Endorsed by:

LEIDEN UNIVERSITY MEDICAL CENTER

Master Class in

Her2-Positive Breast Cancer

Live Webcast 1

HER2-Positive Early Breast Cancer, Diagnosis & Treatment Approaches

BENECKE

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Introduction

Benecke hereby presents a webcast training for medical oncologists. On the locations Jeddah and Riyadh this training will be moderated by Dr. Ahmed Saadeddin and Dr. Meteb Owaish Al-Foheidi. The training is **endorsed** by the **Leids Universitair Medisch Centrum (LUMC)** Leiden, the Netherlands, and consists of 3 educational webcasts and a live meeting.

In the webcasts, leading medical oncologist from Europe and Canada will present compelling topics on breast cancer treatment. Upon completion of the training, after following all 4 sessions, participant will receive a certificate.

The first webcast by Dr. David Miles will be on HER2-Positive Early Breast Cancer, Diagnosis & Treatment Approaches.

The second webcast by Dr. Sunil Verma will put notice on current and future developments in breast cancer.

The third webcast by Dr Fatima Cardoso will be about moving forward with metastatic breast cancer.

Finally, a live meeting will be organized with Professor Hans Gelderblom, Professor Koos van der Hoeven and Professor José Baselga, in which Professor Baselga will participate through a live video conference connection. Professor Gelderblom is a professor in internal medicine, a medical oncologist, and specialized in experimental pharmacotherapy in oncology at the Leids Universitair Medisch Centrum in Leiden, The Netherlands. Professor Koos van der Hoeven is a professor in internal medicine, a medical oncologist and Board member of the Dutch Society for Medical Oncology. Professor Baselga, is Physician-in-Chief of Memorial Sloan-Kettering Cancer Center in New York, United States of America. Professor Gelderblom, Professor van der Hoeven and Professor Baselga will recapitulate the presentations of the adjuvant session and the metastatic session. In addition, they will discuss breast cancer in a broad setting and refer to all major types of breast cancer, HER2 positive, hormone receptor negative and triple negative types. Professor Gelderblom, Professor van der Hoeven and Professor Baselga also will present case studies making use of adjuvantonline.com, an internet program with decision making tools that can help health care professionals to make choices concerning the risks and benefits of adjuvant therapy. Furthermore, gene expression profiling will be addressed. And, the presenters will deliberate about the Sankt Gallen breast cancer guidelines. Hormonal therapy will be assessed as well as chemotherapy and HER2 therapy. Additionally, metastatic breast cancer will be discussed with a focus on new developments in systemic anti cancer treatment. Professor Gelderblom, Professor van der Hoeven and Professor Baselga will describe case studies with notice on European guidelines. And furthermore, state of the art palliative care will be a subject in the live meeting.
Throughout the live session the presenters expect substantial audience participation.

Dr. David Miles, MB, BS, BSc, FRCP, MD

Consultant Medical Oncologist
Mount Vernon Cancer Centre

Dr. David Miles is a medical oncologist with a special interest in the treatment of breast cancer with over 20 years' experience in the field. He was trained at University College London with post-graduate education at Kings College, University College and Guy's and St Thomas's Hospital and completed his doctorate in the biological therapy of breast cancer at the Breast Unit at Guy's Hospital. He was head of the Breast Cancer Biology Group at Guys and more recently moved to be Lead Clinician for breast cancer at the Mount Vernon Cancer Centre.

Dr. Miles is the global Principal Investigator in clinical trials of biological therapies in the treatment of breast cancer and serves on clinical trial steering committees and independent data monitoring committees for studies of novel therapies for the treatment of breast and other cancers.

Dr. Miles advises the National Institute for Health and Clinical Excellence (NICE) on the adoption of new drugs being considered for breast cancer. He was a member of the committee invited by NICE to produce guidelines for the treatment of early stage breast cancer and currently he sits on the NICE quality standards committee for the treatment of breast cancer. He is a module leader and lecturer at the Institute of Cancer Research and frequently lectures internationally. Dr. Miles is an advisor to the charity Breast Cancer Care, a board member of the Cancer Vaccine Institute and sits on the Central Institutional Review Board of Cancer Research UK.

HER2-Positive Early Breast Cancer, Diagnosis & Treatment Approaches - Dr. David Miles

In this webcast Dr. David Miles, consultant medical oncologist from the Mount Vernon Cancer Centre, Middlesex, United Kingdom, will present the latest insights on HER2 positive breast cancer diagnosis and treatment approaches.

Dr. David Miles has a long standing experience in treatment of patients with Her2 positive breast cancer. In his presentation Dr. Miles will speak about Her2 positive breast cancer, diagnosis and treatment approaches.

According to the World Health Organization, breast cancer is by far the most common cancer diagnosed in women worldwide. An estimated 1.38 million women across the world were diagnosed with breast cancer in 2008.

Breast cancer is a heterogeneous disease. However, from a clinical perspective, breast cancer is subdivided into three major groups: hormone receptor positive, Human Epidermal Growth Factor Receptor 2 (HER2) positive and triple negative breast cancer. In the webcast presentation of Dr. Miles focus is on the HER2 positive disease.

HER2

HER2 is a member of the epidermal growth factor receptor (EGFR/ErbB) family and is a known proto-oncogene. It encodes a tyrosine kinase receptor, $p185^{erbB-2}$. This is a trans-membrane receptor. Stimulation of this receptor leads to transduction of an extracellular signal to the nucleus via one of several signaling cascades including the ras/raf/mapk pathway that ultimately leads to gene transcription and cell proliferation. Overstimulation of the signaling cascade leads to uncontrolled cell growth.

In breast cancer that is designated HER2 positive, HER2 is amplified and/or overexpressed. Overexpression of HER2 has been shown to play an important role in the pathogenesis and progression of certain types of breast cancer. This is the case in approximately 20% of breast cancers. Woman whose breast cancers are HER2 positive have a shorter overall survival than HER2 negative cases. HER2 expression is regarded by some as a relevant prognostic factor but now, its identification is important as a target of therapy.

Contemporary cancer research has led to progressions in cancer therapy and the development of the monoclonal antibody trastuzumab.

Trastuzumab targets the HER2 pathway. In early stage HER2-positive breast cancer, it significantly reduces recurrence and mortality. The combined hazard ratios for overall survival and disease-free survival significantly favored the trastuzumab-containing regimens.

The exact mechanism of action of trastuzumab is still unclear. However, trastuzumab binds to the extracellular part of the HER2 receptor, leading to receptor internalization and down-regulation of intracellular signaling. The receptor also flags cells for destruction by the immune system through antibody dependent cell mediated cytotoxicity.

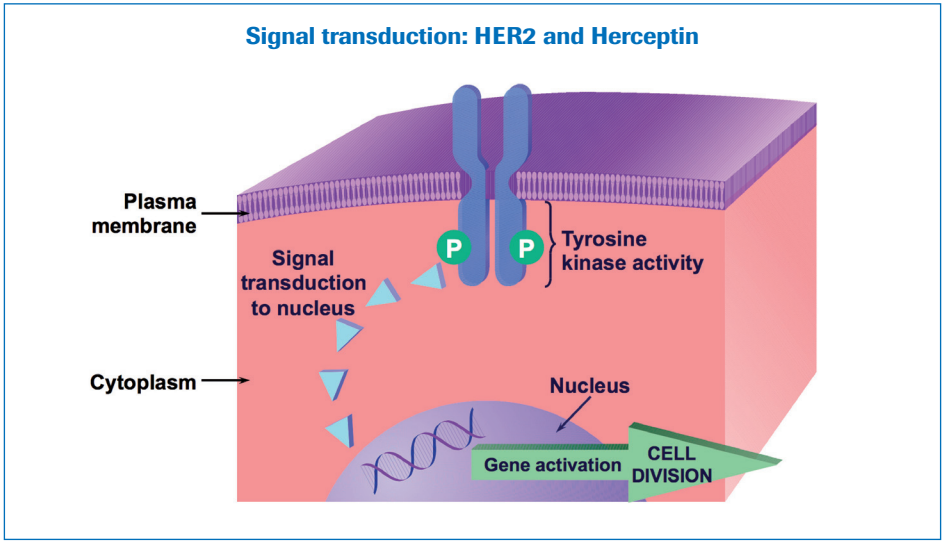

Figure 1: signal transduction by HER2

Adjuvant

In this webcast, latest research results in adjuvant treatment are considered. This additional treatment is intended to increase the relapse free survival rate. Adjuvant therapy for breast cancer can include chemotherapy, hormonal therapy, the targeted drug trastuzumab, radiation therapy, or a combination of treatments. HER2 may serve to direct the selection of optimal adjuvant chemotherapy.
An example of successful adjuvant therapy for early-stage HER2 positive breast cancer is demonstrated by the results of the phase III Herceptin Adjuvant (HERA) trial. The first results of this trial were reported in 2005 by Piccart-Gebhart M.J. et al. and the researcher could conclude that one year of treatment with trastuzumab after adjuvant chemotherapy significantly improves disease-free survival. In 2011, a four years follow-up study of patients enrolled in the HERA trial again showed that treatment with adjuvant trastuzumab for 1 year after chemotherapy is associated with significant clinical benefit.

In the same year (2011) long term follow-up results of trastuzumab plus adjuvant chemotherapy for operable HER2 positive breast cancer from the joint analysis of data from the North Central Cancer Treatment Group (NCCTG N9831 intergroup trail, and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B31 trial, were published. The four year follow-up

data demonstrate consistent disease free survival and overall survival advantages over time.

Based on data from HERA , NSABP B-31 and NCCTG N9831 trials, trastuzumab treatment for one year is now recommended by international guidelines for woman with early stage HER2 positive breast cancer.

On the adjuvant topic, Dr. Miles also will address the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization study, or ALTTO, trial by Metzger-Filho O. et al.. This is an international, phase III clinical trial, of two targeted therapies for HER2-positive breast cancer. And the APHINITY trial, a phase III study, examining the role of dual targeting with pertuzumab and trastuzumab in the adjuvant setting will be discussed.

Neoadjuvant

In his presentation Dr. Miles will also comment on the newest research in neoadjuvant treatment. Neoadjuvant therapy is treatment given before primary therapy and until recently it was used primarily for larger tumors to decrease in size thereby improving the proportion of breast-conserving surgery. However, today is considered a standard option, for patients with HER2-positive disease. Results will be presented from clinical trials in which neoadjuvant setting. A Phase III study called Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimization (neoALTTO) by Baselga J. et al. will be discussed. In this study a comparison was being made by the efficacy of neoadjuvant lapatinib plus paclitaxel, versus trastuzumab plus paclitaxel, versus concomitant lapatinib and trastuzumab plus paclitaxel given as neoadjuvant treatment in HER2/ErbB2 over-expressing and/or amplified primary breast cancer.

Cardiac toxicity

Although the results on efficacy of trastuzumab treatment seem to support its use, there is a potential risk of cardiac toxicities. These risks are going to be discussed as well as the preliminary results of a currently active trial in which trastuzumab is administered concurrently or sequentially to anthracycline-containing adjuvant regimen with respect to cardiac toxicity. Furthermore, newest algorithms for predicting cardiac toxicity in breast cancer patients, based on age, pretreatment, left ventricular ejection fraction. Risk factor for instance can consist of previous or concurrent anthracycline use and age greater than 50 years.

Duration of treatment

Another important issue in treatment of breast cancer is the duration of the therapy. Standard care nowadays is one year of trastuzumab treatment. But the optimal duration of treatments is still a compelling clinical question and is still under research. Different durations of treatment can be, short term approximately between nine and 24 weeks or standard duration which is over 24 weeks and usually 52 weeks. Dr. Miles will report on different duration studies for example the PHARE Trial results (Pivot et al.). In this trial a comparison was made with treatment duration times of 6 to 12 months of trastuzumab in adjuvant early breast cancer.

Tumor gene expression profiles

As was noted earlier, breast cancer is a heterogeneous group of tumors. These tumors can be subdivided on the basis of histopathological features, genetic alterations clinical features or gene-expression profiles. Tumor biopsies from patients used to be classified by histopathology. But histopathological classification does not reflect disease outcome. More recently, subdivision of breast carcinomas is based on molecular techniques, particularly gene-expression analysis. Gene expression profiling helps to refine breast cancer classification and offers the potential of personalized medicine to patients.

The expression profiles of the tumor cells and tissues can be determined with techniques like microarray technology, serial analysis of gene expression (SAGE) or high throughput based sequencing techniques such as RNA-seq. Gene expression analysis reveals a combination of expressed genes, known as genetic signatures, that allows the oncologist to classify tumors into molecular subclasses or predict the prognostic outcome of the patients and their clinical response to the anti-cancer treatment.

Dr. Miles will furthermore inform the participants of the webcasts on the latest results of the above mentioned subjects, as presented on the annual American Society of Clinical Oncology (ASCO) meeting.

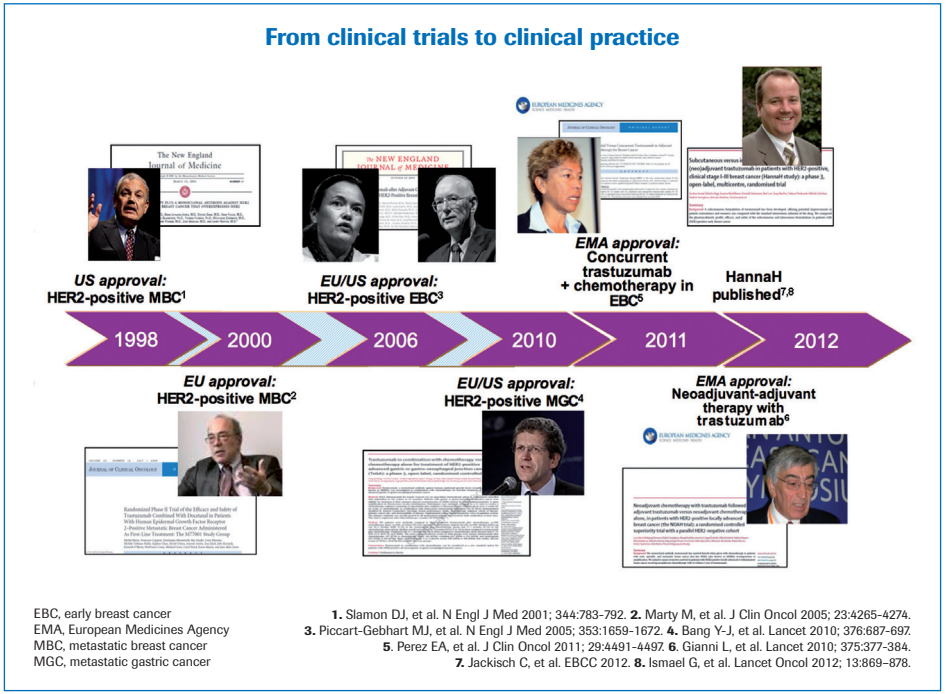

Figure 3. From clinical trials to clinical practice.

Suggested reading list in chronological order

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2. Metzger-Filho O, Procter M, de Azambuja E, Leyland-Jones B, Gelber RD, Dowsett M, Loi S, Saini KS, Cameron D, Untch M, Smith I, Gianni L, Baselga J, Jackisch C, Bell R, Sotiriou C, Viale G, Piccart-Gebhart M. (2013). **Magnitude of Trastuzumab Benefit in Patients With HER2-Positive, Invasive Lobular Breast Carcinoma: Results From the HERA Trial.** *J Clin Oncol.*; 31(16):1954-60.

3. Cancer research UK: World cancer fact sheet CS_FS_WORLD_A4 August 2012: http://publications.cancerresearchuk.org/downloads/product/CS_FS_WORLD_A4.pdf

4. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, D'Amico R. (2012) **Trastuzumab containing regimens for early breast cancer.** Cochrane Database Syst Rev. 18;4:CD006243.

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6. Gianni L, Dafni U, Gelber RD, Azambuja E, Muehlbauer S, Goldhirsch A, Untch M, Smith I, Baselga J, Jackisch C, Cameron D, Mano M, Pedrini JL, Veronesi A,Mendiola C, Pluzanska A, Semiglazov V, Vrdoljak E, Eckart MJ, Shen Z, Skiadopoulos G, Procter M, Pritchard KI, Piccart-Gebhart MJ, Bell R (2011) **Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial.** *Lancet Oncol;* 12(3):236-44.

7. Perez EA, Romond EH, Suman VJ, Jeong JH, Davidson NE, Geyer CE Jr, Martino S, Mamounas EP, Kaufman PA, Wolmark (2011). **Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31.** *J Clin Oncol;* 29(25):3366-73.

8. Costa RB, Kurra G, Greenberg L, Geyer CE. (2010); **Efficacy and cardiac safety of adjuvant trastuzumab-based chemotherapy regimens for HER2-positive early breast cancer.** *Ann Oncol;* 21(11):2153-60.

9. Gianni L, Eiermann W, Semiglazov V, Manikhas A, Lluch A, Tjulandin S, Zambetti M, Vazquez F, Byakhow M, Lichinitser M, Climent MA, Ciruelos E, Ojeda B, Mansutti M, Bozhok A, Baronio R, Feyereislova A, Barton C, Valagussa P, Baselga J. (2010). **Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort.** *Lancet;* 375(9712):377-84.

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12. Plunkett TA, Miles DW (2002). **New biological therapies for breast cancer.** *Int J Clin Pract.* 56(4):261-6.

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15. Houston SJ, Plunkett TA, Barnes DM, Smith P, Rubens RD, Miles DW. (1999) **Overexpression of c-erbB2 is an independent marker of resistance to endocrine therapy in advanced breast cancer.** *Br J Cancer.* 79(7-8):1220-6.

ONLINE AVAILABLE FREE FULL TEXT ARTICLES

1. Perez EA, Romond EH, Suman VJ, Jeong JH, Davidson NE, Geyer CE Jr, Martino S, Mamounas EP, Kaufman PA, Wolmark (2011). **Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31.** *J Clin Oncol;* 29(25):3366-73.

2. Costa RB, Kurra G, Greenberg L, Geyer CE. (2010); **Efficacy and cardiac safety of adjuvant trastuzumab-based chemotherapy regimens for HER2-positive early breast cancer.** *Ann Oncol;* 21(11):2153-60.

3. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, Baselga J, Bell R, Jackisch C, Cameron D, Dowsett M, Barrios CH, Steger G, Huang CS, Andersson M, Inbar M, Lichinitser M, Láng I, Nitz U, Iwata H, Thomssen C, Lohrisch C, Suter TM, Rüschoff J, Suto T, Greatorex V, Ward C, Straehle C, McFadden E, Dolci MS, Gelber RD (2005). **Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.** *N Engl J Med;* 20;353(16):1659-72.

4. Miles DW. (2001). **Update on HER-2 as a target for cancer therapy: herceptin in the clinical setting.** *Breast Cancer Res.* 3(6):380-4.

5. Houston SJ, Plunkett TA, Barnes DM, Smith P, Rubens RD, Miles DW. (1999) **Overexpression of c-erbB2 is an independent marker of resistance to endocrine therapy in advanced breast cancer.** *Br J Cancer.* 79(7-8):1220-6.

Selection of relevant ABSTRACTS

1. Analysis of regional timelines to set up a global phase III clinical trial in breast cancer: the adjuvant lapatinib and/or trastuzumab treatment optimization experience (ABSTRACT)

PURPOSE: This study measured the time taken for setting up the different facets of adjuvant lapatinib and/or trastuzumab treatment optimization (ALTTO), an nternational phase III study being conducted in 44 participating countries.
METHODS: Time to regulatory authority (RA) approval, time to ethics committee/institutional review board (EC/IRB) approval, time from study approval by EC/IRB to first randomized patient, and time from first to last randomized patient were prospectively collected in the ALTTO study. Analyses were conducted by grouping countries into either geographic regions or economic classes as per the World Bank's criteria.
RESULTS: South America had a significantly longer time to RA approval (median: 236 days, range: 21-257 days) than Europe (median: 52 days, range: 0-151 days), North America (median: 26 days, range: 22-30 days), and Asia-Pacific (median: 62 days, range: 37-75 days). Upper-middle economies had longer times to RA approval (median: 123 days, range: 21-257 days) than high-income (median: 47 days, range: 0-112 days) and lower-middle income economies (median: 57 days, range: 37-62 days). No significant difference was observed for time to EC/IRB approval across the studied regions (median: 59 days, range 0-174 days). Overall, the median time from EC/IRB approval to first recruited patient was 169 days (range: 26-412 days).
CONCLUSION: This study highlights the long time intervals required to activate a global phase III trial. Collaborative research groups, pharmaceutical industry sponsors, and regulatory authorities should analyze the current system and enter into dialogue for optimizing local policies. This would enable faster access of patients to innovative therapies and enhance the efficiency of clinical research.

2. Magnitude of Trastuzumab Benefit in Patients With HER2-Positive, Invasive Lobular Breast Carcinoma: Results From the HERA Trial (ABSTRACT).

PURPOSE: To evaluate the benefit of adjuvant trastuzumab in patients diagnosed with human epidermal growth factor receptor 2 (HER2) -positive invasive lobular carcinoma (ILC) enrolled onto the Herceptin Adjuvant (HERA) trial.
PATIENTS AND METHODS: Patients randomly assigned to receive one year of trastuzumab and one year of observation in the HERA trial were included (n = 3,401). Centrally reviewed estrogen receptor (ER), progesterone receptor (PgR), and HER2 copy numbers were used. First site-specific relapse pattern was evaluated for ILC and invasive ductal carcinoma (IDC). The magnitude of trastuzumab benefit was assessed using the Cox proportional hazards

model for disease-free survival (DFS) and overall survival (OS). Results Median follow-up time was 4 years. A total of 187 ILC and 3,213 IDC patients were included. High Allred scores (6 to 8) were more common in patients with ILC than IDC for both ER (36.9% v 22.7%) and PgR (44.1% v 28.5%). A trend toward decreased HER2 copy number was observed in the ILC group. The ILC and IDC subgroups had similar patterns of first site of disease relapse. DFS hazard ratios (HRs) comparing 1 year of trastuzumab versus observation were 0.63 for ILC (95% CI, 0.34 to 1.15) and 0.77 for IDC (95% CI, 0.67 to 0.89; P for interaction = .49). The OS HRs comparing 1 year of trastuzumab versus observation were 0.60 for ILC (95% CI, 0.27 to 1.31) and 0.86 for IDC (95% CI, 0.71 to 1.06; P for interaction = .29).

CONCLUSION: In this retrospective analysis, there was no suggestion that patients in the ILC cohort experienced a different magnitude of benefit from adjuvant trastuzumab than those in the IDC cohort.

4. Trastuzumab containing regimens for early breast cancer (ABSTRACT)

BACKGROUND: Approximately one-fifth of women who develop early breast cancer have HER2-positive tumours, which if untreated, have a worse prognosis than HER2-negative tumours. Trastuzumab is a selective treatment targeting the HER2 pathway. Although the results on efficacy seem to support its use, there are potential cardiac toxicities which need to be considered, especially for women at lower risk of recurrence, or those at increased cardiovascular risk.

OBJECTIVES: To assess the evidence on the efficacy and safety of therapy with trastuzumab, overall and in relation to its duration, concurrent or sequential administration with the standard chemotherapy regimen in patients with HER2-positive early breast cancer.

SEARCH METHODS: We searched the Cochrane Breast Cancer Group's (CBCGs) Specialised Trials Register, and used the search strategy developed by the CBCG to search for randomised controlled trials (RCTs) in CENTRAL, MEDLINE, EMBASE, BIOSIS, TOXNET, and the WHO ICTRP search portal (up to February 2010).

SELECTION CRITERIA: RCTs comparing the efficacy and safety of trastuzumab alone, or in combination with chemotherapy, or no treatment, or standard chemotherapy alone, in women with HER2-positive early breast cancer including women with locally advanced breast cancer.

DATA COLLECTION AND ANALYSIS: We collected data from published and unpublished trials. We used hazard ratios (HRs) for time-to-event outcomes and risk ratio (RRs) for binary outcomes. Subgroup analyses included duration (less or greater than six months) and concurrent or sequential trastuzumab administration.

MAIN RESULTS: We included eight studies involving 11,991 patients. The combined HRs for overall survival (OS) and disease-free survival (DFS) significantly favoured the trastuzumab-containing regimens (HR 0.66; 95% confidence interval (CI) 0.57 to 0.77, P < 0.00001; and HR 0.60; 95% CI 0.50 to 0.71, P < 0.00001, respectively). Trastuzumab significantly increased the risk of congestive heart failure (CHF: RR 5.11; 90% CI 3.00 to 8.72, P < 0.00001); and left ventricular ejection fraction decline (LVEF: RR 1.83; 90% CI 1.36 to 2.47, P = 0.0008). For haematological toxicities, risks did not differ. The two small trials that administered trastuzumab for less than six months did not differ in efficacy from longer studies, but found fewer cardiac toxicities. Studies with concurrent administration gave similar efficacy and toxicity results to sequential studies.

AUTHORS' CONCLUSIONS: Trastuzumab significantly improves OS and DFS in HER2-positive women with early and locally advanced breast cancer, although it also significantly increases the risk of CHF and LVEF decline. The available subgroup analyses are limited by the small number of studies. Studies that administered trastuzumab concurrently or sequentially did not differ significantly in efficacy. Shorter duration of therapy may reduce cardiotoxicity and maintain efficacy, however there is insufficient evidence at present to conclude this due to small numbers of patients in these trials.

5. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial (ABSTRACT)

BACKGROUND: The anti-HER2 monoclonal antibody trastuzumab and the tyrosine kinase inhibitor lapatinib have complementary mechanisms of action and synergistic antitumour activity in models of HER2-overexpressing breast cancer. We argue that the two anti-HER2 agents given together would be better than single-agent therapy.

METHODS: In this parallel groups, randomised, open-label, phase 3 study undertaken between Jan 5, 2008, and May 27, 2010, women from 23 countries with HER2-positive primary breast cancer with tumours greater than 2 cm in diameter were randomly assigned to oral lapatinib (1500 mg), intravenous trastuzumab (loading dose 4 mg/kg [DOSAGE ERROR CORRECTED], subsequent doses 2 mg/kg), or lapatinib (1000 mg) plus trastuzumab. Treatment allocation was by stratified, permuted blocks randomisation, with four stratification factors. Anti-HER2 therapy alone was given for the first 6 weeks; weekly paclitaxel (80 mg/m(2)) was then added to the regimen for a further 12 weeks, before definitive surgery was undertaken. After surgery, patients received adjuvant chemotherapy followed by the same targeted therapy as in the neoadjuvant phase to 52 weeks. The primary endpoint was the rate of pathological complete response (pCR), analysed by intention to treat. This trial is registered with Clinical Trials.gov, NCT00553358.

FINDINGS: 154 patients received lapatinib, 149 trastuzumab, and 152 the combination. pCR rate was significantly higher in the group given lapatinib and trastuzumab (78 of 152 patients [51·3%; 95% CI 43·1–59·5]) than in the group given trastuzumab alone (44 of 149 patients [29·5%; 22·4–37·5]; difference 21·1%, 9·1–34·2, p=0·0001). We recorded no significant difference in pCR between the lapatinib (38 of 154 patients [24·7%, 18·1–32·3]) and the trastuzumab (difference -4·8%, -17·6 to 8·2, p=0·34) groups. No major cardiac dysfunctions occurred. Frequency of grade 3 diarrhoea was higher with lapatinib (36 patients [23·4%]) and lapatinib plus trastuzumab (32 [21·1%]) than with trastuzumab (three [2·0%]). Similarly, grade 3 liver-enzyme alterations were more frequent with lapatinib (27 [17·5%]) and lapatinib plus trastuzumab (15 [9·9%]) than with trastuzumab (11 [7·4%]).

INTERPRETATION: Dual inhibition of HER2 might be a valid approach to treatment of HER2-positive breast cancer in the neoadjuvant setting.

6. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial (ABSTRACT).

BACKGROUND: Treatment with adjuvant trastuzumab for 1 year improves disease-free survival and overall survival in patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer. We aimed to assess disease-free survival and overall survival after a median follow-up of 4 years for patients enrolled on the Herceptin Adjuvant (HERA) trial.
METHODS: The HERA trial is an international, multicentre, randomised, open-label, phase 3 trial comparing treatment with trastuzumab for 1 and 2 years with observation after standard neoadjuvant, adjuvant chemotherapy, or both in patients with HER2-positive early breast cancer. The primary endpoint was disease-free survival. After a positive first interim analysis at a median follow-up of 1 year for the comparison of treatment withtrastuzumab for 1 year with observation, event-free patients in the observation group were allowed to cross over to receive trastuzumab. We report trial outcomes for the 1-year trastuzumab and observation groups at a median follow-up of 48·4 months (IQR 42·0-56·5) and assess the effect of the extensive crossover to trastuzumab. Our analysis was by intention-to-treat. The HERA trial is registered with the European Clinical Trials Database, number 2005-002385-11.
FINDINGS: The HERA trial population comprised 1698 patients randomly assigned to the observation group and 1703 to the 1-year trastuzumabgroup. Intention-to-treat analysis of disease-free survival showed a significant benefit in favour of patients in the 1-year trastuzumab group (4-year disease-free survival 78·6%) compared with the observation group (4-year disease-free survival 72·2%; hazard ratio [HR] 0·76; 95% CI 0·66-0·87; p<0·0001). Intention-to-treat analysis of overall survival showed no significant difference in the risk of death (4-year overall survival 89·3%vs 87·7%, respectively; HR 0·85; 95% CI 0·70-1·04; p=0·11). Overall, 885 patients (52%) of the 1698 patients in the observation group crossed over to receivetra–stuzumab, and began treatment at median 22·8 months (range 4·5-52·7) from randomisation. In a non-randomised comparison, patients in the selective-crossover cohort had fewer disease-free survival events than patients remaining in the observation group (adjusted HR 0·68; 95% CI 0·51-0·90; p=0·0077). Higher incidences of grade 3-4 and fatal adverse events were noted on 1-year trastuzumab than in the observation group. The most common grade 3 or 4 adverse events, each in less than 1% of patients, were congestive cardiac failure, hypertension, arthralgia, back pain, central-line infection, hot flush, headache, and diarrhoea.
INTERPRETATION: Treatment with adjuvant trastuzumab for 1 year after chemotherapy is associated with significant clinical benefit at 4-year median follow-up. The substantial selective crossover of patients in the observation group to trastuzumab was associated with improved outcomes for this cohort.

7. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31 (ABSTRACT).

PURPOSE: Trastuzumab is a humanized monoclonal antibody against the human epidermal growth factor receptor 2 (HER2). The clinical benefits of adjuvant trastuzumab have been demonstrated in interim analyses of four large trials. Initial data of the combined analysis of the North Central Cancer Treatment Group (NCCTG) N9831 Intergroup trial and National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial were reported in 2005. Long-term follow-up results on disease-free survival (DFS) and overall survival (OS) have been awaited.
PATIENTS AND METHODS: Patients with HER2-positive operable breast cancer were randomly assigned to doxorubicin plus cyclophosphamide followed by paclitaxel with or without trastuzumab in the NCCTG N9831 and NSABP B-31 trials. The similar design of both trials allowed data from the control and trastuzumab-containing arms to be combined in a joint analysis.
RESULTS: At 3.9 years of median follow-up, there continues to be a highly statistically significant reduction in DFS event rate in favor of thetrastuzumab-containing arm ($P < .001$). Similarly, there continues to be a statistically significant 39% reduction in death rate in favor of thetrastuzumab-containing arm ($P < .001$).
CONCLUSION: These data demonstrate consistent DFS and OS advantages of adjuvant trastuzumab over time, with the longest follow-up reported to date. The clinical benefits continue to outweigh the risks of adverse effects.

8. Efficacy and cardiac safety of adjuvant trastuzumab-based chemotherapy regimens for HER2-positive early breast cancer (ABSTRACT).

BACKGROUND: Trastuzumab-based adjuvant therapy has become the standard of care for human epidermal growth factor receptor-2 (HER2)-positive early breast cancer (EBC). Both anthracycline- and non-anthracycline-containing trastuzumab regimens are approved in the United States, but cardiotoxicity is increased with anthracycline-containing regimens.
DESIGN: This paper reviews published and reported efficacy and cardiac safety data from the adjuvant trastuzumab trials [National Surgical AdjuvantBreast and Bowel Project (NSABP) B-31/North Central Cancer Treatment Group (NCCTG) N9831, Breast Cancer International Research Group (BCIRG) 006, Herceptin Adjuvant (HERA), FinHer, and Programme Adjuvant Cancer Sein (PACS) 04].
RESULTS: The addition of trastuzumab to adjuvant chemotherapy significantly improved disease-free survival (from 24% to 58%) in five of the six trials. Overall survival was significantly improved (23%-35%) in the large trials. In NSABP B-31/ NCCTG N9831, 5.0%-6.6% of patients who received doxorubicin and cyclophosphamide (AC) were unable to receive trastuzumab. Cardiac event rate was highest in the anthracycline-containingtrastuzumab arms (1.9%-3.8%) and lowest with the regimen of docetaxel, carboplatin, and trastuzumab (TCH) (0.4%).

CONCLUSIONS: Incorporation of trastuzumab into anthracycline and non-anthracycline adjuvant chemotherapy regimens has substantially improved outcomes in HER2-postive EBC. The TCH regimen has the lowest rates of cardiac dysfunction, but uncertainty exists regarding the relative efficacy of TCH compared with anthracycline-containing trastuzumab regimens. Cardiac risk factor assessment can aid in selection of trastuzumab-basedadjuvant therapy regimens.

9. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort (ABSTRACT)

BACKGROUND: The monoclonal antibody trastuzumab has survival benefit when given with chemotherapy to patients with early, operable, and metastatic breast cancer that has HER2 (also known as ERBB2) overexpression or amplification. We aimed to assess event-free survival in patients with HER2-positive locally advanced or inflammatory breast cancer receiving neoadjuvant chemotherapy with or without 1 year of trastuzumab.
METHODS: We compared 1 year of treatment with trastuzumab (given as neoadjuvant and adjuvant treatment; n=117) with no trastuzumab (118), in women with HER2-positive locally advanced or inflammatory breast cancer treated with a neoadjuvant chemotherapy regimen consisting of doxorubicin, paclitaxel, cyclophosphamide, methotrexate, and fluorouracil. Randomisation was done with a computer program and minimisation technique, taking account of geographical area, disease stage, and hormone receptor status. Investigators were informed of treatment allocation. A parallel cohort of 99 patients with HER2-negative disease was included and treated with the same chemotherapy regimen. Primary endpoint was event-free survival. Analysis was by intention to treat. This study is registered, number ISRCTN86043495.
FINDINGS: Trastuzumab significantly improved event-free survival in patients with HER2-positive breast cancer (3-year event-free survival, 71% [95% CI 61-78; n=36 events] with trastuzumab, vs 56% [46-65; n=51 events] without; hazard ratio 0.59 [95% CI 0.38-0.90]; p=0.013). Trastuzumab was well tolerated and, despite concurrent administration with doxo–rubicin, only two patients (2%) developed symptomatic cardiac failure. Both responded to cardiac drugs.
INTERPRETATION: The addition of neoadjuvant and adjuvant trastuzumab to neoadjuvant chemotherapy should be considered for women with HER2-positive locally advanced or inflammatory breast cancer to improve event-free survival, survival, and clinical and pathological tumour responses.

10. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer (ABSTRACT).

BACKGROUND: Trastuzumab, a recombinant monoclonal antibody against HER2, has clinical activity in advanced breast cancer that overexpresses HER2. We investigated its efficacy and safety after excision of early-stage breast cancer and completion of chemotherapy.
METHODS: This international, multicenter, randomized trial compared one or two years of trastuzumab given every three weeks with observation in patients with HER2-positive and either node-negative or node-positive breast cancer who had completed locoregional therapy and at least four cycles of neoadjuvant or adjuvant chemotherapy.
RESULTS: Data were available for 1694 women randomly assigned to two years of treatment with trastuzumab, 1694 women assigned to one year of trastuzumab, and 1693 women assigned to observation. We report here the results only of treatment with trastuzumab for one year or observation. At the first planned interim analysis (median follow-up of one year), 347 events (recurrence of breast cancer, contralateral breast cancer, second nonbreast malignant disease, or death) were observed: 127 events in the trastuzumab group and 220 in the observation group. The unadjusted hazard ratio for an event in the trastuzumab group, as compared with the observation group, was 0.54 (95 percent confidence interval, 0.43 to 0.67; $P<0.0001$ by the log-rank test, crossing the interim analysis boundary), representing an absolute benefit in terms of disease-free survival at two years of 8.4 percentage points. Overall survival in the two groups was not significantly different (29 deaths with trastuzumab vs. 37 with observation). Severe cardiotoxicity developed in 0.5 percent of the women who were treated with trastuzumab.
CONCLUSIONS: One year of treatment with trastuzumab after adjuvant chemotherapy significantly improves disease-free survival among women with HER2-positive breast cancer.

11. Safety and efficacy of the combination of trastuzumab with docetaxel for HER2-positive women with advanced breast cancer. A review of the existing clinical trials and results of the expanded access programme in the UK (ABSTRACT).

Trastuzumab is a humanised monoclonal antibody against the extracellular domain of HER2 (human epidermal growth factor receptor-2) that is overexpressed in about 25% of human breast cancers. It has shown clinical benefit in HER2-positive breast cancer cases when used alone or in combination with chemotherapy. Trastuzumab increases the response rate to chemotherapy and prolongs survival when used in combination with taxanes. In this article, we review the clinical trials where trastuzumab has been administered together with docetaxel, and we present the results of the trastuzumab expanded access programme (EAP) in the UK. Combination of trastuzumab with docetaxel results in similar response rates and time-to-progression with the trastuzumab/paclitaxel combinations. The toxicity of the combination and the risk of heart failure are low. The clinical data for the docetaxel/trastuzumab combination indicate a favourable profile from both the efficacy and the safety point of view and confirm

the feasibility and safety of trastuzumab administration both as monotherapy and in combination with docetaxel.

12. New biological therapies for breast cancer (ABSTRACT)

The exploitation of biological differences between normal and malignant cells is a logical approach to novel treatments for breast cancer. The potential targets for such therapy include the products of proto-oncogenes and oncogenes, inhibition of growth factor receptor signalling and the immunological exploitation of antigenic differences between normal and malignant cells. Monoclonal antibody technology was heralded as a potential 'magic bullet' for cancer therapy following its discovery in the mid-1970s, but it is only in the past few years that such technology has entered mainstream clinical practice. The humanised murine monoclonal antibody to HER2 (trastuzumab) has significant anti-tumour activity but with minimal toxicity, and has been licensed for use in patients with advanced breast cancer. A different approach has been the use of enzyme inhibitors to interfere with the signalling pathways downstream of growth factor receptors (e.g. farnesyl transferase inhibitors). It is likely that effective targets for such therapies will be identified in the next few years. There have been significant advances in our understanding of human immunology which have coincided with the identification of so-called tumour-associated antigens (TAA). These developments have resulted in a resurgence of interest in tumour immunotherapy. Peptides derived from these TAAs have been used to generate tumour-specific immune responses. An alternative strategy has been to immunise patients using viral vectors and plasmid cDNA encoding the TAA. In some studies, notably those in patients with advanced melanoma, significant clinical responses have been observed. Cell-based strategies including autologous tumour cell vaccines, allogeneic tumour cell vaccines and dendritic cell vaccines have been used, and significant responses have been reported in several studies. Few of these methods have so far been applied to breast cancer, but the possible benefits and drawbacks of such an approach will be discussed.

13. Update on HER-2 as a target for cancer therapy: herceptin in the clinical setting (ABSTRACT)

Herceptin is the first therapy for breast cancer which targets an oncogene product. This humanized antibody to HER-2 has been shown to have activity as a single agent in a phase II trial of heavily pre-treated patients with advanced breast cancer and, in phase III studies, its use with chemotherapy is associated with higher response rates, longer time to progression and improved survival when compared with chemotherapy alone. Retrospective analysis of data from these pivotal trials suggests that attributable benefit of herceptin is greater in those patients who express HER-2 at the highest levels, that is 3+ expression by immunohistochemistry. Further analysis also implies that cases which are positive for HER-2 by fluorescent in situ hybridization may also benefit from treatment regardless of whether they express HER-2 at the 2+ or 3+ level. Use of herceptin as first-line therapy for metastatic disease in early

studies suggest that response rates and clinical benefit rate similar to chemotherapy may be achievable and that survival using this sequential approach may not be compromized. Other combinations of herceptin and chemotherapy have been investigated with phase II data suggesting considerable activity with weekly taxol and when combined with navelbine. The non-linear pharmacokinetics of herceptin suggest that, as doses increased, half-life increases and may be feasible on a 3-weekly schedule. The role of herceptin in the adjuvant setting in the management of breast cancer will be tested in randomized studies of patients who express HER-2 at the highest levels; two of these studies have already begun.

14. HER-2 and choice of adjuvant chemotherapy in breast cancer (ABSTRACT).

The amplification or overexpression of HER-2 is a recognized prognostic marker that is associated with poor survival for patients with node-positive breast cancer. Several studies have demonstrated that HER-2 may serve to direct the selection of optimal adjuvant chemotherapy. This article provides a critical review of the studies that offer evidence for the role of HER-2 as a predictor of response to chemotherapy.

15. Overexpression of c-erbB2 is an independent marker of resistance to endocrine therapy in advanced breast cancer (ABSTRACT).

The present study investigated the interaction between c-erbB2 overexpression and the response to first-line endocrine therapy in patients with advanced breast cancer. The primary tumours of 241 patients who were treated at first relapse with endocrine therapy were assessed for overexpression of c-erbB2 by immunohistochemistry. c-erbB2 was overexpressed in 76 (32%) of primary breast cancers and did not correlate with any other prognostic factor. The overall response to treatment and time to progression were significantly lower in patients with c-erbB2-positive tumours compared to those that were c-erbB2-negative (38% vs 56%, $P = 0.02$; and 4.1 months vs 8.7 months, $P < 0.001$, respectively). In multivariate analysis, c-erbB2 status was the most significant predictive factor for a short time to progression ($P = 0.0009$). In patients with ER-positive primary tumours treated at relapse with tamoxifen ($n = 170$), overexpression of c-erbB2 was associated with a significantly shorter time to progression (5.5 months vs 11.2 months, $P < 0.001$). In conclusion, overexpression of c-erbB2 in the primary tumour is an independent marker of relative resistance to first-line endocrine therapy in patients with advanced breast cancer. In patients with ER-positive primary tumours, the overexpression of c-erbB2 defines a subgroup less likely to respond to endocrine therapy.

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