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ABCSG 28 / POSYTIVE

Study Title:
Primary **O**peration in **SY**nchronous me**T**astasized **I**n**V**asiv**E** breast cancer, a multicenter prospective randomized study to evaluate the use of local therapy

Protocol version 4.0 (06.09.20119

Involved Local Ethics committees and their approvals:

- Federal State Salzburg 27 October 2011
- Medical University Innsbruck 18 November 2011
- Federal State Upper Austria 12 January 2012
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- Medical University Graz 20 January 2012
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- Medical University Vienna 10 February 2012
- Federal State Carinthia February 2012

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A Study conducted by the
Austrian Breast & Colorectal Cancer Study Group (ABCSG)

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Sponsor and Coordination

AUSTRIAN BREAST & COLORECTAL CANCER STUDY GROUP
ABCSG Trial Office office@abcsg.at
Nussdorfer Platz 8, A-1190 Vienna, Austria T: +43 1 408 92 30

Academic project directors

Univ. Prof. Dr. Florian Fitzal florian.fitzal@meduniwien.ac.at
Univ. Prof. Dr. Michael Gnant michael.gnant@meduniwien.ac.at
Dept. of Surgery - Division of General Surgery T: +43 1 40400/5621

Univ. Prof. Dr. Günther Steger guenther.steger@meduniwien.ac.at
Dept. of Internal Medicine I/Division of Oncology T: +43 1 40400/5459

Medical University Vienna
Währinger Gürtel 18-20
A-1090 Vienna, Austria

Coordinating Investigator

Univ. Prof. Dr. Florian Fitzal
Medical University Vienna – Dep Surgery

Experts of the trial

Prim. Univ. Prof. Dr. Richard Greil r.greil@salk.at
Paracelsus University Salzburg - St. Johanns-Spital T: +43 662 4482/2879
Head of Dept. of Internal Medicine III/Division of Oncology
Müllner Hauptstraße 48, A-5020 Salzburg, Austria

Univ. Prof. Dr. Hellmut Samonigg hellmut.samonigg@meduni-graz.at
Medical University Graz T: +43 316 385/3115
Dept. of Internal Medicine/Division of Oncology
Auenbruggerplatz 15, A-8036 Graz, Austria

Univ. Prof. Dr. Christian Marth christian.marth@uklibk.ac.at
Medical University Innsbruck christian.marth@i-med.ac.at
Head of Department of Gynecology T: +43 512 504/23051
Innrain 52, A-6020 Innsbruck, Austria

OA Dr Marija Balic Marija.Balic@klinikum-graz.at
Medical University Graz T: +43 316 385/3115
Dept. of Internal Medicine/Division of Oncology
Auenbruggerplatz 15, A-8036 Graz, Austria

OA Dr Vesna Bijelic -Radisic Vesna.Bjelic-Radisic@klinikum-graz.at
Medical University Graz T: +43 316 385/0
Dept. of Gynecology
Auenbruggerplatz 15, A-8036 Graz, Austria

Signatures

Study title: Primary Operation in SYnchronous meTastasized InVasivE breast cancer, a multicenter prospective randomized study to evaluate the use of local therapy

Protocol Number: ABCSG 28 / POSYTIVE

Academic project directors:

[+ Coordinating Investigator]

Florian Fitzal, Prof. MD
Medical University of Vienna
Dept. of Surgery – Division of General Surgery
Währinger Gürtel 18-20, A-1090 Vienna
Phone: +43 1 40400 5621
Fax: +43 1 40400 5641
Email: florian.fitzal@meduniwien.ac.at

Date

Michael Gnant, Prof. MD
Medical University of Vienna
Dept. of Surgery – Division of General Surgery
Währinger Gürtel 18-20, A-1090 Vienna
Phone: +43 1 40400 5646
Fax: +43 1 40400 7603
Email: michael.gnant@meduniwien.ac.at

Date

Günther Steger, Prof. MD
Medical University of Vienna
Dept. of Internal Medicine I - Oncology
Währinger Gürtel 18-20, A-1090 Vienna
Phone: +43 1 40400 5459
Fax: +43 1 40400 6081
Email: guenther.steger@meduniwien.ac.at

Date

Biostatistics:

Christian Fesl, PhD
ABCSG Senior Statistician
Phone: +43 1 408 92 30 - 27
Fax: +43 1 409 09 90
Email: christian.fesl@abcsg.at

Date

Investigator`s Agreement

I have read the preceding protocol *entitled "Primary Operation in SYnchronous meTastasized InVasivE breast cancer, a multicenter prospective randomized study to evaluate the use of local therapy*", and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice (ICH-GCP), Declaration of Helsinki, applicable European Union Guidelines and national regulations.

I agree to ensure that Financial Disclosure Statements will be completed by

- myself and/or
- my sub investigators

before study initiation or during the study if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without prior written consent of ABCSG.

_____ _____

Signature Date

_____

Name of Investigator (in capital letters or typewrite)

Study Summary

Title

Primary Operation in SYnchronous meTastasized InVasivE breast cancer, a multicenter prospective randomized study to evaluate the use of local therapy

Objective

The primary objective is to evaluate the median survival of patients with synchronous metastasized breast cancer and the primary tumor in place comparing arm A with local therapy to the primary tumor versus arm B without local therapy.

The secondary objectives are to evaluate time to distant and local progression as well as in pre-selected centers circulating tumor cells and growth factors in the peripheral blood within the two groups.

Studydesign

This study is a prospective, randomized, multicenter study concerning the influence of local treatment on patients with synchronous metastasized breast cancer. Patients will be stratified at inclusion according to the geographic region, the hormone-receptor status (ER-/PR-/not determinable; any PR and/or ER+), the HER-2 status (positive vs. negative/not determinable), the grading (G1/G2/not determinable vs. G3), location of metastases (visceral ± vs bone only) and use of first line therapy (anthracyclin-based ± any other, except taxan, vs. taxan-based ± any other vs. other therapies, e.g. antihormonal therapy alone). Thereafter patients will be randomly assigned to receive either local therapy of the breast (lumpectomy or mastectomy + axillary surgery /± radiotherapy) versus no local therapy. Surgery of the metastases is not allowed in both treatment regimens and may only be performed on demand. This will be considered as protocol deviation. Systemic therapy will be administered at the centers policy.

Treatment regimens

Therapy arm A, surgical therapy

Local therapy consists of lumpectomy or mastectomy with or without radiotherapy (according to center tumorboard decision) with a resection free margin of at least 1 mm or more demonstrated on paraffin embedded histological sections. Intraoperative frozen sections are allowed but not definitive for margin assessment. For axillary surgery, either axillary dissection level I and II or sentinel node biopsy has to be performed (mandatory) which has only to be followed by axillary dissection in case of macrometastasis of at least one sentinel lymph node..

Therapy arm B, surgery on demand

In arm B (no local therapy) it may be necessary to perform local therapy on demand (surgery, radiotherapy). Reasons may be uncontrolled bleeding or infected exulcerations with a septic component and no treatment benefit from conservative therapy. This will be considered as protocol deviation. However, the patient's follow up is recorded and data are available for analyses as intention to treat.

Radiation therapy

Local radiation therapy of the breast may be given according to center policy in therapy arm A. Radiation therapy of the metastases is allowed according to center policy in both arms.

Systemic therapy

Chemotherapy or anti-hormone therapy is used according to center policy. The following recommendations should be followed:

1. In cases of radiotherapy and chemotherapy (arm A), radiotherapy should not be given later than 6 months after surgery. Radiotherapy is allowed in parallel to anti-hormonal treatment.
2. In premenopausal patients anti-hormonal treatment - if indicated - should always be coupled with ovarian ablation (surgical resection or systemic endocrine treatment, e.g. with goserelin) to ensure complete hormonal blockade.
3. In postmenopausal patients the primary anti-hormonal treatment - if indicated - should be an aromatase inhibitor (if there are no contraindications).
4. Chemotherapy – if indicated - should precede anti-hormonal treatment – if indicated.

Number of patients

254 patients (127 in each group) including a drop out rate of 5%

Inclusion and exclusion criteria

Females whose conditions satisfy all of the following criteria are the only patients eligible for this study.

General inclusion criteria

1. Written informed consent must be obtained and documented prior to beginning any protocol specific procedures and according to local regulatory requirements.
2. Patients age ≥ 18 years
3. Eastern Cooperative Oncology Group Performance Status is 0 -2 (Appendix 3)
4. Able to comply with the protocol requirements during the treatment and follow-up period.

Disease specific inclusion criteria

5. Untreated synchronous metastasized invasive carcinoma of the breast with the primary tumor in situ (bilateral synchronous metastasized breast cancer patients are eligible).
6. The primary tumor must be identified and may be any size, however, primary resection with resection free margins must be possible.
7. Invasive adenocarcinoma of the breast on histological examination.
8. The metastatic site must be identified by radiological assessment (Computer Tomography of the chest and the abdomen OR ultrasound and chest x ray for visceral metastases; bone scan AND/OR computer tomography AND/OR magnetic resonance for bone metastases). A biopsy is not necessary.

Exclusion criteria

1. Patients in whom a R0 resection (microscopic free margins) is clinically questionable
2. Inflammatory cancer
3. Patients with brain metastases
4. Patients who are not eligible for general anesthesia and operations
5. Patients without metastatic breast cancer (patients with a tumor marker value (CEA, CA15-3) above normal levels without the radiological proven evidence of metastases are not eligible for the study)
6. Patients with a second untreated malignancy
7. Any previous malignancy treated with curative intent and the patient has not been disease-free for 5 years – exceptions are:
    a. carcinoma in situ of the cervix
    b. squamous carcinoma of the skin
    c. basal cell carcinoma of the skin
8. Patients with any recurrent cancer disease
9. Pregnant or lactating women
10. Patients are not allowed to be part of another local therapy trial

Stratification

- Geographic region
- Grading
    - G1/G2 **versus** G3/GX
- Receptor status
    - 0/0 **versus** any positive
- Her2neu status
    - FISH amplified/IHC+++ **versus** negative
- Location of metastases
    - visceral ± **versus** bone only
- Planned first line therapy
    - Anthracycline-based ± any other except taxane **versus** taxane-based ± any other **versus** any other therapy

Efficacy evaluation

Median survival
Time to local progression
Time to distant progression
Circulating tumor cells and growth factors in pre-selected centers
Quality of life

Timetable

Planned start date	Q1/10
Planned end enrollment date	Q1/14
Expected follow up end date	Q1/19

Introduction

Background and preliminary data

Overall survival for patients with metastasized breast cancer (stage IV) is limited. Most recent data report about a median survival between 11 and 23 months depending on prognostic factors and systemic therapy [1-6]. As cancer cells have already spread throughout the systemic circulation in stage IV breast cancer disease it is generally believed that systemic therapy may be the only life prolonging treatment. Even in stage I and II breast cancer patients more aggressive local therapy did not improve overall survival [7,8].

Recently a meta-analysis by the Early Breast and Colorectal Trial Collaborative Group (EBCTCG) in 2002 updated in 2005 has shown that the prevention of local recurrence by local therapy significantly correlates with an improvement in overall survival in stage I and II breast cancer patients [9] suggesting an important role of local therapy for overall survival. The first clinical evidence that local therapy may be of benefit in stage IV disease arises from renal-cell cancer patients. Case reports about metastasis shrinkage after primary tumor resection in renal-cell cancer patients were followed by two randomized trials demonstrating that removal of the primary tumor in metastasized renal-cell cancer significantly improved survival [10,11].

Regarding stage IV breast cancer patients Khan et al [4] evaluated 9162 patients accounting for 4.1% of all breast cancer patients entered into the National Cancer Data Base (NCDB) between 1990 and 1993. 43% had systemic treatment only while 57% underwent additional local surgery due to salvage treatment, patients wish or local complications. Local therapy consisted of partial or total mastectomy with or without axillary surgery. The use of radiotherapy has not been evaluated due to lack of data. Patients with surgical removal of the primary tumor had a significant increased 3-year survival rate (17% vs. 35%) with a hazard ratio of 0.61. Similar the Geneva Cancer Registry report from Rapiti et al [5] demonstrated a 40% reduced risk of death with the surgical removal of the primary tumor in 300 stage IV breast cancer patients. A significant improvement in progression free survival by this treatment has been demonstrated in 224 patients with stage IV breast cancer at the MD Anderson Cancer Center [1] and Blanchard et al [2] suggested a significant increase in median survival from 17 to 27 months for the surgical removal of the primary in 427 stage IV breast cancer patients at the Baylor College of Medicine. A retrospective analysis of the Surveillance, Epidemiology and End Results (SEER) program data of 9734 patients also demonstrated a 37% improvement for overall survival in patients with stage IV breast cancer and removal of the primary tumor [6]. These data together strongly suggest an important role for local therapy in stage IV cancer disease. However, this has to be proven in prospective studies. More over the reason for a life extending role of local therapy in metastasized patients is unclear.

Theoretically there are some unproven speculative explanations. The primary tumor may act as a source for ongoing systemic spreading of chemoresistant cancer cells (circulating tumor cells, stem cells) [12-15] or metastases proliferation factors (TGFbeta [16-18], VEGF [19-24]) supporting systemic tumor growth and further metastases proliferation. Resection of the primary tumor may thus down regulate the constant release of circulating tumor cells/stem cells and/or proliferating factors [25,26] reducing the capacity to produce new metastases and decreasing proliferation of metastases.

The reduction of chemoresistant systemic stem cells by resection of the primary tumor may render metastatic cells chemosensitive. Clinically there is evidence that resection of the primary tumor may enhance the response to systemic therapy [11,27,28]

Hypothesis

We first hypothesize that the removal of the primary tumor in stage IV breast cancer patients followed by systemic therapy improves median survival compared with no local therapy. In case that this main thesis proves true we secondly hypothesize that the ultimate reason for the improved survival by local therapy may be due to the reduction of stem cells or circulating proliferation factors such as VEGF or TGF beta in the peripheral system as these cells and factors may origin from the primary cancer. This may reduce metastatic growth kinetics and increase chemosensitivity of visceral and non-visceral metastases and prolong median and progression free survival.

Aim

The aim of the study is to investigate the effect of local therapy to the primary tumor in synchronous metastasized breast cancer patients and to evolve the role of circulating tumor cells and growth factors in the peripheral blood.

Study objectives

The primary study objective is

1. to demonstrate that the resection of the primary breast cancer in synchronous metastasized breast cancer patients increases the median survival.

The secondary study objectives are

1. to investigate the role of the primary breast cancer resection in terms of local and distant time to progression
2. to evaluate the role of peripheral circulating tumor cells and growth factors in synchronous metastasized breast cancer patients and whether there is any association between their detection and the median survival in pre-selcted centers
3. to examine whether the resection of the primary breast cancer influences peripheral circulating tumor cells and growth factors in pre-selcted centers
4. to investigate the quality of life in both groups

Patients

Sample Size Considerations

A sample of 254 patients will be enrolled in this trial (127 in each group) including a drop out rate of 5%. This assumes that there will be a 48-month accrual period. The median survival of patients with local therapy to the primary tumor should be increased by 50% in comparison to patients without local therapy to have 80% power to detect a hazard ratio of 0.666 with a two-sided significance level of 0.05. The recruitment period is assumed with 4 years. The maximum study duration should be 9 years.

Study design (Appendix 1)

This is a prospective multicenter national randomized study. Patients with a histological verified breast cancer are first screened for any metastatic disease. In cases of visceral or non visceral metastatic spreading (International Union against Cancer UICC M1 = stage IV; Appendix 2) the patient is eligible for the study taking into consideration all inclusion and exclusion criteria listed below. After signed informed consent the patient is randomized to either arm A (local treatment) or Arm B (no local treatment, only on demand). In arm A therapy consists of either breast conserving surgery or mastectomy. For axillary surgery, either axillary dissection level I and II or sentinel node biopsy has to be performed (mandatory) which has only to be followed by axillary dissection in case of macrometastasis of at least one sentinel lymph node, followed by radiotherapy (on centers preference). Surgery of the metastases is not allowed in both treatment arms and may only be performed on demand. This will be considered as protocol deviation. Systemic therapy follows surgery on the centers preference. In arm B only systemic therapy is given on the centers preference. Follow up should be done every 3 months during the first 2 years and from then on every 6 months and should include clinical, radiological and laboratory exams. The median survival is the primary endpoint, while the time to local or distant progession are definded as secondary endpoints.

Additional we measure circulating tumor cells and growth factors in the peripheral blood at pre-selcted centers. Therefore 15ml of blood are drawn before surgery and 1-3 days after surgery (arm A only), as well as before first application of systemic therapy, 3-6 months and 12 months after first application of systemic therapy in both arms.

Quality of life questionnaires are handed out to all patients before surgery or first application of systemic therapy as well as every 6 months after enrollment until 42 months visit.

Inclusion and Exclusion Criteria

Females whose conditions satisfy all of the following criteria are the only patients eligible for this study.

General inclusion criteria

1. Written informed consent must be obtained and documented prior to beginning any protocol specific procedures and according to local regulatory requirements.
2. Patients age ≥ 18 years
3. Eastern Cooperative Oncology Group Performance Status is 0 -2 (Appendix 3)
4. Able to comply with the protocol requirements during the treatment and follow-up period.

Disease specific inclusion criteria

5. Untreated synchronous metastasized invasive carcinoma of the breast with the primary tumor in situ (bilateral synchronous metastasized breast cancer patients are eligible).

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1. Patients in whom a R0 resection (microscopic free margins) is clinically questionable
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6. Patients with a second untreated malignancy
7. Any previous malignancy treated with curative intent and the patient has not been disease-free for 5 years – exceptions are:
    a. carcinoma in situ of the cervix
    b. squamous carcinoma of the skin
    c. basal cell carcinoma of the skin
8. Patients with any recurrent cancer disease
9. Pregnant or lactating women
10. Patients are not allowed to be part of another local therapy trial

Stratification

- Geographic region
- Grading
    - G1/G2 **versus** G3/GX
- Receptor status
    - 0/0 **versus** any positive
- Her2neu status
    - FISH amplified/IHC+++ **versus** negative
- Location of metastases
    - visceral ± **versus** bone only
- Planned first line therapy
    - anthracyclinebased ± any other except taxane **versus** taxane based ± any other versus any other therapy

Outcome measurements and statistical analyses

Primary Endpoint

Median survival

Median survival of both groups (Arm A local therapy and Arm B no local therapy) will be compared. Patients are evaluated as intention to treat (thus, patients with surgery on demand are on group B). The median survival is the time point at which 50% of all randomized patient died. For this primary endpoint, the *2-sided log-rank* test

(unstratified) will be used to test for differences between local therapy versus no local therapy at an overall alpha level of 5%. A stratified version of the 2-sided log-rank test will be performed with the stratification factors used for randomization except geographic region. Kaplan-Meier curves and estimates will be provided for each treatment group. Potential confounding effects of the impact of other variables (grading, age, her2-neu expression and so on) will be assessed with the *multiple Cox-Regression analysis*. Data analysis for the primary endpoint is performed on an intention-to-treat basis (ITT). The ITT population includes all randomized subjects who withdraw informed consent and the permission to use their data collected by then. All subjects will be analyzed according to the treatment to which they have been randomized. Subjects who terminate the study before their scheduled final study visits will be censored.

Sample size considerations:

The sample size calculation is based on the following assumptions:

- 4 years recruitment period and a maximum study duration of 9 years
- Control Arm – systemic therapy alone: median survival is 24months
- Experimental Arm – surgery plus systemic therapy: median survival is 36 months (assuming a hazard ratio of 0.666 compared to arm A)
- Overall alpha level of 5% and a power of 80%
- One interim analyses when 50% of the total number of events (death) have occurred

Based on these assumptions and taking into consideration a potential drop-out rate of 5%, 254 patients (127 in each treatment arm) need to be enrolled in order to observe 192 events which should be sufficient to yield 80% power for a two-sided log-rank test at an overall alpha level of 5%.

In order to control the overall type one error at the 5% level, the interim analyses will follow a Lan-DeMets alpha spending approach, using an O'Brien-Fleming boundary function. According to this approach, the study will be stopped after 50% of the total number of events (96 events) due to efficacy (median survival in experimental arm greater than in the control arm) or due to futility (median survival in experimental arm less than in the control arm) at a 2-sided alpha = 0.00306.

Secondary endpoints

Time to distant progression (TTPd)

Time to treatment change due to systemic progression.

Time to local progression (TTPl)

Increase in size >25% of the primary tumor in arm B (no local therapy).
Local recurrence in arm A (local therapy).

For the secondary endpoint, TTPd and TTPl, the *2-sided log-rank test* (unstratified) will be used to test for differences between local versus no local therapy at an overall alpha level of 5%. A stratified version of the 2-sided log-rank test will be performed

with the stratification factors used for randomization except geographic region. Kaplan-Meier curves and estimates will be provided for each treatment group. The multiple analysis will be conducted with a *Cox regression model*. The local recurrence in arm A (local therapy) will be assessed with *univariate and multiple logistic regression analysis*.

Reduction of growth factors, circulating tumor cells, stem cells in pre-selected centers

For the secondary endpoint growth factors, circulating tumor cells, stem cells, post intervention measurements are compared with baseline values and tested with the *repeated measures ANOVA*. Correlations between initial or late drop of growth factors, circulating tumor cells, stem cells and median survival or TTP, respectively, will be calculated with the *Spearman rank order* correlation test. The stem cell and growth factors in the tumor will be correlated with the stem cell and growth factor release into the peripheral circulation and known prognostic factors such as her2neu expression and grading as well as survival time. The association with her2neu expression and grading and categorical variables will be assessed by an *ANOVA*. The association with the survival time will be analysed with a *Cox regression*.

Surgical Therapy

Local therapy consists of lumpectomy or mastectomy with a resection free margin of at least 1 mm or more demonstrated on paraffin embedded histological sections. Intraoperative frozen sections are allowed but not definitive for margin assessment. For axillary surgery, either axillary dissection level I and II or sentinel node biopsy has to be performed (mandatory) which has only to be followed by axillary dissection in case of macrometastasis of at least one sentinel lymph node.

Surgery on demand

In the arm B (no local therapy) it may be necessary to perform local therapy on demand (surgery, radiotherapy). Reasons may be uncontrolled bleeding or infected exulcerations with a septic component and no treatment benefit from conservative therapy. This will be considered as protocol deviation. However, the patient's follow up is recorded and data are available for retrospective analyses as intention to treat.

Radiation therapy

Local radiation therapy of the breast may be given according to center policy in therapy arm A. In arm B this will be considered as protocol deviation. Radiation therapy of the metastases is allowed according to center policy in both arms.

Systemic therapy

Chemotherapy or anti-hormone therapy is used according to center policy. The following recommendations should be followed:

1. In cases of radiotherapy and chemotherapy (arm A), radiotherapy should not be given later than 6 months after surgery. Radiotherapy is allowed in parallel to anti-hormonal treatment.
2. In premenopausal patients anti-hormonal treatment - if indicated - should always be coupled with ovarian ablation (surgical resection or systemic endocrine treatment, e.g. with goserelin) to ensure complete hormonal blockade.

3. In postmenopausal patients the primary anti-hormonal treatment - if indicated - should be an aromatase inhibitor (if there are no contraindications).
4. Chemotherapy – if indicated - should precede anti-hormonal treatment – if indicated.

Follow up (Appendix 4)

Routine laboratory tests for safety assessment of palliative systemic therapy and radiological follow up are performed according to the centers' guidelines with the recommended procedures as follows:

- Clinical examination and laboratory tests (red and white blood cells, Tumor marker CA15-3 and CEA) before and every 2-4 months after randomization. After two years examinations should be done every 5-7 months.
- CT scan of the liver and the lung before and every 2-4 months after randomization. Alternatively a PET-CT scan can be performed. Ultrasound of the liver or chest X-ray is only recommended in cases of contraindication for CT. After two years examinations should be done every 5-7 months.
- CT scan or alternatively PET-CT scan of bone metastases (if diagnosed) before and in case of pre-randomization diagnosed bone metastases every 2-4 months after randomization or in case of suspect new bone metastases anytime after randomisation for diagnostic imaging. After two years examinations should be done every 5-7 months.
- EORTC QLQ-C30 and QLQ-BR23 quality of life (Appendix 5) sheets before and every 6 months after treatment until 24 months visit, then every 12 months until 48 months visit.

Blood specimens in pre-selected centers (Appendix 6)

15ml of blood are drawn before surgery and 1-3 days after surgery (arm A only), as well as before first application of systemic therapy, 3-6 months and 12 months after first application of systemic therapy in arm A and arm B.

Tissue specimens in pre-selected centers

Tumor tissue from core needle biopsies before systemic therapy (arm B no local therapy group) or from surgical resections (arm A local therapy group) are used for further immunhistochemical and flow cytometry analyses. Only in pre-selected centers with experimental background.

Measurements of VEGF and TGF beta in pre-selected centers

Blood

Blood (7.5 ml) is drawn into pre-chilled CTAD-tubes, kept on ice and further processed within 30 min: After an initial centrifugation step at 1000 x g and 4ºC for 10 min, plasma is transferred to microtubes and subjected to further centrifugation at 10000 x g and 4ºC for 10 min (to remove "contaminating" platelets). The supernatant is stored in aliquots at -70ºC to avoid repeated cycles of freezing / thawing prior to analysis. Samples are transported to the University of Vienna surgical research laboratories for further examinations immediately under dry ice. Plasma samples are

analyzed in duplicate by ELISA to determine the concentration of circulating angiogenic factors. Commercially available ELISA tests are applied for VEGF-A, -C, -D (*Quantikine*, R&D Systems, Minneapolis, MN) and TGF-beta,-beta 1,-beta 2 and-beta 3 (R&D System).

Tumor

Specimens from core needle biopsies (arm B) or surgical resected tumors (arm A) are fixed in formaldehyde and sent to the Medical University of Vienna together with the plasma samples. Thereafter blocks are stained with anti-VEGF and anti-TGF beta (R&D Systems) for immunhistochemistry and paraffin blocks are analysed.

Assessment of circulating tumor cells (CTC) and breast cancer stem cells in pre-selected centers

Blood

Peripheral blood (7.5 ml) will be drawn in EDTA-tubes to which a cell preservation solution is added. Probes are shipped to the Medical University of Vienna right away at 4°C. The cells are subjected to immunostaining with appropriate isotype controls or a set of antibodies for evaluation of CTCs (anti-human $CK8^+$, 18^+ and 19^+ and $CD45^-$) or breast cancer stem cells (anti-human ESA^+ $CD44^+$ $CD24^-$ $lineage^-$) within 72 hours. Lineage markers antibodies are anti-CD2, -CD3, -CD10, -CD16, -CD18, -CD31, -CD64, -CD140b. Samples will be analyzed with an EPICS XL-MCL flow cytometer and with acquisition of at least 100000 cells per sample to yield an informative number of events for CTCs (anti-human $CK8^+$, 18^+ and 19^+ and $CD45^-$) and endothelial progenitors ($CD3^-$, $CD19^-$, $CD33^-$, KDR^+, $CD133^+$).

Tumor

Tumor specimens are minced and kept in RPMI medium 1640 under sterile conditions for a maximum of 72 hours. During that time, specimens are shipped to the Medical University of Vienna together with other specimens. Thereafter the tumor pieces are mixed with ultra-pure collagenase III in medium 199 and allowed to incubate at 37°C for 3-4 hours. After incubation, cells are filtered through a 46µl nylon mesh and washed with RPMI/20% FSB, then washed twice with HBSS. Cell are counted and transferred to a 5 ml tube, washed with HBSS and HICS and incubated with Sandoglobin solution for 10 min. After another washing step with HBSS and HICS, antibodies are added. The antibodies are the same as for blood specimen.

Stopping rules (End of Study)

1. Withdrawal of informed consent
2. Death
3. Lost to Follow Up

Risks and Benefits for the patients

Risk of biopsy

Core needle biopsies are routinely performed to preoperatively diagnose breast cancer. Morbidities are bleeding or infections which usually may be treated conservatively. Cell seeding has been demonstrated but the clinical impact is only minor [29].

Risk of blood withdraw

Usually there are no complications with venous blood withdraw, however, a thrombophlebitis or local pain and red skin may result from this invasive diagnostic procedure. The risk is between 1 and 5%. Local cooling packs and sometimes antibiotics and bandages may be necessary to reduce the pain and the infection.

Risks of local treatment

The main risk for the patient is for women in the treatment group A (local therapy) who undergo operation under general anesthesia. In general the local treatment (surgical removal of the primary tumor) has been done throughout more than 100 years in metastasized and non-metastasized patients with excellent results. Recently El-Tamer et al published morbidity and mortality rates of mastectomy and lumpectomy in 3107 patients [30].

30-day mortality was 0 – 0.24% and 30-day morbidity was between 1.8 and 5.7% showing higher numbers for mastectomized patients. The highest morbidity rate was due to superficial wound infections with 3% in the mastectomy group. Wound infection was associated with adipositas (BMI >30). Sever events such as cardiac arrest or pulmonalembolia were seen in 0.06% or 0.24%, respectively. Thrombophlebitis and systemic infections have been seen in 0.07 – 0.24% and 0.07 - 0.3%, respectively. Acute renal insufficiency has been observed in 0.06% of patients undergoing mastectomy.

Bleedings as well as seroma productions are rare and may be observed in 1 to 2% of patients. Most bleedings and hematoma formations may be treated conservatively while only a minority may need to undergo a second operation.

There is, however, a small risk to need a second operation due to positive resection margins. This risk is reduced by the use of intraoperativen frozen section analyses to 6% (Fitzal et al; data submitted).

Benefit for the patients

The benefit for the patient may be a 10% absolute increase in median survival from 24 to 36 months. More over if the hypothesis is true that the resection of the primary tumor in metastasized patients increases overall survival, the knowledge about carcinogenesis increases substantially. If we are able to demonstrate that circulating tumor cells and/or growth factors released from the primary tumor may be at least in part responsible for this improvement, the doors are open to investigate new therapeutic strategies in these patients such as anti-growth factor antibodies or systemic therapies destroying tumor stem cells. No trial has been published so far answering these important questions which may, in fact, guide us to new aspects of cancer therapy.

ADMINISTRATIVE REQUIREMENTS

Good Clinical Practice

- The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected.

Ethical Considerations

- The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (see Appendix 5). The IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients.

Patient Information and Informed Consent

The principal investigators at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained prior to undertaking any trial-related procedure which is not part of the routine clinical management of the patient (i.e. would not be indicated outside the study).

Additionally all consent forms have to be signed and dated by the investigator or authorised delegate. If the patient is unable to read or write, the consent forms should be signed and dated by the investigator and an independent witness, to indicate that the patient apparently understood the information and consented freely.

The written subject information must not be changed without prior release by ABCSG and the approval by IRB/IEC.

The principal investigator(s) must store the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

Patient data protection

The Informed Consent Form will incorporate wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, patients will authorise the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The Informed Consent Form will explain that study data will be stored electronically, maintaining confidentiality in accordance with national data legislation. All data computer processed by ABCSG will be identified by randomization code / study code.

The Informed Consent Form will also explain that for data verification purposes, authorized representatives of ABCSG, a regulatory authority, an IEC may require direct access to parts of the hospital or practice records relevant to the study, including patients' medical history.

Data management

Data management is carried out by ABCSG by the use of the MACRO, InferMed's web based electronic data collection system for clinical trials. MACRO has been designed to support the requirements of internationally recognised ICH Good Clinical Practice and FDA 21 CFR Part 11.

On-site Monitoring

The ABCSG Monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol, completeness, accuracy and consistency of the data and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries in the eCRF.

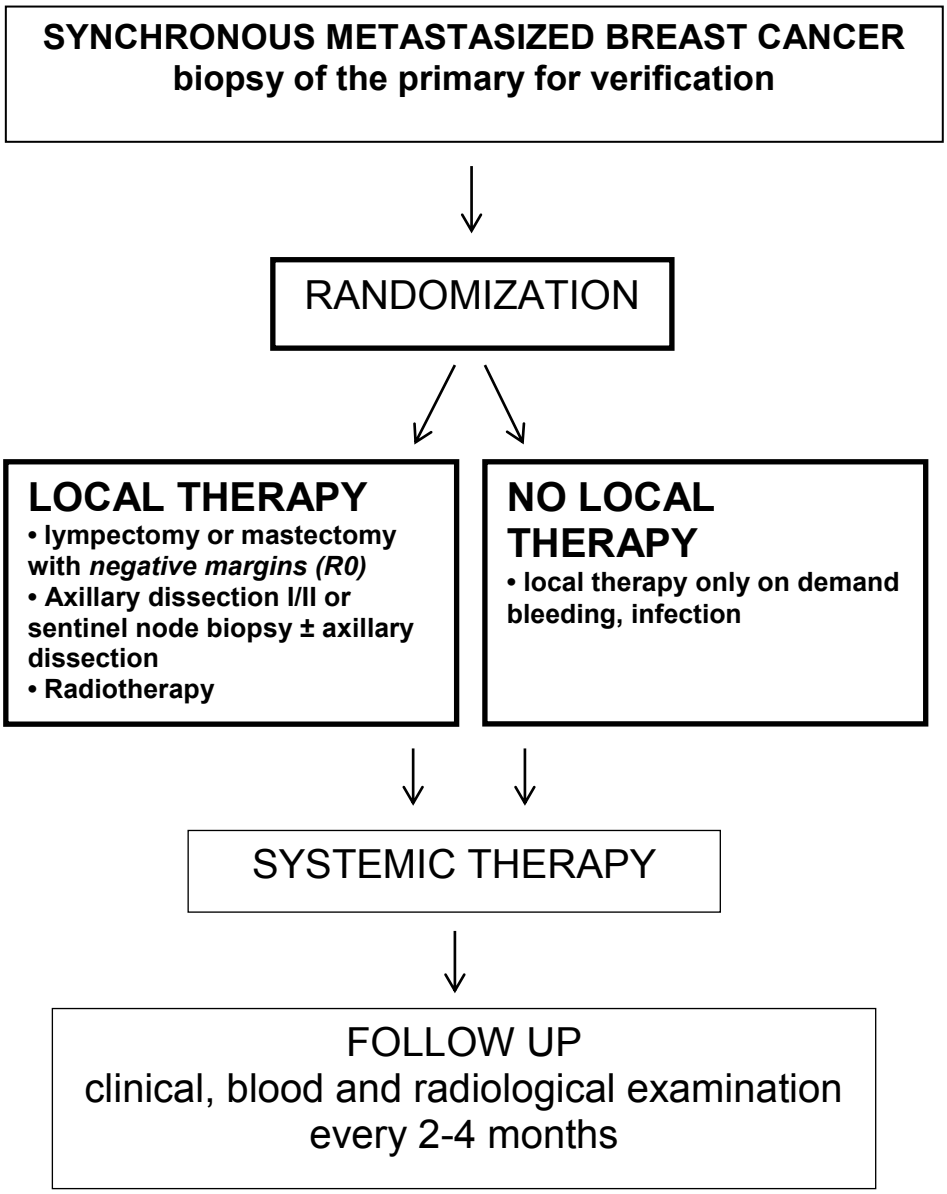
Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 2004), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Appendix 1: Flow chart randomization and groups

Flow chart randomisation and groups



Appendix 2: Union against cancer (UICC 1987) breast cancer stages

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II			
Stage IIa	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIb	T2	N1	M0
	T3	N0	M0
Stage III			
IIIa	T3	N1	M0
	T1,T2,T3	N2	M0
IIIb	T4	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

Appendix 3: Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	**ECOG**
0	**Fully active, able to carry on all pre-disease performance without restriction**
1	**Restricted in physically strenuous activity but ambulatory and able to carry out work of light or sedentary nature, e.g., light house work, office work**
2	**Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours**
3	**Capable of only limited self-care, confined to bed of chair more than 50% of waking hours**
4	**Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair**
5	**Dead**

Oken et al Am J Clin Oncol 5:649-655, 1982

Appendix 4: Follow up Flowchart

recommended Assessments & Investigations	YEAR 1				YEAR 2				YEAR 3		YEAR 4		YEAR 5		RELAPSE/ PROGRESSION
Months (±1 month)	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	
History and Clinical Examination															
Intercurrent Medical History	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
General and Physical Examination	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Quality of Life		•		•		•		•		•		•			
Laboratory (incl CEA, CA 15-3)	**According to systemic therapy but at least every 2-4 months**								**every 5-7 months**						
Imaging															
Breast Imaging (check guidance)	(○)	(○)	(○)	•	(○)	(○)	(○)	•	(○)	•	(○)	•	(○)	•	•
CT[1] Thorax/Abdomen (US/chest X-ray)	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Bone Imaging	**In cases of *pre-randomized diagnosed bone metastases* every 2-4 months, in case of *suspected* bone metastases for staging**								**In cases of *pre-randomized diagnosed bone metastases* every 5-7 months, in case of *suspected* bone metastases for staging**						•
Pregnancy Test [2]	in pre/perimenopausal women according to local policy														

[1] Alternatively a PET-CT scan can be performed
[2] Pregnancy tests have to be performed in pre/perimenopausal women during screening phase and at regular intervalls throughout the trial according to local policy

Appendix 5: EORTC QLQ-C30 (version 3.0), QLQ BR 23

GERMAN

EORTC QLQ-C30 (version 3.0)

Wir sind an einigen Angaben interessiert, die Sie und Ihre Gesundheit betreffen. Bitte beantworten Sie die folgenden Fragen selbst, indem Sie die Zahl ankreuzen, die am besten auf Sie zutrifft. Es gibt keine "richtigen" oder "falschen" Antworten. Ihre Angaben werden streng vertraulich behandelt.

Bitte tragen Sie Ihre Initialen ein: _ _ _ _

Ihr Geburtstag (Tag, Monat, Jahr): _ _ _ _ _ _ _ _

Das heutige Datum (Tag, Monat, Jahr): 3 1 _ _ _ _ _ _ _ _

		Überhaupt nicht	Wenig	Mäßig	Sehr
1.	Bereitet es Ihnen Schwierigkeiten sich körperlich anzustrengen (z.B. eine schwere Einkaufstasche oder einen Koffer zu tragen?)	1	2	3	4
2.	Bereitet es Ihnen Schwierigkeiten, einen längeren Spaziergang zu machen?	1	2	3	4
3.	Bereitet es Ihnen Schwierigkeiten, eine kurze Strecke außer Haus zu gehen?	1	2	3	4
4.	Müssen Sie tagsüber im Bett liegen oder in einem Sessel sitzen?	1	2	3	4
5.	Brauchen Sie Hilfe beim Essen, Anziehen, Waschen oder Benutzen der Toilette?	1	2	3	4

Während der letzten Woche:

		Überhaupt nicht	Wenig	Mäßig	Sehr
6.	Waren Sie bei Ihrer Arbeit oder bei anderen tagtäglichen Beschäftigungen eingeschränkt?	1	2	3	4
7.	Waren Sie bei Ihren Hobbys oder anderen Freizeitbeschäftigungen eingeschränkt?	1	2	3	4
8.	Waren Sie kurzatmig?	1	2	3	4
9.	Hatten Sie Schmerzen?	1	2	3	4
10.	Mussten Sie sich ausruhen?	1	2	3	4
11.	Hatten Sie Schlafstörungen?	1	2	3	4
12.	Fühlten Sie sich schwach?	1	2	3	4
13.	Hatten Sie Appetitmangel?	1	2	3	4
14.	War Ihnen übel?	1	2	3	4
15.	Haben Sie erbrochen?	1	2	3	4

Bitte wenden

GERMAN

Während der letzten Woche:	**Überhaupt nicht**	**Wenig**	**Mäßig**	**Sehr**
16. Hatten Sie Verstopfung?	1	2	3	4
17. Hatten Sie Durchfall?	1	2	3	4
18. Waren Sie müde?	1	2	3	4
19. Fühlten Sie sich durch Schmerzen in Ihrem alltäglichen Leben beeinträchtigt?	1	2	3	4
20. Hatten Sie Schwierigkeiten sich auf etwas zu konzentrieren, z.B. auf das Zeitunglesen oder das Fernsehen?	1	2	3	4
21. Fühlten Sie sich angespannt?	1	2	3	4
22. Haben Sie sich Sorgen gemacht?	1	2	3	4
23. Waren Sie reizbar?	1	2	3	4
24. Fühlten Sie sich niedergeschlagen?	1	2	3	4
25. Hatten Sie Schwierigkeiten, sich an Dinge zu erinnern?	1	2	3	4
26. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Familienleben beeinträchtigt?	1	2	3	4
27. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Zusammensein oder Ihre gemeinsamen Unternehmungen mit anderen Menschen beeinträchtigt?	1	2	3	4
28. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung für Sie finanzielle Schwierigkeiten mit sich gebracht?	1	2	3	4

Bitte kreuzen Sie bei den folgenden Fragen die Zahl zwischen 1 und 7 an, die am besten auf Sie zutrifft

29. Wie würden Sie insgesamt Ihren Gesundheitszustand während der letzten Woche einschätzen?

1	2	3	4	5	6	7
sehr schlecht						ausgezeichnet

30. Wie würden Sie insgesamt Ihre Lebensqualität während der letzten Woche einschätzen?

1	2	3	4	5	6	7
sehr schlecht						ausgezeichnet

GERMAN

EORTC QLQ - BR23

Patienten berichten manchmal die nachfolgend beschriebenen Symptome oder Probleme. Bitte beschreiben Sie, wie stark Sie diese Symptome oder Probleme während der letzten Woche empfunden haben.

Während der letzten Woche:	**Überhaupt nicht**	**Wenig**	**Mässig**	**Sehr**
31. Hatten Sie einen trockenen Mund?	1	2	3	4
32. War Ihr Geschmacksempfinden beim Essen oder Trinken verändert?	1	2	3	4
33. Schmerzten Ihre Augen, waren diese gereizt oder tränten sie?	1	2	3	4
34. Haben Sie Haarausfall?	1	2	3	4
35. Nur bei Haarausfall ausfüllen: Hat Sie der Haarausfall belastet?	1	2	3	4
36. Fühlten Sie sich krank oder unwohl?	1	2	3	4
37. Hatten Sie Hitzewallungen?	1	2	3	4
38. Hatten Sie Kopfschmerzen?	1	2	3	4
39. Fühlten Sie sich wegen Ihrer Erkrankung oder Behandlung körperlich weniger anziehend?	1	2	3	4
40. Fühlten Sie sich wegen Ihrer Erkrankung oder Behandlung weniger weiblich?	1	2	3	4
41. Fanden Sie es schwierig, sich nackt anzusehen?	1	2	3	4
42. Waren Sie mit Ihrem Körper unzufrieden?	1	2	3	4
43. Waren Sie wegen Ihres zukünftigen Gesundheitszustandes besorgt?	1	2	3	4

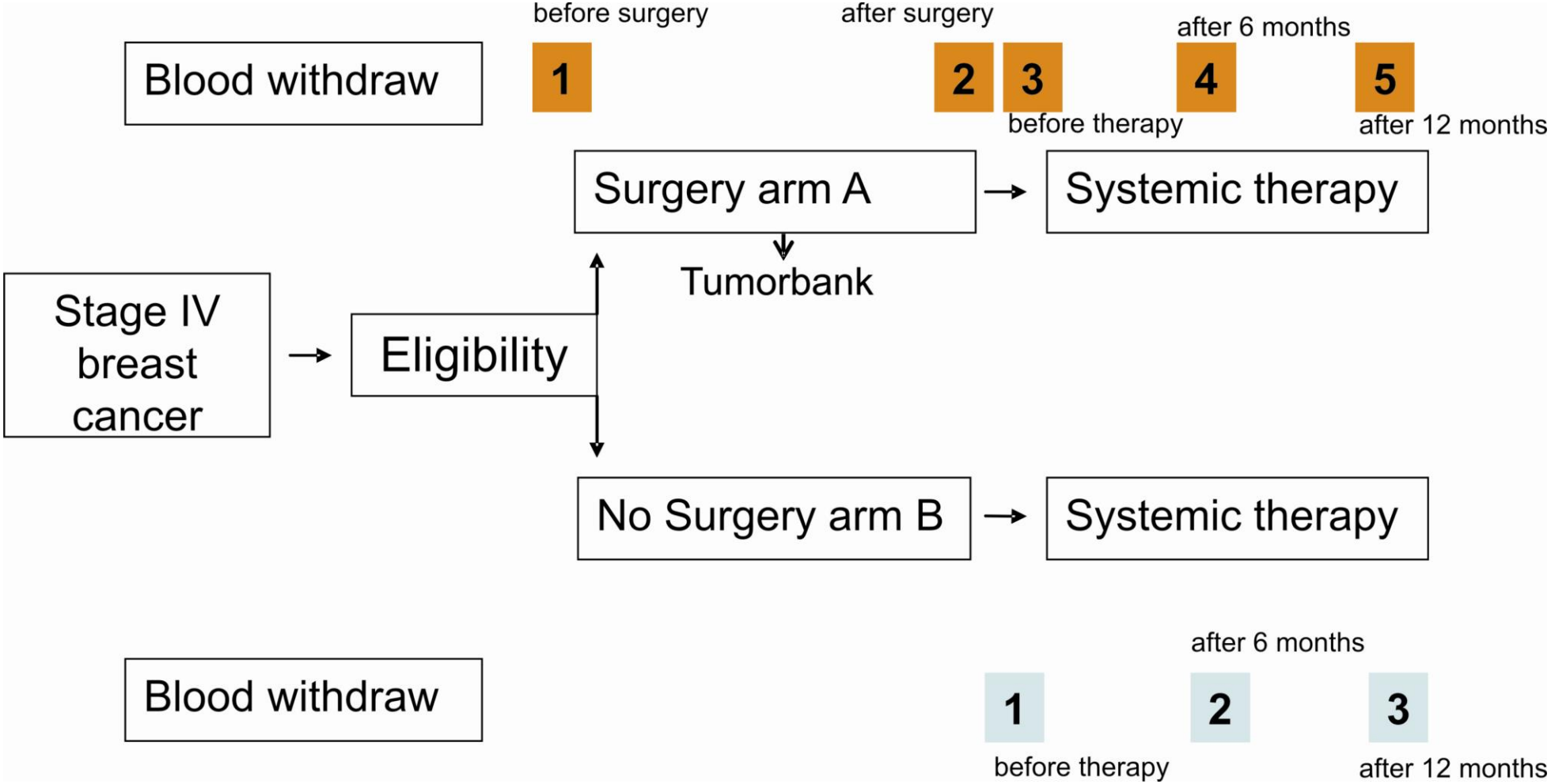
Während der letzten <u>vier</u> Wochen:	**Überhaupt nicht**	**Wenig**	**Mässig**	**Sehr**
44. Wie sehr waren Sie an Sex interessiert?	1	2	3	4
45. Wie sehr waren Sie sexuell aktiv? (mit oder ohne Geschlechtsverkehr)?	1	2	3	4
46. Nur ausfüllen, wenn Sie sexuell aktiv waren: Wie weit hatten Sie Freude an Sex?	1	2	3	4

Bitte wenden

GERMAN

Während der letzten Woche:	Überhaupt nicht	Wenig	Mässig	Sehr
47. Hatten Sie Schmerzen in Arm oder Schulter?	1	2	3	4
48. War Ihr Arm oder Ihre Hand geschwollen?	1	2	3	4
49. War das Heben oder Seitwärtsbewegen des Arms erschwert?	1	2	3	4
50. Hatten Sie im Bereich der betroffenen Brust Schmerzen?	1	2	3	4
51. War der Bereich Ihrer betroffenen Brust angeschwollen?	1	2	3	4
52. War der Bereich der betroffenen Brust überempfindlich?	1	2	3	4
53. Hatten Sie Hautprobleme im Bereich der betroffenen Brust (z.B. juckende, trockene oder schuppende Haut)?	1	2	3	4

Appendix 6: Blood specimen Flow chart in pre-selected centers



Appendix 7: Declaration of Helsinki

Declaration of Helsinki
World Medical Association Declaration of Helsinki:
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically

and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be

allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

11. The subjects must be volunteers and informed participants in the research project.

12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This

does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

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