcomes as defined in the protocol are shown in this table. Reporting was changed into 'cardiac adverse effects' and 'other adverse effects' in the HTA report and evaluated cardiac adverse effects outcomes were extended to incorporate all relevant evidence (see Section 6.1.1).

### 6.1.2 Other sources

In addition to the database searches, the first 33 pages (top 30 records) of a Google Scholar search conducted on 12 June 2023 as well as the reference lists of identified systematic reviews,[38–41]

available HTA reports on topics related to this HTA, and included primary studies were screened for relevant studies not identified through the database searches. Screening, study selection and resolution of disagreements followed the approach described above.

### 6.1.3 Assessment of quality of evidence

**Risk of bias assessment**

Risk of bias was assessed using the Cochrane Risk of Bias (RoB) 2 tool.[42 43] The assessment was conducted for each individual study at the level of individual outcomes (OS, DFS, HRQoL, cardiac and other AEs) and covered the following domains: (a) bias arising from the randomisation process, (b) bias due to deviations from intended interventions, (c) bias due to missing outcome data, (d) bias in measurement of the outcome, and (e) bias in selection of the reported result. These domains were judged with 'low risk of bias', 'some concerns' or 'high risk of bias'. In a non-inferiority setting, per-protocol (PP) analyses are expected to lead to more conservative results (i.e., leading to a lower probability of concluding that there is evidence for non-inferiority), while effect estimates based on intention-to-treat (ITT) analyses tend to be closer to the null effect (i.e., leading to a higher probability of concluding that there is evidence for non-inferiority).[44–46] Ideally, both PP and ITT (and potentially further estimates) should be analysed and reported. Hence, studies solely reporting ITT estimates were considered to be of 'some concerns' in the domain 'bias due to deviations from intended interventions' for OS and DFS. In absence of further issues, studies reporting both PP and ITT estimates for OS and DFS were considered at low risk of bias for this domain. Risk of bias assessment was conducted in duplicate and independently by 2 reviewers, and any disagreements were resolved by consensus.

**Certainty of evidence according to GRADE**

The certainty of evidence for the outcomes of OS, DFS, HRQoL, critical (prioritised) cardiac AEs (congestive heart failure, LVEF <50% and LVEF decrease >10%), and critical other AEs (any severe (grade ≥3) AE, and trastuzumab discontinuation due to any AE) was assessed according to the GRADE approach.[47–49] This involved a standardised assessment of (a) the study limitations (risk of bias), (b) imprecision, (c) inconsistency, (d) indirectness, and (e) publication bias. Based on these criteria, the certainty of evidence for each outcome was categorised as either 'high', 'moderate', 'low', or 'very low'. The results are presented in GRADE GRADE SoF and GRADE Evidence Profile Tables, which were created using the GRADEpro Guideline Development Tool software (McMaster University and Evidence Prime).[50] The GRADE assessment was performed for the primary comparison of ≤6 months (i.e., intervention including 6 months and shorter treatment durations) vs. 12 months of trastuzumab treatment. Additionally, the GRADE assessment was performed for the comparison of 6 months (i.e., intervention including 6 months treatment duration only) vs. 12 months of treatment, since this was considered the most relevant comparison from a policy perspective. The GRADE assessment was conducted in duplicate and independently by 2 reviewers, and any disagreements were resolved by consensus.

### 6.1.4 Methodology data extraction, analysis and synthesis of the domains efficacy and safety

**Data extraction**

Data from identified studies were extracted, per individual study, into a predetermined work sheet. The most recent available information was used if several records for the same study were available. The work sheet was first pilot-tested with 2 selected included studies and subsequently optimised for extraction of all included studies.

For included studies on efficacy and safety, the following information was extracted:

- Study characteristics (i.e., author, year of publication, study type, design, timeframe of participant enrolment, countries in which the study was conducted, sample size, and duration of follow-up)
- Participant characteristics (i.e., age, sex, menopausal status, inclusion criteria including definition of early breast cancer adopted, prognostic factors, Eastern Cooperative Oncology Group (ECOG) performance status)
- Information on intervention and comparator (i.e., adjuvant/neoadjuvant, dose, frequency, treatment duration, concomitant treatments). To enable investigation of the potential effects of concomitant cancer treatments, information on chemotherapy type and duration were also extracted.
- Data on outcomes (i.e., OS, DFS, HRQoL using any validated standardised measure, cardiac AEs, and other AEs), both on an overall study population level and for relevant subgroups (where available)
- Information to assess risk of bias in RCTs according to the Cochrane RoB 2 tool and to assess the certainty of evidence according to the GRADE approach (see Section 6.1.3)
- Information on the non-inferiority margin and whether ITT and/or PP analyses were conducted.

For data published as figures (i.e., where no numerically precise estimates were reported, as was the case for OS and DFS curves and HRQoL), data was extracted using the WebPlotDigitizer (https://automeris.io/WebPlotDigitizer) digitisation tool by 2 reviewers and averages between the 2 extracted datasets were calculated as a basis for the analyses. While this is a common approach for extracting data from original publications, it bears some uncertainty with respect to the extracted data, which is strongly determined by the quality, degree of detail, and presentation of figures.[51]

In the absence of an indication of any relevant missing or additional data (e.g., data on safety outcomes or HRQoL outcomes that were prespecified in trial protocols or registrations), authors of the original articles were not contacted.

All data was extracted in duplicate and independently by 2 reviewers. In case of disagreements, data extraction was verified against the original study reports and disagreements were resolved by consensus.

**Data analysis and synthesis**

Data were analysed using meta-analysis where summarizing results across trials was possible and judged appropriate given the RCTs' clinical and methodological homogeneity. This included OS and DFS, as well as sufficiently similarly defined safety outcomes (AEs). Effect estimates derived from meta-analyses were calculated using inverse variance weighting, according to standard methodology [51] Both common-effects (i.e., fixed-effects) and random-effects estimates (using the Paule-Mandel[52] estimator based on the recommendations by Veroniki et al. (2016)[51]) were calculated. The presented results and discussion in this HTA report are based on random-effects estimates, which were considered as the primary results. This decision was taken since relevant heterogeneity was assumed to be present a priori given the differences in study populations and treatment protocols,[53] in line with methodological guidance.[54 55]

For the time-to-event outcomes of OS and DFS, hazard ratios (HRs) were used as effect measures in order to calculate pooled effects across studies in meta-analyses, in line with relevant guidance[51] HRs lower than 1.0 favour shorter treatment (≤6 months) and HRs larger than 1.0 favour longer treatment (12 months). However, since the current HTA is concerned with non-inferiority of shorter vs. longer treatment in terms of OS and DFS, the analyses refer to a non-inferiority margin instead of a null effect (HR of 1.0) for these outcomes (see also the Section related to non-inferiority margins below). To evaluate the proportional hazards assumption underlying the HRs, published survival curves were inspected visually to determine obvious or severe violations of this assumption alongside assessing Schoenfeld's residuals test (if reported by primary studies). The proportional hazards assumption was likely not sufficiently met by all included studies (due to crossing OS and DFS curves and a $p<0.05$ in Schoenfelds' residuals test in PHARE). Meanwhile, given that the treatment has an effect on survival, the proportionality assumption would likely never be met.[56] Even in case of a violation of the proportional hazards assumption, HRs from Cox regression can still be interpreted as the average treatment effect over the follow-up period and thus likely lead to a valid interpretation of the reported average effects on OS and DFS.[56] To obtain standard errors for HRs for conducting meta-analyses of time-to-event outcomes, the difference between the logarithms of the upper and lower bounds of reported confidence intervals (CIs) were calculated and divided by 3.92 or 3.29 for 95% and 90% CIs, respectively.[51] While PP estimates would be desirable in the context of non-inferiority (see Section 6.1.3), ITT estimates were used in primary analyses for OS and DFS since PP estimates were reported for only 1 trial, but were not reported for the other trials.

For AEs, risk ratios (RRs) were used as the effect measure. RRs greater than 1.0 indicate that shorter treatment (≤6 months) results in a higher risk of AEs compared to longer treatment (12 months) and a RR lower than 1.0 indicates that a shorter treatment is associated with a lower risk

for AEs compared to longer treatment. For AEs, the evidence was evaluated with respect to a difference from a null effect (RR of 1.0; i.e., superiority of shorter treatment compared to longer treatment in terms of safety). AE risks used in meta-analyses were calculated directly from reported event counts and corresponding denominators (study or safety populations).[51]

HRQoL was measured both by continuous (EuroQol visual analogue scale (EQ-VAS)) and categorical outcomes (participants reporting 'poor', 'fair', 'good', or 'very good' health) in included studies, which were analysed on the respective scale (continuous outcomes), or as frequencies and proportions (categorical outcomes). No meta-analysis was conducted, and results were summarised narratively for HRQoL, since results were available for 1 trial only. Given the absence of reporting of estimates for between-group differences, such estimates were calculated as follows: For the EQ-VAS, the differences in means of extracted scale data between groups were calculated (no uncertainty intervals could be calculated based on the extracted data due to the skewed distributions of these scale data). For the categorical outcomes, the difference in the proportion of participants reporting 'good' or 'very good' health (summed) was calculated between groups at different follow-up timepoints, with corresponding 95% confidence interval for proportions.[51]

**Determination of non-inferiority margin**

In the context of non-inferiority trials and non-inferiority meta-analyses, the non-inferiority margins reflect what is deemed a clinically acceptable loss of efficacy. The primary studies included in the review used non-inferiority margins for an absolute risk difference in DFS [6364]ranging between 2% and 8%).[15 16 18–20 57] After consultation with 3 Swiss clinicians with large expertise in the field of systemic breast cancer treatment (2 oncologists and 1 gynaecologist), it was decided that an absolute risk difference of 3% should be used in the HTA report as a non-inferiority margin for the efficacy outcomes of DFS and OS. A non-inferiority margin of a 3% absolute risk difference was also used for DFS in 1 study included in this HTA (the PERSEPHONE trial).[5358] Given the heterogeneity of non-inferiority margins used in the included primary studies, lower (2% absolute risk difference) and higher (4% absolute risk difference) non-inferiority margins were additionally considered in sensitivity analyses, in consultation with the involved experts. Larger non-inferiority margins (e.g. 8% as in the HORG trial[59]) were not considered, as such are unlikely to be acceptable for a change in practice.[53]

To apply non-inferiority margins defined as absolute risk differences to non-inferiority meta-analyses of HRs, corresponding non-inferiority margins on a relative (HR) scale had to be calculated. For this, the survival proportions in the 12-month treatment comparator arms of all included trials at 2, 3, 4, 5, and 7 years after patient enrolment were extracted using digitisation. Then, the average survival proportions ($survival_{12m}$) across trials at these follow-up timepoints were calculated using inverse variance weighting. Pre-specified absolute risk differences of 3% (primary analysis), 2% and 4% (sensitivity analyses) were then subtracted from these survival proportions to calculate the minimal acceptable survival proportions for ≤6 months of treatment (e.g., $survival_{\leq 6m} = survival_{12m}$ - 3%). From this, the resulting HR non-inferiority margins at each timepoint were calculated

according to the formula HR = ln(survival$_{\leq 6m}$) / ln(survival$_{12m}$).[60 61] Estimated average survival proportions for OS and DFS with 12 months of treatment at different follow-up timepoints, calculated minimal acceptable survival proportions, and calculated HR non-inferiority margins assuming a 2%, 3%, and 4% absolute risk difference are demonstrated in Table 2 and Figure 1.

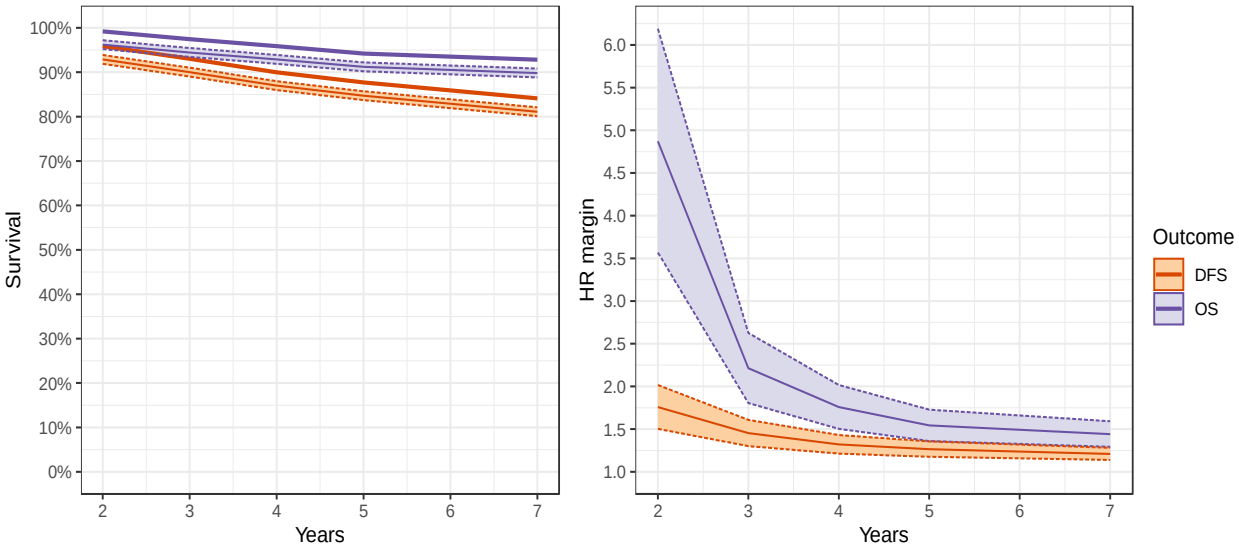
**Table 2: Calculated non-inferiority margins.**

The table summarises the averaged extracted survival of the 12-month treatment groups in the included studies, calculated minimal acceptable survival proportions in the ≤6-month treatment groups (assuming different non-inferiority margins for absolute risk differences), and corresponding calculated relative (hazard ratio) non-inferiority margins. Non-inferiority margins assuming a 3% absolute difference in 5-year OS and DFS were used in primary analyses (in bold).

| | Observed 12 months treatment | Calculated ≤6 months treatment | | | | | |
|---|---|---|---|---|---|---|---|
| | | 2% absolute difference | | 3% absolute difference | | 4% absolute difference | |
| Follow-up timepoint | Survival (average of trial control groups) | Minimal acceptable survival | HR non-inferiority margin | Minimal acceptable survival | HR non-inferiority margin | Minimal acceptable survival | HR non-inferiority margin |
| **DFS** | | | | | | | |
| 2 years | 95.9% | 93.9% | 1.503 | 92.9% | 1.758 | 91.9% | 2.017 |
| 3 years | 93.0% | 91.0% | 1.301 | 90.0% | 1.454 | 89.0% | 1.608 |
| 4 years | 90.0% | 88.0% | 1.213 | 87.0% | 1.321 | 86.0% | 1.431 |
| 5 years | 87.7% | 85.7% | 1.176 | 84.7% | **1.266** | 83.7% | 1.356 |
| 7 years | 84.1% | 82.1% | 1.139 | 81.1% | 1.210 | 80.1% | 1.281 |
| **OS** | | | | | | | |
| 2 years | 99.2% | 97.2% | 3.568 | 96.2% | 4.872 | 95.2% | 6.190 |
| 3 years | 97.5% | 95.5% | 1.805 | 94.5% | 2.214 | 93.5% | 2.627 |
| 4 years | 95.9% | 93.9% | 1.503 | 92.9% | 1.759 | 91.9% | 2.017 |
| 5 years | 94.2% | 92.2% | 1.360 | 91.2% | **1.543** | 90.2% | 1.728 |
| 7 years | 92.8% | 90.8% | 1.293 | 89.8% | 1.442 | 88.8% | 1.592 |

**Legend**: DFS = disease-free survival, HR = hazard ratio, OS = overall survival.

**Figure 1: Calculated non-inferiority margins.**




**Legend**: Bold solid lines in left panel represent averaged OS and DFS with 12 months of treatment at different timepoints. Shaded areas in left panel represent minimal acceptable OS and DFS with ≤6 months of treatment, assuming different non-inferiority margins for absolute differences (solid lines represent a 3% absolute difference, dashed lines represent 2% (top border of shaded area) and 4% (bottom border) absolute differences). Correspondingly, shaded areas in right panel represent calculated relative hazard ratio (HR) margins at different timepoints of follow-up (solid lines represent HR margins assuming a 3% absolute difference, dashed lines represent 2% (bottom border of shaded area) and 4% (top border) absolute differences).

The HRs calculated based on a 3% absolute difference in 5-year OS and DFS were used as non-inferiority margins in the primary analyses. 5-year OS/DFS was selected since it was considered more conservative (with respect to non-inferiority) and more patient-relevant than OS/DFS at shorter follow-up timepoints such as 2 or 3 years. The non-inferiority margins used in primary analyses in this HTA corresponded to a HR of 1.543 for OS (based on an estimated 5-year OS of 94.2%) and a HR of 1.266 for DFS (based on an estimated 5-year DFS of 87.7%).

To further evaluate the sensitivity of the choice of non-inferiority margins, a probabilistic sensitivity analysis using a Monte Carlo simulation was performed to calculate the probability of non-inferiority at different HR non-inferiority margins and for different absolute differences in OS and DFS based on varying assumptions of baseline OS/DFS (i.e., 75%, 80%, 85%, 90%, 95%, and 99% OS/DFS).[62] This was simulated using 1,000,000 random draws from the distribution of the effect estimates derived through meta-analyses, subsequently calculating the proportion of draws that were compatible with non-inferiority at varying non-inferiority margins. Based on this threshold analysis, it was possible to determine the minimum non-inferiority margin that is compatible with a certain probability (e.g., ≥97.5%, corresponding to a 2-sided alpha of 0.05) of non-inferiority based on the currently available evidence.

**Heterogeneity and publication bias**

Heterogeneity between studies was assessed visually and using the $I^2$ statistic. Thereby, different reasons for heterogeneity due to risk of bias, characteristics of underlying study populations, and study design aspects such as trial phase (phase 2 vs. phase 3) and type (non-inferiority vs. superiority), timepoints of participant enrolment, and treatment protocols were considered. An $I^2 \geq 75$ % was considered as considerable heterogeneity.[63] Publication bias was mitigated by ensuring a comprehensive search for eligible studies, including trial registries. Contour-enhanced funnel plots using the non-inferiority margins as a reference are also presented for completeness, although these need to be interpreted with caution due to the low number of included studies (<10 studies included).[51]

**Sensitivity analyses**

Sensitivity analyses were conducted to evaluate the impact of specific aspects related to the included studies on meta-analysis results: risk of bias, differences in characteristics of underlying study populations, and differences in study design aspects. Furthermore, sensitivity analyses regarding the choice of non-inferiority margins were performed.

For the outcomes OS and DFS, sensitivity analyses considered the following aspects: (1) excluding the E2198 trial[23] due to the different study design (phase 2 superiority trial), potentially relevant protocol violations, and potentially relevant attrition in the 12-month treatment group, (2) excluding the E2198 trial[23] and the HORG trial[59] due to including higher-risk breast cancer patients (>75% node-positive early breast cancer), (3) using HR estimates for DFS and OS for the Short-HER trial from Conte et al. [20] instead of the more recent estimate from Conte et al.[64] reported in a conference abstract, and (4) using reported PP estimates (available only from the PHARE trial) instead of ITT estimates. Furthermore, the sensitivity of the choice of the non-inferiority margins was evaluated by (5) using alternative non-inferiority margins based on a 2% and 4% absolute risk difference (both for the ≤6 months vs. 12 months and the 6 months vs. 12 months comparison), as well as (6) using a threshold analysis based on a probabilistic simulation to estimate the probability of non-inferiority at different non-inferiority margins and assuming different baseline risks (see Section "Determination of non-inferiority margin" above). Sensitivity analyses were performed irrespective of the presence of relevant heterogeneity.

No specific sensitivity analyses were conducted for HRQoL and AEs given the limited reported data and since the risk of bias was judged to be of 'some concerns' for these outcomes.

**Subgroup analyses**

Subgroup analyses were conducted for different trastuzumab treatment durations (i.e., 6 months vs. 12 months, 12 weeks vs. 12 months, and 9 weeks vs. 12 months) for all outcomes of interest. Therein, the comparison of 6 months vs. 12 months of trastuzumab treatment was considered the most relevant from a policy perspective and consequently prioritised in the reporting of results

(including GRADE assessment, see Section 6.1.3). Sensitivity analyses outlined above were also conducted for this subgroup.

Further subgroup analyses for the outcomes OS and DFS were conducted for different patient, tumour, and treatment characteristics: age (i.e., women aged ≤50 years vs. women aged >50 years), menopausal status (i.e., pre- vs. peri- vs. postmenopausal), breast cancer grade (i.e., grades I vs. II vs. III), nodal status (i.e., node-negative vs. node-positive), oestrogen receptor status (oestrogen receptor-positive vs. receptor-negative), progesterone receptor status (progesterone receptor-positive vs. receptor-negative), breast cancer size (i.e., <2cm vs. ≥2cm), chemotherapy setting (i.e., adjuvant vs. neoadjuvant chemotherapy), chemotherapy regimen (e.g., anthracycline-based vs. taxane based vs. anthracycline and taxane-based chemotherapy), and timing of trastuzumab administration (i.e., concurrent vs. sequential trastuzumab). No subgroup analyses based on patient, tumour, or treatment characteristics were possible for HRQoL. Subgroup analyses for AEs included an evaluation of the risk of cardiac AEs across participants receiving different chemotherapy regimen.

**Statistical analysis**

All statistical analyses were conducted using R statistical software (v4.2.2), and the *meta* package (v6.5-0) was used for meta-analyses and visualisations.[65 66] Absolute risk differences for time-to-event outcomes presented in GRADE SoF and Evidence Profile tables were calculated according to the formula ARD = $survival_{12m}^{HR}$ - $survival_{12m}$, where '$survival_{12m}$' was the inverse variance weighted average 3-year and 5-year survival (OS or DFS) proportion across 12 month treatment groups of all included RCTs (extracted from survival curves, see Table 2 above) and 'HR' was the corresponding HR (with 95% CI) derived through meta-analysis.[60 61] These analyses assumed proportional hazards over time. Absolute risk differences for adverse effects were calculated according to the formula ARD = $risk_{12m}$ * RR - $risk_{12m}$, where '$risk_{12m}$' was the average risk for the respective AE outcome in the 12 months treatment groups and 'RR' was the corresponding RR (with 95% CI) derived through meta-analysis. Two ARD estimates were calculated for adverse effects: (i) the overall risk in the 12 month treatment group across studies included in the corresponding meta-analysis (total number of events / total number of participants; unweighted approach, not taking into account all reported evidence for subgroup analyses) and (ii) the inverse variance weighted average risk across 12 month treatment groups of all studies reporting data for the respective adverse effect outcome (weighted average of number of events / number of participants across all studies; taking into account evidence also from studies not included in subgroup meta-analyses). As time horizons of reported risks differed between RCTs, risks were assumed to be constant over time for meta-analyses. In subgroup analyses, Cochran's Q tests of subgroup estimates derived through meta-analysis were performed and p-values were calculated assuming a chi-squared distribution to test for subgroup differences.[67] Two-tailed p-values with an alpha of 0.05 were calculated to test non-inferiority with respect to the relevant non-inferiority margins for OS and DFS or to

test superiority (in terms of a lower risk) for AEs. No p-value adjustment for multiple testing was performed.

**Reporting**

For reporting of non-inferiority meta-analyses, we used the classification system by Piaggio et al. (2012)[68] to classify OS and DFS results with shorter treatment as 'superior', 'inferior', 'non-inferior', or 'inconclusive' compared to longer treatment. The term 'inconclusive' in this context describes that the evidence is suggestive of non-inferiority (i.e., the point estimate lies below the specified non-inferiority margin), but that inferiority cannot fully be ruled out (i.e., the confidence interval overlaps with the non-inferiority margin). If results were not 'inconclusive', summary statements were formulated according to GRADE guidance based on the certainty of evidence.[69] In this context, the terms 'likely is', 'may be', and 'very uncertain' apply to contexts where the evidence is of moderate, low, and very low certainty according to GRADE, respectively.

Reporting for AE outcomes not assessed using the GRADE approach as well as for subgroup differences was based on the strength of statistical evidence (instead of dichotomizing into significant or non-significant) based on the framework by Bland ($p \geq 0.1$ no evidence, $0.1 > p \geq 0.05$ weak evidence, $0.05 > p \geq 0.01$ moderate evidence, $0.01 > p \geq 0.001$ strong evidence, $p < 0.001$ very strong evidence).[70 71] Of note, this needs to be distinguished from the assessment of the certainty of evidence based on the GRADE approach described above.

## 6.2 Results efficacy and safety

### 6.2.1 PRISMA flow diagram

Figure 2 provides the PRISMA flow diagram of the study identification, screening, and selection process. In total, 3,791 unique records were identified through literature searches. No additional records were identified through a Google Scholar search and screening of reference lists of relevant systematic reviews, HTA reports, and individual studies (Appendix 2). 103 records were evaluated in full-text for eligibility, and 33 records from 6 RCTs were finally included in the review (Appendix 3).

### 6.2.2 Study characteristics and quality assessment of included studies

**Study characteristics**

The 6 identified RCTs were PHARE,[16 72 73] E2198,[20] HORG,[19 74] Short-HER,[17 75] SOLD,[15] and PERSEPHONE.[18 76] Details of the characteristics of these RCTs are presented in Table 3 and Appendix 4. All identified RCTs compared a shorter treatment duration (≤6 months) with a longer treatment duration (12 months) of trastuzumab, in combination with chemotherapy, in HER2-positive early breast cancer (PICO 1). No RCTs comparing different treatment durations were identified for trastuzumab combined with pertuzumab in HER2-positive early breast cancer (PICO 2).

Among the included RCTs, 3 RCTs evaluated a duration of 6 months, 1 RCT evaluated a duration of 12 weeks, and 2 RCTs evaluated a duration of 9 weeks in the intervention group. All identified RCTs evaluated trastuzumab treatment in the adjuvant setting, while chemotherapy was administered either as an adjuvant treatment or according to investigators' choice (adjuvant or neoadjuvant treatment; PHARE, PERSEPHONE). Chemotherapy was anthracycline- and taxane-based in 4 RCTs and according to investigators' choice (anthracycline- and taxane-based, anthracycline-based, taxane-based, or other) in 2 RCTs (PHARE, PERSEPHONE). While treatment assignment was randomised prior to the start of chemotherapy and trastuzumab therapy in 4 RCTs, participants were randomised after the start of trastuzumab treatment in 2 RCTs (PHARE, PERSEPHONE), allowing participants to have received up to 6 months of trastuzumab treatment at the timepoint of randomisation.

All 6 included studies were multicentric, parallel-design, open-label RCTs, and conducted in European countries or the United States of America (USA). Trial sample sizes ranged from 227 to 4,088 participants, with a total of 11,603 participants included in the systematic review overall. The longest available median follow-up times ranged from 3.9 years to 8.7 years. Among all RCTs, 4 were originally designed as non-inferiority trials with the primary outcome of DFS (Short-HER[22] included OS as a co-primary outcome). Meanwhile, SOLD[20] was originally designed as a superiority trial with DFS as primary outcome but converted to a non-inferiority design after a protocol amendment, and E2198[25] was designed as a phase 2 superiority trial with the primary outcome of cardiac toxicity. Non-inferiority margins for HRs applied in included RCTs ranged from 1.15 to 1.53 (median 1.30) for DFS, based on assumed absolute differences in DFS of 2% to 8% (median 3.5%; varying follow-up timeframes ranging from 2-year to 5-year DFS were used for calculating HRs). A non-inferiority margin for OS was specified only in 1 RCT, determined at HR 1.60 based on a 3% absolute difference in 4-year OS (expected survival not specified).

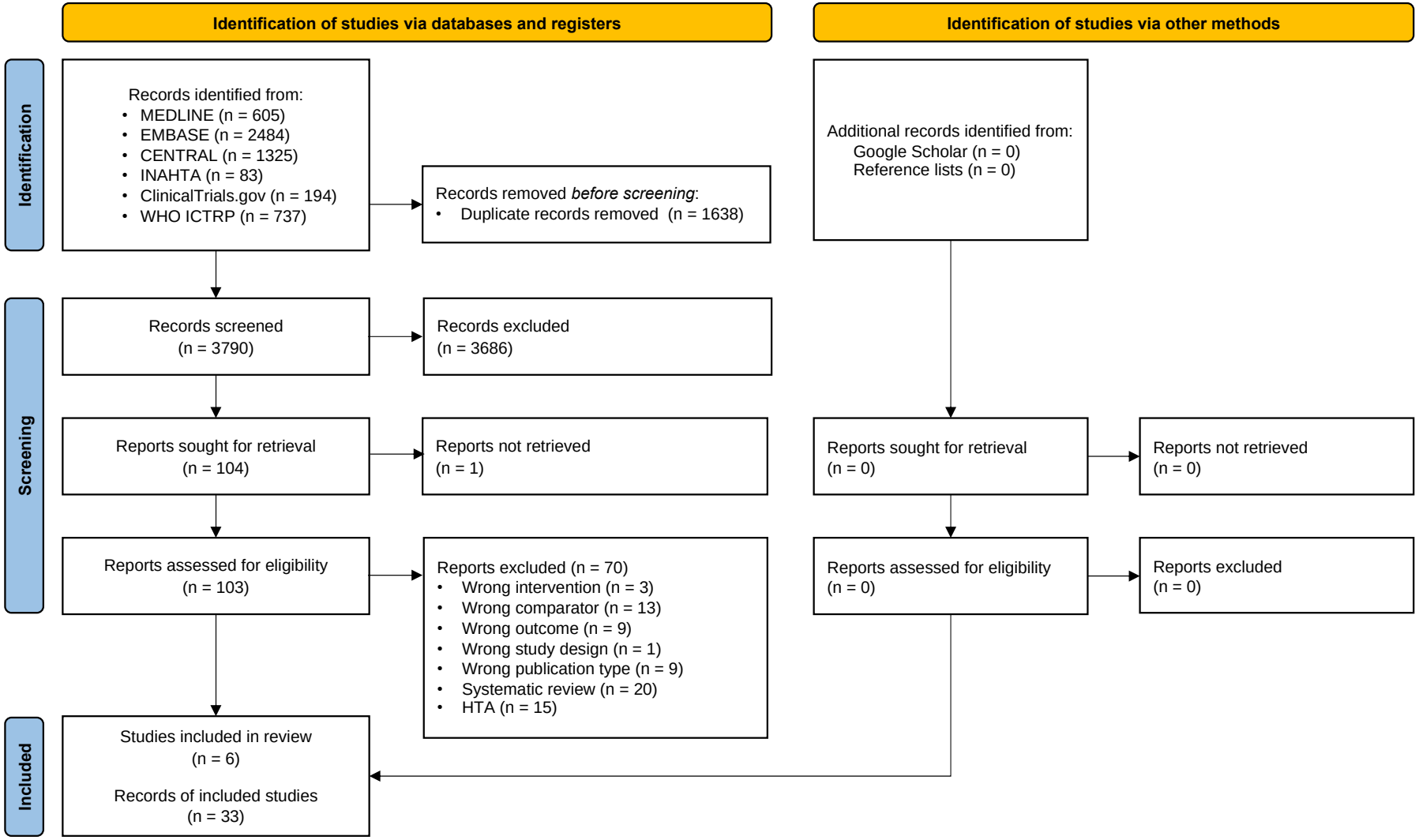
**Participant characteristics**

The characteristics of participants in the included RCTs are shown in Table 4. All RCTs included female breast cancer patients only. The median age of study participants ranged from 48 years to 56 years, including participants between 21 years and 86 years. Where menopausal status was reported (4 RCTs), between 56% and 66% of included women were postmenopausal. Between 60% and 69% had hormone receptor-positive breast cancer. Nodal status was positive in 40% to 47% of women in PHARE, Short-HER, SOLD, and PERSEPHONE, while node-positive breast cancer was more frequent in HORG (79%), and all women were node-positive in E2198. The proportion of women with grade III breast cancer was between 51.5% and 55.8% in PHARE and HORG, while it was between 63% and 67% in SOLD and PERSEPHONE (not reported for E2198 and Short-HER). Information on breast cancer stage at diagnosis and (ECOG) performance status was limited.

**Risk of bias**

The results of the risk of bias assessment of included RCTs are demonstrated in Figure 3. Overall, the risk of bias was judged to be of 'some concern' for almost all studies and outcomes. No issues were identified in the domains related to the randomisation process, selection of the reported result, and missing outcome data. An exception regarding missing outcome data was the evidence related to HRQoL in PERSEPHONE, where data was missing for >30% of participants and important differences in HRQoL between treatment groups were already observed at the start of trastuzumab treatment (no other relevant differences in participant characteristics between groups were observed). Some concerns were raised related to deviations from the intended interventions due to studies primarily reporting ITT estimates for non-inferiority outcomes, with PP estimates only provided by PHARE for DFS. ITT estimates may be biased towards non-inferiority in this context in case of protocol violations. Furthermore, potentially relevant protocol violations occurred in >10% of participants in E2198, PHARE and PERSEPHONE, although these were judged to unlikely have a relevant impact on the effect estimates. Last, the lack of blinding to treatment of both participants and investigators was considered to lead to some concerns regarding risk of bias for HRQoL and AE outcomes, for which responses or recording may be influenced by knowledge of treatment allocation.

**Figure 2: PRISMA flow diagram of the study selection process.**



### 6.2.3 Evidence table

The characteristics of included studies and study participants are presented in Table 3 and Table 4, respectively.

**Table 3: Overview and characteristics of included studies.**

| Name | First author & year of first publication | Study design | Country & enrolment timeframe | Median follow-up (years) | Sample size | Comparison | Main eligibility criteria | Outcomes | Non-inferiority margin |
|---|---|---|---|---|---|---|---|---|---|
| PHARE[16 72 73] | Pivot et al. 2013 | RCT, parallel, open-label, non-inferiority | Multicentric, France 05/2006 to 07/2010 | 7.5 | 3,380 (planned 3,400) | 6 months vs. 12 months | Women ≥18 years with histologically confirmed invasive HER2+ BCa, breast axillary surgery prior to randomisation, have received ≥4 courses of chemotherapy for BCa and trastuzumab for up to 6 months, no prior anti-HER2 therapy, no relevant history of cardiac disease, LVEF ≥50% | Primary: DFS; Secondary: Cardiac safety, OS, MFS | 2% difference in 2-year DFS; HR 1.15 based on 85% 2-year DFS expected with 12 months trastuzumab |
| E2198[20] | Schneider et al. 2015 | RCT, parallel, open-label, superiority* | Multicentric, USA 08/1999 to 11/2013 | 6.42 | 227 (planned 200) | 12 weeks vs. 12 months | Women ≥18 years with histologically confirmed stage II or IIIa (T1-T3, N1-N2, M0) HER2+ BCa, mastectomy or lumpectomy and axillary lymph node dissection within past 12 weeks, no prior chemotherapy, hormonal therapy or radiotherapy for BCa, no relevant history of cardiac disease, LVEF ≥50% | Primary: Cardiac toxicity (CHF or LVEF decrease >10%), CHF, Grade 3-4 myocarditis; Secondary: DFS, OS | No non-inferiority margin specified |

| Name | First author & year of first publication | Study design | Country & enrolment timeframe | Median follow-up (years) | Sample size | Comparison | Main eligibility criteria | Outcomes | Non-inferiority margin |
|---|---|---|---|---|---|---|---|---|---|
| HORG[19 74] | Mavroudis et al. 2015 | RCT, parallel, open-label, non-inferiority | Multicentric, Greece 06/2004 to 05/2012 | 4.3 (Int.) 3.9 (Comp.) | 481 (planned 478) | 6 months vs. 12 months | Women 18-75 years with histologically-confirmed invasive HER2+ BCa with at least 1 positive axillary node, modified radical mastectomy or lumpectomy and axillary lymph node dissection within past 60 days, no prior or concurrent antineoplastic therapy (e.g. hormonal therapy, radiation therapy, chemotherapy, biological agents), no relevant history of cardiac disease, LVEF ≥50% | Primary: DFS; Secondary: OS | 8% difference in 3-year DFS; HR 1.53 based on 85% 3-year DFS expected with 12 months trastuzumab |
| Short-HER[17 75] | Conte et al. 2018 | RCT, parallel, open-label, non-inferiority | Multicentric, Italy 12/2007 to 10/2013 | 8.7 | 1,253 (planned 2,332) | 9 weeks vs. 12 months | Women 18-75 years with histologically confirmed infiltrating primary HER2+ BCa (stage I-IIIA), surgical resection within past 10 weeks, no prior chemotherapy, endocrine therapy or radiotherapy, no relevant history of cardiac disease, LVEF ≥50%, ECOG 0-1 | Primary: DFS, OS; Secondary: Failure rate at 2 years, cardiac safety (definition) | HR 1.29 (DFS; rationale not specified) |
| SOLD[15] | Joensuu et al. 2018 | RCT, parallel, open-label, non-inferiority** | Multicentric, Finland 01/2008 to 12/2014 | 5.2 | 2,174 (planned 2,168*) | 9 weeks vs. 12 months | Women ≥18 years with histologically confirmed invasive HER2+ BCa, no primary systemic cancer therapy prior to BCa diagnosis, no neoadjuvant systemic therapy, no major surgery within 4 weeks prior to | Primary: DFS; Secondary: DDFS, cardiac DFS, OS, treatment safety | 4% difference in 5-year DFS; HR 1.3 based on 85% 5-year DFS expected with 12 months trastuzumab |

| Name | First author & year of first publication | Study design | Country & enrolment timeframe | Median follow-up (years) | Sample size | Comparison | Main eligibility criteria | Outcomes | Non-inferiority margin |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | study treatment start or lack of complete recovery from the effects of major surgery, no relevant history of cardiac disease, LVEF ≥50%, ECOG 0-1 | | |
| PERSEPHONE[18 76] | Earl et al. 2019 | RCT, parallel, open-label, non-inferiority | Multicentric, UK 10/2007 to 07/2015 | 5.4 | 4,088 (planned 4,000) | 6 months vs. 12 months | Women or men ≥18 years with histologically confirmed invasive HER2+ BCa, not having received more than 9 cycles of trastuzumab, no prior chemotherapy or radiotherapy, no relevant history of cardiac disease, LVEF ≥50%, ECOG 0-1 | Primary: DFS; Secondary: OS, health economic analysis, cardiac function (LVEF), HRQoL | 3% difference in 4-year DFS/OS; HR 1.32 (DFS; based on 80% 4-year DFS expected with 12 months trastuzumab) and HR 1.60 (OS; expected survival with 12 months trastuzumab not specified) |

**Legend**: BCa = breast cancer, CHF = congestive heart failure, Comp. = comparator group, DFS = disease-free survival, DDFS = distant disease-free survival, ECOG = Eastern Cooperative Oncology Group performance score, HER2 = human epidermal growth factor receptor 2, HRQoL = health-related quality of life, Int. = intervention group, LVEF = left ventricular ejection fraction, MFS = metastasis-free survival, N = total study population, OS = overall survival, RCT = randomised controlled trial, UK = United Kingdom, USA = United States of America. * E2198 was designed as a superiority trial for safety outcomes, evaluating superiority of shorter trastuzumab treatment over longer treatment in terms of cardiac toxicity. ** SOLD was originally designed as a superiority trial but changed to a non-inferiority trial design (which also affected sample size calculations).

**Table 4: Participant characteristics of included studies.**

| Study | Duration | Female N (%) | Age median (range) | Postmeno-pausal N (%) | UICC/AJCC-Stages N (%) | Grades N (%) | Nodal status N (%) | Hormone receptor status N (%) | ECOG 1+ N (%) |
|---|---|---|---|---|---|---|---|---|---|
| PHARE[16 72 73] | 6 months | 1,690 (100%) | 55 (23-85) | NA | NA | I: 54 (3.3%)<br>II: 672 (40.9%)<br>III: 918 (55.8%) | 0: 915 (54.7%)<br>1-3: 506 (30.2%)<br>4+: 253 (15.1%) | HR+: 1040 (61.5%)<br>ER+: 994 (58.8%)<br>PR+: 701 (41.6%) | NA |
| | 12 months | 1,690 (100%) | 54 (21-86) | NA | NA | I: 52 (3.1%)<br>II: 679 (41%)<br>III: 924 (55.8%) | 0: 927 (55.4%)<br>1-3: 502 (30%)<br>4+: 244 (14.6%) | HR+: 1021 (60.4%)<br>ER+: 974 (57.6%)<br>PR+: 712 (42.4%) | NA |
| E2198[2023] | 12 weeks | 115 (100%) | 49 (26-78) | NA | NA | NA | 0: 0 (0%)<br>1-3: 58 (51%)<br>4+: 57 (49%) | HR+: 69 (60.0%)<br>ER+: 63 (54.8%)<br>PR+: 60 (52.1%) | 14 (12%) |
| | 12 months | 112 (100%) | 48 (22-76) | NA | NA | NA | 0: 0 (0%)<br>1-3: 64 (57%)<br>4+: 48 (43%) | HR+: 71 (63.4%)<br>ER+: 66 (58.9%)<br>PR+: 55 (49.1%) | 12 (11%) |
| HORG[19 74] | 6 months | 240 (100%) | 56 (29-75) | 157 (65%) | NA | I: 10 (4.2%)<br>II: 92 (38.3%)<br>III: 128 (53.3%) | 0: 40 (16.7%)<br>1-3: 107 (44.6%)<br>4+: 93 (38.7%) | HR+: 165 (68.8%) | NA |
| | 12 months | 241 (100%) | 54 (25-75) | 141 (59%) | NA | I: 10 (4.1%)<br>II: 98 (40.7%)<br>III: 124 (51.5%) | 0: 61 (25.3%)<br>1-3: 97 (40.2%)<br>4+: 83 (34.4%) | HR+: 156 (64.7%) | NA |
| Short-HER[17 75] | 9 weeks | 626 (100%) | 55 (25-78) | 403 (64%) | I: 264 (42%)<br>II: 268 (43%)<br>III: 91 (15%) | NA | 0: 332 (53%)<br>1-3: 194 (31%)<br>4+: 100 (16%) | HR+: 427 (68.2%) | NA |
| | 12 months | 627 (100%) | 55 (28-78) | 399 (64%) | I: 245 (39%)<br>II: 281 (45%)<br>III: 100 (16%) | NA | 0: 340 (54%)<br>1-3: 189 (30%)<br>4+: 98 (16%) | HR+: 426 (67.9%) | NA |
| SOLD[1518] | 9 weeks | 1,085 (100%) | 56 (IQR 49-64) | 731 (67%) | I: 427 (39%)<br>II: 529 (49%)<br>III: 129 (12%) | I: 26 (2%)<br>II: 340 (31%)<br>III: 714 (66%) | 0: 647 (59%)<br>1-3: 322 (30%)<br>4+: 116 (11%) | ER+: 711 (65.5%)<br>PR+: 504 (46.5%) | 102 (9%) |
| | 12 months | 1,089 (100%) | 56 (IQR 48-63) | 724 (66%) | I: 430 (39%)<br>II: 528 (48%)<br>III: 131 (12%) | I: 27 (2%)<br>II: 327 (30%)<br>III: 731 (67%) | 0: 649 (60%)<br>1-3: 320 (29%)<br>4+: 120 (11%) | ER+: 723 (66.4%)<br>PR+: 517 (47.5%) | 112 (10%) |
| PERSEPHONE[18 76] | 6 months | 2,043 (100%) | 56 (23-83) | 1070 (52%) | NA | I: 34 (2%)<br>II: 642 (31%)<br>III: 1297 (63%) | 0: 1019 (59%)<br>1-3: 486 (28%)<br>4+: 211 (12%) | ER+: 1411 (69.1%) | NA |
| | 12 months | 2,045 (100%) | 56 (23-82) | 1144 (56%) | NA | I: 29 (1%)<br>II: 628 (31%)<br>III: 1322 (65%) | 0: 1003 (58%)<br>1-3: 479 (28%)<br>4+: 244 (14%) | ER+: 1412 (69.0%) | NA |

**Legend**: ECOG = Eastern Cooperative Oncology Group performance status, ER = oestrogen receptor, HR = hormone receptor, IQR = interquartile range, NA = not available, PR = progesterone receptor.

**Figure 3: Risk of bias of in included studies.**

| Outcome | Study ID | Comparison | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|---|---|
| OS | PHARE | 6 months vs. 12 months | + | ! | + | + | + | ! |
| | E2198 | 12 weeks vs. 12 months | + | ! | + | + | + | ! |
| | HORG | 6 months vs. 12 months | + | ! | + | + | + | ! |
| | Short-HER | 9 weeks vs. 12 months | + | ! | + | + | + | ! |
| | SOLD | 9 weeks vs. 12 months | + | ! | + | + | + | ! |
| | PERSEPHONE | 6 months vs. 12 months | + | ! | + | + | + | ! |
| DFS | PHARE | 6 months vs. 12 months | + | + | + | + | + | + |
| | E2198 | 12 weeks vs. 12 months | + | ! | + | + | + | ! |
| | HORG | 6 months vs. 12 months | + | ! | + | + | + | ! |
| | Short-HER | 9 weeks vs. 12 months | + | ! | + | + | + | ! |
| | SOLD | 9 weeks vs. 12 months | + | ! | + | + | + | ! |
| | PERSEPHONE | 6 months vs. 12 months | + | ! | + | + | + | ! |
| HRQoL | PERSEPHONE | 6 months vs. 12 months | + | ! | ! | ! | + | ! |
| AE | PHARE | 6 months vs. 12 months | + | + | + | ! | + | ! |
| | E2198 | 12 weeks vs. 12 months | + | ! | + | ! | + | ! |
| | HORG | 6 months vs. 12 months | + | + | + | ! | + | ! |
| | Short-HER | 9 weeks vs. 12 months | + | + | + | ! | + | ! |
| | SOLD | 9 weeks vs. 12 months | + | + | + | ! | + | ! |
| | PERSEPHONE | 6 months vs. 12 months | + | + | + | ! | + | ! |

| Legend | | | |
|---|---|---|---|
| + | Low risk | D1 | Randomisation process |
| ! | Some concerns | D2 | Deviations from the intended interventions |
| - | High risk | D3 | Missing outcome data |
| | | D4 | Measurement of the outcome |
| | | D5 | Selection of the reported result |

### 6.2.4 Findings efficacy

#### Overall survival (OS)

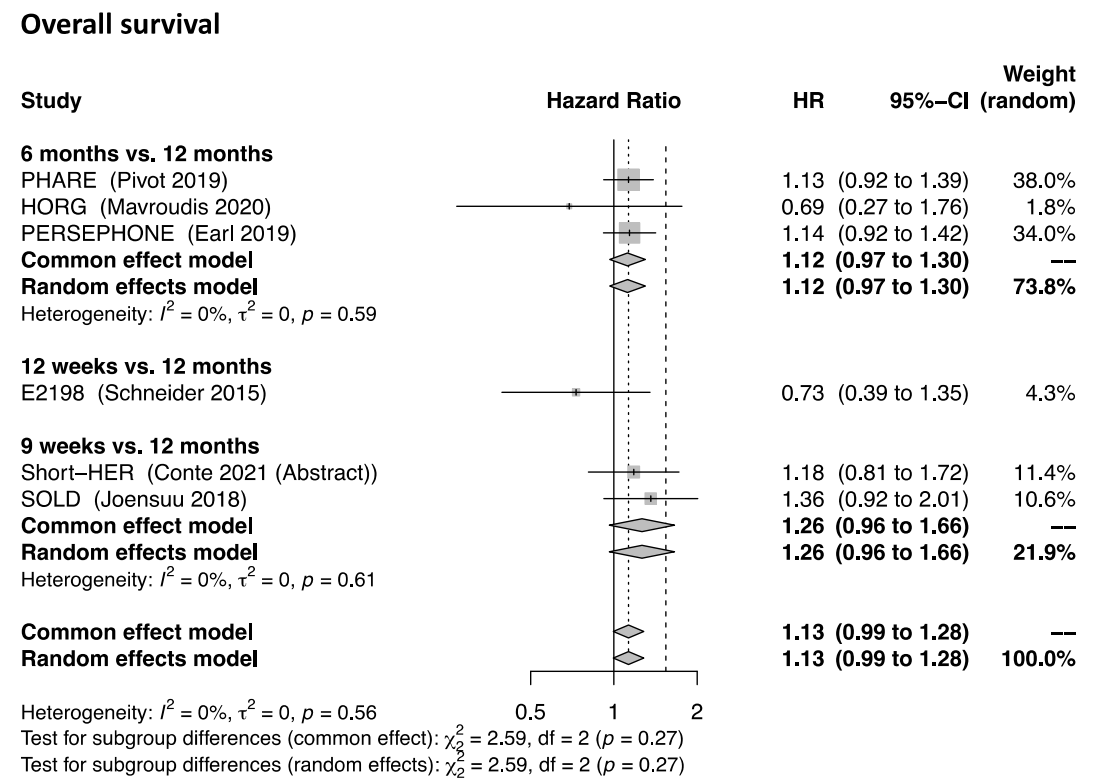
Data for the outcome OS were available from all 6 included RCTs. To the extent that this was possible to evaluate, there was no indication for publication bias regarding OS as published articles were identified for all registered trials (funnel plots are presented for completeness in Appendix 5).

Considering a non-inferiority margin of HR 1.543 for OS, random-effects meta-analyses based on ITT estimates result in a HR of 1.13 (95% CI 0.99 to 1.28, p<0.0001 for non-inferiority, $I^2$ = 0%, 6 RCTs, 11,603 participants; moderate certainty of evidence according to GRADE) with ≤6 months of trastuzumab treatment compared with 12 months of treatment (Figure 4). These results indicate

that OS with ≤6 months of trastuzumab treatment is likely non-inferior to 12 months of treatment (Table 10, Appendix 13).

When assessing the results in terms of superiority and disregarding the non-inferiority margin as a measure for what constitutes a clinically relevant benefit, confidence intervals included a null effect (HR 1.0). Hence, it is uncertain whether OS with 12 months of trastuzumab treatment is on average higher compared to ≤6 months of treatment (irrespective of clinical relevance). The common-effects meta-analysis resulted in the same findings due to the low level of heterogeneity (Figure 4).

**Figure 4: Results from primary meta-analysis for overall survival, including subgroup results for specific durations of trastuzumab treatment.**




**Legend:** Dashed line represents non-inferiority margin (HR 1.543), dotted line represents average effect (based on random-effects model), solid line represents no difference (HR 1.0). HRs greater than 1.0 indicate lower overall survival and HRs lower than 1.0 indicate higher overall survival with shorter treatment compared to 12 months of treatment. Tests for subgroup differences are based on a Q test and p-values indicate the statistical evidence regarding the null hypothesis that there is no difference in effects between subgroups. HR = hazard ratio, CI = confidence interval.

*Sensitivity analyses*

Sensitivity analyses excluding the E2198 trial (study design and risk of bias), excluding the HORG and E2198 trials (higher-risk population), and using an earlier estimate from the Short-HER trial resulted in similar results as in the primary analysis (Appendix 6). Further sensitivity analyses involved testing different non-inferiority margins (2%, 3% and 4% absolute difference in 2-, 3-, 4-, 5-, and 7-year OS), which provided statistical evidence for non-inferiority for all tested margins for the comparison of ≤6 months vs. 12 months of trastuzumab treatment (Appendix 8). A threshold

analysis based on a Monte Carlo simulation demonstrated a ≥97.5% probability of non-inferiority for non-inferiority margins higher or equal to HR 1.29 (Appendix 8).

*Subgroup analyses*

In subgroup analyses regarding OS for different trastuzumab treatment durations, random-effects meta-analyses result in a HR of 1.12 (95% CI 0.97 to 1.30, p<0.0001 for non-inferiority, $I^2$ = 0%, 3 RCTs, 7,949 participants, moderate certainty of evidence; Figure 4). These results indicate that OS with 6 months of trastuzumab treatment is likely non-inferior to 12 months of treatment (Table 11, Appendix 9). Further effect estimates were HR 0.73 (95% CI 0.39 to 1.35, p=0.017 for non-inferiority, 1 RCT) for 12 weeks vs. 12 months of trastuzumab treatment and HR 1.26 (95% CI 0.96 to 1.66, p=0.15 for non-inferiority, $I^2$ = 0%, 2 RCTs) for 9 weeks vs. 12 months of trastuzumab treatment. There was no statistical evidence for a difference between subgroups with different treatment durations (p=0.27).

Subgroup analyses for further patient, tumour, or treatment characteristics for the comparison of ≤6 months vs. 12 months of trastuzumab treatment were limited due to a lack of reporting of subgroup estimates (Table 5, Appendix 9). There was no statistical evidence for a difference in effect estimates between women aged ≤50 years (HR 0.94, 95% CI 0.64 to 1.38) and women aged >50 years (HR 1.25, 95% CI 0.97 to 1.62; p=0.23 for a between-group difference) based on data from 1 study, although effect estimates diverged between the groups. There was evidence for a difference between oestrogen receptor-negative (HR 1.51, 95% CI 1.10 to 2.08) and oestrogen receptor-positive breast cancer patients (HR 0.91, 95% CI 0.68 to 1.21; p=0.02 for a difference) based on 1 study. Effect estimates across subgroups of women with different menopausal status (p=0.78 for a difference based on 1 study) and women with grade 2 or 3 breast cancer (p=0.94 for a difference based on 1 study) were similar. Regarding treatments, there was no evidence for a difference between women receiving adjuvant (HR 1.04, 95% CI 0.81 to 1.33) and neoadjuvant chemotherapy (HR 1.55, 95% CI 0.99 to 2.42; p=0.12 for a difference) based on 1 study, although effect estimates in the 2 groups diverged. Effect estimates for anthracycline- and taxane-based (HR 1.18, 95% CI 0.87 to 1.60) and anthracycline-based chemotherapy (HR 1.00, 95% CI 0.71 to 1.40) were similar, while taxane-based chemotherapy (HR 2.06, 95% CI 1.01 to 4.22) survival was worse with 6 months treatment. However, there was no evidence for a between-group difference (p=0.20) based on 1 study. Last, there was evidence for a difference in effect estimates between concurrent administration of trastuzumab (HR 1.61, 95% CI 1.13 to 2.29) and sequential trastuzumab (HR 0.93, 95% CI 0.71 to 1.22; p=0.016 for a difference) based on 1 study.

**Table 5: Results from subgroup analyses related to patient, tumour, or treatment characteristics for overall survival based on non-inferiority meta-analyses.**

| OS | Trials | HR (95% CI) | p-value for non-inferiority | $I^2$ | Chi-squared for subgroup difference | p-value for subgroup difference |
|---|---|---|---|---|---|---|
| Age | 1 | | | | 1.46 | 0.2277 |
| Age ≤50 years | | 0.94 (0.64 to 1.38) | 0.0115 | – | | |
| Age >50 years | | 1.25 (0.97 to 1.62) | 0.1104 | – | | |
| Oestrogen receptor status | 1 | | | | 5.34 | 0.0208 |
| ER- | | 1.51 (1.10 to 2.08) | 0.8942 | – | | |
| ER+ | | 0.91 (0.68 to 1.21) | 0.0003 | – | | |
| Menopausal status | 1 | | | | 0.49 | 0.7846 |
| Premenopausal | | 0.98 (0.64 to 1.51) | 0.0382 | – | | |
| Perimenopausal | | 0.95 (0.32 to 2.83) | 0.3831 | – | | |
| Postmenopausal | | 1.16 (0.88 to 1.53) | 0.0457 | – | | |
| Breast cancer grade | 1 | | | | 0.01 | 0.9416 |
| Grade 1* | | – | – | – | | |
| Grade 2 | | 1.09 (0.72 to 1.65) | 0.1004 | – | | |
| Grade 3 | | 1.11 (0.86 to 1.43) | 0.0111 | – | | |
| Chemotherapy setting | 1 | | | | 2.38 | 0.1233 |
| Adjuvant chemotherapy | | 1.04 (0.81 to 1.33) | 0.0015 | – | | |
| Neoadjuvant chemotherapy | | 1.55 (0.99 to 2.42) | 0.9841 | – | | |
| Chemotherapy type | 1 | | | | 3.23 | 0.1986 |
| Anthracycline-based | | 1.00 (0.71 to 1.40) | 0.0114 | – | | |
| Taxane-based | | 2.06 (1.01 to 4.22) | 0.4290 | – | | |
| Anthracycline- and taxane-based | | 1.18 (0.87 to 1.60) | 0.0844 | – | | |
| Trastuzumab timing | 1 | | | | 5.84 | 0.0156 |
| Concurrent Trastuzumab | | 1.61 (1.13 to 2.29) | 0.8135 | – | | |
| Sequential Trastuzumab | | 0.93 (0.71 to 1.22) | 0.0002 | – | | |

**Legend**: CI = confidence interval, ER = oestrogen receptor, HR = hazard ratio, OS = overall survival. A non-inferiority margin of HR 1.543 was assumed for overall survival in meta-analyses. * No estimate available due to 0 events in the 12 months treatment group.

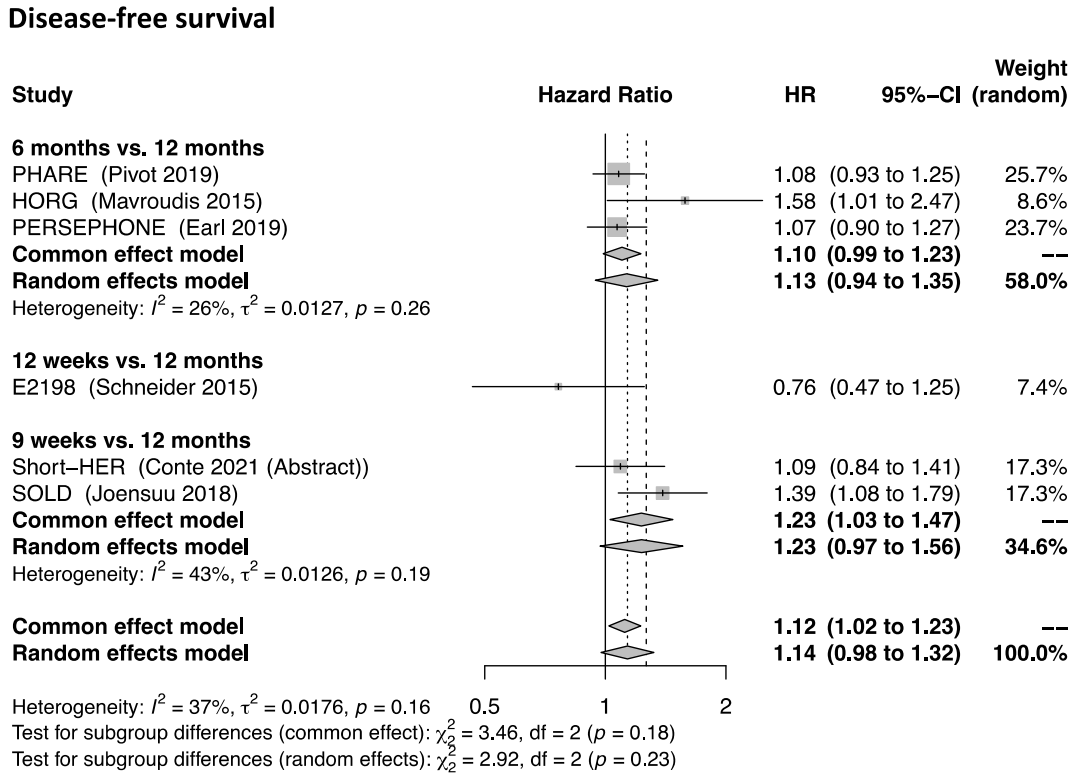
### Disease-free survival (DFS)

Evidence for DFS was available from all 6 included RCTs. There was no indication for publication bias regarding DFS as published articles were identified for all registered trials (funnel plots are presented for completeness Appendix 5).

Considering a non-inferiority margin of HR 1.266 for DFS, random-effects meta-analyses based on ITT estimates resulted in a HR of 1.14 (95% CI 0.98 to 1.32, p=0.22 for non-inferiority, $I^2$ = 37%, 6 RCTs, 11,603 participants, low certainty of evidence) for ≤6 months of trastuzumab treatment compared with 12 months of trastuzumab treatment (Figure 5). These results indicate that the evidence is inconclusive whether DFS with ≤6 months of trastuzumab treatment is non-inferior compared to 12 months of treatment (Table 10, Appendix 13).

When assessing the results in terms of superiority and disregarding the non-inferiority margin as a measure for a clinically relevant benefit, confidence intervals include a null effect (HR 1.0). Hence, the evidence is uncertain whether DFS with 12 months of trastuzumab treatment is on average higher compared to ≤6 months of treatment (irrespective of clinical relevance). The common-effects meta-analysis resulted in a HR of 1.12 (95% CI 1.02 to 1.23, p=0.008 for non-inferiority; Figure 5), which would be compatible with concluding that ≤6 months of trastuzumab treatment is likely non-inferior to 12 months of treatment.

**Figure 5: Results from primary meta-analysis for disease-free survival, including subgroup results for specific durations of trastuzumab treatment.**




**Legend**: Dashed line represents non-inferiority margin (HR 1.266), dotted line represents average effect (based on random-effects model), solid line represents no difference (HR 1.0). HRs greater than 1.0 indicate lower disease-free survival and HRs lower than 1.0 indicate higher disease-free survival with shorter treatment compared to 12 months of treatment. Tests for subgroup differences are based on a Q test and p-values indicate the statistical evidence regarding the null hypothesis that there is no difference in effects between subgroups. HR = hazard ratio, CI = confidence interval.

*Sensitivity analyses*

Sensitivity analyses excluding the E2198 trial (study design and risk of bias), excluding the HORG and E2198 trials (higher-risk population), and using an earlier estimate from the Short-HER trial showed similar results as the primary analysis (Appendix 7). PP estimates were reported only for PHARE, which found no relevant difference in the effect estimate for DFS (HR 1.10, 95% CI 0.93 to 1.30, p=0.15 for non-inferiority for 6 months vs. 12 months of trastuzumab treatment) compared to the ITT analysis. Further sensitivity analyses included the investigation of different non-inferiority margins (2%, 3% and 4% absolute difference in 2-, 3-, 4-, 5-, and 7-year DFS; Appendix 8). Therein, the evidence for non-inferiority was inconclusive when assuming non-inferiority margins corresponding to a 3% absolute difference in 5- or 7-year DFS (or a 2% difference in 3-, 4-, 5-, or 7-year DFS), while there was evidence for non-inferiority at non-inferiority margins corresponding to a 4% absolute difference in 2-, 3-, 4-, or 5-year DFS. A threshold analysis based on a Monte Carlo simulation demonstrated a ≥97.5% probability of non-inferiority for non-inferiority margins higher or equal to HR 1.33 for ≤6 months vs. 12 months of trastuzumab (Appendix 8).

*Subgroup analysis*

In subgroup analyses related to DFS for different trastuzumab treatment durations, random-effects meta-analyses resulted in a HR of 1.13 (95% CI 0.94 to 1.35, p=0.22 for non-inferiority, $I^2$ = 26%, 3 RCTs, 7,949 participants, low certainty of evidence; Table 11). These results indicate that the evidence is inconclusive whether 6 months of trastuzumab treatment is non-inferior to 12 months of treatment (Table 11, Appendix 10). Further effect estimates were HR 0.76 (95% CI 0.47 to 1.25, p=0.045 for non-inferiority, 1 RCT) for 12 weeks vs. 12 months of trastuzumab treatment and HR 1.23 (95% CI 0.97 to 1.56, p=0.81 for non-inferiority, $I^2$ = 43%, 2 RCTs) for 9 weeks vs. 12 months of trastuzumab treatment. There was no statistical evidence for a difference between subgroups with different treatment durations (p=0.23).

Subgroup analyses regarding DFS for further patient, tumour, or treatment characteristics for the comparison of ≤6 months vs. 12 months of trastuzumab treatment (Table 6, Appendix 10) showed no statistical evidence for a difference in effect estimates between women aged <50 years (HR 1.08, 95% CI 0.82 to 1.26) and women aged ≥50 years (HR 1.25, 95% CI 1.01 to 1.55; p=0.29 for a between-group difference) based on data from 4 studies. Furthermore, there was no evidence for a difference between women with oestrogen receptor-negative breast cancer (HR 1.24, 95% CI 1.06 to 1.45) and women with oestrogen receptor-positive breast cancer (HR 1.13, 95% CI 0.90 to 1.41; p=0.52 for a difference) based on 4 studies, and no evidence for a difference between women with progesterone receptor-negative breast cancer (HR 1.10, 95% CI 0.92 to 1.32) and women with progesterone receptor-positive breast cancer (HR 1.18, 95% CI 0.76 to 1.84; p=0.77 for a difference) based on 2 studies. There was no evidence for a difference in effect estimates between women with different menopausal status (premenopausal: HR 1.07, 95% CI 0.79 to 1.46; postmenopausal: HR 1.15, 95% CI 0.86 to 1.53; p=0.55 for a difference) based on 2 studies. Furthermore, there was no evidence for a difference between breast cancer grades (p=0.72 for a difference) based on 2 studies, and no evidence for a difference between women with different nodal status (p=0.74 for a difference) based on 4 studies. There was no evidence for a difference between tumours sized <2cm (HR 0.94, 95% CI 0.72 to 1.23) and tumours sized ≥2cm (HR 1.10, 95% CI 0.91 to 1.32; p=0.35 for a difference) based on 1 study. Regarding treatment, there was weak evidence for a difference in effect estimates between women receiving adjuvant chemotherapy (HR 0.98, 95% CI 0.81 to 1.19) and women receiving neoadjuvant chemotherapy (HR 1.43, 95% CI 1.00 to 2.04; p=0.069 for a difference) based on 1 study. Meanwhile, there was strong evidence for a difference in effect estimates between anthracycline- and taxane-based (HR 1.14, 95% CI 0.90 to 1.44), anthracycline-based (HR 0.86, 95% CI 0.65 to 1.13), and taxane-based chemotherapy (HR 2.47, HR 1.32 to 4.64; p=0.009 for a difference) based on 1 study. And last, there was no evidence for a difference in effect estimates between concurrent (HR 1.25, 95% CI 0.87 to 1.81) and sequential trastuzumab administration (HR 0.97, 95% CI 0.73 to 1.27; p=0.27 for a difference) based on 2 studies.

**Table 6: Results from subgroup analyses related to patient, tumour, or treatment characteristics for disease-free survival based on non-inferiority meta-analyses.**

| DFS | Trials | HR (95% CI) | p-value for non-inferiority | $I^2$ | Chi-squared for subgroup difference | p-value for subgroup difference |
|---|---|---|---|---|---|---|
| Age | 4 | | | | 1.14 | 0.2857 |
| Age ≤50 years* | | 1.08 (0.92 to 1.26) | 0.0468 | 0% | | |
| Age >50 years | | 1.25 (1.01 to 1.55) | 0.8993 | 60% | | |
| Oestrogen receptor status | 4 | | | | 0.41 | 0.5213 |
| ER- | | 1.24 (1.06 to 1.45) | 0.7770 | 14% | | |
| ER+ | | 1.13 (0.90 to 1.41) | 0.3233 | 39% | | |
| Progesterone receptor status | 2 | | | | 0.09 | 0.7688 |
| PR- | | 1.10 (0.92 to 1.32) | 0.1330 | 0% | | |
| PR+ | | 1.18 (0.76 to 1.84) | 0.7659 | 29% | | |
| Menopausal status | 2 | | | | 1.18 | 0.5549 |
| Premenopausal | | 1.07 (0.79 to 1.46) | 0.2839 | 0% | | |
| Perimenopausal | | 0.71 (0.31 to 1.62) | 0.1690 | – | | |
| Postmenopausal | | 1.15 (0.86 to 1.53) | 0.5028 | 12% | | |
| Breast cancer grade | 2 | | | | 0.13 | 0.7230 |
| Grade 1-2** | | 1.12 (0.82 to 1.52) | 0.4277 | 0% | | |
| Grade 3 | | 1.05 (0.85 to 1.28) | 0.0630 | 0% | | |
| Breast cancer size | 1 | | | | 0.88 | 0.3496 |
| Tumor size <2cm | | 0.94 (0.72 to 1.23) | 0.0320 | – | | |
| Tumor size ≥2cm | | 1.10 (0.91 to 1.32) | 0.1396 | – | | |
| Nodal status | 4 | | | | 0.12 | 0.7337 |
| Nodal status 0 | | 1.12 (0.92 to 1.36) | 0.2175 | 8% | | |
| Nodal status ≥1*** | | 1.17 (1.00 to 1.37) | 0.3230 | 0% | | |
| Chemotherapy setting | 1 | | | | 3.31 | 0.0688 |
| Adjuvant chemotherapy | | 0.98 (0.81 to 1.19) | 0.0108 | – | | |
| Neoadjuvant chemotherapy | | 1.43 (1.00 to 2.04) | 0.5017 | – | | |
| Chemotherapy type | 1 | | | | 9.43 | 0.0090 |
| Anthracycline-based | | 0.86 (0.65 to 1.13) | 0.0062 | – | | |
| Taxane-based | | 2.47 (1.32 to 4.64) | 0.0375 | – | | |
| Anthracycline- and taxane-based | | 1.14 (0.90 to 1.44) | 0.3836 | – | | |
| Trastuzumab timing | 2 | | | | 1.23 | 0.2667 |
| Concurrent Trastuzumab | | 0.97 (0.73 to 1.27) | 0.0521 | 67% | | |
| Sequential Trastuzumab | | 1.25 (0.87 to 1.81) | 0.9537 | 79% | | |

**Legend**: CI = confidence interval, DFS = disease-free survival, ER = oestrogen receptor, HR = hazard ratio, PR = progesterone receptor. A non-inferiority margin of HR 1.266 was assumed for disease-free survival in meta-analyses. * Age group definitions in PERSEPHONE differed from other studies (i.e., age ≤50 years vs. age >50 years). ** Estimate for grade 1 group in PERSEPHONE not estimable, includes only grade 2 breast cancer. *** Estimate for nodal status ≥1 in HORG was averaged for nodal status 1-3 and ≥4 groups using inverse variance weighted meta-analysis.

### Health-related quality of life (HRQoL)

HRQoL data were reported in 1 study (PERSEPHONE[21]), which included the EuroQol visual analogue scale (EQ-VAS) and general health status (evaluated using a single-item question). Reporting of this outcome was limited to group-specific results without an evaluation of between-group differences. There was no indication for publication bias regarding HRQoL, as reported estimates were found for all trials that specified the measurement of HRQoL in the trial registration or protocol (if available).

Overall, mean EQ-VAS scores were consistently higher in the group receiving 6 months compared to 12 months, with differences in mean scores ranging from 0.1 points higher to 2.4 points higher on a 0-100 point scale (0 being the worst imaginable health state and 100 being the best imaginable health state) in favour of 6 months treatment compared to 12 months treatment (Table 7). Similarly, the proportion of participants reporting 'good' or 'very good health' was generally higher in the 6

months compared to the 12 months group, with differences in proportions ranging from 0% to 5% higher (differences reported for sum in proportions reporting 'good' or 'very good' health; Table 8).

Given that differences in HRQoL were already observed at baseline (1.5 points higher on EQ-VAS and 5% higher with good or very good health in the group receiving 6 months of trastuzumab compared to the group receiving 12 months of trastuzumab) and inconsistent over time, and due to the concerns raised in the risk of bias assessment, the evidence regarding HRQoL was judged to be very uncertain (very low certainty of evidence).

**Table 7: Results for EuroQol visual analogue scale (EQ-VAS) scores reported in the PERSEPHONE study.**

| Timepoint | 6 months | | | 12 months | | | Difference in mean scores* |
|---|---|---|---|---|---|---|---|
| | N (total N=2,043) | Mean score | Median score (IQR) | N (total N=2,045) | Mean score | Median score (IQR) | |
| Start of trastuzumab | 1,038 | 74 | 76 (64.8 to 84.8) | 1,035 | 72.5 | 75 (60 to 85) | 1.5 higher |
| 3 months | 1,325 | 73.4 | 74.9 (64.8 to 84.8) | 1,263 | 72.4 | 75 (61.9 to 85) | 1.0 higher |
| 6 months | 1,338 | 77.2 | 80.0 (70 to 90) | 1,394 | 75.6 | 80 (69 to 89) | 1.6 higher |
| 9 months | 1,254 | 79.2 | 79.9 (71 to 90) | 1,373 | 76.8 | 80 (70 to 90) | 2.4 higher |
| 12 months | 1,195 | 80.3 | 84.8 (74 to 90) | 1,288 | 78.5 | 80 (70 to 90) | 1.8 higher |
| 18 months | 1,239 | 80.7 | 85 (75 to 94) | 1,237 | 79.8 | 84.9 (70 to 91) | 0.9 higher |
| 24 months | 1,165 | 80.5 | 85 (75 to 93.1) | 1,218 | 80.4 | 84.8 (74.8 to 92.9) | 0.1 higher |

**Legend**: * Difference calculated for 6 months vs. 12 months of trastuzumab treatment (higher means: in favour of 6 months treatment). IQR = interquartile range.

**Table 8: Results for general health status (single-item question) reported in the PERSEPHONE study.**

| Timepoint | 6 months | | | | | 12 months | | | | | Difference in % of participants reporting good or very good health (95% CI)* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N (total N=2,043) | Poor (%) | Fair (%) | Good (%) | Very good (%) | N (total N=2,045) | Poor (%) | Fair (%) | Good (%) | Very good (%) | |
| Start of trastuzumab | 1,038 | 2% | 14% | 49% | 35% | 1,035 | 4% | 17% | 47% | 32% | 5% higher (2% higher to 8% higher) |
| 3 months | 1,325 | 4% | 27% | 51% | 17% | 1,263 | 3% | 29% | 51% | 16% | 1% higher (3% lower to 5% higher) |
| 6 months | 1,338 | 2% | 25% | 55% | 19% | 1,394 | 2% | 24% | 57% | 17% | 0% (no difference; 3% lower to 3% higher) |
| 9 months | 1,254 | 2% | 20% | 57% | 21% | 1,373 | 2% | 25% | 57% | 16% | 5% higher (2% higher to 8% higher) |
| 12 months | 1,195 | 2% | 19% | 53% | 26% | 1,288 | 2% | 23% | 55% | 20% | 4% higher (1% higher to 7% higher) |
| 18 months | 1,239 | 2% | 20% | 52% | 26% | 1,237 | 3% | 20% | 53% | 24% | 1% higher (2% lower to 4% higher) |

| Timepoint | 6 months | | | | | 12 months | | | | | Difference in % of participants reporting good or very good health (95% CI)* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N (total N=2,043) | Poor (%) | Fair (%) | Good (%) | Very good (%) | N (total N=2,045) | Poor (%) | Fair (%) | Good (%) | Very good (%) | |
| 24 months | 1,165 | 3% | 17% | 53% | 28% | 1,218 | 3% | 17% | 52% | 28% | 1% higher (2% lower to 4% higher) |

**Legend**: * Differences in the summed proportion of participants reporting good or very good health and corresponding 95% confidence intervals for proportions were calculated for 6 months vs. 12 months of trastuzumab treatment (higher is in favour of 6 months treatment). CI = confidence interval.

### 6.2.5 Findings safety

#### Cardiac adverse effects

All 6 included RCTs reported results for cardiac AE outcomes, although definitions for specific AEs were heterogenous and data for individual cardiac AE outcomes were generally available only from up to 3 studies (Table 9, Appendix 11).

Random-effects meta-analyses indicated that the risk of congestive heart failure with ≤6 months of trastuzumab treatment is likely lower compared with 12 months of treatment (RR 0.65, 95% CI 0.42 to 1.00, p=0.051, $I^2$ = 0%, 3 RCTs, 5,788 participants, moderate certainty of evidence; Table 10). Meanwhile, the risk of congestive heart failure with 6 months of trastuzumab treatment may be lower compared with 12 months of treatment, but the evidence is very uncertain (RR 0.82, 95% CI 0.34 to 1.97, p=0.65, 1 RCT, 3,380 participants, very low certainty of evidence; Table 11).

The results further indicated that the risk of having a left-ventricular ejection fraction (LVEF) <50% and a decrease in LVEF of >10% with ≤6 months of trastuzumab treatment is likely lower compared with 12 months of treatment (RR 0.76, 95% CI 0.63 to 0.92, p=0.004, $I^2$ = 0%, 3 RCTs, 7,532 participants, moderate certainty of evidence; Table 10). The findings for the comparison of 6 months vs. 12 months of trastuzumab treatment were similar (RR 0.76, 0.62 to 0.93, p=0.008, $I^2$ = 10%, 2 RCTs, 7,298 participants, moderate certainty of evidence; Table 11).

In addition, there was strong to very strong statistical evidence for a reduced risk with ≤6 months of trastuzumab treatment compared with 12 month of treatment for the following cardiac AE outcomes (Table 9): LVEF <50% (RR 0.71, 95% CI 0.57 to 0.89, p=0.003, $I^2$ = 36%, 2 RCTs), clinical cardiac dysfunction (RR 0.64, 95% CI 0.55 to 0.75, p<0.0001, $I^2$ = 0%, 3 RCTs; see Table for definition), and cardiac events (RR 0.33, 95% CI 0.22 to 0.49, p<0.0001, $I^2$ = 0%, 1 RCT; see Table for definition). Although risks were generally lower with shorter treatment, there was considerable statistical uncertainty whether cardiac death (RR 0.57, 95% CI 0.17 to 1.95, p=0.37, 1 RCT) and treatment discontinuation due to cardiac AEs (RR 0.27, 95% CI 0.01 to 8.09, p=0.45, $I^2$ = 79%, 3 RCTs) are reduced with ≤6 months vs. 12 months of treatment. The results for the comparison of 6 months vs. 12 months of treatment were similar for these non-critical cardiac AE outcomes.

Subgroup analyses by chemotherapy regimen could be conducted for the outcome of cardiac events (Appendix 11). Therein, there was no statistical evidence for a difference between anthracycline- and taxane-based (RR 0.36, 95% CI 0.23 to 0.57), anthracycline-based (RR 0.27, 95% CI 0.11 to 0.64), and taxane-based or other chemotherapy (RR 0.35, 95% CI 0.07 to 1.77; p=0.84 for a difference) based on the PHARE study comparing 6 months vs. 12 months of trastuzumab treatment.

**Other adverse effects**

All 6 RCTs reported information on other AE outcomes, with data from up to 5 RCTs available for the individual outcomes (Table 9, Appendix 12).

Based on random-effects meta-analyses, the risk of any severe (grade ≥3) AE with ≤6 months of trastuzumab treatment may be lower compared with 12 months of treatment (RR 0.89, 95% CI 0.72 to 1.09, p=0.25, $I^2$ = 88%, 2 RCTs, 6,007 participants, low certainty of evidence; Table 10). Subgroup results also indicated that the risk of any severe (grade ≥3) AE with 6 months of trastuzumab treatment may be lower compared with 12 months of treatment, with lower statistical uncertainty (RR 0.79, 95% CI 0.70 to 0.90, p=0.0002, 1 RCT, 3,833 participants, low certainty of evidence; Table 11).

The results further indicated that the risk of trastuzumab discontinuation due to any AE with ≤6 months of trastuzumab treatment is likely lower compared with 12 months of treatment (RR 0.37, 95% CI 0.27 to 0.50, p<0.0001, $I^2$ = 66%, 3 RCTs, 6,807 participants, moderate certainty of evidence; Table 10). The results for the comparison of 6 months vs. 12 months of trastuzumab treatment were similar (RR 0.27, 0.19 to 0.39, p<0.0001, 1 RCTs, 3,380 participants, low certainty of evidence; Table 11).

Furthermore, there was statistical evidence for a reduced risk with ≤6 months of trastuzumab treatment compared with 12 month of treatment for fatigue (RR 0.79, 95% CI 0.64 to 0.99, p=0.037, $I^2$ = 22%, 3 RCTs; Table 9). Although risks were generally lower with shorter treatment, there was no statistical evidence for a reduced risk of diarrhea (RR 0.84, 95% CI 0.59 to 1.19, p=0.33, $I^2$ = 19%, 5 RCTs), nausea (RR 0.94, 95% CI 0.48 to 1.86, p=0.87, $I^2$ = 57%, 3 RCTs), vomiting (RR 0.95, 95% CI 0.61 to 1.47, p=0.81, $I^2$ = 0%, 4 RCTs), or rash (RR 0.90, 95% CI 0.51 to 1.58, p=0.71, 1 RCT) for this comparison. No data related to osteoporosis/bone loss or vision/eye problems was reported in identified studies. Results for the comparison of 6 months vs. 12 months of trastuzumab treatment were similar for these non-critical other AE outcomes, with one exception: there was statistical evidence for a reduced risk of nausea with 6 months vs. 12 months of treatment (RR 0.56, 95% CI 0.32 to 0.96, p=0.036, 1 RCT).

**Table 9: Results of meta-analyses of adverse effects outcomes for the comparisons of ≤6 months vs. 12 months of trastuzumab treatment and 6 months vs. 12 months of trastuzumab treatment.**

| Outcome | ≤6 months vs. 12 months | | | | | 6 months vs. 12 months | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Studies | RR (95% CI) | p-value* | Risk with 12 months treatment** | ARD (95% CI) per 1'000 | Studies | RR (95% CI) | p-value* | Risk with 12 months treatment** | ARD (95% CI) per 1'000 |
| **Cardiac AEs** | | | | | | | | | | |
| Congestive heart failure | 3 | 0.65 (0.42 to 1.00) | 0.0514 | 2.7% | -9 (-15 to 0) | 1 | 0.82 (0.34 to 1.97) | 0.6543 | 2.7% | -5 (-18 to 26) |
| LVEF <50% and LVEF decrease >10% | 3 | 0.76 (0.63 to 0.92) | 0.0044 | 6.4% | -15 (-24 to -5) | 2 | 0.76 (0.62 to 0.93) | 0.0080 | 6.4% | -15 (-24 to -4) |
| LVEF <50% | 2 | 0.71 (0.57 to 0.89) | 0.0025 | 8.7% | -25 (-37 to -10) | 2 | 0.71 (0.57 to 0.89) | 0.0025 | 8.7% | -25 (-37 to -10) |
| Clinical cardiac dysfunction** | 3 | 0.64 (0.55 to 0.75) | <0.0001 | 8.7% | -31 (-39 to -21) | 2 | 0.66 (0.56 to 0.77) | <0.0001 | 8.7% | -30 (-38 to -20) |
| Cardiac events*** | 2 | 0.33 (0.25 to 0.44) | <0.0001 | 9.1% | -61 (-69 to -51) | 1 | 0.33 (0.22 to 0.49) | <0.0001 | 9.1% | -61 (-71 to -46) |
| Cardiac death | 1 | 0.57 (0.17 to 1.95) | 0.3726 | 0.3% | -1 (-3 to 3) | 1 | 0.57 (0.17 to 1.95) | 0.3726 | 0.3% | -1 (-3 to 3) |
| Trastuzumab discontinuation due to cardiac AEs | 3 | 0.27 (0.01 to 8.09) | 0.4537 | 5.1% | -37 (-51 to 362) | 3 | 0.27 (0.01 to 8.09) | 0.4537 | 5.1% | -37 (-51 to 362) |
| **Other AEs** | | | | | | | | | | |
| Any severe (grade >=3) AE | 2 | 0.89 (0.72 to 1.09) | 0.2530 | 41.7% | -47 (-116 to 37) | 1 | 0.79 (0.70 to 0.90) | 0.0002 | 41.7% | -86 (-124 to -43) |
| Trastuzumab discontinuation due to any AE | 3 | 0.37 (0.27 to 0.50) | <0.0001 | 13.3% | -84 (-96 to -67) | 1 | 0.27 (0.19 to 0.39) | <0.0001 | 13.3% | -97 (-107 to -81) |
| Fatigue | 3 | 0.79 (0.64 to 0.99) | 0.0373 | 9.8% | -20 (-36 to -1) | 1 | 0.72 (0.60 to 0.87) | 0.0008 | 9.8% | -27 (-39 to -12) |
| Diarrhea | 5 | 0.84 (0.59 to 1.19) | 0.3269 | 3.0% | -5 (-12 to 6) | 2 | 0.93 (0.53 to 1.62) | 0.7887 | 3.0% | -2 (-14 to 19) |
| Nausa | 3 | 0.94 (0.48 to 1.86) | 0.8690 | 2.7% | -1 (-14 to 23) | 1 | 0.56 (0.32 to 0.96) | 0.0362 | 2.7% | -12 (-18 to -1) |
| Vomiting | 4 | 0.95 (0.61 to 1.47) | 0.8128 | 1.9% | -1 (-7 to 9) | 2 | 0.92 (0.55 to 1.56) | 0.7683 | 1.9% | -1 (-8 to 10) |
| Rash | 1 | 0.90 (0.51 to 1.58) | 0.7097 | 1.3% | -1 (-6 to 8) | 1 | 0.90 (0.51 to 1.58) | 0.7097 | 1.3% | -1 (-6 to 8) |

**Legend**: AE = adverse effect, CI = confidence interval, LVEF = left-ventricular ejection fraction, RR = risk ratio. Results are derived from random-effects meta-analysis. * P-values are calculated for superiority in terms of safety. ** The risk with 12 months of trastuzumab treatment was estimated as the inverse variance weighted average risk across 12 months treatment groups of all included RCTs reporting the respective adverse effect outcome. Time horizons of reported risks differed between RCTs and risks were assumed to be constant over time in analyses. *** Clinical cardiac dysfunction was defined as composite outcome in RCTs, with some differences in definitions (PHARE: cardiac death, congestive heart failure, cardiac dysfunction defined as significant LVEF decrease with asymptomatic or mildly symptomatic (NYHA class I-II) status; SOLD: congestive heart failure necessitating medication or medical intervention, myocardial infarction, cardiac or coronary artery surgery, or stenting; PERSEPHONE: symptoms of cardiac disease, signs of congestive heart failure, or use of new medication for cardiac disease). **** Cardiac events were defined as composite outcome in RCTs (PHARE: cardiac death, congestive heart failure, cardiac dysfunction defined as significant LVEF decrease with asymptomatic or mildly symptomatic (NYHA class I-II) status, LVEF <50%, LVEF <50% and LVEF decrease from baseline by >10%, or LVEF ≥50% and LVEF decrease from baseline by >15%; Short-HER: grade ≥2 cardiac AEs according to CTCAE version 3).

### 6.2.6 GRADE Summary of Findings Table

The results of the systematic review, meta-analysis, and GRADE assessment of clinical efficacy and safety are summarised in Table 10 and Appendix 13 for the comparison of ≤6 months vs. 12 months of trastuzumab treatment, and in Table 11 and Appendix 14 for the comparison of 6 months vs. 12 months of trastuzumab treatment.

**Table 10: GRADE summary of findings table for the comparison of ≤6 months vs. 12 months of trastuzumab treatment.**

| Outcomes | № of participants (studies) | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | | Comments |
|---|---|---|---|---|---|---|
| | | | | Risk with 12 months trastuzumab | Risk difference with ≤6 months trastuzumab | |
| **Overall survival (OS)** | 11603 (6 RCTs) | ⊕⊕⊕◯ Moderate[a] | **HR 1.13** (0.99 to 1.28) | **3-year OS*** | | Considering a non-inferiority margin of HR 1.543, OS with 6 months or less of trastuzumab treatment is likely non-inferior to 12 months of trastuzumab treatment. |
| | | | | 975 per 1,000 | **3 fewer survive per 1,000** (7 fewer to 0 fewer) | |
| | | | | **5-year OS*** | | |
| | | | | 942 per 1,000 | **7 fewer survive per 1,000** (16 fewer to 1 more) | |
| **Disease-free survival (DFS)** | 11603 (6 RCTs) | ⊕⊕◯◯ Low[a,b] | **HR 1.14** (0.98 to 1.32) | **3-year DFS*** | | Considering a non-inferiority margin of HR 1.266, the evidence is inconclusive whether DFS with 6 months or less of trastuzumab treatment is non-inferior to 12 months of trastuzumab treatment. |
| | | | | 930 per 1,000 | **9 fewer remain disease free per 1,000** (21 fewer to 1 more) | |
| | | | | **5-year DFS*** | | |
| | | | | 877 per 1,000 | **16 fewer remain disease free per 1,000** (36 fewer to 2 more) | |

| Outcomes | № of participants (studies) | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | | Comments |
|---|---|---|---|---|---|---|
| | | | | Risk with 12 months trastuzumab | Risk difference with ≤6 months trastuzumab | |
| **Health-related quality of life (HRQoL)** | 4088 (1 RCT) | ⊕◯◯◯ Very low[c,d] | Mean EQ-VAS scores were higher in the 6 months compared to the 12 months treatment group (ranging between 0.1 points higher (at 24 months of follow-up) to 2.4 points higher (at 9 months of follow-up)). The proportion of participants reporting good or very good general health was the same or higher in the 6 months compared to the 12 months treatment group (ranging between 0% (at 6 months of follow-up) to 5% (at 9 months of follow-up)). | | | HRQoL with 6 months or less of trastuzumab treatment may be similar or higher compared with 12 months of trastuzumab treatment, but the evidence is very uncertain. |
| **Congestive heart failure** | 5788 (3 RCTs) | ⊕⊕⊕◯ Moderate[e] | **RR 0.65** (0.42 to 1.00) | **Study population**** | | The risk of congestive heart failure with 6 months or less of trastuzumab treatment is likely lower compared with 12 months of trastuzumab treatment. |
| | | | | 18 per 1,000 | **6 fewer experience the AE per 1,000** (10 fewer to 0 fewer) | |
| | | | | **Weighted average**** | | |
| | | | | 27 per 1,000 | **9 fewer experience the AE per 1,000** (15 fewer to 0 fewer) | |
| **LVEF <50% and LVEF decrease >10%** | 7532 (3 RCTs) | ⊕⊕⊕◯ Moderate[e] | **RR 0.76** (0.63 to 0.92) | **Study population**** | | The risk of having a LVEF <50% and a decrease in LVEF of >10% with 6 months or less of trastuzumab treatment is likely lower compared with 12 months of trastuzumab treatment. |
| | | | | 62 per 1,000 | **15 fewer experience the AE per 1,000** (23 fewer to 5 fewer) | |
| | | | | **Weighted average**** | | |
| | | | | 64 per 1,000 | **15 fewer experience the AE per 1,000** (24 fewer to 5 fewer) | |
| **Any severe (grade ≥3) AE** | 6007 (2 RCTs) | ⊕⊕◯◯ Low[e,f] | **RR 0.89** (0.72 to 1.09) | **Study population**** | | The risk of any severe (grade ≥3) AE with 6 months or less of trastuzumab treatment may be lower compared with 12 months of trastuzumab treatment. |
| | | | | 363 per 1,000 | **40 fewer experience the AE per 1,000** (102 fewer to 33 more) | |
| | | | | **Weighted average**** | | |

| Outcomes | № of participants (studies) | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | | Comments |
|---|---|---|---|---|---|---|
| | | | | Risk with 12 months trastuzumab | Risk difference with ≤6 months trastuzumab | |
| | | | | 417 per 1,000 | **46 fewer experience the AE per 1,000** (117 fewer to 38 more) | |
| **Trastuzumab discontinuation due to any AE** | 6807 (3 RCTs) | ⊕⊕⊕◯ Moderate[e] | **RR 0.37** (0.27 to 0.50) | **Study population**** | | The risk of trastuzumab discontinuation due to any AE with 6 months or less of trastuzumab treatment is likely lower compared with 12 months of trastuzumab treatment. |
| | | | | 120 per 1,000 | **76 fewer discontinue per 1,000** (88 fewer to 60 fewer) | |
| | | | | **Weighted average**** | | |
| | | | | 133 per 1,000 | **84 fewer discontinue per 1,000** (97 fewer to 66 fewer) | |

* **For OS and DFS, the anticipated absolute effects** (and their 95% confidence interval) are based on the assumed survival in the 12 months treatment group and the relative effect of the shorter treatment (HR and its 95% CI). **Of note, the absolute effects are for a between-group difference and correspond to a superiority comparison** (i.e., the null hypothesis of HR = 1). Fewer means that less women survive (OS) or remain disease-free (DFS) with shorter treatment compared to 12 months of treatment. However, this **number may be less than what would be deemed clinically relevant based on the prespecified non-inferiority margins of a 3% absolute difference in OS and DFS**, corresponding to 30 fewer per 1,000 women. Please refer to the Comments for the relevant interpretation regarding non-inferiority.

** **For safety outcomes, the anticipated absolute effects** (and their 95% confidence interval) are based on the assumed risk in the 12 months treatment group and the relative effect of the shorter treatment (RR and its 95% CI). The risks in the 12 months treatment group have been calculated using **2 different methods**: (i) the **'study population'** estimate was calculated as the overall risk in the 12 month treatment group across studies included in the corresponding meta-analysis (total number of events / total number of participants; unweighted approach, not taking into account all reported evidence for subgroup analyses), and (ii) the **'weighted average'** estimate was calculated as the inverse variance weighted average risk across 12 month treatment groups of all studies reporting data for the respective adverse effect outcome (weighted average of number of events / number of participants across all studies; taking into account evidence from studies not included in subgroup meta-analyses). Fewer means that less women experience AEs with shorter treatment compared to 12 months of treatment (corresponding to a superiority comparison).

**Legend**: AE = adverse effect, CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, HRQoL = health-related quality of life, LVEF = left-ventricular ejection fraction, OS = overall survival, RR = risk ratio.

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

| Outcomes | № of participants (studies) | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | | Comments |
|---|---|---|---|---|---|---|
| | | | | Risk with 12 months trastuzumab | Risk difference with ≤6 months trastuzumab | |

**Explanations**

a. Risk of bias downgraded by 1 level (resulting in serious risk of bias for OS and DFS): concerns regarding deviations from intended interventions in 3 studies (intention-to-treat effects may be biased towards non-inferiority due to potentially relevant protocol violations in PHARE, E2198 and PERSEPHONE).

b. Imprecision downgraded by 1 level (resulting in serious imprecision for DFS): Considering the specified non-inferiority margin of HR 1.266, the 95% confidence interval includes effects compatible with inferiority.

c. Risk of bias downgraded by 2 levels (resulting in very serious risk of bias for HRQoL): major concerns regarding deviations from intended interventions (due to reporting intention-to-treat estimates with potentially relevant protocol violations), missing outcome data, bias in measurement of the outcome (absence of blinding/placebo control with collection of self-reported outcome data). Differences in HRQoL were observed already at the start of trastuzumab treatment, and no estimates from comparative analyses were provided.

d. Imprecision downgraded by 2 levels (resulting in very serious imprecision for HRQoL): Evidence from single study and no comparative estimates for between-group differences or confidence intervals available; no conclusive assessment possible.

e. Risk of bias downgraded by 1 level (resulting in serious risk of bias): concerns regarding measurement of the outcome (absence of blinding/placebo control with collection of self-reported outcome data).

f. Imprecision downgraded by 1 level (resulting in serious imprecision for safety outcomes): 95% confidence interval is consistent with the possibility of fewer or more events.

**Table 11: GRADE summary of findings table for the comparison of 6 months vs. 12 months of trastuzumab treatment.**

| Outcomes | № of participants (studies) | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | | Comments |
|---|---|---|---|---|---|---|
| | | | | Risk with 12 months trastuzumab | Risk difference with 6 months trastuzumab | |
| **Overall survival (OS)** | 7949 (3 RCTs) | ⊕⊕⊕◯ Moderate[a] | **HR 1.12** (0.97 to 1.30) | **3-year OS*** | | Considering a non-inferiority margin of HR 1.543, OS with 6 months of trastuzumab treatment is likely non-inferior to 12 months of trastuzumab treatment. |
| | | | | 975 per 1,000 | **3 fewer survive per 1,000** (8 fewer to 1 more) | |
| | | | | **5-year OS*** | | |
| | | | | 942 per 1,000 | **7 fewer survive per 1,000** (17 fewer to 2 more) | |
| **Disease-free survival (DFS)** | 7949 (3 RCTs) | ⊕⊕◯◯ Low[a,b] | **HR 1.13** (0.94 to 1.35) | **3-year DFS*** | | Considering a non-inferiority margin of HR 1.266, the evidence is inconclusive whether DFS with 6 months of trastuzumab treatment is non-inferior to 12 months of trastuzumab treatment. |
| | | | | 930 per 1,000 | **9 fewer remain disease free per 1,000** (23 fewer to 4 more) | |
| | | | | **5-year DFS*** | | |
| | | | | 877 per 1,000 | **15 fewer remain disease free per 1,000** (39 fewer to 7 more) | |
| **Health-related quality of life (HRQoL)** | 4088 (1 RCT) | ⊕◯◯◯ Very low[c,d] | Mean EQ-VAS scores were higher in the 6 months compared to the 12 months treatment group (ranging between 0.1 points higher (at 24 months of follow-up) to 2.4 points higher (at 9 months of follow-up)). The proportion of participants reporting good or very good general health was the same or higher in the 6 months compared to the 12 months treatment group (ranging between 0% (at 6 months of follow-up) to 5% (at 9 months of follow-up)). | | | HRQoL with 6 months of trastuzumab treatment may be similar or higher compared with 12 months of trastuzumab treatment, but the evidence is very uncertain. |
| **Congestive heart failure** | 3380 (1 RCT) | ⊕◯◯◯ Very low[e,f] | **RR 0.82** (0.34 to 1.97) | **Study population**** | | The risk of congestive heart failure with 6 months of trastuzumab treatment may be lower compared with 12 months of trastuzumab treatment, but the evidence is very uncertain. |
| | | | | 7 per 1,000 | **1 fewer experience the AE per 1,000** (4 fewer to 6 more) | |
| | | | | **Weighted average**** | | |

| Outcomes | № of participants (studies) | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | | Comments |
|---|---|---|---|---|---|---|
| | | | | Risk with 12 months trastuzumab | Risk difference with 6 months trastuzumab | |
| | | | | 27 per 1,000 | **5 fewer experience the AE per 1,000** (18 fewer to 26 more) | |
| **LVEF <50% and LVEF decrease >10%** | 7298 (2 RCTs) | ⊕⊕⊕◯ Moderate[e] | **RR 0.76** (0.62 to 0.93) | **Study population**** | | The risk of having a LVEF <50% and a decrease in LVEF of >10% with 6 months of trastuzumab treatment is likely lower compared with 12 months of trastuzumab treatment. |
| | | | | 64 per 1,000 | **15 fewer experience the AE per 1,000** (24 fewer to 4 fewer) | |
| | | | | **Weighted average**** | | |
| | | | | 64 per 1,000 | **15 fewer experience the AE per 1,000** (24 fewer to 4 fewer) | |
| **Any severe (grade ≥3) AE** | 3833 (1 RCT) | ⊕⊕◯◯ Low[e,g] | **RR 0.79** (0.70 to 0.90) | **Study population**** | | The risk of any severe (grade ≥3) AE with 6 months of trastuzumab treatment may be lower compared with 12 months of trastuzumab treatment. |
| | | | | 242 per 1,000 | **51 fewer experience the AE per 1,000** (73 fewer to 24 fewer) | |
| | | | | **Weighted average**** | | |
| | | | | 417 per 1,000 | **88 fewer experience the AE per 1,000** (125 fewer to 42 fewer) | |
| **Trastuzumab discontinuation due to any AE** | 3380 (1 RCT) | ⊕⊕◯◯ Low[e,g] | **RR 0.27** (0.19 to 0.39) | **Study population**** | | The risk of trastuzumab discontinuation due to any AE with 6 months of trastuzumab treatment may be lower compared with 12 months of trastuzumab treatment. |
| | | | | 82 per 1,000 | **60 fewer discontinue per 1,000** (67 fewer to 50 fewer) | |
| | | | | **Weighted average**** | | |
| | | | | 133 per 1,000 | **97 fewer discontinue per 1,000** (108 fewer to 81 fewer) | |

| Outcomes | № of participants (studies) | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | | Comments |
|---|---|---|---|---|---|---|
| | | | | Risk with 12 months trastuzumab | Risk difference with 6 months trastuzumab | |

* **For OS and DFS, the anticipated absolute effects** (and their 95% confidence interval) are based on the assumed survival in the 12 months treatment group and the relative effect of the shorter treatment (HR and its 95% CI). **Of note, the absolute effects are for a between-group difference and correspond to a superiority comparison** (i.e., the null hypothesis of HR = 1). Fewer means that less women survive (OS) or remain disease-free (DFS) with shorter treatment compared to 12 months of treatment. However, this **number may be less than what would be deemed clinically relevant based on the prespecified non-inferiority margins of a 3% absolute difference in OS and DFS**, corresponding to 30 fewer per 1,000 women. Please refer to the Comments for the relevant interpretation regarding non-inferiority.

** **For safety outcomes, the anticipated absolute effects** (and their 95% confidence interval) are based on the assumed risk in the 12 months treatment group and the relative effect of the shorter treatment (RR and its 95% CI). The risks in the 12 months treatment group have been calculated using **2 different methods**: (i) the **'study population'** estimate was calculated as the overall risk in the 12 month treatment group across studies included in the corresponding meta-analysis (total number of events / total number of participants; unweighted approach, not taking into account all reported evidence for subgroup analyses), and (ii) the **'weighted average'** estimate was calculated as the inverse variance weighted average risk across 12 month treatment groups of all studies reporting data for the respective adverse effect outcome (weighted average of number of events / number of participants across all studies; taking into account evidence from studies not included in subgroup meta-analyses). Fewer means that less women experience AEs with shorter treatment compared to 12 months of treatment (corresponding to a superiority comparison).

**Legend**: AE = adverse effect, CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, HRQoL = health-related quality of life, LVEF = left-ventricular ejection fraction, OS = overall survival, RR = risk ratio.

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

**Explanations**
a. Risk of bias downgraded by 1 level (resulting in serious risk of bias for OS and DFS): concerns regarding deviations from intended interventions in 3 studies (intention-to-treat effects may be biased towards non-inferiority due to potentially relevant protocol violations in PHARE, E2198 and PERSEPHONE).
b. Imprecision downgraded by 1 level (resulting in serious imprecision for DFS): Considering the specified non-inferiority margin of HR 1.266, the 95% confidence interval includes effects compatible with inferiority.
c. Risk of bias downgraded by 2 levels (resulting in very serious risk of bias for HRQoL): major concerns regarding deviations from intended interventions (due to reporting intention-to-treat estimates with potentially relevant protocol violations), missing outcome data, bias in measurement of the outcome (absence of blinding/placebo control with collection of self-reported outcome data). Differences in HRQoL were observed already at the start of trastuzumab treatment, and no estimates from comparative analyses were provided.
d. Imprecision downgraded by 2 levels (resulting in very serious imprecision for HRQoL): Evidence from single study and no comparative estimates for between-group differences or confidence intervals available; no conclusive assessment possible.
e. Risk of bias downgraded by 1 level (resulting in serious risk of bias): concerns regarding measurement of the outcome (absence of blinding/placebo control with collection of self-reported outcome data).
f. Imprecision downgraded by 2 levels (resulting in very serious imprecision for safety outcomes): evidence from single study and 95% confidence interval is consistent with the possibility of fewer or more events.
g. Imprecision downgraded by 1 level (resulting in serious imprecision for safety outcomes): evidence from single study.

# 7. Costs, cost-effectiveness and budget impact

***Summary statement costs, cost-effectiveness and budget impact***

All published cost-effectiveness studies reported that ≤6 months of trastuzumab treatment is less expensive than 12 months of treatment. Five studies suggested that ≤6 months of trastuzumab is more effective (i.e., lead to more QALYs gained than 12 months of trastuzumab), while 2 studies concluded the opposite. The *de novo* cost-effectiveness analysis conducted for Switzerland suggested that 6 months of trastuzumab treatment resulted in lower costs (CHF -15,047 per patient) compared to 12 months of treatment. At the same time, 6 months of trastuzumab treatment led to a total decrease of 0.62 QALYs per patient, leading to an ICER of CHF 24,242 saved per QALY lost. The budget impact analysis suggested that switching from 12 months to 6 months of trastuzumab treatment would lead to a decrease in total costs of CHF 13.6 million in 2024.

## 7.1 Methodology costs, cost-effectiveness and budget impact

To economically evaluate ≤6 months of trastuzumab treatment vs. 12 months of trastuzumab treatment, a systematic literature review of economic evaluations, followed by a *de novo* cost-effectiveness analysis and a budget impact analysis, was undertaken.

### 7.1.1 Databases and search strategy

The systematic literature search for economic evaluations was conducted in MEDLINE, EMBASE, the INAHTA database, EconLit, and the National Health Service Economic Evaluation Database (NHSEED).

The search string was obtained by integrating and combining the search string used in the clinical part and published search strings for health economic analyses.[77] Unspecific abbreviations such as CUA (for cost-utility analysis) or CBA (for cost-benefit analysis) were not used.

Compared to the inclusion/exclusion criteria for the assessment of clinical efficacy and safety, the economic assessment focused on other study designs (economic evaluations instead of RCTs) and economic outcomes (Table 12). The process of identification of economic studies is graphically summarised using a PRISMA flow diagram.

Table 12: Study inclusion and exclusion criteria for the economic assessment.

| Criterion | Inclusion | Exclusion |
|---|---|---|
| Publication period | No restriction. | - |
| Publication status | Published full text available. | Full text not available.<br>Only conference abstract. |
| Language | English, German, French, Italian | - |
| Setting/Location | No restriction. | - |
| Study design | Health economic analysis, including within-trial or model-based cost minimisation, cost-effectiveness, cost-utility, cost-benefit, and budget impact/cost analyses | Not health economic analyses |
| Population | Females or males (≥18 years) with early breast cancer. | Females or males without breast cancer or with advanced breast cancer.<br>Animal studies |
| Intervention | PICO 1: Adjuvant or neoadjuvant trastuzumab treatment, ≤6 months treatment duration.<br>PICO 2: Adjuvant or neoadjuvant trastuzumab treatment combined with pertuzumab, ≤6 months treatment duration. | Other drugs for the treatment of early breast cancer. |
| Comparator | PICO 1: Adjuvant or neoadjuvant trastuzumab treatment, 12 months treatment duration.<br>PICO 2: Adjuvant or neoadjuvant trastuzumab treatment combined with pertuzumab, 12 months treatment duration. | Other drugs for the treatment of early breast cancer.<br>No drug treatment / placebo. |
| Outcomes | Cost-effectiveness (costs, QALYs, life-years)<br>Budget impact | - |

Search strategies and search results for economic studies are reported in Appendix 15.

### 7.1.2 Assessment of quality of reporting

The quality of reporting of economic studies was assessed according to Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022).[78] However, the assessment was restricted to the following set of key items:

- Item 5: study population (Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).
- Item 7: comparators (Describe the interventions or strategies being compared and why chosen).
- Item 8: perspective (State the perspective(s) adopted by the study and why chosen).
- Item 9: time horizon (State the time horizon for the study and why appropriate).

– Item 23: summary of main results (Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure).

The reason for the restriction to the selected items, is because they are considered fundamental as they confirm that the population, intervention, and comparator in the identified cost-effectiveness analysis are in line with the PICOs of this HTA. Moreover, they also indicate whether other relevant key information has been reported in relation to perspective, time horizon, and cost-effectiveness components.

### 7.1.3 Methodology data extraction, analysis and synthesis of health economic data

*Systematic review of economic evaluations*

One reviewer extracted data into a predefined work sheet. Extracted data was checked by a second reviewer. Any disagreement was solved by consensus. Where consensus could not be reached, a third reviewer was consulted. The following data was extracted:

– Type of economic evaluation
– Type of model used (if applicable)
– Country
– Study population
– Intervention
– Comparator(s)
– Perspective(s) of cost assessment (e.g., healthcare, societal)
– Cost types included
– Time horizon and discount rate
– Clinical and HRQoL-related data sources and assumptions used as input parameters
– Cost, life year, and quality adjusted life year (QALY) results per strategy (including currency and cost year)
– Incremental cost-effectiveness ratio (ICER) or equivalent
– Information to assess the quality of studies and reporting
– Conflicts of interest and funding sources

### 7.1.4 *De novo* health economic modelling

A *de novo* cost-effectiveness analysis was conducted for Switzerland based on PICO 1. To avoid inefficient complexity of the model, the model included only female adult patients with early breast cancer. For the intervention, a treatment duration of 6 months was assumed. Shorter treatment durations (e.g., 9 or 12 weeks) were not included as available evidence seems to be less robust. Moreover, shorter treatment durations were considered clinically less plausible in the Swiss context. Considering that the published evidence did not allow to clearly distinguish between adjuvant and neoadjuvant trastuzumab administration, the present cost-effectiveness analysis was conducted assuming an adjuvant administration of trastuzumab. Therefore, it was assumed that trastuzumab would be administered only after surgery, and costs related to initial surgery were not included in the analyses.

Since evidence concerning combination treatment was not available, pertuzumab treatment was not included in the analysis.

The model was developed in Microsoft Excel.

#### *Population*

Adult women with early breast cancer. In the base case analysis, a starting age of 59 years was used. (The starting age was based on the estimated mean age at diagnosis for early breast cancer in Switzerland according to data collected by NKRS)

#### *Intervention*

The intervention consisted of trastuzumab treatment for a duration of 6 months. An initial trastuzumab dose of 8 mg/kg followed by 6 mg/kg every 3 weeks up to 6 months was assumed. (The most conservative dosage was used. The alternative dosage with initial 4mg/kg followed by 2mg/kg every week would have led to the same total drug consumption, but a higher number of visits due to weekly administrations).

#### *Comparator*

The treatment in the comparator group consisted of trastuzumab treatment for a duration of 12 months. An initial trastuzumab dose of 8 mg/kg followed by 6 mg/kg every 3 weeks up to 12 months was assumed.

#### *Outcomes*

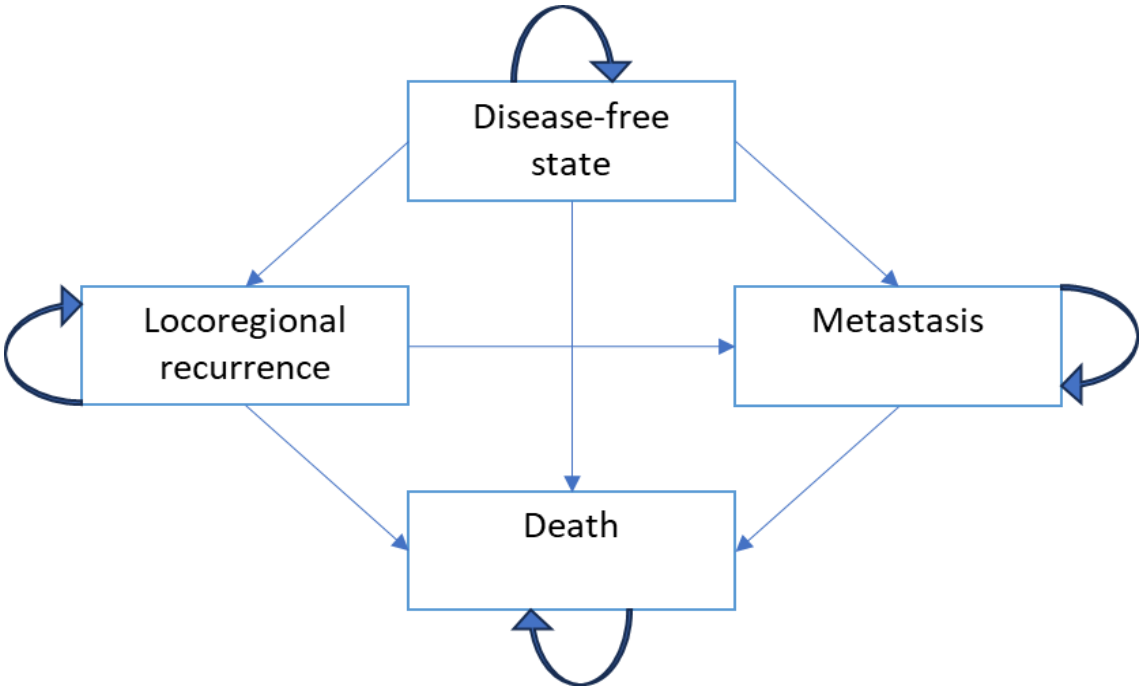
The model assessed lifetime costs (overall, by resource type), life-years, and QALYs, as well as ICERs expressed as costs (CHF) per QALY gained/lost.

The cost-effectiveness analysis was performed from a healthcare payer perspective. The costs of healthcare services covered by the Swiss mandatory health insurance were analysed, irrespective of the actual payer (mandatory health insurance, other social insurance, government, out-of-pocket). The analysis did not include indirect costs due to informal care or productivity losses, or non-medical direct costs such as travel costs (e.g., using public transport).

***Model structure***

A *de novo* health state Markov cohort simulation model with 4 mutually exclusive health states of DFS, locoregional recurrence, distant metastasis, and death was developed (Figure 6). The structure of the model was discussed with clinical experts to ensure it generally reflects daily clinical practice in Switzerland. Nevertheless, it should be emphasised that daily clinical practice may slightly differ.

**Figure 6: Markov model structure.**




***Time horizon and cycle length***

A model cycle length of 3 months including half-cycle correction was used. Half-cycle correction was specifically applied to life-years, QALYs, follow-up consultations and echocardiographies, metastatic costs and terminal care costs. Half-cycle correction was not applied to costs that were assumed to happen during in the first 6 or 12 months of treatment (trastuzumab costs, administration costs, docetaxel costs, radiotherapy, AEs).

A lifetime horizon was adopted. Alternative time horizons (i.e., 5, 10, or 15 years) were explored as part of the scenario analyses.

Costs and utilities were discounted at an annual rate of 3%. Additionally, discount rates of 0% and 5% were explored in the univariate scenario analysis.

***Model inputs***

*Survival (DFS, OS)*

For the first 7 years after start of treatment, DFS and OS were based on the meta-analysis of data extracted in the clinical part of this report. The published survival curves for 6 and 12 months

trastuzumab treatment were digitised, and an average across all trials using inverse variance weighting was calculated. (Table 13). For the timepoint 0 years, it was assumed that all patients would be in a DFS state. Estimated DFS and OS rates for both treatment strategies were converted into transition probabilities as 1 minus the ratio of the survivor function at the end and the beginning of a model cycle.

**Table 13: Average survival for intervention (6 months) and comparator (12 months)**

| Timepoint | Outcome | Intervention (6 months) | Comparator (12 months) |
|---|---|---|---|
| 2 years | DFS | 0.946929 | 0.958958 |
| 3 years | DFS | 0.904903 | 0.930323 |
| 4 years | DFS | 0.877557 | 0.899870 |
| 5 years | DFS | 0.861079 | 0.877169 |
| 7 years | DFS | 0.794967 | 0.840988 |
| | | | |
| 2 years | OS | 0.983493 | 0.992102 |
| 3 years | OS | 0.961056 | 0.974564 |
| 4 years | OS | 0.944165 | 0.958965 |
| 5 years | OS | 0.925751 | 0.942145 |
| 7 years | OS | 0.899003 | 0.928325 |

To cover the time after 7 years of follow-up, 3-month transition probabilities were extracted from the HTA published by Earl et al. in 2020 (Table 14).[53] Among all cost-effectiveness analyses identified in the systematic review, the HTA by Earl at al. seemed to represent the most appropriate source. First, because it clearly reported transition probabilities between the relevant health states (DFS, recurrence, metastasis, and death states). Second, the reported transition probabilities were based on a single, large study (PERSEPHONE). Other cost-effectiveness analyses used estimation from smaller/older trials, sometime combining several sources.

In Earl et al., the reported transition probabilities were applied for up to 5.1 years. Thereafter, a parametric extrapolation was used. Since the resulting transition probabilities beyond 5.1 years were not reported, and since the available data did not allow us to perform a parametric extrapolation, we applied the same transition probabilities from the 7$^{th}$ year of follow up until death. As illustrated in the result section, the fact that OS in the model was comparable to data from the Swiss national cancer registry (see Table 25) supports the validity of this assumption.

**Table 14: 3-month transition probabilities.**

| | | Intervention (6 months) | | Comparator (12 months) | |
|---|---|---|---|---|---|
| **From** | **To** | **Mean** | **SE** | **Mean** | **SE** |
| DFS | Recurrence | 0.001873 | 0.002324 | 0.001439 | 0.000796 |
| DFS | Metastasis | 0.004234 | 0.004889 | 0.003993 | 0.001348 |
| DFS | BC death | 0 | 0 | 0 | 0 |
| DFS | Cardiac death | 0.000048 | 0.000163 | 0.000142 | 0.000292 |
| DFS | Background death | 0.000674 # | 0.000669 # | 0.000692 # | 0.000508 # |
| Recurrence | Metastasis | 0.054839 | 0.048247 | 0.045659 | 0.041194 |
| Recurrence | BC death | 0.009398 | 0.029416 | 0.013969 | 0.023254 |
| Recurrence | Cardiac death | 0.000056 | 0.000222 | 0.002193 | 0.014763 |
| Recurrence | Background death | 0.000209 # | 0.000428 # | 0.000088 # | 0.000269 # |
| Metastasis | BC death | 0.109534 | 0.039779 | 0.09978 | 0.035325 |
| Metastasis | Background death | 0.005066 * | 0.009336 * | 0.003547 * | 0.009777 * |

# Background death from Earl et al. was not used in the model but replaced with Swiss mortality data from the Federal Statistical Office.

For the first 7 years after the start of treatment, background (or general population) mortality was not included since the OS results from the published RCTs were assumed to also cover death due to non-breast cancer-related sources of death (i.e., OS was assumed to represent all-cause mortality). For the following years, breast cancer mortality and cardiac mortality from Earl et al. were combined with background mortality data for the Swiss population published by the Swiss Federal Statistical Office (FSO).[79]

Overall survival rates in the model output were compared with overall survival rates for patients with HER2-positive, early breast cancer patients provided by NKRS).

*Utilities*

As the HTA published by Earl et al., the model included health state utilities for DFS (mean 0.805, SE 0.021), locoregional recurrence (mean 0.708, SE 0.088), and distant metastasis (mean 0.604, SE 0.046).[53 80] The utilities were derived from a cross-sectional survey among 268 patients with stage I-III breast cancer. It is unknown if the 268 patients were HER2-positive and were treated with trastuzumab. Severe cardiac adverse effects were not observed in the patients who participated in the cross-sectional survey. Other potential sources of utility scores used in the published cost-effectiveness analyses were considered less plausible. For example, Lindgren et al. investigated the quality of life of patients with breast cancer (both early and metastatic cancer), estimating

utilities of 0.779 for both DFS and recurrence, and 0.685 for metastatic disease. Although the utility estimate for DFS and metastatic disease were comparable with those used in this report, using the same values for DFS and recurrence in the model seemed implausible. Other utility estimates based on a literature review by Peasgood et al. were considerably lower, with 0.617 for DFS (in the first 10 years after diagnosis) and 0.516 for metastatic disease (utility for recurrence status was not reported).

Utility estimates based on Swiss data were not available. As in other cost-effectiveness analyses, utility decrements due to increasing age were not included in the model. The main reasons behind this decision included the lack of information on age-dependent utility decrement for early breast cancer survivors as well as reduced complexity of the model.

*Adverse effects*

As illustrated in the assessment of clinical efficacy and safety, RCTs comparing 6 vs. 12 months trastuzumab treatment reported results for various cardiac AE outcomes (e.g., congestive heart failure, LVEF <50%, LVEF decrease >10% and LVEF <50%, clinical cardiac dysfunction, cardiac AEs overall), although definitions were heterogenous and only few studies reported on the same outcomes. Overall, 6 months of trastuzumab was judged to likely be associated with a lower risk for cardiac AEs, with low certainty of the evidence. The present analysis includes clinical cardiac dysfunction (based on PHARE and PERSEPHONE), which was assumed to also include congestive heart failure as well as relevant reductions in LVEF. Cardiac AEs overall were not used as only the PHARE trial reported this outcome (with lower frequency if compared to clinical cardiac dysfunction). Similarly, only limited information was available on other AE outcomes. Table 15 illustrates the frequencies of the AEs that were included in the present analysis.

**Table 15: Frequencies of the AE that were included in the present analysis.**

| Adverse effect | Intervention (6 months) | Comparator (12 months) |
|---|---|---|
| Clinical cardiac dysfunction | 0.067466 | 0.100720 |
| Fatigue | 0.086127 | 0.119324 |
| Diarrhea | 0.026027 | 0.031832 |
| Nausea | 0.010315 | 0.018479 |
| Vomiting | 0.012255 | 0.013406 |
| Rash | 0.011862 | 0.013200 |

In the base case analyses, potential costs related to cardiac and other AEs were included in the calculations. In contrast, a potential impact on the quality of life of the patients was not included for the following reasons. First, especially for the cardiac AEs, the outcomes were generally not well defined. Assigning a utility decrement to a poorly defined variable may be problematic. Second, the reversibility, duration, and severity of the reported cardiac AEs was unknown. Therefore, it is not

clear whether a potential utility decrement should be applied only to trastuzumab treatment period (6 or 12 months), for several years, or lifelong.

Although uncertain, the potential impact of a utility decrement was investigated in a scenario analysis in which the utility for patients with clinical cardiac dysfunction was estimated to be 0.600.[80 81] The utility decrement if compared to DFS was thus 0.205 (i.e., 0.805 – 0.600). The utility decrement was only applied to the proportion of patients reporting a cardiac dysfunction. The utility decrement was applied lifelong. It is important to mention that not all cardiac dysfunctions have a lifelong impact on the quality of life of the patients. For example, a decrease in LVEF is reversible and may not lead to lifelong heart failure. In consequence it is very difficult to correctly quantify the impact of cardiac AEs on the quality of life of breast cancer patients. Moreover, the real impact of cardiac AEs remains uncertain: the utility decrement applied in this analysis was based on data from the CArdiac Resynchronisation in Heat Failure (CARE-HF) trial, which assessed the quality of life among patients with heart failure.[81] Whether the utility difference may be similar in a population with breast cancer is unclear.

*Medical resource use*

For the intervention it was assumed that all patients would receive an initial trastuzumab dose of 8 mg/kg followed by 6 mg/kg every 3 weeks over a period of 6 months. Additional data from the Swiss Outpatient Hospital ("Patienten Spital Ambulant") dataset provided by the FOPH were analysed to estimate other costs associated with treatment with trastuzumab (i.e. adjuvant treatment with docetaxel or paclitaxel, and radiotherapy). In this real-world dataset, billing data (as used for reimbursement by Swiss mandatory health insurance) from patients receiving trastuzumab or pertuzumab in the reference year 2019 in an outpatient setting in any Swiss hospital were included. For the estimations, we included only patients who received trastuzumab in 2019, and excluded those whom: (i) were male, (ii) have received pertuzumab alone or in combination with trastuzumab, (iii) have undergone 2 or more gastroscopies and have no other billing code identifying them to likely have breast cancer since trastuzumab may also be administered for HER2-positive gastric cancer or gastro-oesophageal carcinoma (i.e., no breast surgery, no breast biopsy, no mamma sonography, no mamma MRI, no physical mamma examination; TARMED codes 23.01XX, 23.02XX, 39.3430, 39.5130, 23.0010). Billing positions that were subsequently cancelled and negative positions (corresponding to cancellations) were excluded. These criteria yielded 600 eligible participants. Among them, 3.8% (n=23) received adjuvant treatment with docetaxel, while 25.0% (n=150) received paclitaxel. For patients receiving docetaxel, a dosage of 100 mg/m$^2$ docetaxel for a total of 4 cycles was assumed. For those receiving paclitaxel, 175 mg/m$^2$ for a total of 4 cycles was assumed. Overall treatment duration was 6 months. Additional treatments (e.g., cyclophosphamide) were not included in the model. Assuming that such treatments would be prescribed in the first months of early breast cancer treatment in both groups, they would have an impact on the total costs per group but would not affect the budget impact. As in many other cost-effectiveness analyses, treatment

discontinuation was not included in the model. All dosages were based on the recommendation reported in the Specialities list (Spezialitätenliste, www.spezialitätenliste.ch) published by the FOPH.

For the comparator, an identical treatment schedule was assumed, but with a trastuzumab treatment duration of 12 months (in short, patients were assumed to receive the same amount of docetaxel and paclitaxel, but considerably more trastuzumab).

According to data from the Swiss Breast Center DataBase (SBCDB), 71% of the patients with early breast cancer between 2019 and 2021 received concomitant radiotherapy. However, this patient population included all cases, including HER2-negative patients. Additional analyses based on the PSA data suggested that among 600 early breast cancer patients being treated with trastuzumab in 2019, 31.3% received a concomitant radiotherapy, with an average of 19.87 radiotherapy visits per patient. For the present analyses, the estimate based on the PSA dataset was used.

For patients in DFS, a control consultation including an echocardiography every 3 months was assumed in the first 2 years. Thereafter, 1 consultation with echocardiography per year was assumed.

All recurrent patients were assumed to receive a mammectomy.

For all metastatic patients, one-off costs for chemotherapy for metastatic breast cancer were assumed.

*Costs*

Costs included drug acquisition and administration costs, costs of follow-up clinical visits and echocardiography, mammectomy costs for recurrent cases, costs of AE due to trastuzumab treatment, chemotherapy costs for metastatic breast cancer, and terminal care costs (i.e., end-of-life costs). For end-of-life care, 1 terminal care hospitalization at the end of each patient's life was included as a one-off cost, in the base case analysis. It was assumed that such hospitalisation occurred for 65% of the patients. Outpatient end-of-life costs were not considered.

A detailed list of the included costs, the unit costs, assumptions, and sources is provided in section 7.2.4.

***Sensitivity analyses***

Sensitivity analyses were conducted to investigate the impact of uncertainty in relevant input variables on the total costs. Clinical parameters were mainly varied according to reported 95% CIs or standard errors (SEs). For the economic parameters CI or SE were often not available. In these cases, the SE was assumed to be 30% of the base case parameter values. A detailed table with base case, low, and high estimates used in the deterministic sensitivity analysis is provided in section 7.2.4.

For the probabilistic sensitivity analyses, we assigned gamma distributions to unit cost parameters (to prevent values less than zero from being drawn), and beta distributions to utilities and

probabilities. The beta distribution restricted draws to the 0-1 space. A total of 10,000 simulation runs were performed for the main probabilistic sensitivity analysis. For additional exploratory analyses to investigate the impact of the effectiveness assumptions the simulation runs were limited to 500. For technical reasons, the uncertainty related to transition probabilities was investigated exclusively in the probabilistic sensitivity analysis.

In a scenario analysis, the impact of using a Herceptin® (trastuzumab) biosimilar was investigated. Biosimilar purchase prices are reported in section 7.2.4. Further scenario analyses were conducted to evaluate the cost-effectiveness of 6 vs. 12 months of treatment duration over a time horizon of 5, 10, and 15 years. In 2 scenario analyses, the impact of discount rate (0% and 5%) was investigated. In a final scenario, the potential impact of a utility decrement related to clinical cardiac dysfunction was investigated.

### 7.1.5 *De novo* budget impact modelling

The results of the *de novo* cost-effectiveness analysis performed for Switzerland, and in particular the yearly costs in the first 5 years after treatment start, were used as basis for a budget impact analysis. Like the cost-effectiveness analysis, the budget impact analysis focused exclusively on PICO 1.

The population for the budget impact analysis consisted of newly diagnosed adult women with HER2-positive early breast cancer (including locally advanced operable breast cancer). The main source of information on early breast cancer incidence was NKRS (https://nkrs.ch).

Data on early breast cancer incidence were combined with the estimated cost of the intervention and comparator strategies to estimate the yearly budget impact of switching from 12 months of trastuzumab treatment to 6 months of trastuzumab treatment.

The budget impact analysis was performed from a healthcare payer perspective. The costs of healthcare services covered by the Swiss mandatory health insurance were analysed, irrespective of the actual payer (mandatory health insurance, other social insurance, government, out-of-pocket). The analysis did not include indirect costs due to informal care or productivity losses and additional non-medical costs for patients, such as travel costs.

The budget impact analysis was estimated yearly over a period of 5 years (from 2024 to 2028), reflecting a relevant time horizon for decision-making. Only costs happening in the first 5 years after treatment start were included. This means, for example, that the total costs for year 2024 included the costs of patients diagnosed in 2024 (in their first year after treatment start), as well as the costs of those diagnosed in 2023 (in their second year after treatment start), 2022 (in their third year after treatment start), 2021 (in their fourth year after treatment start), and 2020 (in their fifth year after treatment start).

For the budget impact analysis, a discount rate was not applied (in line with standard health economic evaluation practice).

In accordance with the cost-effectiveness analysis, only public prices were considered.

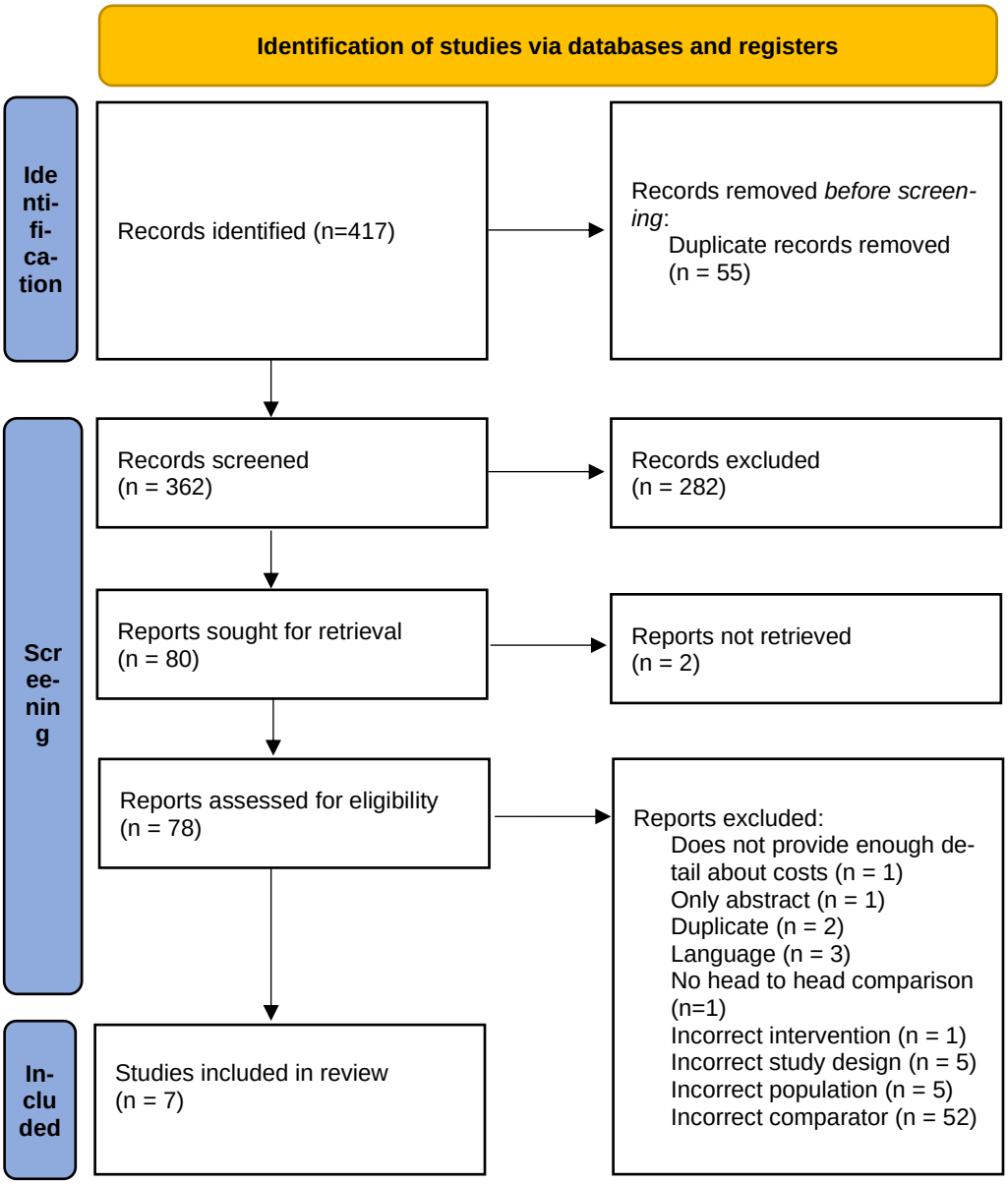
Deterministic sensitivity and scenario analyses were conducted to investigate which input parameters (e.g., estimated number of cases, treatment costs) have the highest impact on the estimated budget impact, and to estimate the impact of alternative assumptions. A scenario analysis using the costs of Herceptin® (trastuzumab) biosimilars was conducted.

## 7.2 Results costs, cost-effectiveness and budget impact

### 7.2.1 PRISMA flow diagram

The study selection process is illustrated in Figure 7. The titles and abstracts of the 362 hits from the systematic search, were screened. From this, 80 studies were included for full text screening. Of these, 7 cost-effectiveness analyses were eligible for inclusion in the systematic review of economic evaluations. The other 73 studies were excluded due to the following reasons: budget impact analysis that does not provide enough detail about costs (item 23 of the CHEERS checklist recommends that such detail is provided) (1 study); only an abstract (1 study); duplicate (2 studies); full-text not available (2 studies); language (3 studies); no head to head comparison (1 study); incorrect intervention (1 study); incorrect study design (5 studies); incorrect population (5 studies); incorrect comparator (52 studies). A list of excluded studies at full-text screening is provided in Appendix 16.

**Figure 7: PRISMA flow diagram for systematic review of economic studies.**




### 7.2.2 Study characteristics and quality assessment of included studies

Methods of the 7 included cost-effectiveness analyses are presented in Table 16 and Table 17. Early cost-effectiveness analyses were published in 2007 (from Australia)[82] and 2008 (from Belgium)[83] respectively. These 2 studies may be considered to be out-of-date, given the lack of available trials at the time (these analyses used data from the FinHer trial to estimate the effectiveness of 9 weeks of trastuzumab). The 5 other cost-effectiveness analyses were published more recently, between 2017 and 2020.

In 4 cost-effectiveness analyses, there clearly appeared to be no conflict of interest by the study authors. In 1 cost-effectiveness analysis from Belgium, no information was provided in regard to whether or not there were competing interests or funding sources.[83] In the remaining 2 cost-

effectiveness analyses from India[84] and Australia[82], one of the authors in each cost-effectiveness analysis reported having some connection to the pharmaceutical industry.

For 6 cost-effectiveness analyses, the perspective used was reflective of the major contributing body/bodies which pay for healthcare in the country (i.e., these 6 cost-effectiveness analyses adopted a “payer” perspective). For 1 cost-effectiveness analysis from India, out-of-pocket patient costs were additionally included, but productivity costs were not included.[84]

The time horizon used varied between cost-effectiveness analyses. For 5 cost-effectiveness analyses, a lifetime horizon was used. For 1 cost-effectiveness analysis from Egypt, a 10-year time horizon was used,[85] while 1 cost-effectiveness analysis from the United Kingdom (UK) used an 18-month time horizon.[53] This cost-effectiveness analysis was a within-trial analysis from the PERSEPHONE trial, which collected follow-up economic data from patients over an 18-month period. A lifetime model-based analysis was also performed in this study.

The model used varied between cost-effectiveness analyses. The cost-effectiveness analysis from Belgium described that a “model” was used without further specification.[83] For 4 cost-effectiveness analyses, a Markov model was used. In 1 cost-effectiveness analysis from the UK, a decision tree model was used for the initial phase, followed by a Markov model for the long-term phase.[86] In the cost-effectiveness analysis published by Earl et al., a within-trial analysis was undertaken. Moreover, a lifetime Markov model was additionally conducted. [53]

Six cost-effectiveness analyses are considered to be cost-utility analyses, as the outcome measure that they used was QALYs. One cost-effectiveness analysis from Belgium used LYs as the outcome measure (i.e., no adjustment for quality of life to LYs was made).[83]

The population in all cost-effectiveness analyses was patients with early breast cancer. In 1 cost-effectiveness analysis by Earl et al., a within-trial analysis of the PERSEPHONE trial, 99% of the patients in the trial were women, and 1% were men.[53] In 1 cost-effectiveness analysis from India, surgically resected early breast cancer patients were the modelled cohort under consideration.[84] In the cost-effectiveness analysis from Belgium, the economic results were presented for early breast cancer stage I, II, and III.[83]

The interventions that were evaluated in the cost-effectiveness analyses were either 12 months, 6 months trastuzumab, or 9 weeks of trastuzumab treatment. The comparators that were evaluated in the cost-effectiveness analyses were either no trastuzumab, or 12 months of trastuzumab treatment. In 3 cost-effectiveness analyses, our research question was directly answered as the intervention of ≤6 months of trastuzumab was directly compared to the comparator of 12 months of treatment. In the 4 other cost-effectiveness analyses, our research question was indirectly answered, as in these cost-effectiveness analyses the costs and outcomes estimated for ≤6 months of trastuzumab as well as 12 months of trastuzumab, were compared with no trastuzumab.

In 5 cost-effectiveness analyses, the currency used matched the local currency of the setting of the cost-effectiveness analysis. This was not exactly the case in 2 cost-effectiveness analyses. In the

cost-effectiveness analysis from Iran, results were presented in Euros.[87] In the cost-effectiveness analysis from India, results were presented in both the local currency as well as US dollars (for this report, only results that were presented in US dollars were extracted).[84]

The discount rate was 3.5% per year in 3 cost-effectiveness analyses and was 3% in 2 other cost-effectiveness analyses. In the cost-effectiveness analysis from Belgium, the discount rate used was 3% for costs, and 1.5% for effects.[83] A discount rate was not applied in 1 cost-effectiveness analysis from the UK (as the time horizon of the analysis was only 18 months).[53]

In 6 cost-effectiveness analyses, the cost year used was or appeared to be close to the year the study was published. In 1 cost-effectiveness analysis from Belgium, the cost year was not stated.[83]

All 7 cost-effectiveness analyses included trastuzumab treatment as a cost item. One cost-effectiveness analysis from India included the cost of clinical and radiologic tests,[84] and 1 cost-effectiveness analysis from Belgium included the cost of the FISH (fluorescence in situ hybridization) test (which is used to measure the level of HER2 gene amplification in cancer cells). In 3 cost-effectiveness analyses from Australia, Belgium, and Iran respectively, the cost related to cardiac events was explicitly included. Costs of recurrence were included in the cost-utility analyses from Iran, Belgium, Australia, and UK. Cost of metastatic cancer were included in the analyses from Belgium and Australia.[82 83]

Utility values in the cost-effectiveness analyses were obtained from a variety of studies. Two cost-effectiveness analyses obtained utility values from a study by Lidgren et al., 1 cost-effectiveness analysis obtained utility values from a systematic review of breast cancer utilities by Peasgood et al. in 2010,[86] and 1 cost-effectiveness analysis obtained utility values from a systematic review of cost-utility analyses in oncology by Earle et al. in 2000.[82] Clinical inputs for the cost-effectiveness analyses were obtained from various trials. The FinHER trial was used as a source of clinical input data in 3 cost-effectiveness analyses of 9 weeks of trastuzumab treatment, and in 1 of these cost-effectiveness analyses the Short-HER trial was also used as a source of clinical input data.[84] The PERSEPHONE trial was used as a source of clinical input data in 3 cost-effectiveness analyses of 6 months of trastuzumab treatment.

For each cost-effectiveness analysis, the quality of reporting using 5 key items from the CHEERS checklist was evaluated. The cost-effectiveness analysis from the UK met the reporting criteria for all 5 items.[53] All included cost-effectiveness analyses met the reporting criteria for population and interventions. The cost-effectiveness analysis from Australia reported the ICER but did not report incremental QALYs or QALYs per strategy.[82] The cost-effectiveness analysis from India reported incremental QALYs but did not report QALYs per strategy.[84] The evaluation of the quality of reporting according to the selected criteria of the CHEERS checklist is available in the Appendix 17.

### 7.2.3 Evidence table

**Table 16: Characteristics of the economic studies included in systematic review.**

| Title | Author Year | Country | Perspective | Time horizon | Model | Analysis | Population | Currency | Cost year | Discount rate |
|---|---|---|---|---|---|---|---|---|---|---|
| Cost effectiveness of trastuzumab for management of breast cancer in India | Gupta 2019 | India | Unclear | Lifetime | Markov model | Cost-effectiveness analysis | Surgically-resected HER2-positive breast cancer at age>=50 years | USD | 2019 (hinted) | 3% |
| Adjuvant trastuzumab therapy for early HER2-Positive Breast Cancer in Iran: A Cost-Effectiveness and Scenario Analysis for an Optimal Treatment Strategy | Ansaripour 2017 | Iran | Healthcare | Lifetime | Markov model | Cost-effectiveness analysis | Early HER2-Positive breast cancer | Euros | 2017 | 3.5% per year |
| Cost-effectiveness of six months versus 1-year adjuvant trastuzumab in HER2 positive early breast cancer in Egypt | Elsisi 2020 | Egypt | Payer | 10 years | Markov | Cost-effectiveness analysis | Aged 18 year or older with a histological diagnosis of invasive early breast cancer with over-expression of HER2 receptor | Egyptian pounds | 2019 | 3.5% annually |
| Trastuzumab in early stage breast cancer: A cost-effectiveness analysis for Belgium | Neyt 2008 | Belgium | Payer | Lifetime | Model' | Cost-effectiveness and budget impact | Early stage breast cancer (Stage 1) | Euros | Not stated | 3% for cost, 1.5% for effects |
| Six versus 12 months' adjuvant trastuzumab in patients with HER2-positive early breast cancer: the PERSEPHONE non-inferiority RCT | Earl 2020 | United Kingdom | NHS and Personal Social Services | 18 months | Within-trial analysis (analysis using lifetime model also produced) | Cost-effectiveness analysis | HER2-positive early breast cancer | Great British pounds | 2017/2018 | No discount rate applied |
| Cost effectiveness of trastuzumab in the adjuvant treatment of early breast cancer: a lifetime model | Millar 2007 | Australia | Australian National Health Service | Lifetime | Markov | Cost-utility analysis | Cohort of patients with HER2-positive breast cancer. The cohort had an age at diagnosis of 50 years. | Australian dollars (AUD) | 2005 | 3% per annum |
| Multi-arm Cost-Effectiveness Analysis (CEA) comparing different durations of adjuvant trastuzumab in early breast cancer, from the English NHS payer perspective | Clarke 2017 | United Kingdom | NHS payer | Lifetime | Decision tree followed by Markov model | Cost-effectiveness analysis | Early breast cancer | Great British pounds | 2017 | 3.5% annual |

**Table 17: Costs considered, effect estimation, and conflict of interests in studies included in systematic review.**

| Title | Author | Year | Cost items | Utilities and clinical inputs | Conflict of interest |
|---|---|---|---|---|---|
| Cost effectiveness of trastuzumab for management of breast cancer in India | Gupta | 2019 | Drug (trastuzumab; chemotherapy); clinical and radiologic tests. | Utilities used were: disease free in first year of 0.749; disease after first year of 0.847; locoregional recurrence of 0.81; metastatic of 0.484. These were based on a study by Chen et al (2009). The HRs for DFS of 1.07 and 1.08 as reported in the PERSEPHONE and PHARE trials, respectively, were applied to the transition probabilities of 1-year trastuzumab use as computed in the base model to derive transition probabilities for 6-month trastuzumab use. Similarly, transition probabilities for 9-week trastuzumab use were computed using hazard rates and cardiac events from 9 weeks vs. 12 months of trastuzumab separately as reported in the Short HER (HR, 1.13) and FinHER trials. | Research funding obtained from various pharmaceutical companies. |
| Adjuvant trastuzumab therapy for early HER2-Positive Breast Cancer in Iran: A Cost-Effectiveness and Scenario Analysis for an Optimal Treatment Strategy | Ansaripour | 2017 | Costs items include: trastuzumab drug, trastuzumab administration; cardiac toxicity; cancer recurrence. | Utilities: baseline (disease-free) is 0.779 based on Lidgren et al; treatment of early stage is 0.779 based on assumption; second primary breast cancer (first year) is 0.700 based on Lidgren et al; advanced (brain) is 0.600 based on Hall et al.Trastuzumab effectiveness: DFS trastuzumab HR (12 months vs. 0 months): 0.62 based on Moja et al. DFS trastuzumab HR (6 months vs. 12 months): 1.28 based on Pivot et al. | No financial support received; no competing interests declared |
| Cost-effectiveness of six months versus 1-year adjuvant trastuzumab in HER2 positive early breast cancer in Egypt | Elsisi | 2020 | Include cost of treatments, day-care, surgery, health states and follow-up visits | Utilities: disease-free survival: 0.696 and patient HER 2 +: 0.779 from Lidgren et al; metastatic relapse: 0.69 (from Lloyd et al). Clinical parameters for 6 months and 12 months were sourced from Earl et al.[53] and included: 4 year disease free survival, local recurrence, probability of distant metastasis, and probability of death. | No funders and nothing to disclose |
| Trastuzumab in early stage breast cancer: A cost-effectiveness analysis for Belgium | Neyt | 2008 | FISH test, trastuzumab treatment, heart failure, metastatic breast cancer treatment, local recurrence, follow-up costs | No utilities as outcome is life-years. Clinical inputs for 9-week trastuzumab based on the FinHer trial; 0.29 is the hazard ratio surviving free of distant recurrence; 0.42 is the hazard ratio surviving free of disease. Clinical inputs for 12-month trastuzumab based on the HERA trial; 0.49 is the hazard ratio surviving free of distant recurrence; 0.54 is the hazard ratio surviving free of disease | No information provided |
| Six versus 12 months' adjuvant trastuzumab in patients with HER2-positive early breast cancer: the PERSEPHONE non-inferiority RCT | Earl | 2020 | Community-based health and social care, including visits or contacts with GPs, district nurses, physiotherapists, occupational therapists, etc.; and hospital services, including outpatients, accident and emergency attendances due to SAEs and hospitalisation costs (inpatients). Cost of trastuzumab drug acquisition and administration was included. | Utilities: EQ-5D-3L questionnaire administered during the PERSEPHONE trial. If a participant died during the trial, it was assumed that his or her utility score was 0 from the date of death until the end date of the trial and the transition to zero from the last non-zero score was linear.<br><br>In the modelling over a lifetime horizon, utilities were identified through a targeted literature review and finally based on a publication by Seferina et al.: DFS: 0.805, Local recurrence: 0.708, Metastasis: 0.604.[80] | Funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme |
| Cost effectiveness of trastuzumab in the | Millar | 2007 | Items include: trastuzumab,treatment of illnesses other than | Average life expectancy (average survival) was derived from the model. Survival was adjusted for quality of life using utility weights from a | The sponsor of trastuzumab in Australia (Roche Products Pty Ltd) had no |

| | | | | | |
|---|---|---|---|---|---|
| adjuvant treatment of early breast cancer: a lifetime model | | | cancer, metastatic cancer after relapse, local or regional recurrence, heart failure screening | published systematic review of cost-utility evaluations in oncology by Earle et al, while utility weights for patients who experienced heart failure were based on authors' assumptions. Transition probabilities for 9-week and 12-month trastuzumab were the same; apart from the primary transition probability derived from the hazard ratio of 'survival free of first distant recurrence' | input to this paper. J.A. Millar has no connection with Roche Products Ltd. M.J. Millward has participated in advisory boards for other anti-cancer pharmaceuticals manufactured by Roche Pharmaceuticals and participated in clinical trials sponsored by Roche Pharmaceuticals. |
| Multi-arm Cost-Effectiveness Analysis (CEA) comparing different durations of adjuvant trastuzumab in early breast cancer, from the English NHS payer perspective | Clarke | 2017 | Include costs for monitoring. recurrence, death, and trastuzumab | Utility values for the health states were derived from regression analyses published as part of a systematic review of utilities for breast cancer patients by Peasgood in 2010. Five-year survival data from the FINHer and BCIRG006 trials were used to populate the decision tree. FinHer trial data was used for 9-week trastuzumab arm. BCIRG006 data was used for 12-month trastuzumab arm. | The authors received no specific funding for this work. The authors have declared that no competing interests exist. |

### 7.2.4 Findings costs

Table 18 summarises the costs used as inputs for the cost-effectiveness and budget impact analyses.

**Table 18: Unit costs and assumptions for the cost-effectiveness model.**

| Cost variable | Unit cost (CHF) | Assumptions/Comments | Sources |
|---|---|---|---|
| Trastuzumab | 4.393 per mg | Mean costs per mg were based on the purchase of "HERCEPTIN Trockensub 440mg c Solv" (CHF 1932.85)<br>Dosage: initial 8mg/kg, then 6mg/kg every 3 weeks | www.spezialitätenliste.ch (accessed 11 Nov 2023) |
| Docetaxel | 3.758 per mg | Mean costs based on "DOCETAXEL Accord Inf Konz 160 mg/8ml 45x20mm" (CHF 601.30)<br>Dosage: 100 mg/m$^2$ for a total of 4 cycles<br>According to PSA data provided by the FOPH, 3.8% of the patients were treated with docetaxel. | www.spezialitätenliste.ch (accessed 11 Nov 2023)<br>Swiss Outpatient Hospital Data ("Patienten Spital Ambulant (PSA)") |
| Paclitaxel | 0.709 per mg | Mean costs based on "PACLITAXEL Accord 600 mg/100ml (CHF 425.15)<br>Dosage: 175 mg/m$^2$ for a total of 4 cycles.<br>According to PSA data provided by the FOPH, 25.0% of the patients were treated with paclitaxel. | www.spezialitätenliste.ch (accessed 11 Nov 2023)<br>Swiss Outpatient Hospital Data ("Patienten Spital Ambulant (PSA)") |
| Drug administration | 360 | Published estimate.<br>Drug administration costs were considered for each trastuzumab cycle | Favre-Bulle et al. 2023 [89] |
| Radiotherapy | 13,482 | Published estimate. One-off costs.<br>Based on PSA data provided by the FOPH, 31.3% of the early breast cancer patients treated with trastuzumab in 2019 received a radiotherapy. Among this patient population (N=188), a total of 3,736 visits for radiotherapy were reported (mean: 19.87 visits per patient). The mean costs per visit were CHF 678. The mean total radiotherapy costs per patient were CHF 13,482.<br>The estimated total costs per radiotherapy according to the PSA data was comparable to the one-off costs used in a recently published study published by Bommer et al. (CHF 10,242) | Swiss Outpatient Hospital Data ("Patienten Spital Ambulant (PSA)")<br>Bommer et al. 2022 [88] |
| Clinical consultation | 127 | Published estimate.<br>For patients in DFS, a consultation including an echocardiography every 3 months was assumed in the first 2 years. Thereafter, 1 consultation with echocardiography per year was assumed. For all patients with local | Bommer et al. 2022 [88] |

| | | | |
|---|---|---|---|
| | | recurrence, 3 additional consultations and echocardiographies were assumed. | |
| Echocardiography | 225 | Tarmed tariff system.<br>For each patient in DFS, an echocardiography every 3 months was assumed in the first 2 years. Thereafter, 1 consultation with echocardiography per year was assumed. For all patients with local recurrence, 3 additional consultations and echocardiographies were assumed. | www.tarmed-browser.ch[94] |
| Mammectomy | 28,318 | One-off costs for all recurrent cases, based on SwissDRG code J01B. | Favre-Bulle 2023 [89]<br>Bommer et al. 2022 [88] |
| Chemotherapy for metastatic breast cancer | 51,204 | Published estimate. One-off costs applied to all metastatic cases. | Favre-Bulle 2023 [89] |
| Terminal care costs | 37,769 | Published estimate. One-off costs.<br>It was assumed that 65% of the patients are hospitalized at the end of life and accrue this cost. Outpatient terminal care costs were not considered. | Bommer et al. 2022 [88] |
| AE costs<br><br><br>Cardiac dysfunction<br>Fatigue<br>Diarrhea<br>Nausea<br>Vomiting<br>Rash | <br><br><br>14,475<br>6,080<br>5,230<br>5,050<br>5,050<br>5,480 | One-off costs, based on SwissDRG codes.<br><br><br>Average of F62A, F62B, F62C, F62D<br>Z65B<br>G71C<br>X64Z<br>X64Z<br>J67Z | SwissDRG 2023 [90] |

In a scenario analysis, the impact of using a Herceptin (trastuzumab) biosimilar was investigated. All biosimilar have the same price, resulting in a cost of CHF 3.606 per mg (i.e., 18% less than the trastuzumab costs used in the base case analysis (Table 19).

**Table 19: Biosimilar to Herceptin (trastuzumab).**

| Biosimilars to Herceptin | CHF | CHF/mg | Source |
|---|---|---|---|
| HERZUMA Trockensub 440 mg c Solv | 1586.75 | 3.606 | www.spezialitätenliste.ch |
| KANJINTI Trockensub 440 mg c Solv | 1586.75 | 3.606 | www.spezialitätenliste.ch |
| OGIVRI Trockensub 440 mg c Solv | 1586.75 | 3.606 | www.spezialitätenliste.ch |
| TRAZIMERA Trockensub 440 mg c Solv | 1586.75 | 3.606 | www.spezialitätenliste.ch |

In the sensitivity analyses, costs and other input parameters were changed as represented in Table 20.

**Table 20: Parameters considered in the deterministic sensitivity analyses.**

| Parameter | Base case | Low estimate | High estimate |
|---|---|---|---|
| Trastuzumab costs, CHF per mg (± 30%) | 4.39 | 3.07 | 5.71 |
| Docetaxel costs, CHF per mg (± 30%) | 3.76 | 2.63 | 4.89 |
| Paclitaxel costs, CHF per mg (± 30%) | 0.71 | 0.50 | 0.92 |
| Administration costs, CHF (± 30%) | 359.5 | 252 | 467 |
| Radiotherapy costs, CHF (± 30%) | 10,242 | 7,170 | 13,315 |
| % of patients receiving radiotherapy (± 30%) | 71% | 50% | 92% |
| Clinical consultation costs, CHF (± 30%) | 127 | 89 | 165 |
| Echocardiography costs, CHF (± 30%) | 225 | 158 | 293 |
| Mammectomy costs, CHF (± 30%) | 28,318 | 19,823 | 36,813 |
| Chemotherapy for metastatic BC costs, CHF (± 30%) | 51,204 | 35,843 | 66,565 |
| Terminal care costs, CHF (± 30%) | 37,769 | 26,439 | 49,100 |
| % of patients hospitalised at the end of life (± 30%) | 65% | 46% | 85% |
| All AE costs, CHF (± 30%) | Various values | Various values | Various values |
| All AE frequencies (95% CI) | Various values | Various values | Various values |
| All utilities (95% CI) | Various values | Various values | Various values |
| Utility DFS (95% CI) | 0.805 | 0.764 | 0.846 |
| Utility Recurrence (95% CI) | 0.708 | 0.536 | 0.880 |
| Utility Metastasis (95% CI) | 0.604 | 0.512 | 0.694 |
| Age, years (95% CI) | 59.46 | 58.95 | 59.97 |

### 7.2.5 Findings cost-effectiveness

**Results of systematic review of economic studies**

This section summarises the main findings from the 7 cost-effectiveness analyses included through the systematic review (Table 21). Two cost-effectiveness analyses from Elisisi et al. (Egypt)[85] and Earl et al. (UK)[53] respectively found that compared with 12 months of trastuzumab, 6 months trastuzumab is dominant (i.e., 6 months of trastuzumab reduces costs and either produces similar QALYs or increases QALYs). This may be because both cost-effectiveness analyses predominantly based their QALY calculation on the PERSEPHONE trial. The PERSEPHONE trial concluded that 6 months of trastuzumab is not clinically inferior to 12 months of trastuzumab and resulted in significantly less cardiac toxicity and fewer severe AEs. Furthermore, 1 other cost-effectiveness analysis from the UK by Clarke et al. found that compared with 12 months of trastuzumab, 9 weeks of trastuzumab is dominant (i.e., 9 weeks of trastuzumab reduces costs and increases QALYs).[86] In another cost-effectiveness analysis published by Millar et al. 2007 (Australia), the authors did not report an ICER estimate for 9 weeks of trastuzumab relative to 12 months of trastuzumab, but instead reported that the ICER for 9 weeks of trastuzumab relative to no trastuzumab, was only AUD 1,700 per QALY gained, and concluded that 9 weeks of trastuzumab is 'economically attractive', while 12 months of trastuzumab has a 'significant budget impact'.[82] In

an additional cost-effectiveness analysis by Neyt et al. (Belgium), 9 weeks of trastuzumab treatment was also considered dominant if compared to 12 months of treatment. [83]

The cost-effectiveness analyses from Gupta et al. (India) [78] and Ansaripour et al. (Iran) [81] estimated that 12 months of trastuzumab produces more QALYs than 6 months of trastuzumab. This may be because both analyses utilised data from the PHARE trial. The PHARE trial concluded that 12 months of trastuzumab is clinically superior to 6 months of trastuzumab. However, both cost-effectiveness analyses concluded that it is cost-effective to reduce the duration of 12 months of trastuzumab treatment, based on the cost savings that are generated.

To summarise, the systematic review of economic evaluations identified 7 cost-effectiveness analyses. All of them indicate that shortening the duration of trastuzumab treatment to either 6 months, or 9 weeks, is cost-effective or even dominant if compared to 12 months of treatment.

**Table 21: Results for studies included in systematic review of economic evaluations.**

| Author Year | Perspective | Country Currency | Intervention | Comparator | Intervention Cost | Comparator Cost | Incremental Cost | Intervention QALYs | Comparator QALYs | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gupta 2019 [84] | Societal | India USD | 9 weeks | 12 months | Not stated | Not stated | -1,345 | Not stated | Not stated | -0.38 | Intervention less costly and less effective |
| Gupta 2019 [84] | Societal | India USD | 6 months | 12 months | Not stated | Not stated | -170 | Not stated | Not stated | -0.20 | Intervention less costly and less effective |
| Ansaripour 2017 [87] | Healthcare | Iran Euros | 6 months | 12 months | 22,442 | 33,160 | -10,718 | 11.71 | 12.22 | -0.51 | Intervention less costly and less effective |
| Elsisi 2020 [85] | Payer | Egypt Egyptian pounds | 6 months | 12 months | 271,647 | 381,248 | -109,601 | 2.99 | 2.93 | 0.06 | 6 months dominant |
| Neyt 2008 [83] | Payer | Belgium Euros | 9 weeks | 12 months | Not stated | Not stated | -31,652 | Not stated | Not stated | 0.68 lifeyears | 9 weeks dominant |
| Earl 2020 [53] | NHS and Personal Social Services | United Kingdom Great British pounds | 6 months | 12 months | 5762 (lifetime: 16,024) | 15,298 (lifetime cost: 25,340) | -9,536 (lifetime: -9,316) | 1.15 (lifetime: 11.12) | 1.14 (lifetime: 11.13) | 0.01 (lifetime: –0.008) | 6 months dominant |
| Millar 2007 [82] | Australian National Health Service | Australia Australian dollars | 9 weeks | 12 months | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported * |
| Clarke 2017 [86] | NHS payer | United Kingdom Great British pounds | 9 weeks | 12 months | 23,662 | 46,859 | -23,197 | 10.0 | 9.2 | 0.80 | 9 weeks dominant |

* The authors did not report differences between 9 weeks and 12 months of trastuzumab treatment. They only reported that 12 months of trastuzumab treatment compared to standard treatment (i.e., no trastuzumab) had an ICER of AUD 21,771 per QALY gained, while 9 weeks vs. standard treatment led to an ICER of AUD 1,700 per QALY gained. As consequence, they concluded that 9 weeks of treatment was the more attractive option

**Results of the *de novo* cost-effectiveness analysis**

The results of the cost-effectiveness analysis, in terms of costs, life-years, and QALY gained per patient for the intervention and comparator groups, as well as the difference between them, are illustrated in Table 22.

Overall, a treatment duration of 6 months of trastuzumab results in lower costs per patient (CHF -15,047) compared to 12 months of treatment. The cost reduction is mainly due to the costs of trastuzumab (CHF -13,415) and its administration (CHF -2,987). Treatment over 6 months also results in lower costs related to consultations (CHF-388) and follow-up echocardiographies (CHF -688). This result is mainly due to the fact that patients with 12 months of treatment have a longer life expectancy and, consequently, have more visits/echocardiographies. Mammectomy costs due to recurrence are in contrast higher for patients treated over 6 months (CHF 993). Concerning AE, 6 months of treatment has lower total costs than 12 months of treatment for both cardiac AEs (CHF -481) and other AEs (CHF -287). In contrast, shorter treatment with trastuzumab results in higher costs related to treatment of metastatic breast cancer (CHF 1,555).

The costs related to docetaxel, paclitaxel, and radiotherapy are identical between intervention and comparator since it was assumed that all patients would receive it at the beginning of the treatment. The undiscounted terminal care costs are also identical since in both group all patients died. However, with the inclusion of discounting, terminal care costs are higher in the intervention group.

**Table 22: Main results of the cost-effectiveness analysis: discouted costs (in CHF), life-years, and QALYs per patient for 6 months and 12 months of trasztuzumab treatment (using a lifetime horizon).**

| | | Intervention (6 months) | Comparator (12 months) | Difference |
|---|---|---|---|---|
| **Total costs** | | 84,045 | 99,092 | -15,047 |
| **Total costs break down (CHF)** | Trastuzumab costs | 16,176 | 29,591 | -13,415 |
| | Drug administration costs | 3,093 | 6,080 | -2,987 |
| | Docetaxel costs | 103 | 103 | - |
| | Paclitaxel costs | 223 | 223 | - |
| | Consultation costs | 7,779 | 8,167 | -388 |
| | Echocardiography costs | 13,781 | 14,469 | -688 |
| | Mammectomy costs | 5,482 | 4,489 | 993 |
| | Radiotherapy costs | 4,220 | 4,220 | - |
| | Cardiac adverse effects costs | 977 | 1,458 | -481 |
| | Other edverse effects costs | 839 | 1,125 | -287 |
| | Costs of chemotherapy for metastatic cancer | 17,454 | 15,900 | 1,555 |

| | | | | |
|---|---|---|---|---|
| | Terminal care costs | 13,920 | 13,268 | 652 |
| **Life-years (undiscounted)** | | 18.18 | 19.55 | -1.37 |
| **Life-years** | | 12.35 | 13.12 | -0.77 |
| **QALYs (undiscounted)** | | 14.31 | 15.41 | -1.1 |
| **QALYs** | | 9.73 | 10.35 | -0.62 |

Concerning quality-adjusted life expectancy, 6 months of trastuzumab treatment leads to a total of 9.73 QALY gained (discounted), while 12 months of treatment leads to 10.35 QALY gained. Therefore, shorted treatment duration leads to a total decrease of 0.62 QALY (discounted) per patient (Table 22). Combining incremental costs and QALYs, in Switzerland the ICER for 6 months of trastuzumab compared to 12 months of treatment would be CHF 24,242 saved per QALY lost. The results are in the lower-left quadrant of the cost-effectiveness plane. In this situation, a low ICER indicates that the amount of money saved per QALY lost is small, while a high ICER suggests high savings per QALY lost. The interpretation does thus differ from that of a cost-effectiveness analysis with results in the upper-right quadrant of the cost-effectiveness plane. If results fall in the upper-right quadrant, the investigated intervention is more expensive and more effective than the comparator(s), and lower ICERs are preferable since they suggest lower costs per additional QALY gained.

Table 23 and Figure 8 illustrate the results of the deterministic sensitivity analyses, which, for technical reasons, disregarded the uncertainty in the transition probabilities. A 30% decrease in trastuzumab costs would lead to a reduction of the cost difference between intervention and comparator (from CHF -15,047 to CHF -11,023). Similarly, a 30% increase would lead to a larger cost difference (CHF -19,072). Variation of other cost parameters would lead to changes in the total costs in both groups. However, the cost difference between groups remains very close to the base case difference (ranging between CHF -14,151 and CHF-15,345 for lower estimates, and between CHF -14,749 and CHF -15,943 for higher estimates).

Concerning variations in utility assumptions, a change in the DFS utility assumptions had the highest impact on overall QALY gained and QALY difference between intervention and comparator. A decrease in DFS utility from 0.805 to 0.764 led to a total of 9.28 QALYs per patient in the intervention group and of 9.87 QALYs per patient in the comparator group. The QALY difference between groups decreased from -0.62 QALY to -0.59 QALY gained.

The scenario analysis investigating the use of trastuzumab biosimilars (i.e., with costs of CHF 3.606 instead of CHF 4.393) led to a cost difference between intervention and comparator of CHF -12,644 (Table 24). Scenario analyses over shorter time horizons suggest that while the total costs per patient increase over time for both groups, the cost difference between groups remains similar

(CHF -15,562 at 5 years, CHF -14,188 at 10 years, CHF -14,127 at 15 years). In contrast, the amount of QALY gained in both groups as well as the difference between groups increases with longer time horizons. The QALY difference between intervention and comparator was -0.05 QALYs at 5 years, -0.19 QALYs at 10 years, and -0.33 QALYs at 15 years (in the base case analysis using a lifetime horizon the QALY difference was -0.67). This observation emphasises the importance of the time horizon (the relative ICERs were CHF 303,836 saved per QALY lost at 5 years, CHF 76,014 saved per QALY lost at 10 years, and CHF 42,620 saved per QALY lost at 15 years).

The inclusion of a utility decrement due to cardiac AEs led to a decrease in the total number of QALYs gained of 0.15 in the intervention group and 0.25 in the comparator group. In consequence, the difference between the 2 groups decreased from -0.62 QALYs to -0.53 QALYs (Table 24).

**Table 23: Deterministic sensitivity analyses.**

| Varied parameter | Lower estimate | | | | | | Higher estimate | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intervention | | Comparator | | Difference | | Intervention | | Comparator | | Difference | |
| | Costs (CHF) | QALYs | Costs (CHF) | QALYs | Costs (CHF) | QALYs | Costs (CHF) | QALYs | Costs (CHF) | QALYs | Costs (CHF) | QALYs |
| Trastuzumab costs per mg (± 30%) | 79,193 | 9.73 | 90,215 | 10.35 | -11,023 | -0.62 | 88,898 | 9.73 | 107,970 | 10.35 | -19,072 | -0.62 |
| Drug administration costs (± 30%) | 83,117 | 9.73 | 97,269 | 10.35 | -14,151 | -0.62 | 84,973 | 9.73 | 100,916 | 10.35 | -15,943 | -0.62 |
| Docetaxel costs (± 30%) | 84,014 | 9.73 | 99,062 | 10.35 | -15,047 | -0.62 | 84,076 | 9.73 | 99,123 | 10.35 | -15,047 | -0.62 |
| Paclitaxel costs (± 30%) | 83,978 | 9.73 | 99,026 | 10.35 | -15,047 | -0.62 | 84,112 | 9.73 | 99,159 | 10.35 | -15,047 | -0.62 |
| Radiotherapy costs (± 30%) | 82,779 | 9.73 | 97,827 | 10.35 | -15,047 | -0.62 | 85,311 | 9.73 | 100,358 | 10.35 | -15,047 | -0.62 |
| % of patients receiving radiotherapy (± 30%) | 82,779 | 9.73 | 97,827 | 10.35 | -15,047 | -0.62 | 85,311 | 9.73 | 100,358 | 10.35 | -15,047 | -0.62 |
| Clinical consultation costs (± 30%) | 81,712 | 9.73 | 96,642 | 10.35 | -14,931 | -0.62 | 86,379 | 9.73 | 101,543 | 10.35 | -15,164 | -0.62 |
| Echocardiography costs (± 30%) | 79,911 | 9.73 | 94,752 | 10.35 | -14,841 | -0.62 | 88,180 | 9.73 | 103,433 | 10.35 | -15,254 | -0.62 |
| Mammectomy costs (± 30%) | 82,401 | 9.73 | 97,746 | 10.35 | -15,345 | -0.62 | 85,690 | 9.73 | 100,439 | 10.35 | -14,749 | -0.62 |
| *All AE frequencies (95% CI)* | 82,978 | 9.73 | 97,574 | 10.35 | -14,596 | -0.62 | 85,113 | 9.73 | 100,611 | 10.35 | -15,499 | -0.62 |
| *All AE costs (± 30%)* | 83,501 | 9.73 | 98,317 | 10.35 | -14,817 | -0.62 | 84,590 | 9.73 | 99,867 | 10.35 | -15,278 | -0.62 |
| Chemotherapy for metastatic BC costs (± 30%) | 78,809 | 9.73 | 94,323 | 10.35 | -15,514 | -0.62 | 89,282 | 9.73 | 103,862 | 10.35 | -14,581 | -0.62 |
| Terminal care costs (± 30%) | 79,869 | 9.73 | 95,112 | 10.35 | -15,243 | -0.62 | 88,221 | 9.73 | 103,073 | 10.35 | -14,852 | -0.62 |
| % of patients hospitalized at the end of life (± 30%) | 79,869 | 9.73 | 95,112 | 10.35 | -15,243 | -0.62 | 88,221 | 9.73 | 103,073 | 10.35 | -14,852 | -0.62 |
| *Utility DFS (0.764-0.846)* | 84,045 | 9.28 | 99,092 | 9.87 | -15,047 | -0.59 | 84,045 | 10.18 | 99,092 | 10.83 | -15,047 | -0.65 |
| *Utility Recurrence (0.536-0.880)* | 84,045 | 9.61 | 99,092 | 10.23 | -15,047 | -0.63 | 84,045 | 9.85 | 99,092 | 10.47 | -15,047 | -0.61 |
| *Utility Metastasis (0.514-0.694)* | 84,045 | 9.66 | 99,092 | 10.29 | -15,047 | -0.62 | 84,045 | 9.80 | 99,092 | 10.42 | -15,047 | -0.62 |
| *All Utilities (95% CI)* | 84,045 | 9.09 | 99,092 | 9.69 | -15,047 | -0.59 | 84,045 | 10.37 | 99,092 | 11.02 | -15,047 | -0.65 |
| Age (95% CI) | 84,176 | 9.78 | 99,226 | 10.41 | -15,051 | -0.63 | 83,910 | 9.67 | 98,954 | 10.29 | -15,044 | -0.61 |

Note: for technical reasons, the uncertainty related to transition probabilities was investigated exclusively in the probabilistic sensitivity analysis.

**Figure 8. Tornado diagram of the deterministic sensitivity analysis**

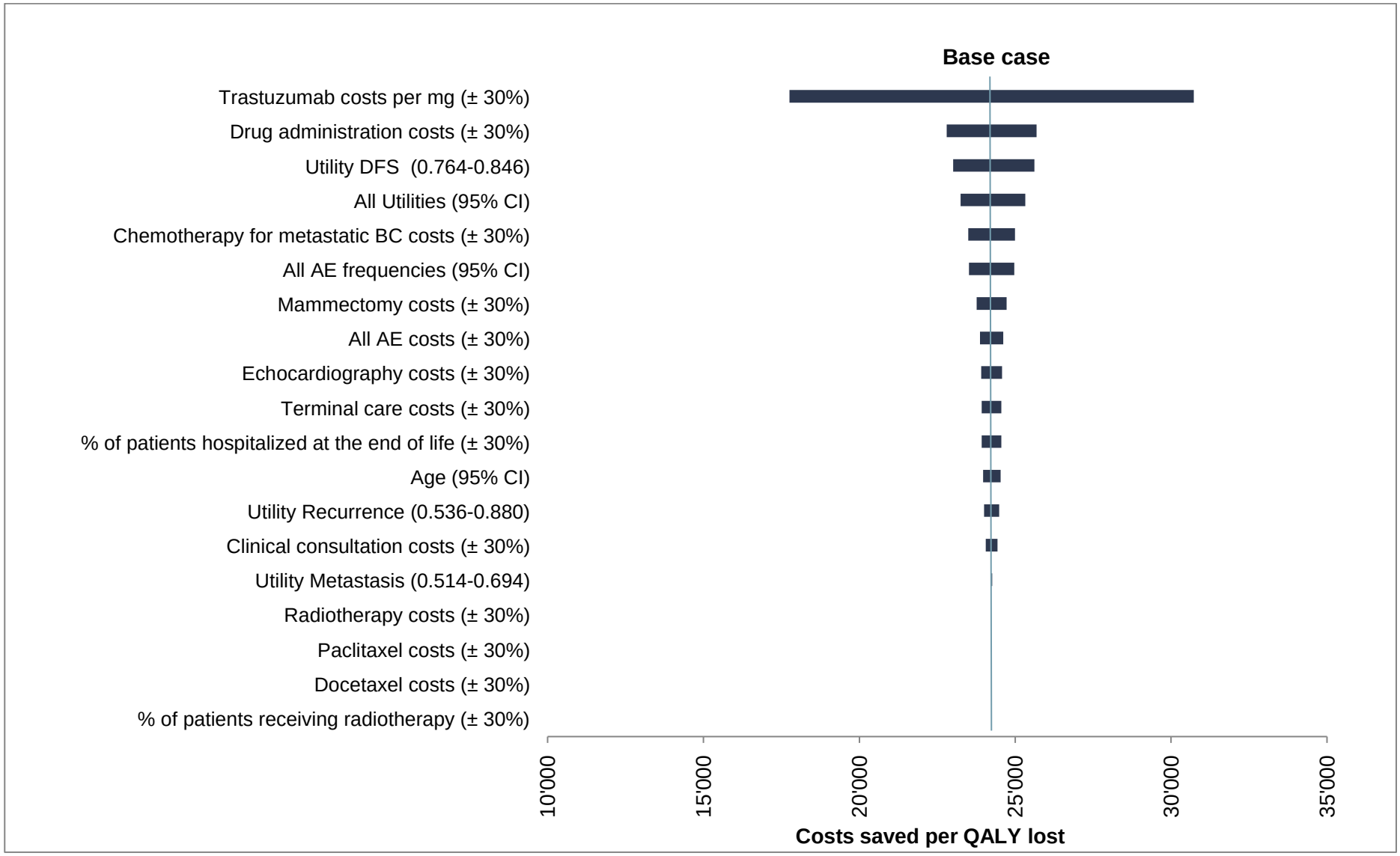


**Table 24. Scenario analyses for the base case.**

| | Intervention | | Comparator | | Difference | |
|---|---|---|---|---|---|---|
| | Costs (CHF) | QALYs | Costs (CHF) | QALYs | Costs (CHF) | QALYs |
| Base case | 84,045 | 9.73 | 99,092 | 10.35 | -15,047 | -0.62 |
| Biosimilar costs | 81,148 | 9.73 | 93,792 | 10.35 | -12,644 | -0.62 |
| Time horizon 5 years | 47,923 | 3.38 | 63,485 | 3.43 | -15,562 | -0.05 |
| Time horizon 10 years | 61,800 | 5.76 | 75,988 | 5.94 | -14,188 | -0.19 |
| Time horizon 15 years | 70,068 | 7.37 | 84,195 | 7.70 | -14,127 | -0.33 |
| Discount rate 0% | 112,050 | 14.31 | 128,347 | 15.41 | -16,297 | -1.10 |
| Discount rate 5% | 76,570 | 8.47 | 91,364 | 8.96 | -14,794 | -0.50 |
| Utility decrement due to cardiac adverse effects | 84,045 | 9.58 | 99,092 | 10.10 | -15,047 | -0.53 |

The modeled patient survival is comparable with survival rates of HER2-positive, early breast cancer patients in Switzerland provided by NKRS. Table 25 illustrates the survival rates at 1, 5, 10, and 15 years. Please note that this includes patients with and without trastuzumab (and pertuzumab) treatment including a high-risk setting, who may have received trastuzumab at varying durations of treatment (if such was received). Hence, it includes a mixture of patients and is not limited to those receiving 12 months of trastuzumab.

**Table 25. Overall survival rates in the model and according to the the National Agency for Cancer Registration (NKRS).**

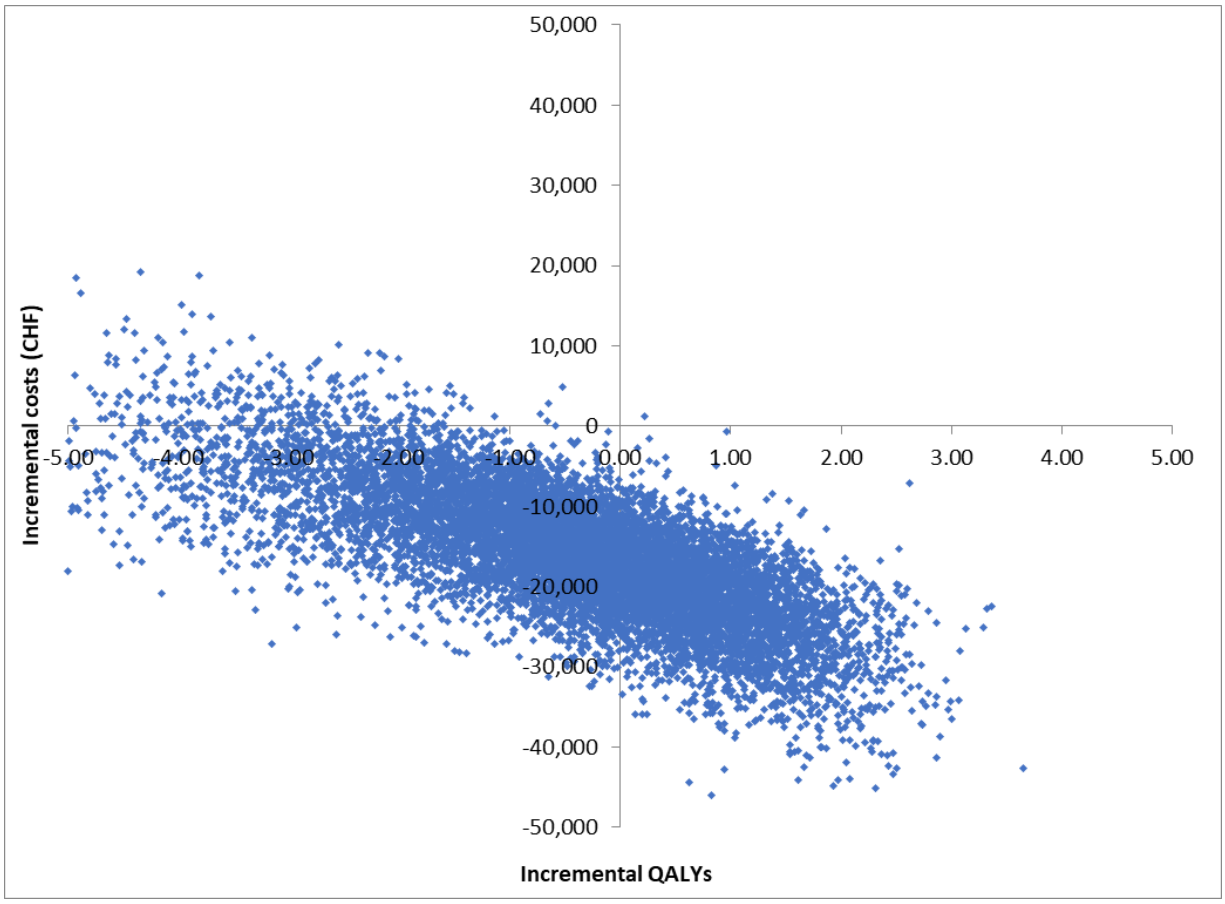
| Time horizon | 1 year | 5 years | 10 years | 15 years |
|---|---|---|---|---|
| Survival rates in the model | 0.994 | 0.890 | 0.750 | 0.616 |
| Survival rates according to NKRS | 0.975 | 0.837 | 0.704 | 0.567 |

The probabilistic sensitivity analysis suggests that the variation of the input parameters has an important impact on the results (Figure 9). The impact is particularly strong on the estimated number of QALYs, with values ranging from ca. 5 QALYs lost to almost 4 QALYs gained (for 6 months compared to 12 months of trastuzumab). In 56.6% of the cases the results indicate a QALY loss, while in 43.4% of the cases there is an increase in QALYs. The cost variation ranges from ca. CHF 20,000 to CHF -48,000, with 96.8% of the cases suggesting a reduction of the total costs. The distribution across the 4 quadrants of the cost-effectiveness plane is 53.4% in the lower-left (i.e., 6 months treatment is less expensive and less effective than 12 months treatment), 43.4% in the lower-right (i.e., 6 months treatment is less expensive and more effective than 12 months treatment), 3.2% in the upper left (i.e., 6 months treatment is more expensive and less effective than 12

months treatment), and 0.01 in the upper-right (i.e., 6 months is more expensive and more effective than 12 months treatment).

Over a total of 10,000 simulations, the mean costs of 6 months compared to 12 months of treatment are CHF -16,105 per patient, with mean QALYs of -0.41 (i.e., 0.41 QALY lost per patient). The resulting ICER is thus CHF 38,909 per QALY lost.

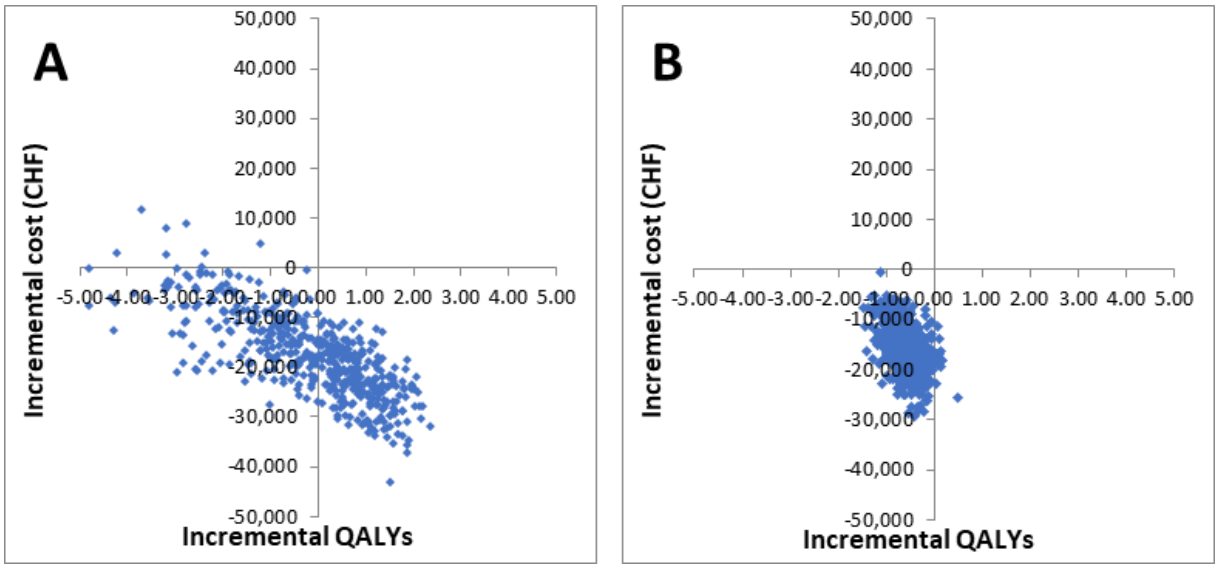
**Figure 9. Probabilistic sensitivity analysis**




Although more pronounced, the variation in the probabilistic sensitivity analysis (95%CI -3.25, 2.40) is comparable to the results reported in the HTA by Earl et al. (95%CI -2.09, 1.19). In Earl et al. the uncertainty in the transition probabilities for the 6 months treatment (used in the present model from the 7$^{th}$ year onwards) were identified as main responsible for variation in the probabilistic sensitivity analysis. The wide distribution of the results may also be due to the fact that in the PSA transition probabilities of both strategies were varied independently instead of using hazard ratios (the UK study also reported that survival analysis was conducted by arm). To further investigate the impact of the variation in the transition probabilities in the present model, additional analyses in which only the transition probabilities of the 6 months treatment were varied, were conducted. As illustrated in Figure 10, the variation of the transition probabilities according to the published SEs has a

significant impact on the distribution of the results. In particular, while the incremental costs remain concentrated between CHF 0 and CHF -30,000, the distribution of incremental QALYs changes. With the 12 months transition probabilities kept constant, and 6 months transition probabilities varied according to the SEs, the incremental QALYs range from -5 to almost 3 (range: 8). In contrast, if both the 6 months and 12 months transition probabilities are kept constant, the incremental QALYs are concentrated between -1.5 and 0.5 (range: 2). These results confirm that the variation in the transition probabilities in the 6 months treatment has a high impact on the results.

**Figure 10. Probabilistic sensitivity analyses to investigate the impact of the variation in transition probabilities.**




Legend: A – Results with 12 months transition probabilities constant, while 6 months transition probabilities (and other input parameters) are varied. B – Results with 6 months and 12 months transition probabilities constant, while other input parameters are varied.

Exploratory probabilistic sensitivity analyses were conducted to investigate the impact of the adopted time horizons on the results distribution. In general, the distribution of the clouds for different time horizons (5, 10, and 15 years) remains similar for the costs. In contrast there is a clear variation for the QALYs. Using a 5-years time horizon, the PSA suggests a mean cost difference of -15,887 and a mean QALY difference of -0.05. Mean ICER is CHF 304,449 saved per QALY lost. The cost difference ranges from ca CHF 18,000 to CHF -40,000, while QALYs range from -0.87 to 0.23. 67% of the simulations are in the lower-left, 31.5% in the lower right, and 1.5% in the upper-left quadrant (see Appendix 18 for a graphical representation). Using a 10-years time horizon, the PSA suggests a mean cost difference of -14,855 and a mean QALY difference of -0.17. The mean ICER is CHF 86,853 saved per QALY lost. Cost difference ranges again from ca CHF 18,000 to CHF -40,000, while QALYs range from -2.2 to 0.88. Overall, 59.7% of the simulations are in the lower-left, 35% in the lower right, and 5.3% in the upper-left quadrant (see Appendix 18 for a graphical representation). Using a 15-years time horizon, the PSA suggests a mean cost difference of -15,096 and a mean QALY difference of -0.27. Mean ICER is CHF 56,043 saved per

QALY lost. The cost difference ranges again from ca CHF 18,000 to CHF -40,000, while QALYs range from -4.3 to 1.7. Overall, 55.2% of the simulations are in the lower-left, 38.4% in the lower right, and 6.4% in the upper-left quadrant (see Appendix 18 for a graphical representation).

### 7.2.6 Findings budget impact

According to data from NKRS, the mean yearly number of patients newly diagnosed with early breast cancer was 5,564 between 2018 and 2020 (range: 5,429-5,770). Among them, 13.2% were HER2-positive. Considering the ageing of the Swiss population, it is estimated that the number of newly diagnosed HER2-positive early breast cancer patients will increase from 758 in 2024 to 783 in 2028 (Table 26).

According to data from the SBCDB, it was assumed that 96% of the patients receive trastuzumab therapy. Therefore, the number of HER2-patients assumed to receive treatment with trastuzumab increases from 728 in 2024 to 752 in 2028. Although in reality there is a time shift with treatment overlapping years (i.e., a patient who start a 12 months treatment in June will have half of the trastuzumab treatment in 1 year, and half in the following year), it was assumed that all costs of the first year happens in the year of starting treatment. It was assumed that this potential time shift would have a very limited impact on the budget impact analysis.

**Table 26: Estimated number of newly diagnosed HER2-positive early breast cancers per year.**

| Year | 2024 | 2025 | 2026 | 2027 | 2028 |
|---|---|---|---|---|---|
| Number of early breast cancers | 5,757 | 5,804 | 5,848 | 5,893 | 5,942 |
| Number of HER2-positive early breast cancers | 758 | 765 | 771 | 776 | 783 |
| Number of HER2-positive early breast cancers treated with trastuzumab | 728 | 734 | 740 | 745 | 752 |

Cost data for the first 5 years after treatment start were extracted from the cost-effectiveness analyses. Table 27 summarises the assumed costs for both treatment strategies. All costs related to trastuzumab/docetaxel treatment, drug administration, radiotherapy, and adverse effects were assumed to happen in the first year of treatment.

**Table 27: Annual costs per patient in the first 5 years after treatment start according to treatment strategy (in CHF).**

| Costs (CHF) 6 months treatment | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Year** | **Trastuzumab** | **Drug administration** | **Docetaxel** | **Paclitaxel** | **Consultation** | **Echocardiography** | **Radiotherapy** | **Mammectomy** | **Cardiac adverse effects** | **Other adverse effects** | **Chemotherapy for metastatic cancer** | **Terminal care** | **Total** |
| Year 1 | 16,236 | 3,106 | 103 | 223 | 1,326 | 2,349 | 556 | 4,220 | 977 | 839 | 697 | 185 | 30,816 |
| Year 2 | - | - | - | - | 1,476 | 2,614 | 709 | - | - | - | 1,112 | 387 | 6,297 |
| Year 3 | - | - | - | - | 483 | 856 | 960 | - | - | - | 1,285 | 763 | 4,345 |
| Year 4 | - | - | - | - | 457 | 809 | 727 | - | - | - | 1,455 | 851 | 4,297 |
| Year 5 | - | - | - | - | 430 | 762 | 423 | - | - | - | 1,468 | 920 | 4,003 |
| | | | | | | | | | | | | | |
| **Costs (CHF) 12 months treatment** | | | | | | | | | | | | | |
| **Year** | **Trastuzumab** | **Drug administration** | **Docetaxel** | **Paclitaxel** | **Consultation** | **Echocardiography** | **Radiotherapy** | **Mammectomy** | **Cardiac adverse effects** | **Other adverse effects** | **Chemotherpay for metastatic cancer** | **Terminal care** | **Total** |
| Year 1 | 29,946 | 6,159 | 2,706 | 893 | 1,328 | 2,352 | 431 | 4,220 | 1,458 | 1,125 | 642 | 101 | 51,361 |
| Year 2 | - | - | - | - | 1,486 | 2,633 | 555 | - | - | - | 975 | 254 | 5,904 |
| Year 3 | - | - | - | - | 487 | 864 | 687 | - | - | - | 1,087 | 602 | 3,728 |
| Year 4 | - | - | - | - | 469 | 830 | 730 | - | - | - | 1,201 | 727 | 3,956 |
| Year 5 | - | - | - | - | 414 | 734 | 380 | - | - | - | 1,268 | 670 | 3,466 |

Total costs for 6 months of trastuzumab treatment and 12 months of treatment as well as the yearly budget impact are reported in Table 28. Switching from 12 months of trastuzumab treatment to 6 months of treatment would lead to a decrease in total costs ranging between CHF 13.6 million in 2024 and CHF 14.1 million in 2028.

**Table 28: Total costs according to treatment strategy and budget impact (in million CHF).**

| Year | 2024 | 2025 | 2026 | 2027 | 2028 |
|---|---|---|---|---|---|
| 6 months treatment | 36.129 | 36.270 | 36.555 | 36.838 | 37.137 |
| 12 months treatment | 49.721 | 49.993 | 50.383 | 50.771 | 51.187 |
| Budget impact | -13.592 | -13.723 | -13.828 | -13.933 | -14.050 |

The sensitivity analyses suggest that lower trastuzumab costs would lead to a decrease in the budget impact (savings) resulting from the switch from 12 months to 6 months of trastuzumab treatment (from CHF-13.6 million in 2024 to CHF-8.5 million) (Table 29). On the opposite side, higher trastuzumab costs would lead to a higher budget impact (savings). The use of biosimilar costs (CHF 3.606 per mg instead of CHF 4.393) would lead to a budget impact ranging between CHF-11.8 million in 2024 and CHF-12.2 million in 2028.

The number of HER2-positive early breast cancer cases also has a high impact on the total costs: a 30% decrease in the number of cases would lead to a budget impact of CHF-9.5 million in 2024, while a 30% increase would lead to a budget impact of CHF-17.7 million. Changes in other input parameters (e.g., administration costs or AE costs) lead to small changes in the budget impact.

**Table 29: Sensitivity analyses.**

| Changed parameter | 2024 | 2025 | 2026 | 2027 | 2028 |
|---|---|---|---|---|---|
| Base case | -13.592 | -13.723 | -13.828 | -13.933 | -14.050 |
| Trastuzumab costs -30% | -8.501 | -8.591 | -8.656 | -8.722 | -8.795 |
| Trastuzumab costs +30% | -20.480 | -20.668 | -20.825 | -20.984 | -21.159 |
| Biosimilar costs | -11.804 | -11.921 | -12.011 | -12.103 | -12.204 |
| Number of cases -30% | -9.514 | -9.606 | -9.679 | -9.753 | -9.835 |
| Number of cases +30% | -17.669 | -17.840 | -17.976 | -18.113 | -18.265 |

| | | | | | |
|---|---|---|---|---|---|
| Administration costs -30% | -12.925 | -13.051 | -13.150 | -13.251 | -13.361 |
| Administration costs +30% | -14.259 | -14.396 | -14.505 | -14.616 | -14.738 |
| Chemotherapy for metastatic breast cancer costs -30% | -13.774 | -13.905 | -14.011 | -14.118 | -14.236 |
| Chemotherapy for metastatic breast cancer costs +30% | -13.409 | -13.542 | -13.645 | -13.749 | -13.864 |
| Clinical consultation costs -30% | -13.589 | -13.721 | -13.825 | -13.930 | -14.047 |
| Clinical consultation costs +30% | -13.594 | -13.726 | -13.831 | -13.936 | -14.053 |
| Echocardiography costs -30% | -13.587 | -13.718 | -13.823 | -13.928 | -14.045 |
| Echocardiography costs +30% | -13.597 | -13.728 | -13.833 | -13.938 | -14.055 |
| All adverse effects costs -30% | -13.424 | -13.554 | -13.657 | -13.762 | -13.876 |
| All adverse effects costs +30% | -13.760 | -13.893 | -13.998 | -14.105 | -14.223 |

# 8. Ethical, legal, social and organisational issues

***Summary statement ethical, legal, social and organisational issues***

There is very little literature on ELSO in relation to the specific question of reducing the duration of cancer treatment. Application of the principles of biomedical ethics in a normative analysis reveals that shortening the course of trastuzumab is largely compatible with the principles of beneficence, nonmaleficence, and justice. No serious ELSO issues were found in the literature. A few ethical issues emerging from the analysis concern uncertainties with respect to non-inferiority in DFS, potential harms to a subset of patients, informing patients about these potential harms, and respecting patient's autonomy with regard to treatment choice.

## 8.1 Methodology ethical, legal, social and organisational issues

This part of the HTA report describes and analyses the ethical, legal, social, and organisational (ELSO) issues associated with moving from 12 months of trastuzumab treatment compared to 6 months of treatment so as to inform the wider conclusions of the report. A literature review was conducted to identify relevant issues, but only indirectly relevant issues were detected. Therefore, the following normative analysis focuses on ethical issues emerging from application of the EUNetHTA checklist to the research question, along with consideration of the foundational principles of biomedical ethics in this context.

This part of the report has 4 main sections. First, the methodology for the literature review and normative analysis, respectively, are described. Next, the results of the review and analysis are provided, with the relevant evidence referred to in relation to each emerging issue. The normative analysis provided here draws on the empirical evidence regarding clinical effectiveness and cost-effectiveness in the preceding parts of this report, as well as the available literature on the specific issues. The ethical analysis applies the 4 principles of biomedical ethics and was conducted in accordance with the EUNetHTA Ethical, Legal, and Social Issues (ELSI) checklist for HTAs.[91] The main ethical issues emerging from the analysis concern individual prospective harms and benefits for patients, the disclosure of related evidence to patients, and respecting patients' autonomy in terms of access to treatment. Overall, however, it was concluded that shortening the course of trastuzumab to 6 months would be compatible with the 4 principles of biomedical ethics.

### 8.1.1 Literature review methodology

Given the narrow nature of the research question and the lack of studies on these specific issues, a purposive scoping review including grey literature was undertaken.

Literature was identified using purposive sampling on PubMed and Google Scholar using the search terms "breast cancer treatment", "ethical issues", "legal issues" "social issues", "organisational issues" and "ELSI". No date range was set to maximise the number of hits. Further papers were then identified via relevant references and screening of abstracts. Few papers were identified, so the search was widened to include grey literature via Google. Ultimately, literature included qualitative and quantitative studies, legal and ethical analysis articles, policy reports, and summaries of court proceedings.

### 8.1.2 Normative analysis methodology

The analysis was conducted in accordance with the EUNetHTA Ethical, Legal, and Social Issues (ELSI) checklist for HTAs (Table 30).[91] This checklist asks essentially the same question for each of the 4 domains: does the intervention pose any new ethical, legal social or organisational issues in contrast with the comparator? And: does the comparison indicate any differences that may be relevant?

**Table 30: EUNetHTA Ethical, Legal, and Social Issues (ELSI) checklist.**

| | |
|---|---|
| *Ethical* | Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?<br>Does comparing the new medicine to the defined, existing comparators point to any difference that may be ethically relevant? |
| *Organisational* | Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparators point to any differences that may be organisationally relevant? |

| | |
|---|---|
| | Does comparing the new medicine to the defined, existing comparator(s) point to any differences that may be organisationally relevant? |
| *Social* | Does the introduction of the new medicine and its potential use/non-use instead of the defined existing comparator(s) give rise to any new social issues?<br>Does comparing the new medicine to the defined, existing comparator(s) point to any differences that may be socially relevant? |
| *Legal* | Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issue?<br>Does comparing the new medicine to the defined, existing comparators point to any differences that may be legally relevant? |

Given the highly specific nature of the intervention – moving from 12 to 6 months of trastuzumab – it is both appropriate and necessary to consider the ethical issues from the perspective of the principles of biomedical ethics. Developed by Beauchamp and Childress decades ago, these 4 principles are widely regarded as the most important ones to consider when addressing ethical issues in clinical care.[92] No one principle is more important than any other, though their relative significance can change depending on the context and specific issue under consideration. Considering the intervention through the lens of the principles enables identification of any new ethical issues that might be relevant, in line with the EUNetHTA Ethical, Legal, and Social Issues (ELSI) checklist.

In no particular order, the principle of respect for autonomy requires that patients' wishes regarding their treatment are followed and that they are given all relevant information regarding their care. The principles of beneficence and nonmaleficence, respectively, require that physicians aim to benefit patients and avoid harming them. The principle of justice requires fair treatment of patients, including non-discrimination, and just allocation of resources.

In the normative analysis the principles are applied to the case of a "typical" patient, but it should be borne in mind that the ethical evaluation will depend on the individual actual patient and her diagnosis, prognosis and preferences.

## 8.2 Results ethical, legal, social and organisational issues

### 8.2.1 Results of literature review

No literature concerning specific **social** or **organisational issues** was identified in the search, so the results section touches briefly on legal issues (2 sources) before focusing on the ethical issues identified (7 sources).

The literature concerning **legal issues** associated with trastuzumab relate to historical court cases where patients sought access to treatment. When first introduced as a treatment for advanced

breast cancer, the drug was very expensive, and access was limited to a small number of patients. In the UK, 1 patient with early breast cancer took legal action arguing that denial of trastuzumab treatment violated her human rights. [93] At the time, the drug was not yet licenced for patients with early-stage cancer, and the hospital rejected the argument that this patient's circumstances were exceptional. The case reached the High Court, which rejected her argument. However, this decision was then reversed by the Court of Appeal, which found that the hospital trust had acted "irrationally and unlawfully".[93] However, in making this ruling the court determined that the hospital trust could indeed deny trastuzumab treatment to the patient under certain circumstances, but in this particular case the reasoning provided by the hospital trust was flawed as it did not provide a sufficient rationale. [94] These legal issues are not directly relevant to the issue of shortening the course of treatment. However, the issue of access remains relevant despite the current wider availability of the drug: if patients were denied access to either 6 or 12 months of treatment or were not informed about the relevant facts regarding either course of treatment, this could of course result in potential complaints and litigation. This may be unlikely to occur in Switzerland but is still a relevant ethical issue here and in other jurisdictions.

As with the legal literature, the main focus of the evidence regarding **ethical issues** is on concerns about the cost of trastuzumab treatment when it was first introduced, and related concerns regarding access to the drug and circumvention of normal approval processes. Prior to the 2006 legal case in the UK mentioned above, the Health Secretary effectively ordered NICE (the UK National Institute for Health and Care Excellence) to approve the drug and hospital trusts to provide it.[95] In response, an editorial in the *Lancet* urged caution in the approval of new medicines, arguing that "They must be free from political, special interest, or media influence, no matter how well meaning." [96]

One paper provided a (historical, indirectly relevant) ethical analysis of a similarly controversial decision to offer an extremely shortened course of trastuzumab (9 weeks rather than 12 months) in New Zealand.[97] In this case, the New Zealand's pharmaceutical management agency argued that the longer course was not justified in terms of cost-effectiveness, instead funding the cheaper and shorter course on the grounds that there was "insufficient evidence of additional long-term health benefits from the longer treatment course." Ultimately this led to the government bypassing its own pharmaceutical agency and authorising the funding of the full 12 months regimen, a decision which was analysed from the perspective of social science in another paper.[98] This case is of some relevance because it concerned a shorter course of trastuzumab. However, the ethical issues involved are quite different because of the context, the evolution in evidence over the last decade, and the 2-month rather than 6-month course involved. However, the substantial media and political profile of the New Zealand and UK cases indicates the high societal interest in breast cancer care in general and trastuzumab treatment specifically.

One historical, indirectly relevant interview study with physicians about the provision of trastuzumab found that they faced extreme constraints on autonomy in deciding which patients should receive the drug due to its cost.[99] However, this study was conducted soon after the drug was introduced, and given easier access to the drug nowadays this particular issue is not relevant to the focus of this HTA. One ethical point of interest is that, given that a 6-month course significantly reduces the cost per patient of treatment, shortening the course to 6 months could conceivably widen access in any healthcare systems where the drug is not yet widely available.

Though there is no further ethical literature specifically about the ethics of shortening the course of trastuzumab, there is some indirectly relevant evidence from more general papers about doctors' views on high-cost drugs and the relative value of cancer care. One study found that "Common barriers to the use of trastuzumab included issues related to insurance coverage, drug availability and cost to the patient".[100] In Switzerland today, these issues are not relevant. However, in some other countries, any patient paying for some or all of the cost of trastuzumab would also benefit financially if the course were reduced to 6 months.

One other ethical issue mentioned in relation to trastuzumab is the labelling of patients using HER2-status: "this means to categorise breast cancer patients as either "good responders", "non-responders" or "difficult to treat", which is at least a potential cause of discrimination."[101] However, this issue applies to all trastuzumab treatments, regardless of the length of the course, and is not directly relevant here.

### 8.2.2 Results of normative analysis

The results of the literature review revealed no relevant social or organisational issues for this analysis, and the preceding clinical and economic parts of this report do not reveal any relevant differences between 12 months and 6 months (or less) of trastuzumab treatment in terms of these 2 domains. As already mentioned, only if patients were denied information about the evidence regarding 12 vs. 6 months of treatment would any potential legal issues arise, and these would not be new legal issues, but merely typical complaints regarding lack of informed consent or transparency. The remainder of this normative analysis therefore focuses on the relevant ethical issues.

**The principle of beneficence**

What conclusions does consideration of the principles of biomedical ethics yield with regard to a 6-month (or less) course of trastuzumab vs. a 12-month course? The preceding parts of this report show that a treatment course of 6 months or less of trastuzumab is likely non-inferior to a 12-month course in terms of OS, while the evidence is inconclusive for non-inferiority for DFS (i.e., the effect estimate was below the non-inferiority margin, but inferiority could not be fully ruled out statistically). Furthermore, it is uncertain whether 12 months was superior to a shorter treatment course in terms of either OS or DFS, if non-inferiority margins (i.e., what constitutes a minimal (clinically) important

effect) are not considered. (Note that this ethical analysis focuses on the PICO 1 population, as evidence was not available for the PICO 2 population.)
In terms of the principles, these findings mean that patients (generally) benefit to the same extent from the shorter course of treatment in terms of survival, assuming that the non-inferiority margins represent a minimal important effect. Therefore, the principle of beneficence is satisfied to the same extent as with a 12-month course (with some caveats; see next paragraph). Meanwhile, it cannot be ruled out that on average, patients may benefit more (to a clinically relevant extent) from longer treatment in terms of DFS, as the evidence for non-inferiority regarding this outcome was inconclusive.

**The principle of nonmaleficence**

Equally, the evidence suggests that there may be a reduction in severe (grade ≥3) adverse events with shorter treatment courses (371 instead of 417 for ≤6 months vs. 12 months, Table 10), meaning that the risk of harm to patients may be expected to be reduced. There were also reductions in the risk for specific other AEs on a shorter course. Furthermore, there would likely be 9 fewer congestive heart failures per 1,000 (18 instead of 27) and 15 less women with a LVEF <50% and a decrease in LVEF of >10% per 1,000 (49 instead of 64) with ≤6 months of treatment compared to 12 months of treatment. Treatment discontinuations due to any AE are also likely reduced with shorter treatment compared to 12 months of treatment. In terms of the principle of nonmaleficence, a treatment course of 6 months or less of trastuzumab is therefore preferable to a 12-month course because of fewer harms associated with AEs. (The evidence is very uncertain regarding self-reported HRQoL, so that cannot be factored into the ethical evaluation.)

However, an important caveat to this is that despite the conclusion of non-inferiority, there is an absolute decrease in OS and DFS with a ≤6-month course (Table 10), meaning that the likelihood of harm will increase for some women, relative to a 12-month course. According to the assessment of efficacy and safety, this can be quantified as around 16 more patients per 1,000 (15 per 1000 for a 6-month course) experiencing recurrence and 7 extra women per 1,000 dying within 5 years, a 12% increase. From the health economics perspective “6 months of trastuzumab treatment led to a total of 9.73 QALY gained (discounted), while 12 months of treatment led to 10.35 QALYs gained. Therefore, shortened treatment duration led to a total decrease of 0.62 QALY per patient.” (Table 22). Thus, the (average) OS and DFS do decrease, despite the overall conclusion of non-inferiority (i.e., to a lesser extent than what was predetermined as clinically relevant at the population level). As stated in the discussion of this report, information on patient preferences and the overall benefit-harm balance may also be used in determining relevant non-inferiority margins. This is also an important ethical point: some patients may have different personal thresholds for perceived inferiority.

**The principle of respect for autonomy**

The principle of respect for autonomy is also relevant here, though it simply requires that patients be given all relevant information about one treatment course vs. the other. Patients should be informed about the evidence, and if a 6-month course becomes the standard of care, care must be taken in the shared decision-making process to ensure that patients who are aware of the previous standard of care are not unnecessarily worried about this change. In other words, a potential issue is that patients fear they are getting "second-rate" treatment so the healthcare system can save money. This can be addressed through informing patients of the evidence base and stressing the (general) non-inferiority and decreased toxicity of shortened regime, along with the fact that treatment is typically stopped early in case of adverse events in any case.

In some cases, however, patients might want to run the risks of the longer treatment if maximising the chances of survival is of utmost importance to them. In line with the principle of respect for autonomy (and respect for individual inferiority thresholds, as mentioned above), those who prefer longer treatment should have this wish granted, though the potential downsides of this choice should also be made clear to them. However, an issue (both ethical and legal) could arise if a hospital or healthcare system only provided one treatment course or the other; a patient might claim that his or her autonomy is being violated because they would prefer the shorter or the longer course. In any case, great care should always be taken in the shared decision-making process. The UK National Institute for Health and Care Excellence (NICE) guidelines on shared decision-making state that the healthcare professional should "openly discuss the risks, benefits and consequences of each option, making sure the person knows this includes choosing no treatment, or no change to what they are currently doing".[102] In terms of 12 months vs. 6 months of treatment this means that patients should be informed about the relative prospective harms and benefits of the different durations of treatment in a comprehensible format, even if the standard course changes to 6 months.

**The principle of justice**

Finally, assuming patients are treated fairly and equitably in a non-discriminatory manner, the principle of justice is informative mainly with regard to resource allocation. Reducing the course of treatment from 12 to 6 months would decrease healthcare costs (saving CHF 15,047 per patient for a similar level of benefit in terms of survival and reduced harm), enabling those resources to be spent elsewhere.

### 8.2.3 Discussion

Overall, if a 6-month (or shorter) course offers similar benefit to most patients, does less harm, and represents more just use of resources, then it is consistent with 3 of the 4 principles of biomedical ethics (beneficence, non-maleficence, and justice) to switch to a 6-month course as the standard

of care. However, the decrease in OS and DFS for some patients on the shorter course and the uncertainty about non-inferiority regarding DFS are important issues from an ethical perspective, both of which would have to be addressed carefully in shared decision making with patients if the standard of care was changed to shorter treatment.

The validity of this assessment can be checked with reversal test.[103] Given the evidence presented in this report, would it be ethical to continue with a 12-month course as the standard? Doing so would slightly increase survival, and would increase the risk of adverse events, while also costing more. This would be contrary to the principles of nonmaleficence and justice, and also to the principle of respect for autonomy, if patients were not informed of the possibility of the 6-month option, the uncertainty regarding DFS, and its reduced risk of AEs.

One other ethical issue that could theoretically arise is that producers of the treatment drug might increase its cost if patients are only receiving a 6-month course. If this occurred, the savings made by moving to 6 months could be reduced. However, this is unlikely for several reasons. In Switzerland, prices are already fixed, and the price is set based on across-country comparisons and across-indication comparisons with other drugs. Additionally, several different manufacturers can produce the drug generically and there are already several biosimilar treatments. In any case, even if this did occur, the benefits to patients in terms of reduced risk of adverse events and potential improvement in HRQoL might in themselves be sufficient to justify the change to a 6-month course.

Finally, it should also be noted that although no literature on specific organisational issues in this area was identified, reducing the duration of treatment is likely to have effects at an organisational level. It is probable that the reduced treatment duration also reduced organisational burden for hospitals and patients. For example, it may result in fewer visits to the hospital for the patient, as well as more appointment slots available for other patients in the hospitals. This can be seen as an advantage that complements the conclusion with regard to the principle of justice (organisational resource savings). It is important to emphasize that organisational changes may also have an economic impact on the hospitals: although the additional resources will presumably be allocated to the treatment of other patients, it is unknown whether these patients will be economically equivalent (i.e., the remuneration of inpatient and outpatient treatments may not by the same).

### 8.2.4 Conclusion

The preceding normative analysis reveals that changing from 12 months to 6 months of trastuzumab treatment would generally be in alignment with the principles of biomedical ethics as it would reduce harm overall while offering similar survival benefit and saving resources (at least for the PICO 1 population).

There are 3 closely linked ethical issues involved in making this change that must be carefully considered though. First, OS and DFS may be lower for some women with shorter treatment, meaning that in individual cases a 12-month course may still be preferable from the patient perspective. The problem is that it is not possible to say who these individual patients are while making treatment decisions. Furthermore, the evidence was inconclusive regarding non-inferiority in terms of DFS. Therefore, the second ethical issue is that shared decision-making is of utmost importance in discussing treatment with patients, to ensure that they receive all the relevant facts about potential treatments (and their duration). Finally, respect for autonomy does not consist merely in the provision of information to patients, but also enabling access to the treatment that is preferred, as far as possible within the context of inevitable resource constraints.

# 9. Additional issues

**Current clinical practice guidelines**

Current clinical practice guidelines for the treatment of HER2-positive early breast cancer recommend treatment with 12 months of trastuzumab over shorter courses (6 months or less), although they discuss the possibility of using shorter courses in individual cases. The reasons for recommending 12 months of trastuzumab over shorter courses like 6 months include:

- Guidelines from the German Guideline Program in Oncology (S3-Leitlinien)[104] published in 2021 recommend 12 months of trastuzumab as the standard treatment: *"Adjuvant treatment with trastuzumab is generally indicated for patients with node-positive tumours and node-negative tumours ≥ 1 cm in diameter with HER2 overexpression. The duration of therapy is one year. The infusions can be given at weekly or 3-weekly intervals. Additional studies were conducted on the duration of therapy. The two-year arm of the Hera study showed no significant difference compared to the one-year arm. The Phare study compared half a year with one year of trastuzumab and it could not be shown that the shorter duration was not inferior. Thus, one year of trastuzumab therapy remains the standard."*
- Guidelines from the European Society for Medical Oncology (ESMO)[105] from 2019 state: *"A few studies compared shorter versus standard 12-month administration of trastuzumab, but only the largest Persephone trial was able to show the non-inferiority of the shorter 6-month regimen, although this could not be demonstrated in the other studies. Therefore, a duration of 1 year remains the standard, although in highly selected low-risk patients, who receive anthracycline/taxane-based chemotherapy [...], shortening trastuzumab duration to 6 months may be discussed. Further data and longer follow-up are needed and several questions are still open regarding de-*

*escalation of anti-HER2 therapy, ChT [chemotherapy] or both in HER2-positive early breast cancer."*

– Recommendations from the St. Gallen International Consensus Conference for the Primary Therapy of Individuals with Early Breast[106] Cancer from 2023 state:[113] *"Studies investigating the non-inferiority of a shorter duration of trastuzumab (6 months versus 12 months) support evidence of 6 months of treatment for patients with low risk of relapse and comorbidities as an option. The decision regarding the duration of trastuzumab should consider the balance between the benefits of 12 months versus 6 months and the baseline risk of recurrence, particularly in resource-constrained settings with limited treatment capacity."*

Of note, for stage II and stage III HER2-positive breast cancers, most recent clinical consensus from the St. Gallen International Consensus Conference 2023 recommends the combination treatment with trastuzumab and pertuzumab. ESMO guidelines[106] and guidelines from the German Guideline Program in Oncology (S3-Leitlinien)[104] also recommend the use of the combination treatment with trastuzumab and pertuzumab in patients with breast cancer at elevated risk of recurrence (defined as node-positive disease or oestrogen receptor-negative disease by ESMO, and as node-positive disease or tumour size >2cm by the German Guidelines). These recommendations may limit the applicability of the findings of this HTA to low-risk or node-negative HER2-positive early breast cancer.

**Ongoing studies**

No ongoing studies with unpublished results have been identified in the systematic reviews conducted within this HTA. Meanwhile, some of the studies included in this HTA are still ongoing and it is possible that additional results with longer follow-up may be published in the future. Furthermore, an individual participant data meta-analysis is currently ongoing (preliminary results described below).[53] [107]

# 10. Discussion

**Summary of main results**

This HTA aimed to investigate the clinical efficacy, safety, cost-effectiveness, budget impact, and ethical, legal, social, and organisational aspects of ≤6 months compared with 12 months of trastuzumab treatment and of ≤6 months compared with 12 months of combination treatment with trastuzumab and pertuzumab in women with HER2-positive early breast cancer. 6 RCTs including a total of 11,603 women were identified for the comparison of ≤6 months of trastuzumab vs. 12 months of trastuzumab treatment. No RCTs were identified comparing different treatment durations for the combination of trastuzumab and pertuzumab. The included RCTs reported data on OS, DFS, HRQoL, and treatment-related adverse effects, and evaluated treatment durations of 6 months (3 RCTs), 12 weeks (1 RCT), and 9 weeks (2 RCTs).

The analyses conducted in this HTA resulted in the following findings:

- **Overall survival (OS)**: Considering a non-inferiority margin of HR 1.543 (corresponding to a 3% absolute difference for an assumed 5-year OS of 94.2%), OS with 6 months or less of trastuzumab treatment is likely non-inferior to 12 months of trastuzumab treatment (HR 1.13, 95% CI 0.99 to 1.28, p<0.0001 for non-inferiority, $I^2$ = 0%, 6 RCTs, 11,603 participants, moderate certainty of evidence).
- **Disease-free survival (DFS)**: Considering a non-inferiority margin of HR 1.266 (corresponding to a 3% absolute difference for an assumed 5-year DFS of 87.7%), the evidence is inconclusive whether DFS with 6 months or less of trastuzumab treatment is non-inferior to 12 months of trastuzumab treatment (HR 1.14, 95% CI 0.98 to 1.32, p=0.22 for non-inferiority, $I^2$ = 37%, 6 RCTs, 11,603 participants, low certainty of evidence).
- **Health-related quality of life (HRQoL)**: HRQoL with 6 months or less of trastuzumab treatment may be similar or higher compared with 12 months of trastuzumab treatment, but the evidence is very uncertain (1 RCT, 4,088 participants, very low certainty of evidence).
- **Cardiac adverse effects (AEs)**:
  - **Congestive heart failure**: The risk of congestive heart failure with 6 months or less of trastuzumab treatment is likely lower compared with 12 months of trastuzumab treatment (RR 0.65, 95% CI 0.42 to 1.00, p=0.051, $I^2$ = 0%, 3 RCTs, 5,788 participants, moderate certainty of evidence).
  - **Left-ventricular ejection fraction (LVEF) <50% and LVEF decrease >10%**: The risk of having a LVEF <50% and a decrease in LVEF of >10% with 6 months or less of trastuzumab treatment is likely lower compared with 12 months of trastuzumab

treatment (RR 0.76, 95% CI 0.63 to 0.92, p=0.004, $I^2$ = 0%, 3 RCTs, 7,532 participants, moderate certainty of evidence).

- **Other adverse effects (AEs)**:
  - **Any severe (grade ≥3) AE**: The risk of any severe (grade ≥3) AE with 6 months or less of trastuzumab treatment may be lower compared with 12 months of trastuzumab treatment (RR 0.89, 95% CI 0.72 to 1.09, p=0.25, $I^2$ = 88%, 2 RCTs, 6,007 participants, low certainty of evidence).
  - **Trastuzumab discontinuation due to any AE**: The risk of trastuzumab discontinuation due to any AE with 6 months or less of trastuzumab treatment is likely lower compared with 12 months of trastuzumab treatment (RR 0.37, 95% CI 0.27 to 0.50, p<0.0001, $I^2$ = 61%, 3 RCTs, 6,807 participants, moderate certainty of evidence).
  - All cost-effectiveness studies identified in the systematic review report that ≤6 months of trastuzumab treatment is less expensive than 12 months of treatment. The effects on QALYs are discordant, with 5 studies suggesting that ≤6 months treatment is more effective (i.e., lead to more QALY gained than 12 months of trastuzumab), and 2 studies concluding that ≤6 months of trastuzumab is less effective (i.e., the QALY difference compared to 12 months was negative),
- **Costs, cost-effectiveness and budget impact**
  - The ***de novo*** **cost-effectiveness analysis** conducted for Switzerland suggests that a treatment duration of 6 months of trastuzumab results in lower costs (CHF -15,047) compared to 12 months of treatment. At the same time, trastuzumab treatment over 6 months leads to a total decrease of 0.62 QALY per patient. As a consequence, an ICER of CHF 24,242 saved per QALY lost is estimated.
  - The **budget impact analysis** suggests that switching from 12 months to 6 months of trastuzumab treatment would lead to a decrease in total costs ranging between CHF 13.6 million in 2024 and CHF 14.1 million in 2028.
- **Ethical, legal, social and organisational issues (ELSO)**
  - The analysis of **ELSO** issues and the principles of biomedical ethics show that shortening the course of trastuzumab would be ethical for most patients, given little reduction in benefit, reduction of AEs, and reduction of resources. However, 3 ethical issues arise concerning the possibly lower OS and DFS with shorter treatment in some women, informing women about this evidence, and facilitating informed choices regarding treatment.

**Evidence in context**

One further HTA report investigating 6 months vs. 12 months of trastuzumab treatment was identified, conducted within the National Institute of Health Research (NIHR) Health Technology Assessment Programme in the UK.[53] This report mainly focused on the PERSEPHONE study results but also included data from PHARE, HORG, Short-HER and SOLD. The authors' conclusion was based on a meta-analysis of aggregate data from PHARE and PERSEPHONE. The report referred to a non-inferiority margin for DFS of HR 1.19, based on a 2% absolute difference in 4-year DFS. The reported results showed that 6 months of trastuzumab treatment is non-inferior to 12 months of treatment in terms of DFS (HR 1.08, 90% CI 0.98 to 1.18). Of note, the conclusions of this report were based on a 90% CI with a 1-sided alpha of 0.05 and excluding HORG (because the authors argued that the risk of disease recurrence in this study was higher due to the larger proportion of participants with node-positive breast cancer). In contrast to this report, our analysis was based on a 95% CI (with a 2-sided alpha of 0.05), leading to a lower probability for concluding non-inferiority than a 90% CI).

Furthermore, 4 systematic reviews and meta-analyses published in the last 3 years with similar approaches to ours were identified. [39–42] Wang et al.[42] (2021) investigated OS, DFS, and safety in studies comparing 6 months vs. 12 months of trastuzumab treatment, including evidence from PHARE, HORG and PERSEPHONE. Similar to this HTA, they found the evidence to be inconclusive for DFS (HR 1.18, 95% CI 0.97 to 1.44), while they found non-inferiority for OS (HR 1.14, 95% CI 0.98–1.32) with 6 months vs. 12 months of trastuzumab treatment, based on non-inferiority margins of HR 1.20 and HR 1.43 for DFS and OS (3% absolute difference), respectively. Of note, the authors used an incorrect estimate for OS (corrected in a corrigendum in 2020) [19 74], Stewart et al.[42] (2020) evaluated OS and DFS with ≤6 months vs. 12 months of trastuzumab treatment, including the PHARE, HORG (using the corrected OS estimate [22 80]), Short-HER, SOLD, and PERSEPHONE trials. They concluded that shorter treatment was non-inferior for DFS (HR 1.13, 95% CI 1.03 to 1.24) and the evidence was inconclusive for non-inferiority for OS (HR 1.14, 95% CI 1.00 to 1.30), based on non-inferiority margins of HR 1.29 (median of included studies, corresponding to 3.9% absolute difference in 5-year DFS) for both DFS and OS, respectively. Gulia et al.[43] (2020) reconstructed individual participant data based on published data from PHARE, E2198 (not included in individual participant data meta-analysis), HORG, Short-HER, SOLD, and PERSEPHONE, and used this as a basis for meta-analysis. They evaluated OS, DFS and cardiac AEs for ≤6 months vs. 12 months of trastuzumab treatment. Based on reconstructed individual participant data, the authors found shorter treatment to be non-inferior for DFS (HR 1.14, 95% CI,1.03 to 1.25) based on a non-inferiority margin of HR 1.30 for DFS (determined as median of included studies), and similar effect estimate for OS (HR 1.17, 95% CI 1.02 to 1.34) as other systematic reviews. Of note, the OS effect estimate used for HORG in this analysis was incorrect and the data from the 6-month treatment arm was misattributed to the 12-month arm in reconstructed individual participant data meta-analyses, and effect estimates from E2198 in meta-analyses were also misattributed to 6 months vs. 12 months of treatment instead of 12 months vs. 6 months of treatment, which both

lead to a decreased probability of concluding non-inferiority for OS compared to our analysis. They further reported that the risk of congestive heart failure (RR 0.53, 95% CI 0.38 to 0.74, p<0.001) and asymptomatic LVEF decline (RR 0.71, 95% CI 0.50 to 1.00, p=0.049) was significantly reduced with ≤6 months of treatment compared to 12 months of trastuzumab treatment. Furthermore, Eiger et al. (2020)[41] assessed several cardiac AE outcomes for ≤6 months vs. 12 months of trastuzumab treatment, including data from all 6 trials included in the current HTA. For their primary outcome of 'clinical cardiac dysfunction', they used a different definition to the one used in this HTA (based on the definition used in the included studies), which was broader and allowed to pool further results from other studies under that outcome (this was not done in this HTA since the outcome definitions were considered too heterogenous to be pooled). They found substantial heterogeneity for their outcome definition ($I^2$=65.7%), which was not the case based on the definition used in this HTA ($I^2$=0%). The authors found that patients receiving 12 months of trastuzumab showed a higher risk (higher odds ratios (OR)) for 'clinical cardiac dysfunction' compared to those receiving 6 months of trastuzumab (OR 1.57, 95% CI 1.30 to 1.90, p<0.001) and those receiving ≤6 months of trastuzumab (OR 1.90, 95% CI 1.37 to 2.64, p<0.001). Similarly, they found a higher risk of congestive heart failure (OR 1.22, 95% CI 0.51 to 2.96, p-value not reported) and for low LVEF (OR 1.45, 95% CI 1.19 to 1.75, p<0.001) with 12 months vs. 6 months of trastuzumab. Overall, their findings are similar to the results of the assessment of clinical efficacy and safety conducted within this HTA. Last, an individual participant data meta-analysis is currently ongoing, for which preliminary results have been published in a conference abstract.[107] Such an analysis may account for between-trial differences in participant characteristics. Therein, the authors concluded that there was inconclusive evidence for non-inferiority in DFS for ≤6 months vs. 12 months of trastuzumab (HR 1.14, 95% credible interval (CrI) 0.88 to 1.47, p=0.37 for non-inferiority). However, they concluded that DFS for 6 months vs. 12 months of trastuzumab was non-inferior (HR 1.07, 90% CrI 0.98 to 1.17, p=0.02 for non-inferiority) based on a non-inferiority margin of a 2% absolute difference or a HR of 1.19. Of note, the latter conclusion was based on a 90% CrI (equivalent to assuming a 1-sided alpha of 0.05). No previous systematic review has evaluated the evidence on HRQoL in the context of HER2-positive early breast cancer. Overall, the results from different systematic reviews are similar, although there were differences in the choices of non-inferiority margins, included studies, the treatment durations of interest (6 months or ≤6 months vs. 12 months of trastuzumab), and the applied alpha threshold (1-sided or 2-sided alpha of 0.05; 90% or 95% CI). These differences impact the authors' conclusions regarding non-inferiority between ≤6 months and 12 months of trastuzumab treatment for the outcomes OS and DFS.

One further note pertains to the interpretation of the meta-analysis results from the assessment of clinical efficacy and safety: The estimated effects (HRs) for OS and DFS were smaller than the respective prespecified non-inferiority margins. At the same time, the estimated effects were different from a null effect (HR 1.0), although there was substantial statistical uncertainty and estimates were still compatible with a null effect (i.e., 95% CIs overlapped with 1.0) for both outcomes based on random-effects models and ITT estimates. Assuming that the point estimates are correct, this

would mean that the magnitude of the estimated potential benefit in terms of OS and DFS would be considered not to be clinically important based on the non-inferiority margins, but that there would still be some benefit in OS and DFS on average were the results interpreted in terms of superiority. This needs to be kept in mind when interpreting the results from the cost-effectiveness analysis and the ELSO assessment.

Regarding the economic assessment, no prior systematic review comparing ≤6 months with 12 month of trastuzumab treatment has been identified. The economic literature comparing ≤6 months with 12 month of trastuzumab treatment is also very limited.

The current systematic review identified only 7 cost-effectiveness analyses. Two of them were published more than 15 years ago (Millare et al. 2007[76], from Australia; Neyt et al. 2008[77], from Belgium) and can be considered as outdated, given the lack of available trials at the time (these 2 cost-utility analyses used data from the FinHer trial to estimate the effectiveness of 9 weeks of trastuzumab). The 5 other cost-effectiveness analyses were published more recently (between 2017 and 2020). Two of them were conducted in the UK (Earl et al. [53], Clarke et al. [86]), while the other 3 were conducted in India (Gupta et al. [84]), Iran (Ansaripour et al. [87]) and Egypt (Elsisi et al. [85]). When comparing the results of these studies with the data derived from the current HTA report, different aspects have to be considered, including the different settings they were conducted for. In all models many assumptions concerning the (effectiveness) parameters were made. One point that is common to all cost-effectiveness analyses is the fact that 6 months of trastuzumab treatment resulted in being less expensive than 12 months of treatment (despite many differences in healthcare settings, cost assumptions, time horizon, discount rate, etc.). In contrast, results concerning the effectiveness in terms of QALYs are discordant, with 5 cost-effectiveness analyses concluding that ≤6 months treatment is more effective (i.e., lead to more QALY gained than 12 months of trastuzumab), and 3 cost-effectiveness analyses (including the economic analysis conducted for this report) concluding that 6≤ months of trastuzumab is less effective (i.e., the QALY difference compared to 12 months was negative). Among the 4 cost-effectiveness analyses suggesting that ≤6 months treatment is more effective than 12 months of treatment, in 2 studies the QALY difference in favour of a shorter treatment was very small (0.06 QALYs in Elsisi et al, 0.01 QALYs in Earl et al.),[53 85] while in the other 2 studies the difference was larger (0.68 Lys in Neyt et al., 0.80 QALY in Clarke et al.)[83 86]. The underlying assumptions concerning the assumed frequencies of cardiac and non-cardiac AEs as well as the utility decrements associated with them may have played a major role in the conducted analyses. In the base case analysis of this HTA, the potential impact of AEs on the quality of life of the patients was not included for 2 reasons. First, especially for the cardiac AEs, the outcomes reported in the RCTs were generally not well defined. Assigning a utility decrement to a poorly defined variable may be problematic. Second, the reversibility, duration, and severity of the reported cardiac AEs was unknown. Therefore, it was not clear whether a potential utility decrement should be applied only to the trastuzumab treatment period (6 or 12 months), for several years, or lifelong. Nevertheless, the potential impact of a utility decrement was investigated in a scenario analysis in which the utility for patients with clinical cardiac

dysfunction was estimated to be 0.600. As consequence the utility decrement if compared to DFS was 0.205 (i.e., 0.805 – 0.600). The inclusion of a utility decrement due to cardiac AEs led to a decrease in the total number of QALYs gained of 0.15 in the intervention group and 0.25 in the comparator group. The difference between the 2 groups decreased from -0.62 QALYs to -0.53 QALYs. The inclusion of additional utility decrements for other AEs may further decrease the difference between intervention and comparator.

**Evidence gaps**

Only very limited data were identified for HRQoL outcomes, and reporting of data related to AE outcomes was limited. Furthermore, the definitions of AE outcomes were heterogenous. These shortcomings precluded any clear statements on HRQoL benefits or detriments for patients and led to some uncertainty with respect to the safety of ≤6 months compared to 12 months of trastuzumab treatment. Given the importance of HRQoL as a patient-relevant outcome in oncology trials, a systematic elicitation and reporting of HRQoL data and full reporting of AE data could have substantially strengthened the results of the assessment of clinical efficacy and safety. Hence, better reporting should be strongly encouraged – if not mandated – for all future trials, particularly in the field of oncology. It is unlikely that additional HRQoL or AE data at acceptable risk of bias would become available from the trials included in this HTA.

Further, given the context-dependency of the choice of non-inferiority margins in oncological settings, there is no clear consensus of an acceptable non-inferiority margin for OS and DFS in the setting of (HER2-positive) early breast cancer. The identified studies used non-inferiority margins ranging from a 2% to an 8% absolute difference in DFS over 2 to 5 years. The choices made in this HTA resulted in HR non-inferiority margins that were well in line with those used in these studies, with a tendency of being more conservative (i.e., closer to a HR of 1.0). While the determination of non-inferiority margins – including in this HTA – primarily takes into account what constitutes a minimal (clinically) important difference for an individual patient (absolute difference in risk of death or disease recurrence), information on patient preferences and the overall benefit-harm balance may also be used in determining relevant non-inferiority margins. For instance, research that asks patients whether they are willing to forego some potential survival to have fewer AEs can provide important information to help decide on the acceptable limits for non-inferiority. Moreover, research that considers both the possible benefits in OS and DFS alongside the potential risks and harms of treatment (such as quantitative benefit-harm assessments which weigh the expected benefits of a treatment against its potential harms), can assist in making informed decisions. This kind of study can help us better understand the trade-offs patients might need to consider, such as choosing between longer or shorter durations of trastuzumab treatment in the context of this HTA.

Last, in this HTA, no data was identified from RCTs comparing ≤6 months of combination treatment with trastuzumab and pertuzumab with 12 months of treatment. Evidence from RCTs or strong observational studies evaluating this research question would be required to allow the evaluation of a potential shortening of treatment courses for combination treatment (PICO 2).

**Applicability of this HTA**

Some important aspects need to be considered regarding the applicability of this HTA. First, the applicability of the study populations in the included RCTs requires consideration. Little information is available from Switzerland regarding the distributions of stage, hormone receptor status, and further characteristics of patients with HER2-positive early breast cancer. Based on data provided by NKRS (https://nkrs.ch), 68.5% of patients with HER2-positive breast cancer in 2018-2020 were oestrogen receptor-positive and 50.1% were progesterone receptor-positive (70.0% were hormone receptor-positive overall). This compares relatively well with the studies included in the assessment of clinical efficacy and safety, especially PERSEPHONE, SOLD, Short-HER, and HORG. No further data was available to assess the applicability of the study populations to the Swiss context. It may generally be expected that patients included in RCTs are on average younger and have less comorbidities compared to the overall population.[108] This also means that OS in the overall Swiss patient population may be lower than in the included RCTs (see Table 25), which would lead to a lower probability of concluding non-inferiority when assuming a 3% absolute difference in 5-year survival as the non-inferiority margin. Meanwhile, the sensitivity analyses presented in Appendix 8 allow to explore the probability of non-inferiority under different assumptions about baseline survival given the current state of evidence.

Second, the applicability of the HTA research questions in current clinical practice needs to be considered. For HER2-positive early breast cancers at high risk of recurrence, combination treatment with trastuzumab and pertuzumab for 12 months is currently recommended (see Section 9, Current clinical practice guidelines). No data was identified for the comparison of ≤6 months vs. 12 months of combination treatment. Since high-risk patients correspond to those with a tumour size >2 cm or with node-positive disease (according to the Swissmedic approval for combination treatment with trastuzumab and pertuzumab; further aspects such as breast cancer stage or oestrogen receptor status may be additionally considered based on specific guidelines [106]), a large proportion of patients newly diagnosed with HER2-positive early breast cancer may fall into this category. Hence, these patients may also fall outside of the scope of the evidence identified in this HTA, thus limiting the applicability of its findings for this population.

**Strengths and limitations of this HTA**

This HTA included a comprehensive evaluation of the efficacy, safety, cost-effectiveness, budget impact, and ethical, legal, social, and organisational aspects. Several limitations need to be considered. First, the systematic evidence reviews relied on published information. Additional information may be available to pharmaceutical suppliers or regulatory bodies if such information has been submitted as part of the drug approval process for the indication of HER2-positive early breast cancer. This may, for example, include additional information on the safety or cost-effectiveness of trastuzumab. However, it is unlikely that such information would have been submitted since approval of trastuzumab and pertuzumab has been established for a 12-month treatment duration in this setting. Furthermore, the original study authors were not contacted in the absence of an

indication that relevant additional data would be available. Even if available, it was deemed unlikely that such information would lead to changes in the findings or conclusions of this report. Second, as in any systematic review, relevant publications may have been missed in the systematic searches based on the search strategy or inclusion criteria (e.g., language restrictions). However, given the literature identified and feedback from involved clinical experts, it was considered highly unlikely that relevant published information was missed. Third, data from observational studies was not considered in the assessment related to the clinical efficacy and safety. While additional information may have been available from such studies, such was considered to be at very high risk of bias in a non-randomised setting since treatment duration can be assumed to be strongly driven by participant characteristics (i.e., confounding by indication) and tolerance of trastuzumab treatment (i.e., discontinuation due to (cardiac) AEs). Fourth, data from OS and DFS curves and HRQoL was extracted using digitization, which may introduce some uncertainty regarding the corresponding estimates. However, this uncertainty was considered negligible in the context of this HTA, since resulting OS and DFS estimates were well in line with those reported in the original articles (for the few timepoints where such were available), and HRQoL estimates were considered very uncertain regardless of their precision. Fifth, meta-analysis relies on several assumptions that need to be fulfilled to make valid inferences. In this report, the combination of the identified evidence in meta-analysis was deemed justified in this setting and sensitivity analyses were conducted leading to the same conclusions. The use of HRs in meta-analyses for OS and DFS assumed proportional hazards. While this assumption was likely not sufficiently met in the included trials, their use was nevertheless considered justified since HRs can be interpreted as the average relative effect over the follow-up and thus could be used for interpreting the overall effects across trials.[56] Furthermore, the use of RRs in meta-analyses for AEs assumed constant risks for AEs over the follow-up in the trials. This also needs to be considered when interpreting the corresponding results, as this assumption may not hold for all of the AEs. Sixth, the conclusions of the non-inferiority meta-analyses for OS and DFS are influenced by the choice of the non-inferiority margin used in analysis. While different choices could be deemed sensible, the non-inferiority margins used in this HTA were derived based on a pre-specified absolute risk difference and a systematic approach to calculating resulting (relative) HRs based on the available evidence. In addition, various sensitivity analyses were conducted based on different assumptions, allowing readers to make their own conclusions. Seventh, PP estimates were generally not reported and meta-analyses for OS and DFS therefore relied on ITT estimates. Since ITT estimates may be biased towards concluding non-inferiority, this is an important limitation to the findings, as also reflected in the risk of bias assessment. Eighth, the *de novo* cost-effectiveness analysis was based on a health state Markov cohort simulation model with 4 mutually exclusive health states of DFS, locoregional recurrence, distant metastasis, and death. Although the structure of the model generally reflects daily clinical practice in Switzerland, it should be emphasised that daily clinical practice may slightly differ. Ninth, the probabilistic sensitivity analysis suggested that the variation of the transition probabilities had an important impact on the results. In particular, the variations in the 6 months treatment group led to considerable

changes in the incremental QALYs. This was due to the high uncertainty of the transition probabilities. As reported in Table 14, the published SE for most transition probabilities were very large (up to 6.7 times higher than the mean estimate). Moreover, like in the UK study, the PSA transition probabilities of both strategies were varied independently instead of using hazard ratios (the UK study also reported that survival analysis was conducted by arm). The wide variation, especially using long time horizons, may then be an artefact and may not correctly reflect the real uncertainty. An additional limitation concerning the probabilistic sensitivity analysis is the fact that the input parameters were varied randomly, without taking into account that some of them (e.g., transition probabilities) may be connected. Tenth, additional treatments (e.g., cyclophosphamide) were not included in the economic model. It was assumed that such treatments would be prescribed similarly in the first months of early breast cancer treatment in both groups. Therefore, although they would have an impact on the total costs per group, they would not significantly affect the budget impact. Finally, the impact of AEs on HRQoL is highly uncertain. In a scenario analysis, the inclusion of a utility decrement due to cardiac AEs led to a decrease in the total number of QALYs gained of 0.15 in the intervention group and 0.25 in the comparator group. The difference between the 2 groups decreased from -0.62 QALYs to -0.53 QALYs. The inclusion of additional utility decrements for other AEs may further reduce the difference between the 2 groups.

# 11. Conclusions

This HTA evaluating ≤6 months of trastuzumab compared to 12 month of trastuzumab treatment in HER2-positive early breast cancer found that 6 months or less of treatment is likely non-inferior compared with 12 months of treatment for OS, whereas the evidence for non-inferiority is inconclusive for DFS. While the evidence is very uncertain for HRQoL, the risk of cardiac AEs and trastuzumab discontinuation due to any AE is likely lower and the risk of any severe (grade ≥3) AEs may be lower with a shorter treatment duration. Furthermore, the *de novo* cost-effectiveness analysis suggests that 6 months compared to 12 months of trastuzumab treatment reduces costs but also reduces QALYs. The budget impact analysis suggests that switching from 12 months to 6 months of trastuzumab would lead to a decrease in total costs. Due to a lack of evidence, the comparison of ≤6 months of adjuvant combination treatment with trastuzumab and pertuzumab compared to 12 months of combination treatment could not be assessed in this HTA.

# 12. References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# 13. Appendices

**Appendix 1: Search strategies and search results for the systematic review related to the clinical efficacy and safety.**

MEDLINE (accessed via Ovid)

| | |
|---|---|
| 1 | exp Breast Neoplasms/ |
| 2 | ((breast* or mamma*) adj4 (cancer* or neoplasm* or malignanc* or tumor* or tumour* or carcinoma* or adenocarcinoma*)).ti,ab. |
| 3 | 1 or 2 |
| 4 | exp Chemotherapy, Adjuvant/ or exp Neoadjuvant Therapy/ |
| 5 | (adjuvant or neoadjuvant).ti,ab. |
| 6 | 4 or 5 |
| 7 | exp Trastuzumab/ or (trastuzumab or herceptin).ti,ab. |
| 8 | (duration or timing or time or short* or long* or course* or cycle* or length or ((compar* or difference or versus or vs*) adj4 (year* or month* or week* or day*))).ti,ab. |
| 9 | 7 and 8 |
| 10 | (pertuzumab or perjeta).ti,ab. |
| 11 | 9 or 10 |
| 12 | Clinical Trials as Topic/ or (randomized controlled trial or controlled clinical trial).pt. or (randomi?ed or randomly).ab. or (trial).ti. |
| 13 | exp Animals/ not Humans/ |
| 14 | 12 not 13 |
| 15 | 3 and 6 and 11 and 14 |

EMBASE (accessed via Elsevier)

| | |
|---|---|
| #1 | 'breast cancer'/exp |
| #2 | ((breast* OR mamma*) NEAR/4 (cancer* OR neoplasm* OR malignanc* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma*)):ti,ab |
| #3 | #1 OR #2 |
| #4 | 'adjuvant chemotherapy'/exp OR 'neoadjuvant chemotherapy'/exp |
| #5 | (adjuvant or neoadjuvant):ti,ab |
| #6 | #4 OR #5 |
| #7 | 'trastuzumab'/exp OR (trastuzumab or herceptin):ti,ab |
| #8 | (duration OR timing OR time OR short* OR long* OR course* OR cycle* OR length OR ((compar* OR difference OR versus OR vs*) NEAR/4 (year* OR month* OR week* OR day*))):ti,ab |
| #9 | #7 AND #8 |
| #10 | 'pertuzumab'/exp OR (pertuzumab or perjeta):ti,ab |
| #11 | #9 OR #10 |
| #12 | 'clinical trial'/exp OR ('randomized controlled trial' OR 'controlled clinical trial'):it OR (randomi?ed OR randomly):ab OR (trial):ti |
| #13 | 'animals'/exp NOT 'humans'/exp |
| #14 | #12 NOT #13 |
| #15 | #3 AND #6 AND #11 AND #14 |

CENTRAL (accessed via the Cochrane Library)

| | |
|---|---|
| #1 | MeSH descriptor: [Breast Neoplasms] explode all trees |
| #2 | ((breast* OR mamma*) NEAR/4 (cancer* OR neoplasm* OR malignanc* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma*)) |
| #3 | #1 OR #2 |
| #4 | MeSH descriptor: [Chemotherapy, Adjuvant] explode all trees |
| #5 | MeSH descriptor: [Neoadjuvant Therapy] explode all trees |
| #6 | (adjuvant or neoadjuvant) |
| #7 | #4 OR #5 OR #6 |
| #8 | MeSH descriptor: [Trastuzumab] explode all trees |
| #9 | (trastuzumab or herceptin) |
| #10 | duration OR timing OR time OR short* OR long* OR course* OR cycle* OR length OR ((compar* OR difference OR versus OR vs*) NEAR/4 (year* OR month* OR week* OR day*)) |
| #11 | (#8 OR #9) AND #10 |
| #12 | (pertuzumab or perjeta) |
| #13 | #11 OR #12 |
| #14 | #3 AND #7 AND #13 |

INAHTA HTA Database (accessed via INAHTA)

| |
|---|
| (((Breast Neoplasms)[mhe]) OR (breast cancer* OR breast neoplasm* OR breast tumor* OR breast tumour*)) AND ((Trastuzumab)[mhe] OR (trastuzumab OR herceptin) OR (pertuzumab OR perjeta)) |

ClinicalTrials.gov (accessed via ClinicalTrials.gov)

| | |
|---|---|
| Condition | Breast Cancer |
| Other terms | trastuzumab or pertuzumab |
| Study type | Interventional Studies (Clinical Trials) |
| Study results | All Studies |

WHO ICTRP (accessed via WHO)

| | |
|---|---|
| Title | breast cancer and (trastuzumab or pertuzumab) |
| Condition | breast cancer |
| Intervention | (trastuzumab or pertuzumab) |
| Recruitment status | ALL |

Search results

| **Database** | **Search Portal** | **Search Date** | **Records** |
|---|---|---|---|
| MEDLINE | Ovid | 07 May 2023 | 605 |
| EMBASE | Elsevier | 07 May 2023 | 2484 |
| CENTRAL | Cochrane Library | 07 May 2023 | 1325 |
| INAHTA HTA Database | INAHTA | 07 May 2023 | 83 |
| ClinicalTrials.gov | ClinicalTrials.gov | 07 May 2023 | 194 |
| WHO ICTRP | WHO | 07 May 2023 | 737 |
| *Subtotal* | | | *5428* |
| *Duplicates* | | | *-1638* |
| Google Scholar | Google | 12 June 2023 | 0 |
| Reference lists | – | – | 0 |
| **Total** | | | **3790** |

**Appendix 2: List of identified records for studies included in the systematic review related to the clinical efficacy and safety.**

| Study & article type | Title | Author (if available) & year | Journal / registry | Link |
|---|---|---|---|---|
| **PHARE (7 records)** | | | | |
| Trial registration | Trastuzumab for 6 Months or 1 Year in Treating Women With Nonmetastatic Breast Cancer That Can Be Removed By Surgery | 2006 | ClinicalTrials.gov | https://clinicaltrials.gov/show/NCT00381901 |
| Abstract | PHARE Trial results of subset analysis comparing 6 to 12 months of trastuzumab in adjuvant early breast cancer | Pivot et al. 2012 | Cancer Research | https://doi.org/10.1158/0008-5472.SABCS12-S5-3 |
| Full article | 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial | Pivot et al. 2013 | The Lancet Oncology | https://doi.org/10.1016/S1470-2045(13)70225-0 |
| Full article | Trastuzumab duration effects within patient prognostic subgroups in the PHARE trial | Kramar et al. 2014 | Annals of Oncology | https://doi.org/10.1093/annonc/mdu177 |
| Full article | Cardiac toxicity events in the PHARE trial, an adjuvant trastuzumab randomised phase III study | Pivot et al. 2015 | European Journal of Cancer | https://doi.org/10.1016/j.ejca.2015.05.028 |
| Abstract | PHARE randomized trial final results comparing 6 to 12 months of trastuzumab in adjuvant early breast cancer | Pivot et al. 2019 | Cancer Research | https://doi.org/10.1158/1538-7445.SABCS18-GS2-07 |
| Full article | 6 months versus 12 months of adjuvant trastuzumab in early breast cancer (PHARE): final analysis of a multicentre, open-label, phase 3 randomised trial | Pivot et al. 2019 | The Lancet | https://doi.org/10.1016/S0140-6736(19)30653-1 |
| **E2198 (2 records)** | | | | |
| Trial registration | Chemotherapy Plus Monoclonal Antibody Therapy in Treating Women With Stage II or Stage IIIA Breast Cancer That Overexpresses HER2 | 1999 | ClinicalTrials.gov | https://clinicaltrials.gov/show/NCT00003992 |
| Full article | Pilot trial of paclitaxel-trastuzumab adjuvant therapy for early stage breast cancer: a trial of the ECOG-ACRIN cancer research group (E2198) | Schneider et al. 2015 | British Journal of Cancer | https://doi.org/10.1038/bjc.2015.405 |
| **HORG (3 records)** | | | | |
| Trial registration | Six vs 12 Months of Trastuzumab With Docetaxel Following FEC as Adjuvant Treatment in N+ Breast Cancer | 2008 | ClinicalTrials.gov | https://clinicaltrials.gov/show/NCT00615602 |
| Full article | Six versus 12 months of adjuvant trastuzumab in combination with dose-dense chemotherapy for women with HER2-positive breast cancer: a multicenter randomized study by the Hellenic Oncology Research Group (HORG) | Mavroudis et al. 2015 | Annals of Oncology | https://doi.org/10.1093/annonc/mdv213 |
| Corrigendum | Corrigendum to Six versus 12 months of adjuvant trastuzumab in combination with dose-dense chemotherapy for women with HER2-positive breast cancer: a multicenter randomized study by the Hellenic Oncology Research Group (HORG) | Mavroudis et al. 2020 | Annals of Oncology | https://doi.org/10.1016/j.annonc.2020.01.004 |
| **Short-HER (10 records)** | | | | |

| Study & article type | Title | Author (if available) & year | Journal / registry | Link |
|---|---|---|---|---|
| Trial registration | SHORT-HER: Multicentric randomised phase III trial of adjuvant chemotherapy plus 3 vs 12 months of trastuzumab in breast cancer patients with HER2 positive disease | 2007 | EUCTR | https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2007-004326-25-IT |
| Protocol | Multicentric, randomized phase III trial of two different adjuvant chemotherapy regimens plus three versus twelve months of trastuzumab in patients with HER2-positive breast cancer (Short-HER Trial; NCT00629278) | Guarneri et al. 2008 | Clinical Breast Cancer | https://doi.org/10.3816/CBC.2008.n.056 |
| Trial registration | Combination Chemotherapy and Trastuzumab in Treating Women With Stage I, Stage II, or Stage III HER2-Positive Breast Cancer | 2008 | ClinicalTrials.gov | https://clinicaltrials.gov/show/NCT00629278 |
| Abstract | Abstract P5-12-05: 9 Weeks vs 1 Year Adjuvant Trastuzumab in Combination with Chemotherapy: preliminary Cardiac Safety Data of the Phase III Multicentric Italian Study Short-HER | Guarneri et al. 2010 | Cancer Research | https://doi.org/10.1158/0008-5472.SABCS10-P5-12-05 |
| Abstract | Final analysis of the phase III multicentric Italian study Short-HER: 9 weeks vs 1 year adjuvant trastuzumab for HER21 early breast cancer | Conte et al. 2017 | Annals of Oncology | https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01439798/full |
| Abstract | 9 weeks vs 1 year adjuvant trastuzumab in combination with chemotherapy: results of the phase III multicentric Italian study Short-HER | Conte et al. 2017 | Journal of Clinical Oncology | https://doi.org/10.1200/JCO.2017.35.15_suppl.501 |
| Full article | Nine weeks versus 1 year adjuvant trastuzumab in combination with chemotherapy: final results of the phase III randomized Short-HER study | Conte et al. 2018 | Annals of Oncology | https://doi.org/10.1093/annonc/mdy414 |
| Abstract | 9 weeks versus 1 year adjuvant trastuzumab for HER2+ early breast cancer: subgroup analysis of the ShortHER trial allows to identify patients for whom a shorter trastuzumab administration may have a favourable risk/benefit ratio | Conte et al. 2018 | Annals of Oncology | https://doi.org/10.1093/annonc/mdy424.005 |
| Full article | Validation of the AJCC prognostic stage for HER2-positive breast cancer in the ShortHER trial | Dieci et al. 2019 | BMC Medicine | https://doi.org/10.1186/s12916-019-1445-z |
| Abstract | 41O Nine weeks vs 1-year adjuvant trastuzumab: long term outcomes of the ShortHER randomised trial | Conte et al. 2021 | Annals of Oncology | https://doi.org/10.1016/j.annonc.2021.03.055 |
| **SOLD (3 records)** | | | | |
| Trial registration | A randomized phase III study comparing trastuzumab plus docetaxel (HT) followed by 5-FU, epirubicin, and cyclophosphamide (FEC) to the same regimen followed by single-agent trastuzumab as adjuvant treatments for early breast cancer - SOLD | 2007 | EudraCT | https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-002016-26 |
| Trial registration | The Synergism Or Long Duration (SOLD) Study | 2008 | ClinicalTrials.gov | https://clinicaltrials.gov/show/NCT00593697 |
| Full article | Effect of Adjuvant Trastuzumab for a Duration of 9 Weeks vs 1 Year With Concomitant Chemotherapy for | Joensuu et al. 2018 | JAMA Oncology | https://doi.org/10.1001/jamaoncol.2018.1380 |

| Study & article type | Title | Author (if available) & year | Journal / registry | Link |
|---|---|---|---|---|
| | Early Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: the SOLD Randomized Clinical Trial | | | |
| **PERSEPHONE (8 records)** | | | | |
| Trial registration | Persephone: duration of Herceptin with chemotherapy 6 versus 12 months | 2007 | ISRCTN | http://isrctn.com/ISRCTN52968807 |
| Trial registration | Persephone : duration of Trastuzumab with Chemotherapy in patients with early breast cancer: six months versus twelve | 2007 | EUCTR | https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2006-007018-39-GB |
| Trial registration | Trastuzumab in Treating Women With HER2-Positive Early Breast Cancer | 2008 | ClinicalTrials.gov | https://clinicaltrials.gov/show/NCT00712140 |
| Full article | Trastuzumab-associated cardiac events in the Persephone trial | Earl et al. 2016 | British Journal of Cancer | https://dx.doi.org/10.1038/bjc.2016.357 |
| Abstract | PERSEPHONE: a randomised phase 3 non-inferiority trial of 6 versus 12 months (m) of adjuvant trastuzumab in patients with HER2 positive (+) early breast cancer (EBC) | Earl et al. 2018 | British Journal of Cancer | https://doi.org/10.1038/s41416-018-0299-z |
| Abstract | PERSEPHONE: 6 versus 12 months (m) of adjuvant trastuzumab in patients (pts) with HER2 positive (+) early breast cancer (EBC): randomised phase 3 non-inferiority trial with definitive 4-year (yr) disease-free survival (DFS) results | Earl et al. 2018 | Journal of Clinical Oncology | https://doi.org/10.1200/JCO.2018.36.15_suppl.506 |
| Full article | 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial | Earl et al. 2019 | The Lancet | https://doi.org/10.1016/S0140-6736(19)30650-6 |
| Short article | Six versus 12 months, adjuvant trastuzumab in patients with HER2-positive early breast cancer: The PERSEPHONE non-inferiority RCT | Earl et al. 2020 | Health Technology Assessment | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7505360/ |

**Appendix 3: List of excluded records including reasons for exclusion at full-text screening for the systematic review related to the clinical efficacy and safety.**

| Title | Authors | Year | Journal | Reason for exclusion |
|---|---|---|---|---|
| Trastuzumab for the treatment of primary breast cancer in HER2-positive women: a single technology appraisal | Ward et al. | 2009 | Health technology assessment | Fulltext not available |
| A Study Comparing the Efficacy of TCbHP and ECHP-THP in the Neoadjuvant Treatment of HER2-positive Breast Cancer | Liu et al. | 2022 | https://clinicaltrials.gov/show/NCT05474690 | Wrong comparator |
| First FDA approval of neoadjuvant therapy for breast cancer: pertuzumab for the treatment of patients with HER2-positive breast cancer | Amiri-Kordestani et al. | 2014 | Clinical cancer research | Wrong publication type |
| Impact of lapatinib (La) treatment duration and endocrine therapy (ET) addition on the efficacy of primary dual HER2 blockage with La and trastuzumab (T) for HER2+ breast cancer (BC) patients | Bando et al. | 2015 | European journal of cancer | Wrong intervention |
| Short-duration versus 1-year adjuvant trastuzumab in early HER2 positive breast cancer: A meta-analysis of randomized controlled trials | Chen et al. | 2019 | Cancer treatment reviews | Systematic review |
| Serum her2 ECD levels in two different adiuvant chemotherapy regimens of trastuzumab in primary breast cancer | Cocco et al. | 2013 | Biochimica Clinica | Wrong outcome |
| Serum HER2-ECD during trastuzumab based therapy in women with primary breast cancer: Preliminary results of an italian multicentric study (short-her) | Cocco et al. | 2011 | Clinical Chemistry and Laboratory Medicine | Wrong outcome |
| PAM50 HER2-enriched subtype as an independent prognostic factor in early-stage HER2+ breast cancer following adjuvant chemotherapy plus trastuzumab in the ShortHER trial | Conte et al. | 2019 | Journal of clinical oncology | Wrong outcome |
| Preliminary working paper for health technology assessment of trastuzumab (Herceptin) as adjuvant treatment of early breast cancer after surgical treatment - accelerated assessment | Danish Centre for Evaluation and Health Technology Assessment | 2005 | https://database.inahta.org/article/5449 | HTA |
| Trastuzumab as adjuvant treatment of early breast cancer after surgical treatment | Danish Centre for Evaluation and Health Technology Assessment | 2006 | https://database.inahta.org/article/13049 | HTA |
| Six Months vs. 12 Months of Adjuvant Trastuzumab Among Women With HER2-Positive Early-Stage Breast Cancer: A Meta-Analysis of Randomized Controlled Trials | Deng et al | 2020 | Frontiers in oncology | Systematic review |
| Type of adjuvant endocrine therapy and disease-free survival in patients with early HR-positive/HER2-positive BC: analysis from the phase III randomized ShortHER trial | Dieci et al. | 2023 | NPJ breast cancer | Wrong comparator |
| Validation of the American Joint Committee on Cancer new prognostic stage groups for HER2-positive breast cancer patients treated with adjuvant chemotherapy and trastuzumab in the prospective ShortHER trial | Dieci et al. | 2019 | Annals of Oncology | Wrong outcome |
| Type of endocrine therapy and DFS in patients with early HER2+/HR+ BC: Analysis from the phase III randomized ShortHER trial | Dieci et al. | 2022 | Journal of Clinical Oncology | Wrong comparator |
| Association of tumor-infiltrating lymphocytes with distant disease-free survival in the ShortHER randomized adjuvant trial for patients with early HER2+ breast cancer | Dieci et al. | 2019 | Annals of oncology | Wrong comparator |
| Tumor-infiltrating lymphocytes (TILs) as an independent prognostic factor for early HER21 breast cancer patients treated with adjuvant chemotherapy and trastuzumab in the randomized shortHER trial | Dieci et al. | 2018 | Annals of Oncology | Wrong comparator |
| Persephone: Suration of trastuzumab with chemotherapy in women with HER2 positive early breast cancer | Earl et al. | 2012 | Cancer Research | Wrong outcome |
| LBA11 Individual patient data meta-analysis of 5 non-inferiority RCTs of reduced duration single agent adjuvant trastuzumab in the treatment of HER2 positive early breast cancer | Earl et al. | 2021 | Annals of Oncology | Systematic review |

| Title | Authors | Year | Journal | Reason for exclusion |
|---|---|---|---|---|
| Cardiotoxicity of trastuzumab given for 12 months compared to shorter treatment periods: a systematic review and meta-analysis of six clinical trials | Eiger et al. | 2020 | ESMO open | Systematic review |
| What is the optimal duration and treatment sequence of trastuzumab in the adjuvant setting? | Garcia | 2006 | Women's Oncology Review | Wrong publication type |
| Addition of pertuzumab (P) to trastuzumab (H)-based neoadjuvant chemotherapy significantly improves pathological complete response in women with HER2-positive early breast cancer: Result of a randomised phase II study (NEOSPHERE) | Gianni et al. | 2011 | Breast | Wrong comparator |
| 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial | Gianni et al. | 2016 | The Lancet Oncology | Wrong comparator |
| Deescalating Adjuvant Trastuzumab in HER2-Positive Early-Stage Breast Cancer: A Systemic Review and Meta-Analysis | Goldvaser et al. | 2019 | JNCI cancer spectrum | Systematic review |
| De-escalating adjuvant trastuzumab in human epidermal growth factor receptor 2 (HER2)-positive early-stage breast cancer: A systemic review and meta-analysis | Goldvaser et al. | 2019 | Journal of Clinical Oncology | Systematic review |
| 19P PIK3CA mutations in HER2-positive early breast cancer patients enrolled in the adjuvant randomized short-HER study | Guarneri et al. | 2020 | Annals of Oncology | Wrong comparator |
| PIK3CA Mutation in the ShortHER randomized adjuvant trial for patients with early HER2+ breast cancer: Association with prognosis and integration with PAM50 subtype | Guarneri et al. | 2020 | Clinical Cancer Research | Wrong comparator |
| Evaluation of 1-Year vs Shorter Durations of Adjuvant Trastuzumab Among Patients With Early Breast Cancer: An Individual Participant Data and Trial-Level Meta-analysis | Gulia et al. | 2020 | JAMA network open | Systematic review |
| Duration of adjuvant trastuzumab in HER2 positive breast cancer: Overall and disease free survival results from meta-analyses of randomized controlled trials | Gyawali et Niraula | 2017 | Cancer treatment reviews | Systematic review |
| Adjuvant trastuzumab duration trials in HER2 positive breast cancer - what results would be practice-changing? Persephone investigator questionnaire prior to primary endpoint results | Hiller et al. | 2018 | BMC cancer | Wrong study design |
| Cost effectiveness analyses of 6 versus 12 months of adjuvant trastuzumab in patients with HER2 positive early breast cancer: Results from the PERSEPHONE trial | Hulme et al. | 2018 | British Journal of Cancer | Wrong outcome |
| PERSEPHONE: 6 versus 12 months (m) of adjuvant trastuzumab in patients (pts) with HER2 positive (1) early breast cancer (EBC): Cost effectiveness analysis results | Hulme et al. | 2018 | Annals of Oncology | Wrong outcome |
| HTA of trastuzumab in early stage breast cancer | Huybrechts et al. | 2006 | https://database.inahta.org/article/6361 | HTA |
| One year versus a shorter duration of adjuvant trastuzumab for HER2-positive early breast cancer: a systematic review and meta-analysis | Inno et al. | 2019 | Breast cancer research and treatment | Systematic review |
| Addendum zum Auftrag A13-10 (Pertuzumab) | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen | 2013 | https://www.iqwig.de/download/A13-28_Addendum-zum-Auftrag-A13-10_Pertuzumab.pdf | HTA |
| Pertuzumab | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen | 2013 | https://www.iqwig.de/download/A13-10_Pertuzumab_Nutzenbewertung-35a-SGB-V.pdf | HTA |

| Title | Authors | Year | Journal | Reason for exclusion |
|---|---|---|---|---|
| Pertuzumab - Addendum zum Auftrag A15-34 | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen | 2016 | https://www.iqwig.de/download/A16-01_%20Pertuzumab_Addendum-zum-Auftrag-A15-34.pdf | HTA |
| Pertuzumab (Mammakarzinom, adjuvant) | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen | 2022 | https://www.iqwig.de/download/a22-103_pertuzumab_nutzenbewertung-35a-sgb-v_v1-0.pdf | HTA |
| Pertuzumab (Mammakarzinom) | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen | 2018 | https://www.iqwig.de/download/A18-41_Pertuzumab_Nutzenbewertung-35a-SGB-V_V1-0.pdf | HTA |
| Pertuzumab (Mammakarzinom) - Addendum zum Auftrag A18-41 | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen | 2018 | https://www.iqwig.de/download/A18-76_Pertuzumab_Addendum-zum-Auftrag-A18-41_V1-0.pdf | HTA |
| Pertuzumab (neues Anwendungsgebiet) | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen | 2015 | https://www.iqwig.de/download/A15-34_Pertuzumab-neues-AWG_Nutzenbewertung-35a-SGB-V.pdf | HTA |
| Pertuzumab/Trastuzumab (Mammakarzinom, adjuvant) | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen | 2021 | https://www.iqwig.de/download/a21-11_pertuzumab-trastuzumab_nutzenbewertung-35a-sgb-v_v1-0.pdf | HTA |
| Pertuzumab/Trastuzumab (Mammakarzinom, neoadjuvant) | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen | 2021 | https://www.iqwig.de/download/a21-10_pertuzumab-trastuzumab_nutzenbewertung-35a-sgb-v_v1-0.pdf | HTA |
| Herceptin | Israeli Center for Technology Assessment in Health Care | 1999 | https://database.inahta.org/article/838 | HTA |

| Title | Authors | Year | Journal | Reason for exclusion |
|---|---|---|---|---|
| A randomized phase III study of adjuvant trastuzumab for a duration of 9 weeks versus 1 year, combined with adjuvant taxane-anthracycline chemotherapy, for early HER2-positive breast cancer (the SOLD study) | Joensuu et al. | 2018 | Cancer research | Wrong outcome |
| Adjuvant and neoadjuvant breast cancer treatments: A systematic review of their effects on mortality | Kerr et al. | 2022 | Cancer treatment reviews | Systematic review |
| Adjuvant anti-HER2 therapy, treatment-induced amenorrhea (TIA) and survival in premenopausal patients (pts) with HER2-positive (HER21) early breast cancer (EBC): analysis from the ALTTO trial (BIG 2-06) | Lambertini et al. | 2017 | Annals of oncology | Wrong comparator |
| Risk of Congestive Heart Failure in Early Breast Cancer Patients Undergoing Adjuvant Treatment With Trastuzumab: A Meta-Analysis | Long et al. | 2016 | The oncologist | Systematic review |
| Optimum adjuvant trastuzumab duration for human epidermal growth factor receptor-2 positive breast cancer: a network meta-analysis of randomized trials | Ma et al. | 2021 | Translational cancer research | Systematic review |
| Efficacy and safety of trastuzumab, lapatinib, and paclitaxel neoadjuvant treatment with or without prolonged exposure to anti-HER2 therapy, and with or without hormone therapy for HER2-positive primary breast cancer: a randomised, five-arm, multicentre, open-label phase II trial | Masuda et al. | 2018 | Breast cancer | Wrong intervention |
| Can estrogen receptor status predict for shorter duration of adjuvant trastuzumab in early-stage breast cancer? | Mathew et Erqou | 2018 | Annals of oncology | Wrong publication type |
| A multicenter randomized study comparing 6 versus 12 months of trastuzumab in combination with dose-dense docetaxel following FEC as adjuvant treatment of women with axillary node-positive or high-risk, node-negative breast cancer overexpressing HER2 | Mavroudis et al. | 2014 | Journal of Clinical Oncology | Wrong outcome |
| Combination Chemotherapy With or Without Capecitabine and/or Trastuzumab Before Surgery in Treating Women With Stage I, Stage II, or Stage III Breast Cancer | German Breast Group | 2006 | https://clinicaltrials.gov/show/NCT00288002 | Wrong publication type |
| Pertuzumab (Perjeta) with chemotherapy and trastuzumab for HER2-positive early breast cancer - adjuvant therapy | NIHR | 2016 | https://database.inahta.org/article/17406 | HTA |
| Duration of adjuvant trastuzumab in HER-2 positive breast cancer: Pooled results of overall, and disease-free survivals from meta-analyses of randomized controlled trials | Niraula et Gyawali | 2018 | Cancer Research | Systematic review |
| Optimal duration of adjuvant trastuzumab in treatment of early breast cancer: a meta-analysis of randomized controlled trials | Niraula et Gyawali | 2019 | Breast cancer research and treatment | Systematic review |
| How to strengthen the French breast cancer clinical research: The example of the PHARE trial | Pauporte et al. | 2009 | Oncologie | Wrong publication type |
| Phare trial results comparing 6 to 12 months of trastuzumab in adjuvant early breast cancer | Pivot et al. | 2012 | Annals of Oncology | Wrong comparator |
| Efficacy of short-course adjuvant trastuzumab in early stage breast cancer | Saifo et Nikoula | 2019 | Cancer research | Wrong intervention |
| Concurrent administration of trastuzumab and anthracyclines as adjuvant regimen for HER2-positive breast cancer: a randomised controlled trial | Shen et al. | 2017 | Oncotarget | Wrong comparator |
| Short versus long duration of adjuvant trastuzumab (T) in HER2+ breast cancer: A systematic review and meta-analysis of randomized controlled trials (RCTs) | Sipra et al. | 2019 | Journal of Clinical Oncology | Systematic review |
| Pertuzumab for the Neoadjuvant Treatment of Early-Stage HER2-Positive Breast Cancer: An Evidence Review Group Perspective of a NICE Single Technology Appraisal | Squires et al. | 2018 | PharmacoEconomics; https://dx.doi.org/10.1007/s40273-017-0556-7 | HTA |
| Do all patients with HER2 positive breast cancer require one year of adjuvant trastuzumab? A systematic review and meta-analysis | Stewart et al. | 2020 | Breast | Systematic review |

| Title | Authors | Year | Journal | Reason for exclusion |
|---|---|---|---|---|
| Do all patients with HER2-positive breast cancer require one year of adjuvant trastuzumab?: A systematic review and meta-analysis | Stewart et al. | 2019 | Journal of Clinical Oncology | Systematic review |
| Adjuvant trastuzumab: does time really matter? | Swain et al. | 2013 | The oncologist | Wrong publication type |
| Risk of recurrence and death in patients with early HER2-positive breast cancer who achieve a pathological complete response (pCR) after different types of HER2-targeted therapy: A retrospective exploratory analysis | Swain et al. | 2020 | Cancer Research | Wrong comparator |
| Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): A randomised multicentre, open-label, phase 2 trial: Commentary | Thill | 2012 | Breast Care | Wrong publication type |
| Adjuvant trastuzumab in the treatment of her-2-positive early breast cancer: a meta-analysis of published randomized trials | Viani et al. | 2007 | BMC cancer | Systematic review |
| 6 versus 12,Äämonths of adjuvant trastuzumab in HER2+ early breast cancer: A systematic review and meta-analysis | Wang et al. | 2021 | Medicine | Systematic review |
| Her2/neu in focus: Novel therapeutic options | Welt | 2014 | Oncology Research and Treatment | Wrong publication type |
| HERA - new lessons from a new trial | Wilcken | 2003 | Cancer forum | Wrong publication type |
| Tailored duration of adjuvant trastuzumab for early human epidermal growth factor receptor 2-positive breast cancer | Yu et al. | 2020 | Cancer Research | Systematic review |

**Appendix 4: Further characteristics of included studies in the systematic review related to clinical efficacy and safety.**

| Name | First author & year of first publication | Study design | Timepoint of participant randomisation | Treatment setting | Treatment schedule intervention | Treatment schedule comparator |
|---|---|---|---|---|---|---|
| PHARE[16 72 73 19 77 78] | Pivot et al. 2013 | RCT, parallel, open-label, non-inferiority | After surgery, after start of (neo)adjuvant chemotherapy, after 3-6 months of trastuzumab therapy | Adjuvant trastuzumab treatment | Initial treatment: Trastuzumab IV (loading 8mg/kg, then 6mg/kg) q3w, chemotherapy ± radiation therapy ± hormone therapy according to investigators' choice; Continuation: Trastuzumab IV q3w until completion of 6 months | Initial treatment: Trastuzumab IV (loading 8mg/kg, then 6mg/kg) q3w, chemotherapy ± radiation therapy ± hormone therapy according to investigators' choice; Continuation: Trastuzumab IV q3w until completion of 12 months |
| E2198[2023] | Schneider et al. 2015 | RCT, parallel, open-label | After surgery, before start of chemotherapy and trastuzumab therapy | Adjuvant trastuzumab treatment | Cycles 1-4: Paclitaxel q3w + Trastuzumab IV (loading 4mg/kg, then 2mg/kg) q1w; Cycles 5-8: Doxorubicin + Cyclophosphamide q3w Continuation: None. | Cycles 1-4: Paclitaxel q3w + Trastuzumab IV (loading 4mg/kg, then 2mg/kg) q1w; Cycles 5-8: Doxorubicin + Cyclophosphamide q3w; Continuation: Trastuzumab IV (loading 4mg/kg, then 2mg/kg) q1w for 1 year |
| HORG[19 74 22 79] | Mavroudis et al. 2015 | RCT, parallel, open-label, non-inferiority | After surgery, before start of chemotherapy and trastuzumab therapy | Adjuvant trastuzumab treatment | Cycles 1-4: 5-Fluorouracil + Epirubicin + Cyclophosphamide (FEC) q2w; Cycles 5-8: Docetaxel + Trastuzumab IV (loading 6mg/kg, then 4mg/kg) q2w; Continuation: Trastuzumab IV (6mg/kg) q3w until completion of 6 months | Cycles 1-4: 5-Fluorouracil + Epirubicin + Cyclophosphamide (FEC) q2w; Cycles 5-8: Docetaxel + Trastuzumab IV (loading 6mg/kg, then 4mg/kg) q2w; Continuation: Trastuzumab IV (6mg/kg) q3w until completion of 12 months |
| Short-HER[17 75 20 71] | Conte et al. 2018 | RCT, parallel, open-label, non-inferiority | After surgery, before start of chemotherapy and trastuzumab therapy | Adjuvant trastuzumab treatment | Cycles 1-3: Docetaxel + Trastuzumab IV (loading 4mg/kg, then 2mg/kg) q3w; Cycles 4-6: 5-Fluorouracil + Epidoxorubicin + Cyclophosphamide q3w Continuation: None. | Cycles 1-4: Doxorubicin + Cyclophosphamide q3w or Epidoxorubicin + Cyclophosphamide q3w; Cycles 5-8: Paclitaxel q3w + Trastuzumab IV (loading 8mg/kg, then 6mg/kg) q3w for 18 doses or Docetaxel q3w + Trastuzumab IV (loading 8mg/kg, then 6mg/kg) q3w Continuation: Trastuzumab IV (6mg/kg) q3w up to total 18 doses |

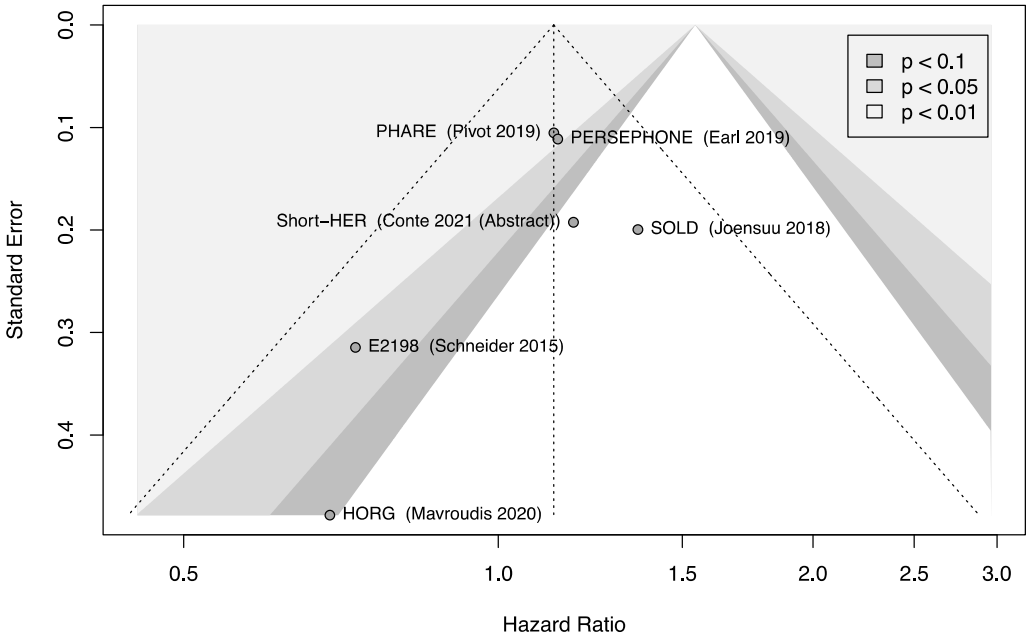
| Name | First author & year of first publication | Study design | Timepoint of participant randomisation | Treatment setting | Treatment schedule intervention | Treatment schedule comparator |
|---|---|---|---|---|---|---|
| SOLD[1518] | Joensuu et al. 2018 | RCT, parallel, open-label, non-inferiority* | Before start of chemotherapy and trastuzumab therapy | Adjuvant trastuzumab treatment | Cycles 1-3: Docetaxel q3w + Trastuzumab IV q1w or q3w or SC q3w (q1w IV: loading 4mg/kg, then 2mg/kg; q3w IV: loading 8mg/kg, then 6mg/kg; q3w SC: each dose 600mg regardless of body weight); Cycles 4-6: Fluorouracil + Epirubicin hydrochloride + Cyclophosphamide (FEC) q3w<br>Continuation: None. | Cycles 1-3: Docetaxel q3w + Trastuzumab IV q1w or q3w or SC q3w (q1w IV: loading 4mg/kg, then 2mg/kg; q3w IV: loading 8mg/kg, then 6mg/kg; q3w SC: each dose 600mg regardless of body weight); Cycles 4-6: Fluorouracil + Epirubicin hydrochloride + Cyclophosphamide (FEC) q3w;<br>Continuation: Trastuzumab IV or SC q3w (IV: loading 8mg/kg, then 6mg/kg; SC: each dose 600mg regardless of body weight) started 3 weeks after the last FEC cycle for total 14 doses |
| PERSEPHONE[18 76 21 80] | Earl et al. 2019 | RCT, parallel, open-label, non-inferiority | Initially before start of (neo)adjuvant chemotherapy and trastuzumab therapy; After protocol amendment at any time up to and including the ninth cycle (6 months) of trastuzumab | Adjuvant trastuzumab treatment | Trastuzumab IV or SC (IV: loading 8mg/kg, then 6mg/kg; SC: 600mg regardless of body weight) q3w over 6 months with chemotherapy (concurrently or sequentially) ± radiation therapy ± hormone therapy according to investigators' choice | Trastuzumab IV or SC (IV: loading 8mg/kg, then 6mg/kg; SC: 600mg regardless of body weight) q3w over 12 months with chemotherapy (concurrently or sequentially) ± radiation therapy ± hormone therapy according to investigators' choice |

**Legend**: DFS = disease-free survival, HR = hazard ratio, IV = intravenous administration, OS = overall survival, qXw = every X weeks, RCT = randomised controlled trial, SC = subcutaneous administration. * SOLD was originally designed as a superiority trial but changed to a non-inferiority trial design.

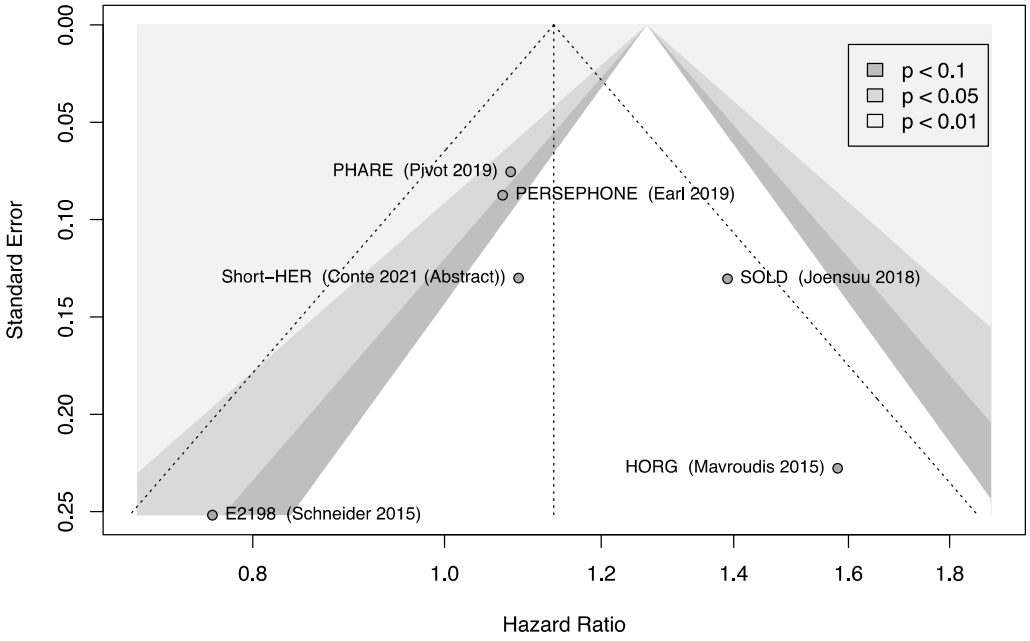
**Appendix 5: Funnel plots for overall survival and disease-free survival.**

Panel (A) depicts the contour-enhanced funnel plot overall survival (OS) and panel (B) for disease-free survival (DFS). Dotted lines represent the funnel for the average results from random-effects meta-analysis. Shaded areas determine results where statistical evidence reaches different p-value thresholds for non-inferiority, based on non-inferiority margins of HR 1.543 for OS and HR 1.266 for DFS. Funnel plots need to be interpreted with caution due to the low number of included studies.

**A Overall survival**

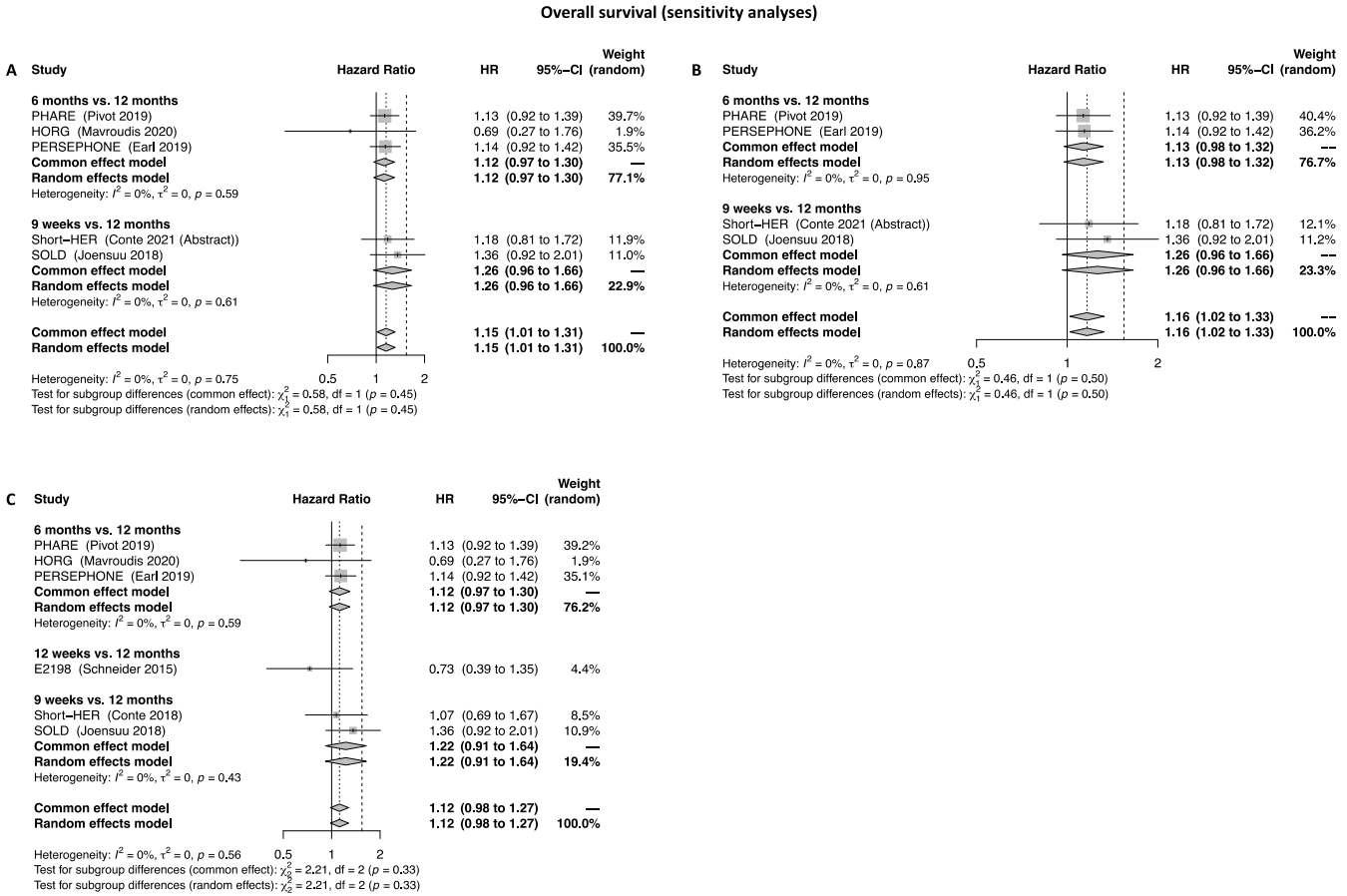



**B Disease-free survival**



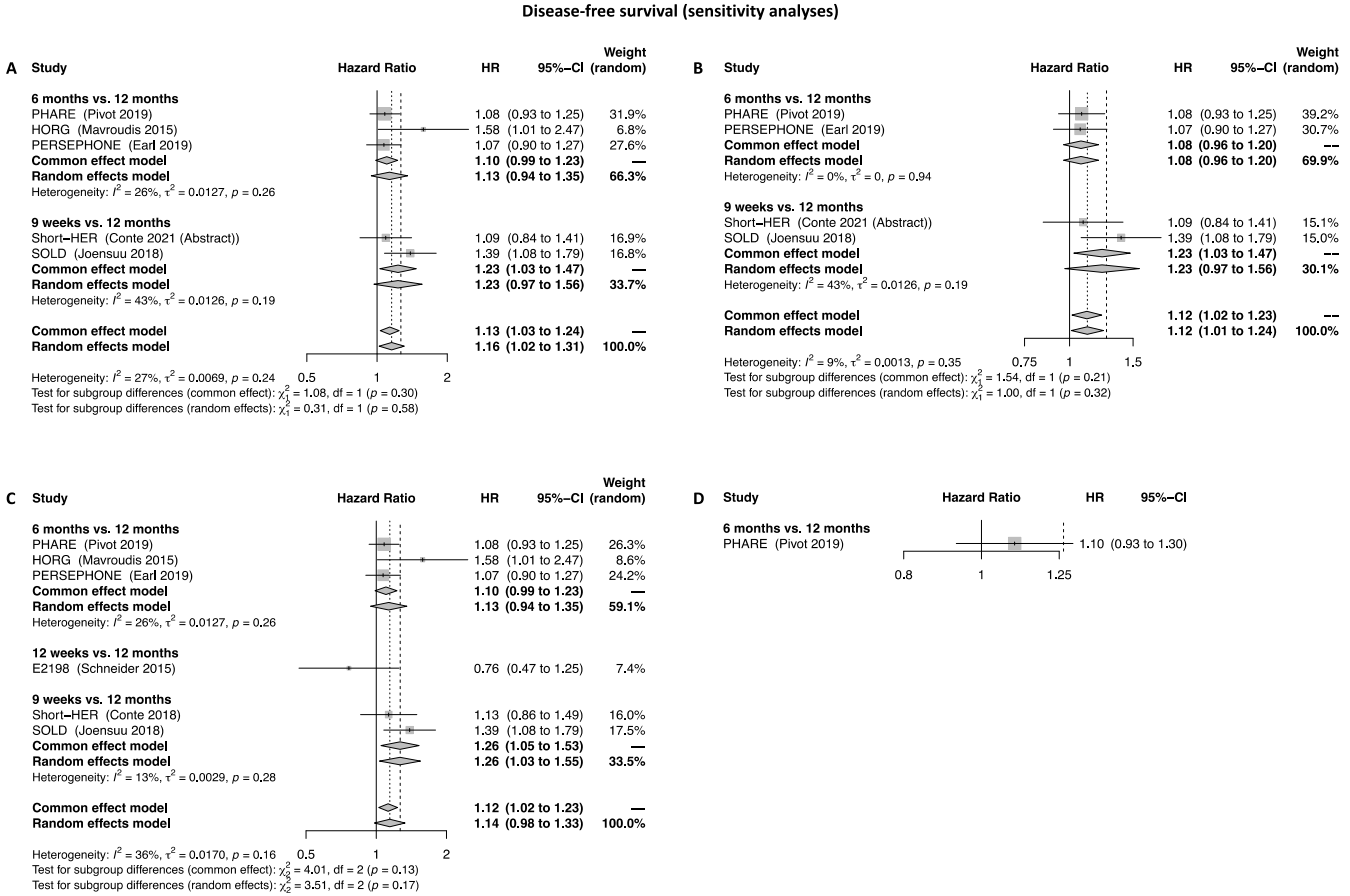
## Appendix 6: Sensitivity analysis results for overall survival.

Sensitivity analysis results from meta-analyses for overall survival (OS). In panel (A), the E2198 trial was omitted due to the different (phase 2 superiority) design, potentially relevant protocol violations and potentially relevant attrition in the 12-month treatment group. In panel (B), the HORG trial and the E2198 trial were omitted due to the higher-risk patient population (>75% node-positive). In panel (C), a different effect estimate was included in meta-analysis for the Short-HER trial (publication by Conte et al. 2018 instead of the conference abstract by Conte et al. 2021).



## Appendix 7: Sensitivity analysis results for disease-free survival.

Sensitivity analysis results from meta-analyses for disease-free survival (DFS). In panel (A), the E2198 trial was omitted due to the different (phase 2 superiority) design, potentially relevant protocol violations and potentially relevant attrition in the 12-month treatment group. In panel (B), a different effect estimate was included in meta-analysis for the Short-HER trial (publication by Conte et al. 2018 instead of the conference abstract by Conte et al. 2021). In panel (C), only reported per-protocol estimates were used instead of intention-to-treat estimates (available only for the PHARE trial).



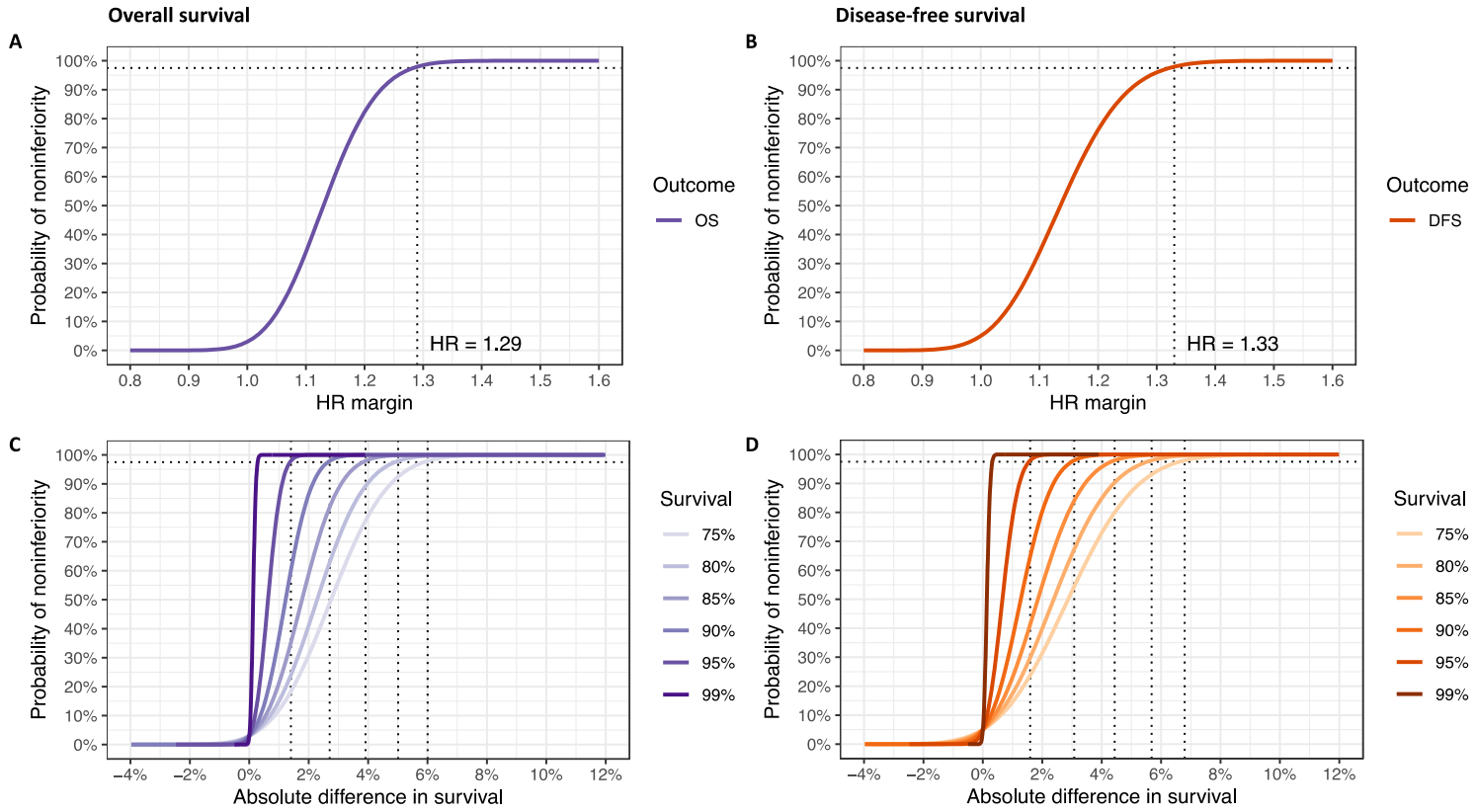
**Appendix 8: Sensitivity analyses related to non-inferiority margins for overall survival and disease-free survival.**

Results from primary meta-analysis for overall survival (OS) and disease-free survival (DFS) for the comparisons of ≤6 months vs. 12 months and 6 months vs. 12 months of trastuzumab treatment were tested against different non-inferiority margins. In primary analyses, HR non-inferiority margins derived for 5-year OS and 5-year DFS based on an absolute difference in survival of 3% were used (marked with *). This table presents the test results for non-inferiority assuming the different HR non-inferiority margins derived for 2-, 3-, 4-, 5-, and 7-year OS and DFS with corresponding interpretation of the results regarding non-inferiority, assuming that a 2%, 3%, and 4% absolute difference in survival is clinically relevant.

| **Overall survival** | | | | **Disease-free survival** | | | |
|---|---|---|---|---|---|---|---|
| **≤6 months vs. 12 months** | | | | | | | |
| **Timepoint** | **2% absolute difference** | **3% absolute difference** | **4% absolute difference** | **Timepoint** | **2% absolute difference** | **3% absolute difference** | **4% absolute difference** |
| 2-year OS | HR 3.568: p<0.0001 likely non-inferior | HR 4.872: p<0.0001 likely non-inferior | HR 6.190: p<0.0001 likely non-inferior | 2-year DFS | HR 1.503: p=0.0003 likely non-inferior | HR 1.758: p<0.0001 likely non-inferior | HR 2.017: p<0.0001 likely non-inferior |
| 3-year OS | HR 1.805: p<0.0001 likely non-inferior | HR 2.214: p<0.0001 likely non-inferior | HR 2.627: p<0.0001 likely non-inferior | 3-year DFS | HR 1.301: p=0.0786 inconclusive | HR 1.454: p=0.0014 likely non-inferior | HR 1.608: p<0.0001 likely non-inferior |
| 4-year OS | HR 1.503: p<0.0001 likely non-inferior | HR 1.759: p<0.0001 likely non-inferior | HR 2.017: p<0.0001 likely non-inferior | 4-year DFS | HR 1.213: p=0.3931 inconclusive | HR 1.321: p=0.0499 likely non-inferior | HR 1.431: p=0.0028 likely non-inferior |
| 5-year OS | HR 1.360: p=0.0043 likely non-inferior | **HR 1.543: p<0.0001*** likely non-inferior | HR 1.728: p<0.0001 likely non-inferior | 5-year DFS | HR 1.176: p=0.6507 inconclusive | **HR 1.266: p=0.1609*** inconclusive | HR 1.356: p=0.0216 likely non-inferior |
| 7-year OS | HR 1.293: p=0.0377 likely non-inferior | HR 1.442: p=0.0002 likely non-inferior | HR 1.592: p<0.0001 likely non-inferior | 7-year DFS | HR 1.139: p=0.9688 inconclusive | HR 1.210: p=0.4129 inconclusive | HR 1.281: p=0.1180 inconclusive |
| **6 months vs. 12 months** | | | | | | | |
| **Timepoint** | **2% absolute difference** | **3% absolute difference** | **4% absolute difference** | **Timepoint** | **2% absolute difference** | **3% absolute difference** | **4% absolute difference** |
| 2-year OS | HR 3.568: p<0.0001 likely non-inferior | HR 4.872: p<0.0001 likely non-inferior | HR 6.190: p<0.0001 likely non-inferior | 2-year DFS | HR 1.503: p=0.0019 likely non-inferior | HR 1.758: p<0.0001 likely non-inferior | HR 2.017: p<0.0001 likely non-inferior |
| 3-year OS | HR 1.805: p<0.0001 likely non-inferior | HR 2.214: p<0.0001 likely non-inferior | HR 2.627: p<0.0001 likely non-inferior | 3-year DFS | HR 1.301: p=0.1249 inconclusive | HR 1.454: p=0.0060 likely non-inferior | HR 1.608: p=0.0001 likely non-inferior |
| 4-year OS | HR 1.503: p=0.0001 likely non-inferior | HR 1.759: p<0.0001 likely non-inferior | HR 2.017: p<0.0001 likely non-inferior | 4-year DFS | HR 1.213: p=0.4408 inconclusive | HR 1.321: p=0.0882 inconclusive | HR 1.431: p=0.0100 likely non-inferior |
| 5-year OS | HR 1.360: p=0.0104 likely non-inferior | **HR 1.543: p<0.0001*** likely non-inferior | HR 1.728: p<0.0001 likely non-inferior | 5-year DFS | HR 1.176: p=0.6657 inconclusive | **HR 1.266: p=0.2174*** inconclusive | HR 1.356: p=0.0467 likely non-inferior |
| 7-year OS | HR 1.293: p=0.0585 inconclusive | HR 1.442: p=0.0009 likely non-inferior | HR 1.592: p<0.0001 likely non-inferior | 7-year DFS | HR 1.139: p=0.9340 inconclusive | HR 1.210: p=0.4586 inconclusive | HR 1.281: p=0.1708 inconclusive |

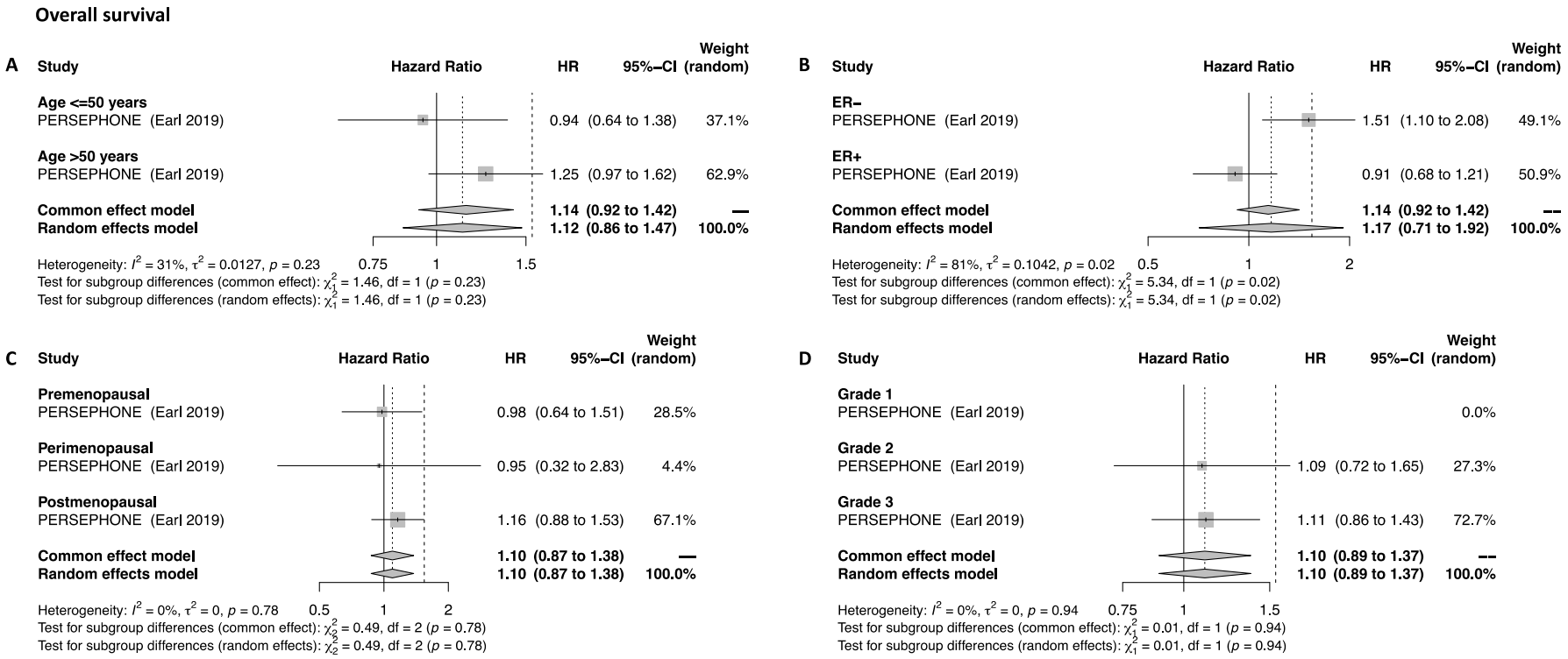
**Legend**: DFS = disease-free survival, HR = hazard ratio, OS = overall survival. * Non-inferiority HR margin used in primary analyses in the assessment of clinical efficacy and safety.

Results from threshold sensitivity analyses for non-inferiority of overall survival (OS) and disease-free survival (DFS) based on a Monte Carlo simulation for the meta-analysis results comparing ≤6 months vs. 12 months of trastuzumab treatment. Panels (A) and (B) show the probability of non-inferiority with varying HR non-inferiority margins for OS and DFS, respectively. For OS, the threshold where a ≥97.5% probability (corresponding to an alpha of 0.05) of non-inferiority would be reached is HR 1.29. For DFS, this threshold is at HR 1.33. Correspondingly, the probability of non-inferiority at other HR non-inferiority margins can be read from the figure. Panels (C) and (D) demonstrate the probability of non-inferiority with varying non-inferiority margins in terms of the absolute differences in OS and DFS, respectively, using various assumptions for the baseline survival rates. This allows to determine the minimum absolute threshold at X years that would have to be chosen with a certain baseline OS after X years where non-inferiority could be concluded with ≥97.5% probability. Correspondingly, the probability of non-inferiority at a set absolute difference margin (e.g., 2%) after X years (e.g., 4 years) with a certain baseline X-year survival (e.g., 90% 4-year DFS) can be read from the figure (e.g., probability of non-inferiority of 80%).

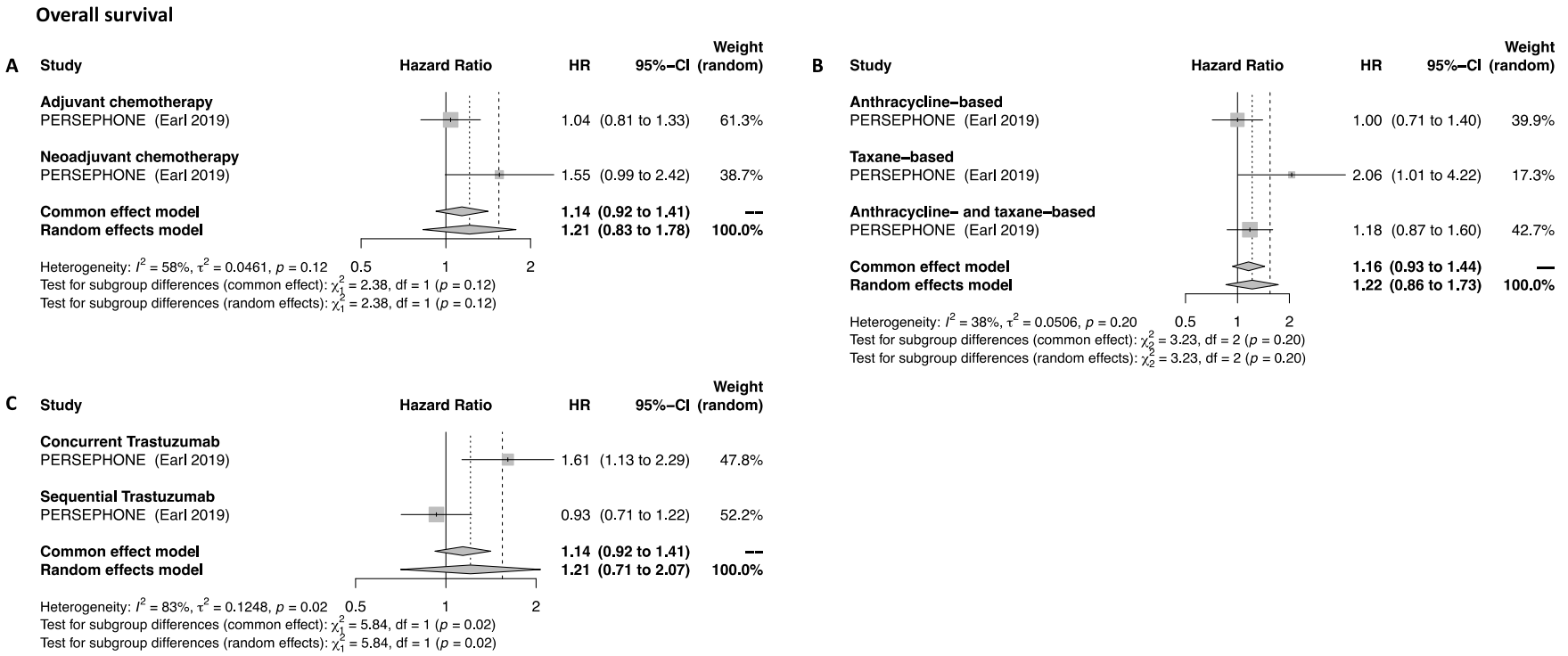


## Appendix 9: Subgroup analyses for overall survival.

Results from meta-analyses for overall survival (OS) for relevant participant subgroups: (A) participant age, (B) oestrogen receptor status, (C) menopausal status, and (D) breast cancer grade. Legend: CI = confidence interval, ER = oestrogen receptor, HR = hazard ratio.

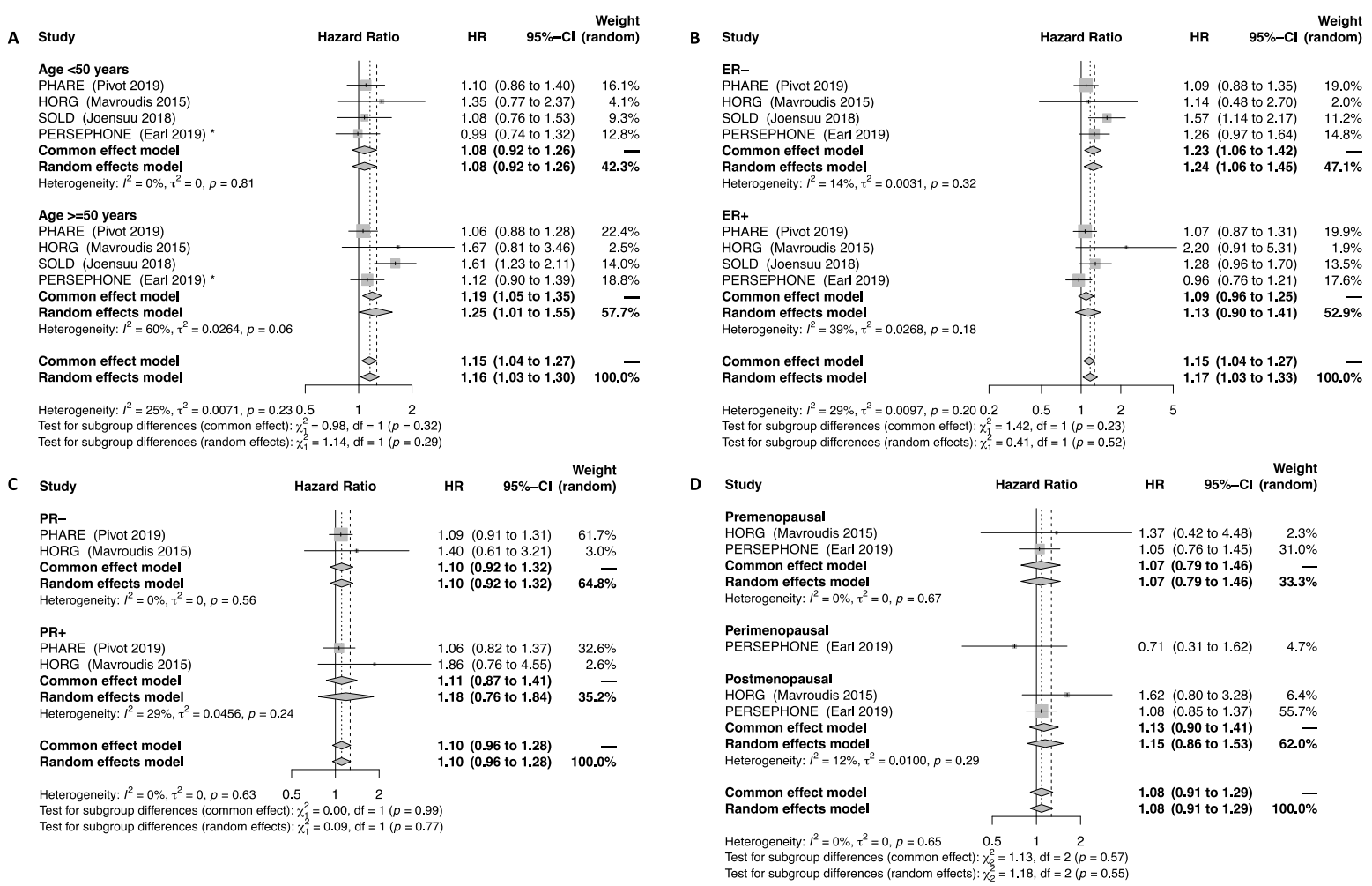


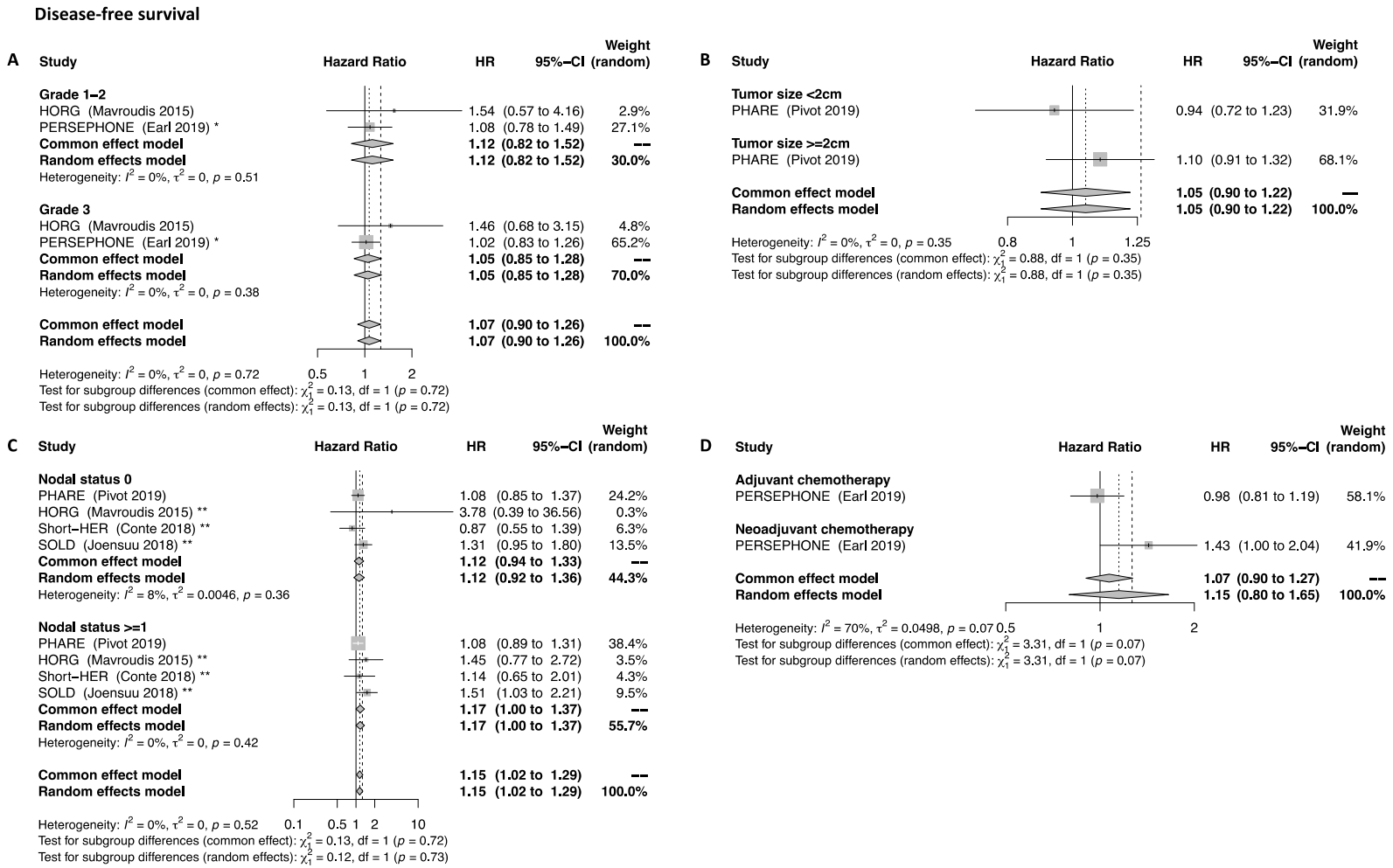
Results from meta-analyses for overall survival (OS) for relevant treatment subgroups: (A) chemotherapy setting, (B) chemotherapy regimen, and (C) timing of trastuzumab administration. Legend: CI = confidence interval, HR = hazard ratio.



## Appendix 10: Subgroup analyses for disease-free survival.

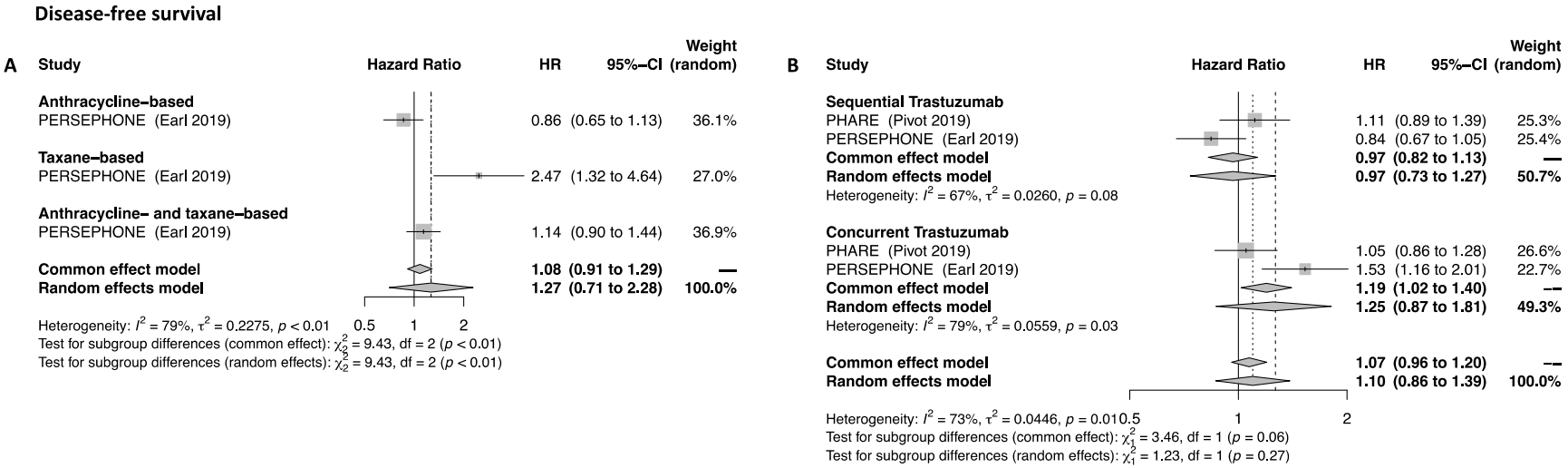
Results from meta-analyses for disease-free survival (DFS) for relevant participant subgroups: (A) participant age, (B) oestrogen receptor status, (C) progesterone receptor status, and (D) menopausal status. Legend: CI = confidence interval, ER = oestrogen receptor, HR = hazard ratio, PR = progesterone receptor. * Age group definitions in PERSEPHONE differed from other studies (i.e., age ≤50 years vs. age >50 years).





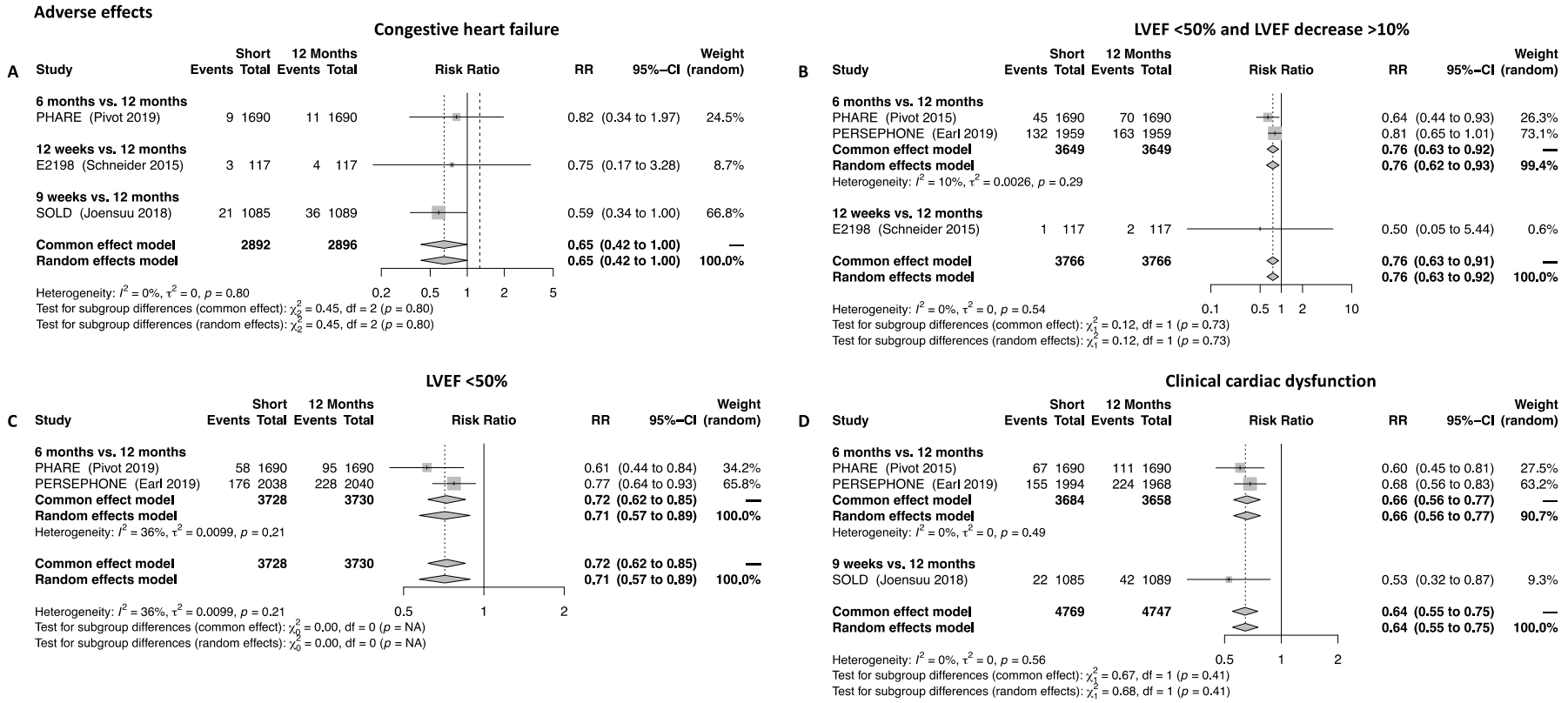

Results from meta-analyses for disease-free survival (DFS) for relevant participant and treatment subgroups: (A) breast cancer grade, (B) tumour size, (C) nodal status, and (D) chemotherapy setting. Legend: CI = confidence interval, HR = hazard ratio. * Estimate for grade 1 group in PERSEPHONE not estimable, includes only grade 2 breast cancer. ** Estimate for nodal status ≥1 in HORG was averaged for nodal status 1-3 and ≥4 groups using inverse variance weighted meta-analysis.

Results from meta-analyses for disease-free survival (DFS) for relevant treatment subgroups: (A) chemotherapy regimen and (B) timing of trastuzumab administration. Legend: CI = confidence interval, HR = hazard ratio.

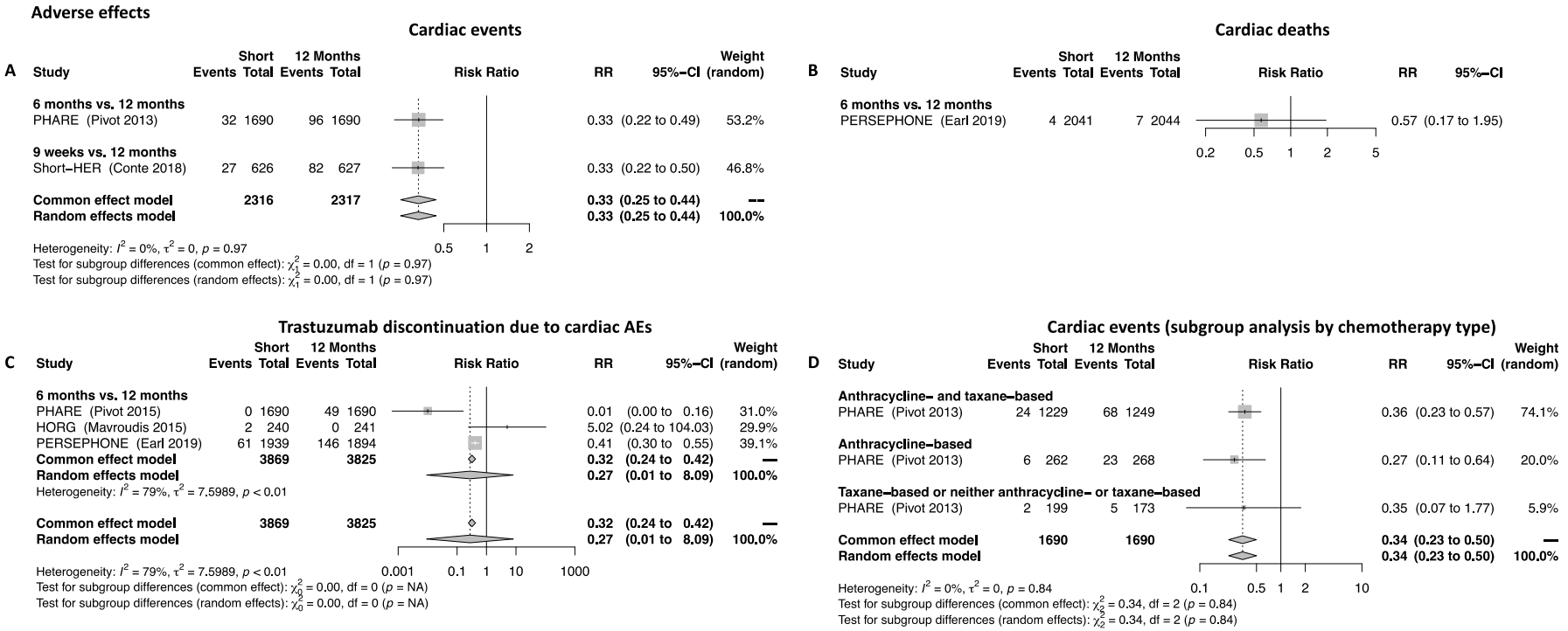


## Appendix 11: Analysis results for cardiac adverse effects.

Results from meta-analyses for cardiac adverse effects (AEs): (A) congestive heart failure, (B) left ventricular ejection fraction (LVEF) <50% and LVEF decrease >10%, (C) LVEF <50%, and (D) clinical cardiac dysfunction. Clinical cardiac dysfunction was defined as as composite outcome in RCTs, with some differences in definitions (PHARE: cardiac death, congestive heart failure, cardiac dysfunction defined as significant LVEF decrease with asymptomatic or mildly symptomatic (NYHA class I-II) status; SOLD: congestive heart failure necessitating medication or medical intervention, myocardial infarction, cardiac or coronary artery surgery, or stenting; PERSEPHONE: symptoms of cardiac disease, signs of congestive heart failure, or use of new medication for cardiac disease). Legend: CI = confidence interval, RR = risk ratio.

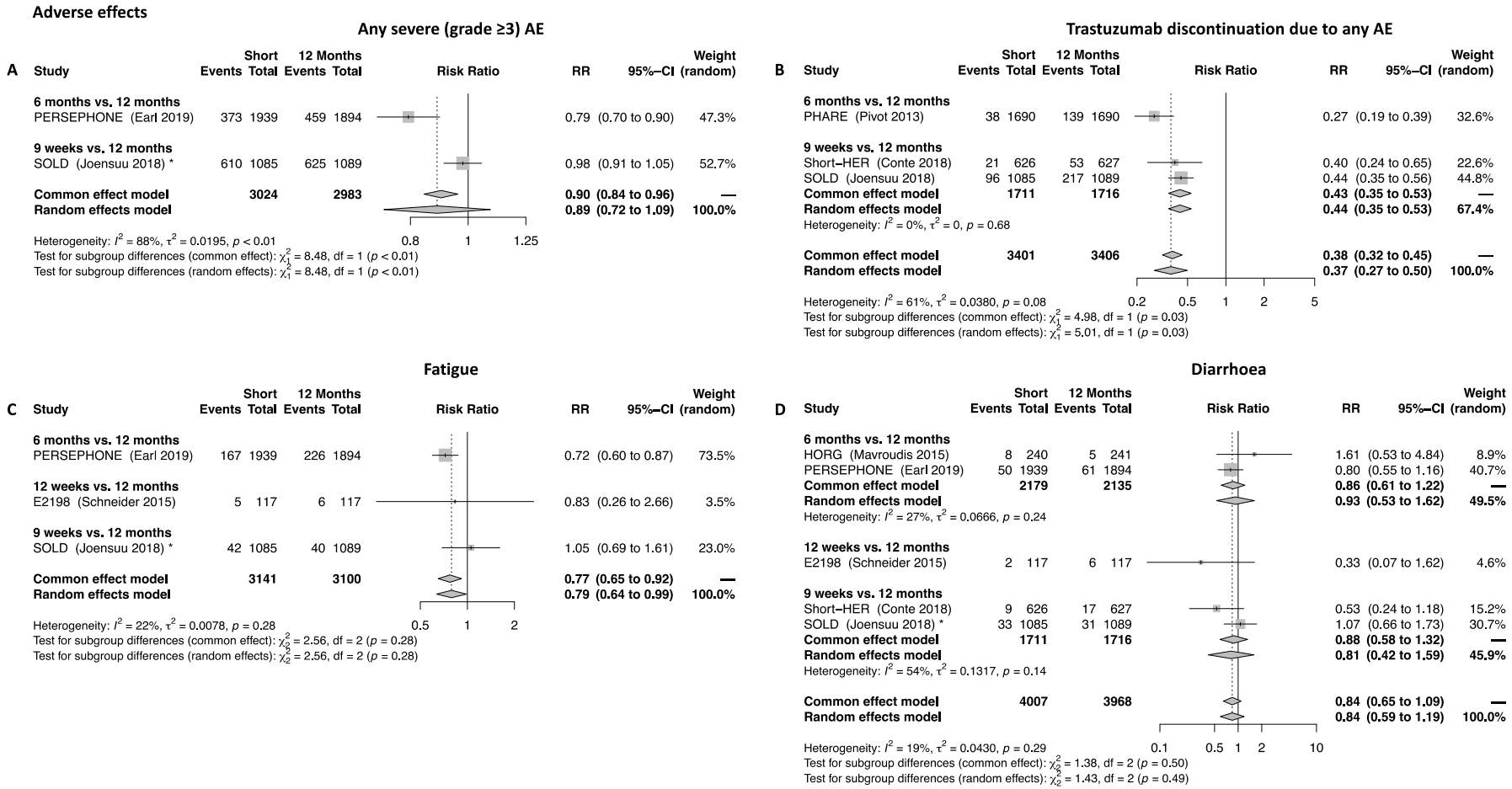


Results from meta-analyses for cardiac adverse effects (AEs): (A) cardiac events, (B) cardiac death, and (C) trastuzumab discontinuation due to cardiac AEs. Panel D demonstrates a subgroup analysis for cardiac events (grade ≥3) based on concomitant chemotherapy regimen. Cardiac events were defined as composite outcome in RCTs (PHARE: cardiac death, congestive heart failure, cardiac dysfunction defined as significant LVEF decrease with asymptomatic or mildly symptomatic (NYHA class I-II) status, LVEF <50%, LVEF <50% and LVEF decrease from baseline by >10%, or LVEF ≥50% and LVEF decrease from baseline by >15%; Short-HER: grade ≥2 cardiac AEs according to CTCAE version 3).Legend: CI = confidence interval, RR = risk ratio.

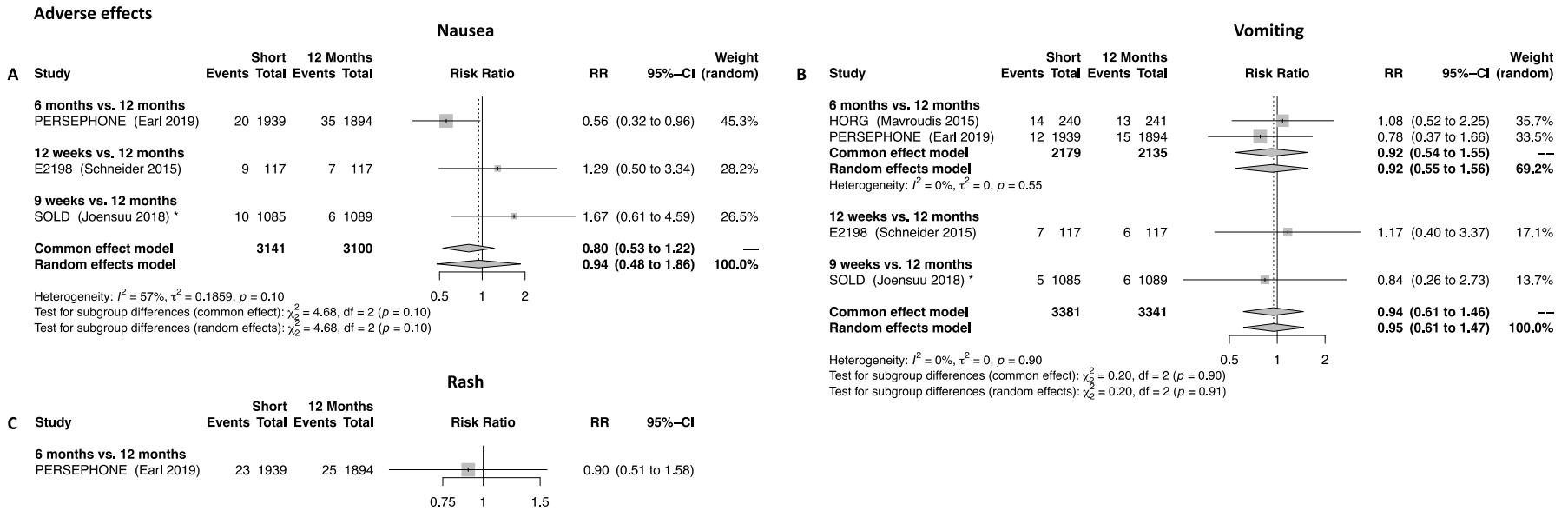


## Appendix 12: Analysis results for other adverse effects.

Results from meta-analyses for other adverse effects (AEs): (A) any severe (grade ≥3) AE, (B) trastuzumab discontinuation due to any AE, (C) fatigue, and (D) diarrhoea. Legend: CI = confidence interval, RR = risk ratio.



Results from meta-analyses for other adverse effects (AEs): (A) nausea, (B) vomiting, and (C) rash. No evidence was identified for osteoporosis/bone loss and vision/eye problems. Legend: CI = confidence interval, RR = risk ratio.



**Appendix 13: GRADE evidence profile for the comparison of ≤6 months vs. 12 months of trastuzumab treatment from the assessment of clinical efficacy and safety.**

| Certainty assessment | | | | | | | № of participants | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | ≤6 months trastuzumab | 12 months trastuzumab | Relative (95% CI) | Absolute (95% CI) | | |
| **Overall survival (OS)** | | | | | | | | | | | | |
| 6 | randomised trials | serious[a] | not serious | not serious | not serious | none | 5799 | 5804 | **HR 1.13** (0.99 to 1.28) | - | ⨁⨁⨁◯ Moderate | CRITICAL |
| | | | | | | | - | **3-year OS***: 97.5% | | **3 fewer survive per 1,000** (from 7 fewer to 0 fewer)* | | |
| | | | | | | | - | **5-year OS***: 94.2% | | **7 fewer survive per 1,000** (from 16 fewer to 0 fewer)* | | |
| **Disease-free survival (DFS)** | | | | | | | | | | | | |
| 6 | randomised trials | serious[a] | not serious | not serious | serious[b] | none | 5799 | 5804 | **HR 1.14** (0.98 to 1.32) | - | ⨁⨁◯◯ Low | CRITICAL |
| | | | | | | | - | **3-year DFS***: 93.0% | | **9 fewer remain disease free per 1,000** (from 21 fewer to 2 more)* | | |
| | | | | | | | - | **5-year DFS***: 87.7% | | **15 fewer remain disease free per 1,000** (from 36 fewer to 3 more)* | | |
| **Health-related quality of life (HRQoL)** | | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of participants | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | ≤6 months trastuzumab | 12 months trastuzumab | Relative (95% CI) | Absolute (95% CI) | | |
| 1 | randomised trials | very serious[c] | not serious | not serious | very serious[d] | none | Mean EQ-VAS scores were higher in the 6 months compared to the 12 months treatment group (ranging between 0.1 points higher (at 24 months of follow-up) to 2.4 points higher (at 9 months of follow-up)). The proportion of participants reporting good or very good general health was the same or higher in the 6 months compared to the 12 months treatment group (ranging between 0% (at 6 months of follow-up) to 5% (at 9 months of follow-up)). | | | | ⊕◯◯◯ Very low | CRITICAL |
| **Congestive heart failure** | | | | | | | | | | | | |
| 3 | randomised trials | serious[e] | not serious | not serious | not serious | none | 33/2892 (1.1%) | 51/2896 (1.8%)** (study population) | **RR 0.65** (0.42 to 1.00) | **6 fewer experience the AE per 1,000** (from 10 fewer to 0 fewer)** | ⊕⊕⊕◯ Moderate | CRITICAL |
| | | | | | | | | 2.7%** (weighted average) | | **9 fewer experience the AE per 1,000** (from 15 fewer to 0 fewer)** | | |
| **LVEF <50% and LVEF decrease >10%** | | | | | | | | | | | | |
| 3 | randomised trials | serious[e] | not serious | not serious | not serious | none | 178/3766 (4.7%) | 235/3766 (6.2%)** (study population) | **RR 0.76** (0.63 to 0.92) | **15 fewer experience the AE per 1,000** (from 23 fewer to 5 fewer)** | ⊕⊕⊕◯ Moderate | CRITICAL |
| | | | | | | | | 6.4%** (weighted average) | | **15 fewer experience the AE per 1,000** (from 5 fewer to 24 fewer)** | | |
| **Any severe (grade ≥3) AE** | | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of participants | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | ≤6 months trastuzumab | 12 months trastuzumab | Relative (95% CI) | Absolute (95% CI) | | |
| 2 | randomised trials | serious[e] | not serious | not serious | serious[f] | none | 983/3024 (32.5%) | 1084/2983 (36.3%)** (study population) | **RR 0.89** (0.72 to 1.09) | **40 fewer experience the AE per 1,000** (from 102 fewer to 33 more)** | ⊕⊕◯◯ Low | CRITICAL |
| | | | | | | | | 41.7%** (weighted average) | | **47 fewer experience the AE per 1,000** (from 116 fewer to 37 more)** | | |
| **Trastuzumab discontinuation due to any AE** | | | | | | | | | | | | |
| 3 | randomised trials | serious[e] | not serious | not serious | not serious | none | 155/3401 (4.6%) | 409/3406 (12.0%)** (study population) | **RR 0.37** (0.27 to 0.50) | **76 fewer discontinue per 1,000** (from 88 fewer to 60 fewer)** | ⊕⊕⊕◯ Moderate | CRITICAL |
| | | | | | | | | 13.3%** (weighted average) | | **84 fewer discontinue per 1,000** (from 96 fewer to 67 fewer)** | | |

* **For OS and DFS, the anticipated absolute effects** (and their 95% confidence interval) are based on the assumed survival in the 12 months treatment group and the relative effect of the shorter treatment (HR and its 95% CI). **Of note, the absolute effects are for a between-group difference and correspond to a superiority comparison** (i.e., the null hypothesis of HR = 1). Fewer means that less women survive (OS) or remain disease-free (DFS) with shorter treatment compared to 12 months of treatment. However, this **number may be less than what would be deemed clinically relevant based on the prespecified non-inferiority margins of a 3% absolute difference in OS and DFS**, corresponding to 30 fewer per 1,000 women. Please refer to the Comments for the relevant interpretation regarding non-inferiority.

** **For safety outcomes, the anticipated absolute effects** (and their 95% confidence interval) are based on the assumed risk in the 12 months treatment group and the relative effect of the shorter treatment (RR and its 95% CI). The risks in the 12 months treatment group have been calculated using **2 different methods**: (i) the **'study population'** estimate was calculated as the overall risk in the 12 month treatment group across studies included in the corresponding meta-analysis (total number of events / total number of participants; unweighted approach, not taking into account all reported evidence for subgroup analyses), and (ii) the **'weighted average'** estimate was calculated as the inverse variance weighted average risk across 12 month treatment groups of all studies reporting data for the respective adverse effect outcome (weighted average of number of events / number of participants across all studies; taking into account evidence from studies not included in subgroup meta-analyses). Fewer means that less women experience AEs with shorter treatment compared to 12 months of treatment (corresponding to a superiority comparison).

**Legend**: AE = adverse effect, CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, HRQoL = health-related quality of life, LVEF = left-ventricular ejection fraction, OS = overall survival, RR = risk ratio.

| Certainty assessment | | | | | | | № of participants | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | ≤6 months trastuzumab | 12 months trastuzumab | Relative (95% CI) | Absolute (95% CI) | | |

**Grades of evidence after the GRADE working group**:
**High certainty**: we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty**: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty**: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty**: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

**Explanations**
a. Risk of bias downgraded by 1 level (resulting in serious risk of bias for OS and DFS): concerns regarding deviations from intended interventions in 3 studies (intention-to-treat effects may be biased towards non-inferiority due to potentially relevant protocol violations in PHARE, E2198 and PERSEPHONE).
b. Imprecision downgraded by 1 level (resulting in serious imprecision for DFS): Considering the specified non-inferiority margin of HR 1.266, the 95% confidence interval includes effects compatible with inferiority.
c. Risk of bias downgraded by 2 levels (resulting in very serious risk of bias for HRQoL): major concerns regarding deviations from intended interventions (due to reporting intention-to-treat estimates with potentially relevant protocol violations), missing outcome data, bias in measurement of the outcome (absence of blinding/placebo control with collection of self-reported outcome data). Differences in HRQoL were observed already at the start of trastuzumab treatment, and no estimates from comparative analyses were provided.
d. Imprecision downgraded by 2 levels (resulting in very serious imprecision for HRQoL): Evidence from single study and no comparative estimates for between-group differences or confidence intervals available; no conclusive assessment possible.
e. Risk of bias downgraded by 1 level (resulting in serious risk of bias): concerns regarding measurement of the outcome (absence of blinding/placebo control with collection of self-reported outcome data).
f. Imprecision downgraded by 1 level (resulting in serious imprecision for safety outcomes): 95% confidence interval is consistent with the possibility of fewer or more events.

**Appendix 14: GRADE evidence profile for the comparison of 6 months vs. 12 months of trastuzumab treatment from the assessment of clinical efficacy and safety.**

| Certainty assessment | | | | | | | № of participants | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | 6 months trastuzumab | 12 months trastuzumab | Relative (95% CI) | Absolute (95% CI) | | |
| **Overall survival (OS)** | | | | | | | | | | | | |
| 3 | randomised trials | serious[a] | not serious | not serious | not serious | none | 3973 | 3976 | **HR 1.12** (0.97 to 1.30) | - | ⊕⊕⊕◯ Moderate | CRITICAL |
| | | | | | | | - | **3-year OS***: 97.5% | | **3 fewer survive per 1,000** (from 7 fewer to 1 more)* | | |
| | | | | | | | - | **5-year OS***: 94.2% | | **7 fewer survive per 1,000** (from 17 fewer to 2 more)* | | |
| **Disease-free survival (DFS)** | | | | | | | | | | | | |
| 3 | randomised trials | serious[a] | not serious | not serious | serious[b] | none | 3973 | 3976 | **HR 1.13** (0.94 to 1.35) | - | ⊕⊕◯◯ Low | CRITICAL |
| | | | | | | | - | **3-year DFS***: 93.0% | | **9 fewer remain disease free per 1,000** (from 23 fewer to 4 more)* | | |
| | | | | | | | - | **5-year DFS***: 87.7% | | **15 fewer remain disease free per 1,000** (from 40 fewer to 6 more)* | | |
| **Health-related quality of life (HRQoL)** | | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of participants | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | 6 months trastuzumab | 12 months trastuzumab | Relative (95% CI) | Absolute (95% CI) | | |
| 1 | randomised trials | very serious[c] | not serious | not serious | very serious[d] | none | Mean EQ-VAS scores were higher in the 6 months compared to the 12 months treatment group (ranging between 0.1 points higher (at 24 months of follow-up) to 2.4 points higher (at 9 months of follow-up)). The proportion of participants reporting good or very good general health was the same or higher in the 6 months compared to the 12 months treatment group (ranging between 0% (at 6 months of follow-up) to 5% (at 9 months of follow-up)). | | | | ⊕◯◯◯ Very low | CRITICAL |
| **Congestive heart failure** | | | | | | | | | | | | |
| 1 | randomised trials | serious[e] | not serious | not serious | very serious[f] | none | 9/1690 (0.5%) | 11/1690 (0.7%)** (study population) | **RR 0.82** (0.34 to 1.97) | **1 fewer experience the AE per 1,000** (from 4 fewer to 6 more)** | ⊕◯◯◯ Very low | CRITICAL |
| | | | | | | | | 2.7%** (weighted average) | | **5 fewer experience the AE per 1,000** (from 18 fewer to 26 more)** | | |
| **LVEF <50% and LVEF decrease >10%** | | | | | | | | | | | | |
| 2 | randomised trials | serious[e] | not serious | not serious | not serious | none | 177/3649 (4.9%) | 233/3649 (6.4%)** (study population) | **RR 0.76** (0.62 to 0.93) | **15 fewer experience the AE per 1,000** (from 24 fewer to 4 fewer)** | ⊕⊕⊕◯ Moderate | CRITICAL |
| | | | | | | | | 6.4%** (weighted average) | | **15 fewer experience the AE per 1,000** (from 4 fewer to 24 fewer)** | | |
| **Any severe (grade ≥3) AE** | | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of participants | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | 6 months trastuzumab | 12 months trastuzumab | Relative (95% CI) | Absolute (95% CI) | | |
| 1 | randomised trials | serious[e] | not serious | not serious | serious[g] | none | 373/1939 (19.2%) | 459/1894 (24.2%)** (study population) | **RR 0.79** (0.70 to 0.90) | **51 fewer experience the AE per 1,000** (from 73 fewer to 24 fewer)** | ⨁⨁◯◯ Low | CRITICAL |
| | | | | | | | | 41.7%** (weighted average) | | **86 fewer experience the AE per 1,000** (from 43 fewer to 124 fewer)** | | |
| **Trastuzumab discontinuation due to any AE** | | | | | | | | | | | | |
| 1 | randomised trials | serious[e] | not serious | not serious | serious[g] | none | 38/1690 (2.2%) | 139/1690 (8.2%)** (study population) | **RR 0.27** (0.19 to 0.39) | **60 fewer discontinue per 1,000** (from 67 fewer to 50 fewer)** | ⨁⨁◯◯ Low | CRITICAL |
| | | | | | | | | 13.3%** (weighted average) | | **97 fewer discontinue per 1,000** (from 81 fewer to 107 fewer)** | | |

* **For OS and DFS, the anticipated absolute effects** (and their 95% confidence interval) are based on the assumed survival in the 12 months treatment group and the relative effect of the shorter treatment (HR and its 95% CI). **Of note, the absolute effects are for a between-group difference and correspond to a superiority comparison** (i.e., the null hypothesis of HR = 1). Fewer means that less women survive (OS) or remain disease-free (DFS) with shorter treatment compared to 12 months of treatment. However, this **number may be less than what would be deemed clinically relevant based on the prespecified non-inferiority margins of a 3% absolute difference in OS and DFS**, corresponding to 30 fewer per 1,000 women. Please refer to the Comments for the relevant interpretation regarding non-inferiority.

** **For safety outcomes, the anticipated absolute effects** (and their 95% confidence interval) are based on the assumed risk in the 12 months treatment group and the relative effect of the shorter treatment (RR and its 95% CI). The risks in the 12 months treatment group have been calculated using **2 different methods**: (i) the **'study population'** estimate was calculated as the overall risk in the 12 month treatment group across studies included in the corresponding meta-analysis (total number of events / total number of participants; unweighted approach, not taking into account all reported evidence for subgroup analyses), and (ii) the **'weighted average'** estimate was calculated as the inverse variance weighted average risk across 12 month treatment groups of all studies reporting data for the respective adverse effect outcome (weighted average of number of events / number of participants across all studies; taking into account evidence from studies not included in subgroup meta-analyses). Fewer means that less women experience AEs with shorter treatment compared to 12 months of treatment (corresponding to a superiority comparison).

**Legend**: AE = adverse effect, CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, HRQoL = health-related quality of life, LVEF = left-ventricular ejection fraction, OS = overall survival, RR = risk ratio.

| Certainty assessment | | | | | | | № of participants | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | 6 months trastuzumab | 12 months trastuzumab | Relative (95% CI) | Absolute (95% CI) | | |

**Grades of evidence after the GRADE working group**:
**High certainty**: we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty**: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty**: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty**: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

**Explanations**
a. Risk of bias downgraded by 1 level (resulting in serious risk of bias for OS and DFS): concerns regarding deviations from intended interventions in 3 studies (intention-to-treat effects may be biased towards non-inferiority due to potentially relevant protocol violations in PHARE, E2198 and PERSEPHONE).
b. Imprecision downgraded by 1 level (resulting in serious imprecision for DFS): Considering the specified non-inferiority margin of HR 1.266, the 95% confidence interval includes effects compatible with inferiority.
c. Risk of bias downgraded by 2 levels (resulting in very serious risk of bias for HRQoL): major concerns regarding deviations from intended interventions (due to reporting intention-to-treat estimates with potentially relevant protocol violations), missing outcome data, bias in measurement of the outcome (absence of blinding/placebo control with collection of self-reported outcome data). Differences in HRQoL were observed already at the start of trastuzumab treatment, and no estimates from comparative analyses were provided.
d. Imprecision downgraded by 2 levels (resulting in very serious imprecision for HRQoL): Evidence from single study and no comparative estimates for between-group differences or confidence intervals available; no conclusive assessment possible.
e. Risk of bias downgraded by 1 level (resulting in serious risk of bias): concerns regarding measurement of the outcome (absence of blinding/placebo control with collection of self-reported outcome data).
f. Imprecision downgraded by 2 levels (resulting in very serious imprecision for safety outcomes): evidence from single study and 95% confidence interval is consistent with the possibility of fewer or more events.
g. Imprecision downgraded by 1 level (resulting in serious imprecision for safety outcomes): evidence from single study.

**Appendix 15: Search strategies and search results for economic studies.**

MEDLINE (accessed via Ovid), 02. May 2023

| | | |
|---|---|---|
| 1 | exp Breast Neoplasms/ or ((breast* or mamma*) adj4 (cancer* or neoplasm* or malignanc* or tumor* or tumour* or carcinoma* or adenocarcinoma*)).ti,ab. | 485262 |
| 2 | exp Chemotherapy, Adjuvant/ or exp Neoadjuvant Therapy/ or (adjuvant or neoadjuvant).ti,ab. | 220596 |
| 3 | (exp Trastuzumab/ or (trastuzumab or herceptin).ti,ab.) and (duration or timing or time or short* or long* or course* or cycle* or length or ((compar* or difference or versus or vs*) adj4 (year* or month* or week* or day*))).ti,ab. | 5233 |
| 4 | (pertuzumab or perjeta).ti,ab. | 1440 |
| 5 | 3 or 4 | 6179 |
| 6 | exp Animals/ not Humans/ | 5117568 |
| 7 | 5 not 7 | 6086 |
| 8 | Economics/ | 27500 |
| 9 | exp "Costs and Cost Analysis"/ | 264059 |
| 10 | Economics, Nursing/ | 4013 |
| 11 | Economics, Medical/ | 9245 |
| 12 | Economics, Pharmaceutical/ | 3100 |
| 13 | exp Economics, Hospital/ | 25703 |
| 14 | Economics, Dental/ | 1920 |
| 15 | exp "Fees and Charges"/ | 31350 |
| 16 | exp Budgets/ | 14101 |
| 17 | budget*.ti,ab,kf. | 35645 |
| 18 | (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. | 277841 |
| 19 | (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 | 374965 |
| 20 | (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. | 206192 |
| 21 | (value adj2 (money or monetary)).ti,ab,kf. 15. exp models, economic/ | 2999 |
| 22 | economic model*.ab,kf. | 16201 |
| 23 | markov chains/ | 4153 |
| 24 | markov.ti,ab,kf. | 15939 |
| 25 | monte carlo method/ | 28662 |
| 26 | monte carlo.ti,ab,kf. | 32103 |
| 27 | exp Decision Theory/ | 59482 |
| 28 | (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. | 13197 |
| 29 | or/8-28 | 36782 |
| 30 | 1 and 2 and 7 and 29 | 103 |

EMBASE (accessed via Elsevier), 02. May 2023

| | | |
|---|---|---|
| #1 | 'breast cancer'/exp OR (((breast* OR mamma*) NEAR/4 (cancer* OR neoplasm* OR malignanc* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma*)):ti,ab) | 722863 |
| #2 | 'adjuvant chemotherapy'/exp OR 'neoadjuvant chemotherapy'/exp OR adjuvant:ti,ab OR neoadjuvant:ti,ab | 332434 |
| #3 | ('trastuzumab'/exp OR trastuzumab:ti,ab OR herceptin:ti,ab) AND (duration:ti,ab OR timing:ti,ab OR time:ti,ab OR short*:ti,ab OR long*:ti,ab OR course*:ti,ab OR cycle*:ti,ab OR length:ti,ab OR (((compar* OR difference OR versus OR vs*) NEAR/4 (year* OR month* OR week* OR day*)):ti,ab)) | 17621 |
| #4 | 'pertuzumab'/exp OR (pertuzumab or perjeta):ti,ab | 7614 |
| #5 | #3 OR #4 | 22632 |
| #6 | 'animals'/exp NOT 'humans'/exp | 5946677 |
| #7 | #5 NOT #6 | 22081 |
| #8 | 'economics' | 455782 |
| #9 | 'costs and cost analysis'/exp | 402413 |
| #10 | economic NEAR/2 model | 6717 |
| #11 | 'cost minimi*':ti,ab OR 'cost utilit*':ti,ab OR 'health utilit*':ti,ab OR 'economic evaluation':ti,ab OR 'economic review':ti,ab OR 'cost outcome*':ti,ab OR 'cost analys*s':ti,ab OR 'economic analys*s':ti,ab OR 'budget impact analysis':ti,ab,kw | 54167 |
| #12 | 'cost-effective*':ti,kw OR 'pharmacoeconomic*':ti,kw OR 'pharmaco-economic*':ti,kw OR 'cost benefit':ti,kw OR costs:ti,kw | 127547 |
| #13 | 'life year':ab,kw OR 'life years':ab,kw OR 'qaly*':ab,kw OR 'cost-benefit analys*s':ab,kw OR 'cost effectiveness analys*s':ab,kw | 59480 |
| #14 | (cost:ti,kw OR economic*:ti,kw) AND (costs:ab OR 'cost-effectiveness':ab OR 'markov':ab OR 'monte carlo':ab OR 'model':ab OR 'modeling':ab OR 'modelling':ab) | 124210 |
| #15 | #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 | 880602 |

| | | |
|---|---|---|
| #16 | #1 AND #2 AND #7 AND #15 | 265 |

International Network of Agencies for Health Technology Assessment (INAHTA), 02. May 2023

| | | |
|---|---|---|
| 1 | Breast cancer or breast neoplasms or breast carcinoma | 1427 |
| 2 | (trastuzumab or Herceptin or pertuzumab or Perjeta) | 89 |
| 3 | (costs or cost-effectiveness or cost-utility or cost-benefit or cost-minimization or budget or economic) | 4277 |
| 4 | 1 AND 2 AND 3 | 15 |

EconLit, 02. May 2023

| | | |
|---|---|---|
| 1 | Breast cancer or breast neoplasms or breast carcinoma | 392 |
| 2 | trastuzumab or Herceptin or pertuzumab or Perjeta | 5 |
| 3 | 1 AND 2 | 3 |

National Health Service Economic Evaluation Database (NHSEED), 02. May 2023

| | | |
|---|---|---|
| 1 | Breast cancer or breast neoplasms or breast carcinoma | 602 |
| 2 | trastuzumab or Herceptin or pertuzumab or Perjeta | 45 |
| 3 | 1 AND 2 | 31 |

**Appendix 16: List of excluded records at full-text screening for systematic review of economic studies.**

| Author | Year | Title | Reason for exclusion |
|---|---|---|---|
| N. Ttc and N. Ttt | 2014 | Cost-Effectiveness Analysis of 1-Year Adjuvant Trastuzumab Therapy of Early-Stage Her2-Positive Breast Cancer. | Abstract only |
| | | PERSEPHONE - duration of trastuzumab study with chemotherapy in early breast cancer: six versus twelve months | Duplicate |
| C. Attard, A. Pepper, S. Brown, M. Thompson, P. Thuresson, S. Yunger, S. Dent, A. Paterson and G. C. N.-. Wells | 2014 | Cost-effectiveness analysis of neoadjuvant pertuzumab and trastuzumab therapy for locally advanced, inflammatory, or early HER2-positive breast cancer in Canada | Duplicate |
| T. T. Purmonen, P. K. Auvinen and J. A. Martikainen | 2010 | Budget impact analysis of trastuzumab in early breast cancer: a hospital district perspective. | Exclude- Q23 CHEERS |
| Ecri | 2005 | Trastuzumab [Herceptin (R)] for the treatment of breast cancer | Full text not available |
| | | Trastuzumab emtansine for the treatment of locally advanced or metastatic HER2 - positive breast cancer after treatment with trastuzumab and a taxane (ID603) | Incorrect comparator |
| A. Aboutorabi, M. Hadian, H. Ghaderi, M. Salehi and M. Ghiasipour | 2014 | Cost-effectiveness analysis of trastuzumab in the adjuvant treatment for early breast cancer. | Incorrect comparator |
| Anonymous | 2019 | Cost-Effectiveness Analysis of Pertuzumab With Trastuzumab and Chemotherapy Compared to Trastuzumab and Chemotherapy in the Adjuvant Treatment of HER2-Positive Breast Cancer in the United States. | Incorrect comparator |
| S. Atikah, F. SS, M. AR, A. AAR and I. MMG | 2021 | Targeted therapies in combination with neoadjuvant chemotherapy for HER2-positive breast cancer and economic evaluation | Incorrect comparator |
| C. L. Attard, A. N. Pepper, S. T. Brown, M. F. Thompson, P.-O. Thuresson, S. Yunger, S. Dent, A. H. Paterson and G. A. Wells | 2015 | Cost-effectiveness analysis of neoadjuvant pertuzumab and trastuzumab therapy for locally advanced, inflammatory, or early HER2-positive breast cancer in Canada. | Incorrect comparator |
| C. H. Botelho, M. D. P. Estevez-Diz and A. G. Campolina | 2022 | Cost-effectiveness analysis of trastuzumab for early breast cancer in Brazil. | Incorrect comparator |
| S. Boutayeb, A. Boutayeb, N. Ahbeddou, W. Boutayeb, E. Ismail, M. Tazi and H. Errihani | 2010 | Estimation of the cost of treatment by chemotherapy for early breast cancer in Morocco. | Incorrect comparator |
| J. A. Buendia, C. Vallejos and A. Pichon-Riviere | 2013 | An economic evaluation of trastuzumab as adjuvant treatment of early HER2-positive breast cancer patients in Colombia. | Incorrect comparator |
| A. Buja, E. Perissinotto, A. Compostella, A. Tramarin, V. Rebba, D. Pastorelli, F. Grigoletto, C. Gallo, G. Rausa and D. C. N.-. Gregori | 2011 | Taking decisions on expenditure for high-cost drugs at the regional level: a model for evaluating the overall impact of trastuzumab in the Veneto Region of Italy | Incorrect comparator |
| A. Cesarec and R. Likic | 2017 | Budget Impact Analysis of Biosimilar Trastuzumab for the Treatment of Breast Cancer in Croatia | Incorrect comparator |
| W. Chen, Z. Jiang, Z. Shao, Q. Sun and K. Shen | 2009 | An economic evaluation of adjuvant trastuzumab therapy in HER2-positive early breast cancer. | Incorrect comparator |
| L. Chicaiza-Becerra, M. Garcia-Molina, O. Gamboa and C. C. N.-. Castaneda-Orjuela | 2014 | ErbB2+ metastatic breast cancer treatment after progression on trastuzumab: a cost-effectiveness analysis for a developing country | Incorrect comparator |
| M. D. Danese, D. Lalla, M. Brammer, Q. Doan and K. Knopf | 2010 | Estimating recurrences prevented from using trastuzumab in HER-2/neu-positive adjuvant breast cancer in the United States. | Incorrect comparator |
| G. J. de Lima Lopes | 2011 | Societal costs and benefits of treatment with trastuzumab in patients with early HER2neu-overexpressing breast cancer in Singapore. | Incorrect comparator |

| Author | Year | Title | Reason for exclusion |
|---|---|---|---|
| K. J. Dedes, T. D. Szucs, P. Imesch, A. Fedier, M. K. Fehr and D. Fink | 2007 | Cost-effectiveness of trastuzumab in the adjuvant treatment of early breast cancer: a model-based analysis of the HERA and FinHer trial. | Incorrect comparator |
| T. N. Doan and J. Barendregt | 2019 | Adjuvant trastuzumab chemotherapy in early breast cancer: meta-analysis of randomised trials and cost-effectiveness analysis. | Incorrect comparator |
| E. Dvortsin, J. Gout-Zwart, E.-L. M. Eijssen, J. van Brussel and M. J. Postma | 2016 | Comparative Cost-Effectiveness of Drugs in Early versus Late Stages of Cancer; Review of the Literature and a Case Study in Breast Cancer. | Incorrect comparator |
| B. A. B. Essers, S. C. Seferina, V. C. G. Tjan-Heijnen, J. L. Severens, A. Novák, M. Pompen, U. H. Oron and M. A. Joore | 2010 | Transferability of model-based economic evaluations: the case of trastuzumab for the adjuvant treatment of HER2-positive early breast cancer in the Netherlands. | Incorrect comparator |
| F. Fagnani, X. Colin, P. Arveux, B. Coudert and J.-L. Misset | 2007 | [Cost/effectiveness analysis of adjuvant therapy with trastuzumab in patients with HER2 positive early breast cancer]. | Incorrect comparator |
| A. Farolfi, P. Silimbani, D. Gallegati, E. Petracci, A. Schirone, M. Altini and C. Masini | 2017 | Resource utilization and cost saving analysis of subcutaneous versus intravenous trastuzumab in early breast cancer patients. | Incorrect comparator |
| N. Fleeman, A. Bagust, S. Beale, K. Dwan, R. Dickson, C. Proudlove and e. al. | 2013 | Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer: a single technology appraisal | Incorrect comparator |
| L. P. J. Garrison, D. Lalla, M. Brammer, J. B. Babigumira, B. Wang and E. A. Perez | 2013 | Assessing the potential cost-effectiveness of retesting IHC0, IHC1+, or FISH-negative early stage breast cancer patients for HER2 status. | Incorrect comparator |
| L. P. J. Garrison, D. Lubeck, D. Lalla, V. Paton, A. Dueck and E. A. Perez | 2007 | Cost-effectiveness analysis of trastuzumab in the adjuvant setting for treatment of HER2-positive breast cancer. | Incorrect comparator |
| L. P. J. Garrison and D. L. Veenstra | 2009 | The economic value of innovative treatments over the product life cycle: the case of targeted trastuzumab therapy for breast cancer. | Incorrect comparator |
| A. J. Genuino, U. Chaikledkaew, A. M. Guerrero, T. Reungwetwattana and A. Thakkinstian | 2019 | Cost-utility analysis of adjuvant trastuzumab therapy for HER2-positive early-stage breast cancer in the Philippines. | Incorrect comparator |
| N. Gershon, Y. Berchenko, P. S. Hall and D. A. Goldstein | 2019 | Cost effectiveness and affordability of trastuzumab in sub-Saharan Africa for early stage HER2-positive breast cancer. | Incorrect comparator |
| M. J. Hassett, H. Li, H. J. Burstein and R. S. Punglia | 2020 | Neoadjuvant treatment strategies for HER2-positive breast cancer: cost-effectiveness and quality of life outcomes. | Incorrect comparator |
| L. Hedden, S. O'Reilly, C. Lohrisch, S. Chia, C. Speers, L. Kovacic, S. Taylor and S. Peacock | 2012 | Assessing the real-world cost-effectiveness of adjuvant trastuzumab in HER-2/neu positive breast cancer. | Incorrect comparator |
| B. E. Hillner and T. J. Smith | 2007 | Do the large benefits justify the large costs of adjuvant breast cancer trastuzumab? | Incorrect comparator |
| P.-H. Hsieh, A. J. Kacew, M. Dreyer, A. V. Serritella, R. W. Knoebel, G. W. Strohbehn and M. J. Ratain | 2022 | Alternative trastuzumab dosing strategies in HER2-positive early breast cancer are associated with patient out-of-pocket savings. | Incorrect comparator |
| S. S. Ioannou, Y. Marcou, E. Kakouri and M. A. Talias | 2020 | Real-World Setting Cost-Effectiveness Analysis Comparing Three Therapeutic Schemes of One-Year Adjuvant Trastuzumab in HER2-Positive Early Breast Cancer from the Cyprus NHS Payer Perspective. | Incorrect comparator |
| R. Kongsakon, S. Lochid-Amnuay, N. Kapol and O. Pattanaprateep | 2019 | From Research to Policy Implementation: Trastuzumab in Early-Stage Breast Cancer Treatment in Thailand. | Incorrect comparator |
| T. Konishi, M. Fujiogi, N. Michihata, H. Ohbe, H. Matsui, K. Fushimi, M. Tanabe, Y. Seto and H. Yasunaga | 2022 | Cost-effectiveness analysis of trastuzumab monotherapy versus adjuvant chemotherapy plus trastuzumab in elderly patients with HER2-positive early breast cancer. | Incorrect comparator |
| N. Kunst, S.-Y. Wang, A. Hood, S. S. Mougalian, M. P. DiGiovanna, K. Adelson and L. Pusztai | 2020 | Cost-Effectiveness of Neoadjuvant-Adjuvant Treatment Strategies for Women With ERBB2 (HER2)-Positive Breast Cancer. | Incorrect comparator |

| Author | Year | Title | Reason for exclusion |
|---|---|---|---|
| A. W. Kurian, R. N. Thompson, A. F. Gaw, S. Arai, R. Ortiz and A. M. Garber | 2007 | A cost-effectiveness analysis of adjuvant trastuzumab regimens in early HER2/neu-positive breast cancer. | Incorrect comparator |
| N. L. Liberato, M. Marchetti and G. Barosi | 2007 | Cost effectiveness of adjuvant trastuzumab in human epidermal growth factor receptor 2-positive breast cancer. | Incorrect comparator |
| M. Lidgren, B. Jönsson, C. Rehnberg, N. Willking and J. Bergh | 2008 | Cost-effectiveness of HER2 testing and 1-year adjuvant trastuzumab therapy for early breast cancer. | Incorrect comparator |
| M. J. H. G. M. c. J. M. K. K. Zeghal | 2018 | Le trastuzumab dans le traitement du cancer du sein HER2 positif au stade précoce et localement avancé | Incorrect comparator |
| J. Norum, J. A. Olsen, E. A. Wist and P. E. Lønning | 2007 | Trastuzumab in adjuvant breast cancer therapy. A model based cost-effectiveness analysis. | Incorrect comparator |
| A. Parthan, E. Santos, L. Becker, A. Small, D. Lalla, M. Brammer and A. Teitelbaum | 2014 | Health care utilization and costs by site of service for nonmetastatic breast cancer patients treated with trastuzumab. | Incorrect comparator |
| S. D. Reed and K. A. Schulman | 2009 | Cost utility of sequential adjuvant trastuzumab for HER2/Neu-positive breast cancer. | Incorrect comparator |
| S. C. Seferina, B. L. T. Ramaekers, M. de Boer, M. W. Dercksen, F. van den Berkmortel, R. J. W. van Kampen, A. J. van de Wouw, A. C. Voogd, V. C. G. Tjan Heijnen and M. A. Joore | 2017 | Cost and cost-effectiveness of adjuvant trastuzumab in the real world setting: A study of the Southeast Netherlands Breast Cancer Consortium. | Incorrect comparator |
| C. Skedgel, D. Rayson and T. Younis | 2009 | The cost-utility of sequential adjuvant trastuzumab in women with Her2/Neu-positive breast cancer: an analysis based on updated results from the HERA Trial. | Incorrect comparator |
| J. A. Sussell, J. A. Roth, C. S. Meyer, A. Fung and S. A. Hansen | 2022 | Assessment of the Cost-Effectiveness of HER2-Targeted Treatment Pathways in the Neoadjuvant Treatment of High-Risk HER2-Positive Early-Stage Breast Cancer. | Incorrect comparator |
| Y. Takumoto, T. Shiroiwa, K. Shimozuma, H. Iwata, M. Takahashi, S. Baba, K. Kobayashi, Y. Hagiwara, T. Kawahara, Y. Uemura, H. Mukai, N. Taira and M. Sawaki | 2022 | Cost-Effectiveness of Trastuzumab With or Without Chemotherapy as Adjuvant Therapy in HER2-Positive Elderly Breast Cancer Patients: A Randomized, Open-Label Clinical Trial, the RESPECT Trial. | Incorrect comparator |
| I. Van Vlaenderen, J. L. Canon, V. Cocquyt, G. Jerusalem, J. P. Machiels, P. Neven, M. Nechelput, I. Delabaye, M. Gyldmark and L. Annemans | 2009 | Trastuzumab treatment of early stage breast cancer is cost-effective from the perspective of the Belgian health care authorities. | Incorrect comparator |
| S. Ward, H. Pilgrim and D. Hind | 2009 | Trastuzumab for the treatment of primary breast cancer in HER2-positive women: a single technology appraisal. | Incorrect comparator |
| C. National Horizon Scanning | 2010 | Trastuzumab (Herceptin) for HER2 positive early, locally advanced and inflammatory breast cancer - neoadjuvant treatment | Incorrect comparator (assume NICE TA) |
| C. National Horizon Scanning | 2011 | Trastuzumab SC (Herceptin SC) for breast cancer, early or metastatic, HER2 positive - monotherapy or combination therapy, including neo-adjuvant and adjuvant use | Incorrect comparator (assume NICE TA) |
| C. C. N.-. National Horizon Scanning | 2011 | Trastuzumab-DM1 (Herceptin-DM1) for breast cancer, locally advanced or metastatic, HER2 positive - second or third line | Incorrect comparator (assume NICE TA) |
| H. Nihr | 2016 | Pertuzumab (Perjeta) with chemotherapy and trastuzumab for HER2-positive early breast cancer – adjuvant therapy | Incorrect comparator (assume NICE TA) |

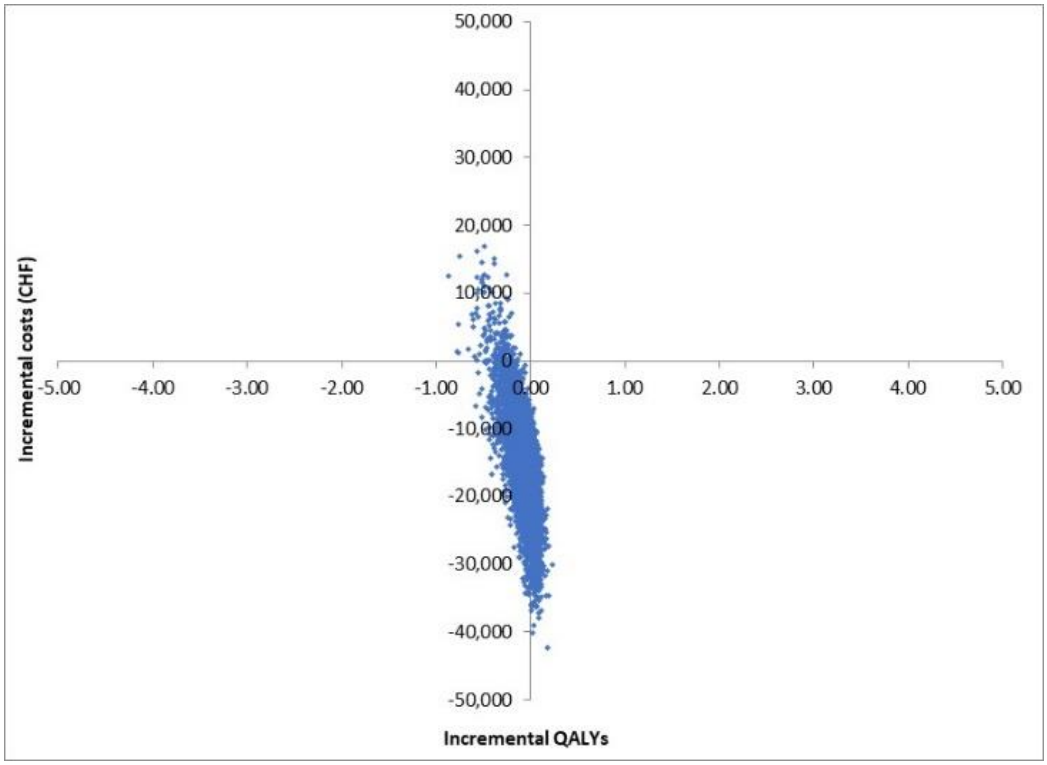
| Author | Year | Title | Reason for exclusion |
|---|---|---|---|
| H. S. C. Nihr | 2014 | Pertuzumab (Perjeta) for HER2-positive locally advanced, inflammatory or early breast cancer – neo-adjuvant in combination with trastuzumab and docetaxel | Incorrect comparator (assume NICE TA) |
| H. S. C. Nihr | 2012 | Trastuzumab (Herceptin) for HER2 positive early breast cancer – two year regimen | Incorrect intervention (assume NICE TA) |
| K. Athanasakis and J. Kyriopoulos | 2012 | A cost-effectiveness analysis of trastuzumab plus docetaxel vs. docetaxel alone for the treatment of HER2-positive metastatic breast cancer in the Greek healthcare setting | Incorrect population |
| S. Ballali, D. Chiffi, M. P. Trojniak, D. Gregori, F. Grigoletto, E. Perissinotto, A. Buja, A. Tramarina, C. Gallo, A. Compostella, D. Pastorelli and G. Rausa | 2013 | Evaluating trastuzumab and lapatinib's economic impact in the treatment of metastatic breast cancer in Veneto region cohort | Incorrect population |
| A. Canadian Coordinating Office for Health Technology | 1998 | Herceptin: monoclonal antibody therapy for metastatic breast cancer | Incorrect population |
| E. B. Elkin, K. C. Weinstein, E. P. Winer, K. M. Kuntz, S. J. Schnitt and J. C. C. N.-. Weeks | 2004 | HER-2 testing and trastuzumab therapy for metastatic breast cancer: a cost-effectiveness analysis | Incorrect population |
| A. Nachtnebel, K. Hintringer and C. Marth | 2012 | Pertuzumab (Omnitarg/Perjeta®) for the first-line therapy of metastatic HER2 positive breast cancer | Incorrect population |
| N. S. Nair, S. Gupta, J. Ghosh, S. Desai, V. Parmar, T. Shet, G. Chitkara, S. Siddique and R. A. Badwe | 2022 | Access to HER2-targeted therapy at a tertiary care center in India: An evolution. | Incorrect study design |
| N. Oestreicher | 2009 | Costs of adjuvant breast cancer treatments. | Incorrect study design |
| T. Younis and C. Skedgel | 2008 | Is trastuzumab a cost-effective treatment for breast cancer? | Incorrect study design |
| T. Younis and C. Skedgel | 2011 | Adjuvant trastuzumab for breast cancer: uncertainties in clinical and economic evidence following early stopping of the HERA trial. | Incorrect study design |
| Nhsc | 2006 | Trastuzumab as adjuvant therapy for early stage breast cancer - horizon scanning review | Incorrect study design (assume NICE TA) |
| L. Lindner, A. Vieta, C. Rodriguez, A. Barnadas, P. Sanchez-Rovira and I. Martin | 2013 | [Cost-effectiveness analysis of adjuvant therapy with trastuzumab for the treatment of early-stage breast cancer] | Language |
| S. J. Martins and C. A. Yamamoto | 2008 | [Clinical and economic issues in adjuvant chemotherapy for HER-2 positive breast cancer]. | Language |
| E. J. Vos, S. C. Linn and S. Rodenhuis | 2006 | [Effects and costs of adjuvant chemotherapy for operable lymph node positive breast cancer with HER2/neu overexpression]. | Language |
| S. Metcalfe, J. Evans and G. Priest | 2007 | PHARMAC funding of 9-week concurrent trastuzumab (Herceptin) for HER2-positive early breast cancer. | No head to head comparison |
| E. Danish Centre for and A. Health Technology | 2006 | [Trastuzumab as adjuvant treatment of early breast cancer after surgical treatment] | Text unavailable |

**Appendix 17: Quality of reporting of economic studies according to Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022).**

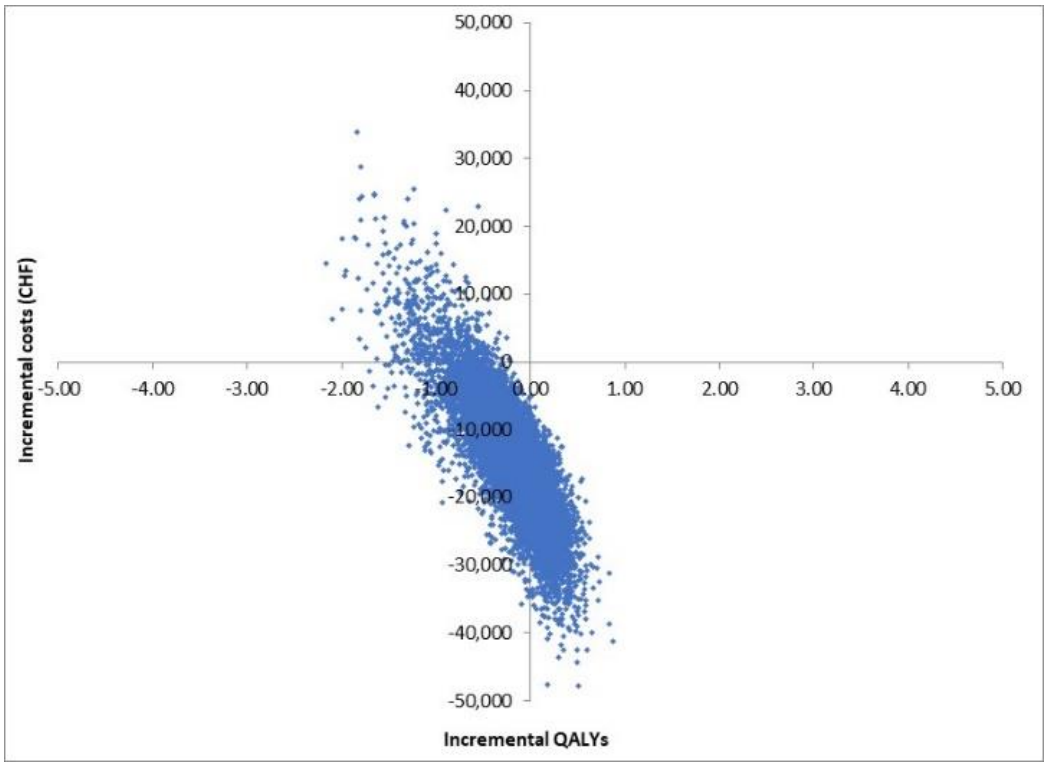
| Title | Author | Year | CHEERS Q5 | CHEERS Q7 | CHEERS Q8 | CHEERS Q9 | CHEERS Q23 |
|---|---|---|---|---|---|---|---|
| Cost effectiveness of trastuzumab for management of breast cancer in India | Gupta | 2019 | 5 Yes | 7 Yes | 8 Partial | 9 Partial | 23 No |
| Adjuvant trastuzumab therapy for early HER2-Positive Breast Cancer in Iran: A Cost-Effectiveness and Scenario Analysis for an Optimal Treatment Strategy | Ansaripour | 2017 | 5 Yes | 7 Yes | 8 Yes | 9 Maybe | 23 No |
| Cost-effectiveness of six months versus 1-year adjuvant trastuzumab in HER2 positive early breast cancer in Egypt | Elsisi | 2020 | 5 Yes | 7 Yes | 8 Partial | 9 Yes | 23 Partial |
| Trastuzumab in early stage breast cancer: A cost-effectiveness analysis for Belgium | Neyt | 2008 | 5 Yes | 7 Yes | 8 Yes | 9 Yes | 23 Partial |
| Six versus 12 months' adjuvant trastuzumab in patients with HER2-positive early breast cancer: the PERSEPHONE non-inferiority RCT | Earl | 2020 | 5 Yes | 7 Yes | 8 Yes | 9 Yes | 23 Yes |
| Cost effectiveness of trastuzumab in the adjuvant treatment of early breast cancer: a lifetime model | Millar | 2007 | 5 Yes | 7 Yes | 8 Partial | 9 Partial | 23 Partial |
| Multi-arm Cost-Effectiveness Analysis (CEA) comparing different durations of adjuvant trastuzumab in early breast cancer, from the English NHS payer perspective | Clarke | 2017 | 5 Yes | 7 Yes | 8 Partial | 9 Partial | 23 Partial |

**Appendix 18: Probabilistic sensitivity analyses using different time horizons**

PSA using 5y time horizon.




PSA using 10y time horizon.



PSA using 15y time horizon.