Clinical Study Report

planB

Randomised comparison of adjuvant Docetaxel / Cyclophosphamide with sequential adjuvant EC / Docetaxel chemotherapy in patients with HER2/neu negative early breast cancer
6 x TC vs. 4 x EC ➔ 4 x Doc

WSG-AM04
2008-004263-19

15.05.2018 / 19.12.2018

CONFIDENTIAL

Signature pages for clinical study report

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Signed:  Date: 27.03.2019

Coordinating Investigator
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1 TITLE PAGE

Study title: planB

Name of Test Drug:	N/A, commercial ware: Docetaxel, Cyclophosphamide, Epirubicin
Indication studied:	Early breast cancer
Study description:	**planB -** Randomised comparison of adjuvant Docetaxel / Cyclophosphamide with sequential adjuvant EC / Docetaxel chemotherapy in patients with HER2/neu negative early breast cancer 6 x TC vs. 4 x EC ➔ 4 x Doc
Sponsor:	Westdeutsche Studiengruppe GmbH, WSG
Protocol:	WSG-AM04
Clinical Phase:	Prospective, multi-centre, controlled, non-blinded, randomised phase III
Study dates:	First patient in: 05.02.2009, last patient out: 01.03.2017
Coordinating Investigator:	Prof. Dr. med. Ulrike Nitz (UN), Ev. Krankenhaus Bethesda Brustzentrum Niederrhein, Ludwig-Weber-Str. 15, 41061 Mönchengladbach, Germany
Sponsor signatory:	Dr. Iris Reiser, Westdeutsche Studiengruppe, Ludwig-Weber-Str. 15, 41061 Mönchengladbach, Germany
GCP Statement:	This study was performed in compliance with ICH Good Clinical Practice (GCP) including the archiving of essential documents
Date of report:	15.05.2018 / 19.12.2018

2 SYNOPSIS

NAME OF SPONSOR WSG **NAME OF FINISHED PRODUCT** N/A **NAME OF ACTIVE INGREDIENT(S)** N/A		**(FOR NATIONAL AUTHORITY USE ONLY)**

Title of Study	**planB -** Randomised comparison of adjuvant Docetaxel / Cyclophosphamide with sequential adjuvant EC / Docetaxel chemotherapy in patients with HER2/neu negative early breast cancer 6 x TC vs. 4 x EC ➔ 4 x Doc		
Investigator(s) / Study centre(s)	This study was conducted at 90 sites in Germany.		
Publication	Manuscript Draft: Prospective WSG Phase III PlanB trial: Adjuvant 4xEC-4xT versus 6xTC in Triple Negative and Intermediate or High Genomic Risk HR+/HER2-negative Early Breast Cancer (Journal of Clinical Oncology)		
Study period	From: February 2009 To: March 2017	Clinical Phase	Phase III
Objectives	Primary objective • To compare disease-free survival in patients treated with either 6 cycles of docetaxel / cyclophosphamide chemotherapy or 4 cycles of EC followed by 4 cycles of docetaxel as adjuvant treatment Secondary objectives • To compare overall survival between the two arms • To compare the toxicity between the two arms • To evaluate survival in the observation arm • To perform translational research regarding prognostic and predictive factors		
Methodology	Prior to randomisation for all patients with HR positive disease OncotypeDX® will be performed. HR positive patients with RS<11 and 0 to 3 positive nodes should not receive chemotherapy and will be followed up for DFS and OS only. The following patients will be randomised to receive chemotherapy within the planB trial: • Patients with HR positive disease and either RS>11 and 0-3 positive nodes • Patients with HR positive disease and 4 or more positive nodes regardless of RS • Patients with HR negative disease Patients will be randomised to one of the following treatment arms: Arm A: 6 cycles of docetaxel / cyclophosphamide chemotherapy with docetaxel 75 mg/m² on day 1 every 3 weeks and cyclophosphamide 600 mg/m² on day 1 every 3 weeks Arm B: 4 cycles of EC chemotherapy with epirubicin 90 mg/m² on day 1 every 3 weeks and cyclophosphamide 600 mg/m² on day 1 every 3 weeks followed by 4 cycles docetaxel with docetaxel 100 mg/m² on day 1 every 3 weeks Dose delay and dose adjustment in case of severe or unacceptable toxicity. Patients with hormone sensitive disease (estrogen and/or progesterone receptor positive) will receive antihormonal therapy according to national standards as defined by AGO guidelines. Patients will be followed every 3 months during the first year after end of treatment and every 6 months until year 5 or until relapse to document Supportive treatment: Dexamethasone according to SmPC docetaxel G-CSF according to AGO guidelines to avoid dose delay and dose adjustment due to febrile neutropenia and infection. It is highly recommended to use Neulasta® as G-CSF treatment.		

	Translational Research Protocol: Within the planB study, a central tumor bank will be built and central pathology will be performed for all patients. Each participating patient donates one paraffin-embedded tumor block to WSG for RS assessment and further translational projects at screening. Selected sites will participate in evaluation of circulating tumor cells (Early Breast Cancer Trialists' Collaborative Group and EBCTCG.).
Number of patients	Planned: 2448 patients (1224 patients per each treatment arm) will be enrolled to receive chemotherapy. Analysed: 3198 patients (Arm A: 1222; Arm B: 1227) Observation arm: 337 patients
Diagnosis and main criteria for inclusion	HER2/neu negative eartly breast cancer; The following patients will be randomised to receive chemotherapy within the planB trial: • Patients with HR positive disease and either RS>11 and 0-3 positive nodes • Patients with HR positive disease and 4 or more positive nodes regardless of RS • Patients with HR negative disease **General Inclusion Criteria (Screening):** • Female patients, age at diagnosis: 18 - 75 years • Histologically confirmed unilateral primary invasive carcinoma of the breast • Adequate surgical treatment with complete resection of the tumor (R_0) and resection of ≥ 10 axillary nodes or SLN in clinically N_0 patients • T1 - T4 (if operable, *inflammatory breast cancer is excluded*) • Her2 non-over expressing tumor confirmed by IHC/FISH • Estrogen and/or progesterone receptor analysis performed on the primary tumor prior to randomisation. Results must be known at the time of randomisation • Node positive disease or node negative disease with at least one other risk factor (tumor size ≥ 2 cm, grade ≥ 2, ER and PR negative, high uPA//PAI-1 levels) • No evidence for distant metastasis (M_0) after conventional staging • Performance Status ECOG ≤ 1 or KI ≥ 80 % • The patient must be accessible for treatment and follow-up • Written informed consent for shipping of tumor block for central pathology review and evaluation of Recurrence Score (HR positive) and participation in the planB trial prior to beginning specific protocol procedures, including expected cooperation of the patients for the treatment and follow-up, must be obtained and documented according to the local regulatory requirements HR positive patients must also meet all of the following clinical inclusion criteria: • Patient willingness to participate in adjuvant chemotherapy planB trial if RS > 11 • Indication for chemotherapy given provided either ≥ 4 involved lymph nodes or RS > 11 in 1-3 lymph nodes or N0 disease **Additional Inclusion Criteria (Randomisation):** All patients with HR negative breast cancer and patients with HR positive (ER and/or PR) tumors and node-positive disease with ≥ 4 involved lymph nodes or 0-3 involved lymph nodes with RS > 11 will be randomised for chemotherapy question if they are meeting all of the following additional inclusion criteria prior to randomisation: • Laboratory requirements (within 21 days prior to randomisation): ○ Leucocytes ≥ 3.5 10^9/L

	○ Platelets ≥ 100 10^9/L ○ Haemoglobin ≥ 10 g/dL ○ Total bilirubin ≤ 1 ULN ○ ASAT (SGOT) and ALAT (SGPT) ≤ 2.5 ULN ○ Creatinine ≤ 175 □mol/L (2 mg/dL) • Negative pregnancy test (urine or serum) within 7 days prior to randomisation in premenopausal patients • LVEF within normal limits of each institution measured by echocardiography or MUGA scan and normal ECG (within 42 days prior to randomisation)
Test product, dose and mode of administration, batch number	**Arm A: Docetaxel-Cyclophosphamide (TC)** **TC** treatment will consist of 6 cycles of docetaxel and cyclophosphamide. Docetaxel will be given first: Dose: 75 mg/m², day 1 Route: 1 hour intravenous infusion. During the first 5 minutes, the infusion must be done drop by drop in order to reduce the incidence of acute hypersensitivity reaction (AHSR). Schedule: Every 3 weeks Followed by cyclophosphamide: Dose: 600 mg/m², day 1 Route: 5 to 60 minutes intravenous bolus injection (as per hospital policy) Schedule: Every 3 weeks This is called a cycle of treatment and will be given 6 times. In the event of relapse during treatment, unacceptable toxicities or withdrawn consent, treatment shall finish earlier. **Arm B: EC → Docetaxel (EC-DOC)** **EC Segment:** Epirubicin Dose: 90 mg/m², day 1 Route: 5 - 15 minute intravenous bolus injection (as per hospital policy) Schedule: Every 3 weeks Followed by cyclophosphamide Dose: 600 mg/m², day 1 Route: 5 to 60 minutes intravenous bolus injection (as per hospital policy) Schedule: Every 3 weeks This is called a cycle of treatment and is to be given 4 times. Following completion of 4 cycles, the patient will enter the docetaxel segment for this arm of treatment. **Docetaxel Segment:** Three weeks after the last course of EC, docetaxel will be given Dose: 100 mg/m², day 1 Route: 1 hour intravenous infusion. During the first 5 minutes, the infusion must be done drop by drop in order to reduce the incidence of acute hypersensitivity reaction (AHSR). Schedule: Every 3 weeks This is called a cycle of treatment and is to be given 4 times. In the event of relapse during treatment, unacceptable toxicities or withdrawn consent, treatment shall finish earlier. **Prophylactic Premedication Regimen for Docetaxel-related Hypersensitivity Reactions and Fluid Retention**

	The following premedication regimen must be administered for all patients treated with docetaxel. **Dexamethasone** Day before chemotherapy: Morning and evening dose of 8 mg p.o. Day of docetaxel infusion: Morning dose of 8 mg p.o. 8 mg i.v. prior to infusion of docetaxel Evening dose of 8 mg p.o. Day after chemotherapy: Morning and evening dose of 8 mg p.o. Dexamethasone 8 mg equivalent may be used (Dexamethasone 8 mg = Methylprednisolone 40 mg = Prednisone 50 mg = Prednisolone 50 mg).
Duration of treatment	**Arm A: Docetaxel-Cyclophosphamide (TC)** TC treatment will consist of 6 cycles of docetaxel and cyclophosphamide. Patients will receive 6 cycles of adjuvant therapy; each cycle will last for 3 weeks. The duration of the study treatment during adjuvant therapy is 18 weeks from cycle 1 to 6. **Arm B: EC → Docetaxel (EC-DOC)** EC treatment will consist of 4 cycles of epirubicin and cyclophosphamide. Patients will receive 4 cycles of adjuvant therapy; each cycle will last for 3 weeks. The duration of the study treatment during adjuvant therapy is 12 weeks from cycle 1 to 4. Following completion of 4 cycles, the patient will enter the docetaxel segment for this arm of treatment. Patients will receive 4 cycles of adjuvant therapy; each cycle will last for 3 weeks. The duration of the study treatment during adjuvant therapy is 12 weeks from cycle 1 to 4. **Follow-up per patient**: 5 years
Criteria for evaluation	**Efficacy:** • **Primary efficacy parameters**: The primary efficacy parameter will be 5 year disease-free survival. The disease-free survival is defined as the interval from the date of randomisation to the date of local, regional or metastatic relapse or the date of second primary cancer (with the exception of curatively treated non-melanoma skin cancer or in situ carcinoma of the cervix) or death from any cause whichever occurs first. • **Secondary efficacy parameters:** Secondary efficacy parameters will consist of the comparison between groups based on overall survival and toxicity. **Safety**: <u>Interim Safety Evaluation</u> When the data of the first 100 patients per each treatment arm are completely evaluable for the whole chemotherapy treatment period one safety interim analysis will be performed. The results will be reviewed by the IDMSC. Overall Safety Evaluation <u>Grading of Adverse Events</u> The National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 3.0 and the corresponding grading system will be used to grade adverse events for recording in the CRF. For all adverse events not classified by the NCI-CTC a COSTART grading classification (FDA 1989) will be performed (severity as 1: mild, 2: moderate, 3: severe, and 4 life threatening). <u>Populations to be analysed</u> The safety analysis will be conducted on all patients who started at least one infusion of the study treatment. <u>Statistical Methods</u> Adverse events will be compared using two-tailed χ^2 tests or, when expected counts are low, Fisher's exact test or one of its generalisations. In view of the anticipated large number of statistical tests, p-values will not be interpreted in the usual sense

	but will be used as a “flagging device” to highlight differences worth further attention. Descriptive statistics will be given on the number of patients in whom the study medication had to be replaced, delayed or permanently stopped.
Statistical methods	The Kaplan-Meier product limit method will be used to estimate the disease-free survival and the overall survival. The log rank test, stratified for nodal status (N0, N1-3 versus N4+), for hormonal receptor status (estrogen and/or progesterone receptor positive versus negative) and age (<50 / ≥50), will be used to perform all pair wise comparisons between the two treatment arms with respect to disease-free survival and overall survival. Confidence intervals of the median disease-free and overall survival will be calculated using the method of Simon. To test the equivalence of both study treatments, the confidence interval method for the difference in survival probabilities derived from the usual logrank test based upon the observed number of events at each time point and the number expected in the new treatment proposed by PJA Skaff, JA Sloan (1998) will be used. The evaluation will be done by SAS® 9.1 using the algorithms developed for this publication. Cox’s proportional hazards regression analysis will be performed for disease-free survival and overall survival in order to adjust the treatment comparison for the major prognostic factors. These factors include age, menopausal status, type of surgery, histopathological findings, tumor size, pathological markers and molecular markers. Such adjusted analysis, for instance by nodal status (N0, N1-3 versus N4+) will be reported with appropriate caveat. In the statistical analysis, a centre will correspond to a participating institution. It is expected to have at the end of the study a large number of centres with few patients per centre. It is consequently not planned to include any centre effect in the analyses. However, should there be centres with a large recruitment, it is planned to compare the consistence of the results between this (these) large centre(s) and the entire study results, in terms of major baseline characteristics and the primary endpoint. Prospectively planned analyses include analysis of primary endpoint disease-free survival according to topoisomerase II protein (different assay formats), triple negativity (ER -, PR -, HER2 -), etc.

NAME OF COMPANY WSG **NAME OF FINISHED PRODUCT** N/A **NAME OF ACTIVE INGREDIENT(S)** N/A		**(FOR NATIONAL AUTHORITY USE ONLY)**

SUMMARY CONCLUSIONS

EFFICACY RESULTS

From 2009 to 2011, 3,198 patients were registered, of whom 348 (RS≤11) omitted chemotherapy and 401 were not randomized. The intent-to-treat population included 2,449 patients (EC-T/TC): postmenopausal, 62.2%/60.8%; pN0, 58.2%/59.5%; pT1, 57.6%/52.3%; HR+, 81.4%/82.2%; RS>25 (in HR+ patients), 26.2%/27.5%. Overall, 87% of the 1,227 EC-T and 93% of the 1,222 TC patients completed therapy. After a
60-months median follow-up, 5-year DFS and OS rates were similar in the EC-T and TC arms. DFS: 89.6% (95% confidence interval, 87.9%-91.5%) v 89.9% (88.1%- 91.8%); OS: 94.5% (93.1%-95.9%) v 94.7% (93.3%-96.1%). The DFS difference was within the non-inferiority margin of the original trial design. Five treatment-related deaths were reported for TC (one for EC-T), despite a trend towards more severe adverse events in the EC-T arm. RS was not predictive for efficacy in EC-T versus TC. No efficacy differences were observed between triple-negative, luminal A/B-like, and pN2/3 tumors.

SAFETY RESULTS

Six treatment-related deaths were observed within the study: Five in the TC arm (0.4%) and one (0.1%) in the EC-T arm (*P*=.2). Five of them were due to infections/septicaemia. The EC-T arm, compared to the TC arm, was characterized by significantly more dose reductions (78 [6.6%] *v* 230 [19.7%]; *P*<.001) and dose delays (>7 days) (78 [6.7%] *v* 47 [4.0%]; *P*=.004). Overall, 87% and 93% of patients in these respective arms completed therapy by protocol. Grade 3-4 leukopenia, neutropenia, nausea, vomiting, (peripheral) polyneuropathy, hand-foot syndrome, mucositis/stomatitis, arthralgia, myalgia, and fatigue were observed in significantly more EC-T than TC-treated patients (Table 3). Only a nonsignificant trend towards higher frequency of grade 3-4 infections and febrile neutropenia was seen within the TC arm. Use of primary granulocyte-colony stimulating factor during the first cycle of therapy was documented in 14.9% and 4.9% of patients in the TC and EC-T arms, respectively (*P*<.001). Febrile neutropenia rates were significantly lower in patients with primary prophylaxis during first cycle of therapy in the TC arm (primary prophylaxis *v* not: 1.7% *v* 6.0%; *P*=.02). In further follow-up, four deaths (TC/EC-T: 2/2) were observed due to heart failure and one due to acute myeloid leukemia (EC-T arm).

CONCLUSION

In WSG PlanB, 5-year DFS and OS for TC and EC-T were equally excellent. Thus, for EBC patients at intermediate risk of recurrence, 6xTC is a safe and effective chemotherapy option.

DATE OF THE REPORT: 15.05.2018 / 19.12.2018

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4 LIST OF ABBREVIATIONS & DEFINITION OF TERMS

A	Doxorubicin
AE	Adverse Event
AHSR	acute hypersensitivity reaction
ALAT	Alanine transaminase
AML	Acute myeloid leukemia
ANC	Absolute Neutrophile Count
ASAT	Aspartate aminotransferase
BC	Breast cancer
BP	Blood pressure
BSA	Body surface area
CBC	Complete Blood Count
CHF	Congestive heart failure
CI	Confidence Intervall
CRF	Case Report Form
CRO	Clinical Research Organization
CTC	Common Toxicity Criteria and Circulating Tumor Cell
D(oc)	Docetaxel
DFS	Disease Free Survival
DMP	Data Management Plan
DSF	Disease-Free Survival
DVP	Data Validation Plan
E	Epirubicin
ECG	Electrocardiogram
EOT	End of Treatment
ET	Endocrine Therapy
F	5-Fluoruracil
FDA	Food and Drug Administration
FNP	Febrile Neutopenia
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
H	Herceptin®
HR	Hazard Ratio
HR+ / HR-	Hormone Receptor Positive / Hormone Receptor Negative

ICH	International Conference on Harmonisation
IRB/EC	Independent Review Board / Ethic Committee
ITT	Intention-to-treat
LVEF	Left Ventricular Ejection Fraction
M	Methrotrexat
MDS	Myelodysplastic Syndromes
MUGA	Multiple Uptake Gated Acquisition Scan
NCI	National Cancer Institute
OR	Overall Response
OS	Overall Survival
P	Paclitaxel
RDE	Remote Data Entry
RFS	Relapse Free Survival
RR	Response Rate
RS	Recurrence Score
SAE	Serious Adverse Event
SAL	Secondary Acute Leukemia
SLN	Sentinel Lymph Node
SLND	Sentinel Lymph Node Dissection
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standardized uptake value
T	Docetaxel
TCbH	Taxotere®/Carboplatin/Herceptin®
UNL	Upper normal limit
WBC	With Blood cell count
WHO	World Health Organisation

5 ETHICS AND REGULATORY APPROVAL

5.1 INDEPENDENT ETHICS COMMITTEE APPROVAL

The study protocol and all its amendments, and the patient information sheet(s) were reviewed and approved by the appropriate independent ethics committees as detailed in 16.1.3.

Ethics-approval by the lead ethics committee of the Aertzekammer Nordrhein:

- Initial approval on 23.12.2008, protocol version 1.0/1.1
- Approval on Amendment 1, 22.06.2009, protocol version 2.0
- Approval on Amendment 2, 24.05.2011, protocol version 3.0 and patient information sheet version 3.0

All mentioned versions of the protocol were also approved by the local ethics committees.

5.2 ETHICAL CONDUCT OF THE STUDY

The study was performed in accordance with the current version of the declaration of Helsinki (52nd WMA General Assembly, Edinburgh, Scotland, October 2000). The trial was conducted in agreement with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practise (GCP).

5.3 PATIENT INFORMATION AND CONSENT

All patients provided written informed consent to participate in the study prior to being screened. Patients signed a separate written informed consent for study participation and tissue samples. Study participation was independently from the willingness to provide tissue or blood samples, or participation in the project “circulating tumor cells”.

The patient information sheet detailed the procedures involved in the study (aims, methodology, potential risks, anticipated benefits) and the investigator explained these to each patient. The patient signed the consent form to indicate that the information had been explained and understood. The patient was then allowed time to consider the information presented before signing and dating the informed consent form to indicate that they fully understood the information, and willingly volunteered to participate in the study. The patient was given a copy of the informed consent form for their information. The original copy of the informed consent was kept in a confidential file in the Investigators centre records. A sample of the patient information sheet and consent form can be found at appendix 0.

5.4 REGULATORY APPROVAL

The study was conducted only in Germany. The study was performed in compliance with the requirements of the regulatory authorities. The study gained full regulatory approval from the Federal Institute for Drugs and Medical Devices on 26.08.2009 (0).

- Approval on Amendment 1, 26.08.2009, protocol version 2.0.1
- Approval on Amendment 2, 24.05.2011, protocol version 3.0

The study gained full approval from lead ethics committee of the Aerztekammer Nordrhein on 23.12.2008 as described in section 5.1.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Table 1 shows the principal study personnel involved in the study.

Table 1: Principal study personnel

Title	Name and affiliation
Coordinating investigator	Prof. Dr. med. Ulrike Nitz, Ev. Krankenhaus Bethesda Brustzentrum Niederrhein, Ludwig-Weber-Str. 15, 41061 Mönchengladbach, Germany
Steering committee	• **Prof. Dr. Christoph Thomssen**, Universitätsklinikum Halle (Saale), Ernst-Gruber-Str. 40, 06120 Halle, Germany • **PD Dr. Toralf Reimer**, Universitäts-Frauenklinik am Klinikum Südstadt Rostock, Südring 81, 18059 Rostock, Germany • **Prof. Dr. Dirk Elling**, Sana Klinikum Lichtenberg, Fanningerstraße 32, 10365 Berlin, Germany • **PD Dr. Carsten Oberhoff**, Kath. Kliniken Essen-Nord-West gGmbH, Hospitalstr. 24, 45329 Essen • **Prof. Dr. Andreas Schneeweiss**, Universitäts-Frauenklinik, Voss-Str. 9, 69115 Heidelberg, Germany • **Dr. Mathias Warm**, Brustzentrum Krankenhaus Holweide, Neufelder Str. 34, 51067 Köln, Germany • **Dr. John Hackmann**, Marien-Hospital Witten gGmbH, Brustzentrum, Marienplatz 2, 58452 Witten, Germany • **Prof. Dr. Michael Untch**, HELIOS Klinikum Berlin-Buch, Schwanebecker Chaussee 50, 13125 Berlin, Germany • **Prof. Dr. Christian Jackisch**, Klinikum Offenbach GmbH, Starkenburgring 66, 63069 Offenbach, Germany • **Prof. Dr. Volker Möbus**, Städt. Kliniken Frankfurt a.M.-Höchst, Gotenstr. 6-8, 65929 Frankfurt a. M., Germany • **Prof. Dr. Hans-Joachim Lück**, Gynäkologisch-onkologische Praxis, Pelikanplatz 23, 30177 Hannover, Germany • **Prof. Dr. Pia Wülfing**, Universitätsklinikum Münster, Albert-Schweitzer-Str. 33, 48149 Münster, Germany
Monitoring committee	**Prof. Dr. Jens Huober**, Senologie-Zentrum Ostschweiz, Kantonsspital, 9007 St. Gallen, Switzerland ***Dr. Fatima Cardoso**, Institut Jules Bordet, 121 Blvd de Waterloo, 1000 Brussels, Belgium (affirmation pending)* ***Dr. Henry Roche,** Institut Claudius Regaud, 20/24 rue du Pont St Pierre, 31052 Toulouse, France (affirmation pending)* **Prof. Dr. Wolfgang Janni**, Universitätsklinikum Düsseldorf, Moorenstr. 5, 40225 Düsseldorf, Germany
Scientific Board	**Prof. Dr. Nadia Harbeck (Chair SC, Scientific Co-Chair of planB),** Universitätsklinik Köln, Kerpener Str. 34, 50931 Köln, Germany **Prof. H. H. Kreipe (Co-Chair SC)**, Institut für Pathologie an der Medizinischen Hochschule Hannover, Postfach 610140, 30601 Hannover, Germany

	Prof. Dr. Nils Brünner, Royal University, Copenhagen, Denmark **PD Dr. Sherko Kümmel**, Kliniken Essen Mitte, Frauenklinik, Henricistr. 92, 45136 Essen, Germany **Prof. Dr. E. Stickeler**, Universitäts-Frauenklinik, Hugstetter Straße 55, 79106 Freiburg, Germany **Dr. Oleg Gluz,** Bethesda Krankenhaus, Klinik für Frauenheilkunde, Hainstr. 35, 42109 Wuppertal, Germany **Dr. N. Gottschalk**, Universitätsklinikum Essen, Klinik für Frauenheilkunde und Geburtshilfe, Hufelandstr. 55, 45122 Essen, Germany **Dr. C. Liedtke,** Universitätsklinikum Münster, Albert-Schweitzer-Str. 33, 48149 Münster, Germany **Dr. E. Kantelhardt,** Universitätsklinikum Halle (Saale), Ernst-Gruber-Str. 40, 06120 Halle, Germany **Dr. M. Vetter,** Universitätsklinikum Halle (Saale), Ernst-Gruber-Str. 40, 06120 Halle, Germany **Prof. Dr. T. Fehm**, Universitäts-Frauenklinik, Gynäkoonkologie, Calwerstr. 7, 72076 Tübingen, Germany
Statistician	**Prof. Dr. Dr. Ivan Zuna**, Steinbachweg 37, 69118 Heidelberg **Dr. Ronald E. Kates**, Palnmaker Str. 49, 83624 Otterfing
Central laboratory facilities	Dept. of Pathology at the University Clinics in Hannover, Germany
Contract research organization (CRO)	• HZM Pharmaservice GmbH, Kranzplatz 1, 65183 Wiesbaden • palleos healthcare GmbH, Taunusstraße 5a, 65183 Wiesbaden, Germany
Sponsor	Westdeutsche Studiengruppe GmbH, Ludwig-Weber-Str. 15b, 41061 Mönchengladbach (Dr. Corinna Bühne)
Project Managers	Dr. Iris Reiser, Westdeutsche Studiengruppe GmbH, Ludwig-Weber-Str. 15b, 41061 Mönchengladbach
Clinical Research Associate(s)	• HZM Pharmaservice GmbH, Kranzplatz 1, 65183 Wiesbaden • Westdeutsche Studiengruppe GmbH, Ludwig-Weber-Str. 15b, 41061 Mönchengladbach
Medical Advisor	PD Dr. med. Oleg Gluz, Westdeutsche Studiengruppe GmbH, Ludwig-Weber-Str. 15b, 41061 Mönchengladbach
Data Management	pallas healthcare consulting GmbH, Wilhelmstr. 62, 65183 Wiesbaden, Germany

7 INTRODUCTION

7.1 THERAPEUTIC AREA

Breast cancer is a leading cancer site in women around the world. In the United States, 182460 new cases of female breast cancer (26 % of all cancers in US women) and 40480 deaths (14.9 % of all cancer deaths in women) are estimated to occur in the year 2008 (Jemal et al., 2008). In Canada, an estimated 22300 new cases of breast cancer will be diagnosed (30.7 % of all cancer) with an estimated 5300 deaths from breast cancer (18.8 % of all cancer) for the year 2007. In Europe, an estimated 429960 new cases per year (13.5 % of all cancer cases) and 131900 recorded deaths per year are reported (Ferlay et al., 2007).

Surgery is the main modality of treatment in patients with breast cancer. Surgery and/or radiotherapy can control local-regional diseases in the majority of patients. However, more than 60 % will ultimately die due to widespread disease.

In the past 30 years, adjuvant antihormonal therapy or cytostatic treatment has been increasingly used (Veronesi U et al., 2005). Ongoing studies show that adjuvant treatment can prolong time to recurrence and survival in breast cancer patients (Early Breast Cancer Trialists' Collaborative Group and EBCTCG., 2005).

7.2 RATIONALE FOR THE STUDY

Anthracycline based chemotherapy is standard in adjuvant therapy of breast cancer. Data from single prospective randomised recent (taxane containing) trials (*Slamon DJ* et al., 2007) and a meta-analysis including trial data of first and second generation regimens (Gennari et al., 2008) suggest that benefit from anthracyclines is mainly restricted to HER2/neu over expressing tumors. Major toxicity of anthracyclines is cardiac toxicity, which may cause long-term symptomatic cardiac dysfunction in a patient with a priori high curative potential (Pinder et al., 2007).

A recent trial comparing an anthracycline-free taxane containing regimen versus an ancient standard 4 x AC demonstrates superiority of the taxane based regimen in HER2/neu over expressing and non over expressing patients with early breast cancer (Jones S et al., 2007).

The planned trial compares an anthracycline-free taxane based regimen versus a modern third generation (anthracycline/taxane-based) regimen in HER2/neu non-over expressing tumors. The aim is to define a further anthracycline-free standard and to spare anthracycline toxicity to a patient, who will only have a modest benefit from this compound.

8 STUDY OBJECTIVES

8.1 PRIMARY OBJECTIVE

The primary study objective was:

- To compare disease-free survival in patients treated with either 6 cycles of docetaxel / cyclophosphamide chemotherapy or 4 cycles of EC followed by 4 cycles of docetaxel as adjuvant treatment

8.2 SECONDARY OBJECTIVE

Secondary objectives were:

- To compare overall survival between the two arms
- To compare the toxicity between the two arms
- To evaluate survival in the observation arm

- To perform translational research regarding prognostic and predictive factors

9 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN

This was a multi-centre, controlled, prospective, open, randomised phase III trial.
Prior to enrolment for all HR positive patients, Recurrence Score (RS) will be evaluated. Patients with node-negative disease or with 1-3 positive LN and with a low risk Recurrence Score (<11) should omit chemotherapy. Follow-up data for these patients will be obtained regularly, i.e. annually, for DFS and OS.

The treatment assigned was based on a dynamic minimisation procedure using centre, status of axillary lymph nodes (N0, N1-3 versus N4+), and hormonal receptor status (estrogen and/or progesterone receptor positive versus negative) as factors in the minimisation algorithm, which will use a stochastic treatment allocation algorithm based on the variance method.

Patients meeting the inclusion criteria were stratified at enrolment into 4 groups according to institution, the number of axillary lymph nodes involved (0, 1-3 nodes vs. 4+ nodes), age (<50 / ≥50) and by estrogen and/or progesterone receptor status (positive or negative) and will be randomly assigned to receive adjuvant treatment with either:

Arm A: 6 cycles of docetaxel / cyclophosphamide chemotherapy with docetaxel 75 mg/m² on day 1 every 3 weeks and cyclophosphamide 600 mg/m² on day 1 every 3 weeks (→ total duration: 18 weeks)

Arm B: 4 cycles of EC chemotherapy with epirubicin 90 mg/m² on day 1 every 3 weeks and cyclophosphamide 600 mg/m² on day 1 every 3 weeks followed by 4 cycles docetaxel 100 mg/m² on day 1 every 3 weeks (→ total duration: 24 weeks)

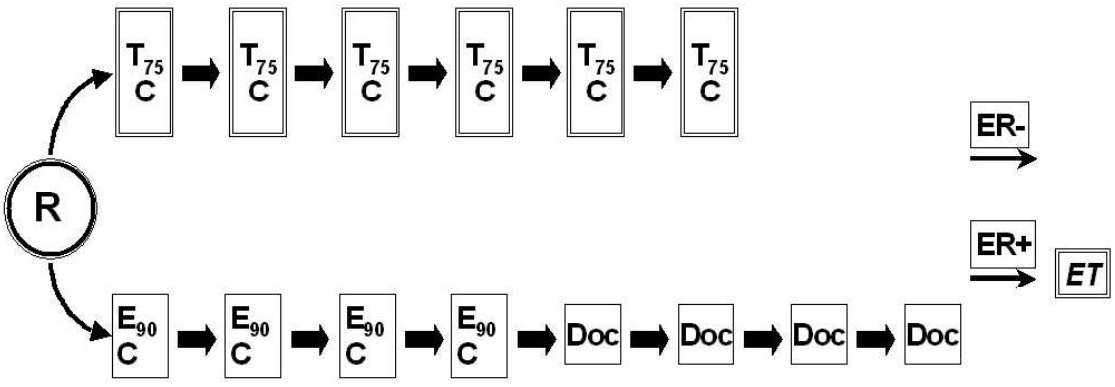

Figure 1: Design planB trial

Patients with hormone sensitive disease (estrogen and/or progesterone receptor positive) will receive antihormonal therapy according to national standards as defined by AGO guideline.

Recruitment of patients: 05.02.2009 to 08.12.2011

Pre-randomisation period:
Follow-.up: 5 years

9.2 DISCUSSION OF STUDY DESIGN; INCLUDING THE CHOICE OF CONTROL GROUPS

The PlanB-Study was a multi-centre, controlled, prospective, open, randomised phase III trial to compare disease-free survival in patients treated with either 6 cycles of docetaxel / cyclophosphamide chemotherapy or 4 cycles of EC followed by 4 cycles of docetaxel as adjuvant treatment.
From 2009 to 2011, 3,198 patients were registered, of whom 348 (RS≤11) omitted chemotherapy and 401 were not randomized. The intent-to-treat population included 2,449 patients (EC-T/TC): postmenopausal, 62.2%/60.8%; pN0, 58.2%/59.5%; pT1, 57.6%/52.3%; HR+, 81.4%/82.2%; RS>25 (in HR+ patients), 26.2%/27.5%.
All patients who signed the informed consent, successfully complete screening and met the eligibility criteria where enrolled in consecutive order. No selection for treatments or treatment time was taken.

9.3 SELECTION OF STUDY POPULATION

9.3.1 Inclusion Criteria

HER2/neu negative eartly breast cancer;
The following patients will be randomised to receive chemotherapy within the planB trial:

- Patients with HR positive disease and either RS>11 and 0-3 positive nodes
- Patients with HR positive disease and 4 or more positive nodes regardless of RS
- Patients with HR negative disease

General Inclusion Criteria (Screening):
Patients may be considered to participate in the planB trial in case that all of the following inclusion criteria are met:

1. Female patients, age at diagnosis 18 - 75 years
2. Histologically confirmed unilateral primary invasive carcinoma of the breast
3. Adequate surgical treatment with complete resection of the tumor (R_0) and resection of $\geq$ 10 axillary nodes or SLN in clinically N_0 patients
4. T1 - T4 (if operable, *inflammatory breast cancer is excluded*)
5. Her2 non-over expressing tumor confirmed by IHC/FISH
6. Estrogen and/or progesterone receptor analysis performed on the primary tumor prior to randomisation. Results must be known at the time of randomisation.
7. Node positive disease or node negative disease with at least one other risk factor (tumor size $\geq$ 2 cm, grade $\geq$ 2, ER and PR negative, high uPA//PAI-1 levels)
8. No evidence for distant metastasis (M_0) after conventional staging
9. Performance Status ECOG $\leq$ 1 or KI $\geq$ 80 %
10. The patient must be accessible for treatment and follow-up
11. Written informed consent for shipping of tumor block for central pathology review and evaluation of Recurrence Score (HR positive) and participation in the planB trial prior to beginning specific protocol procedures, including expected cooperation

of the patients for the treatment and follow-up, must be obtained and documented according to the local regulatory requirements

HR positive patients must also meet all of the following clinical inclusion criteria:

12. Patient willingness to participate in adjuvant chemotherapy planB trial if RS > 11
13. Indication for chemotherapy given provided either ≥ 4 involved lymph nodes or RS > 11 in 1-3 lymph nodes or N0 disease

Additional Inclusion Criteria (Randomisation):
All patients with HR negative breast cancer and patients with HR positive (ER and/or PR) tumors and node-positive disease with ≥ 4 involved lymph nodes or 0-3 involved lymph nodes with RS > 11 will be randomised for chemotherapy question if they are meeting all of the following additional inclusion criteria prior to randomisation:

14. Laboratory requirements (within 21 days prior to randomisation):
    - Leucocytes ≥ 3.5 10^9/L
    - Platelets ≥ 100 10^9/L
    - Haemoglobin ≥ 10 g/dL
    - Total bilirubin ≤ 1 ULN
    - ASAT (SGOT) and ALAT (SGPT) ≤ 2.5 ULN
    - Creatinine ≤ 175 □mol/L (2 mg/dL)
15. Negative pregnancy test (urine or serum) within 7 days prior to randomisation in premenopausal patients
16. LVEF within normal limits of each institution measured by echocardiography or MUGA scan and normal ECG (within 42 days prior to randomisation)

9.3.2 Exclusion Criteria

General Exclusion Criteria (Screening):
Patients who meet one of the following exclusion criteria will not be eligible for the planB trial:

1. HER2 over expression confirmed by IHC/FISH/CISH
2. Known hypersensitivity reaction to the compounds or incorporated substances
3. Known polyneuropathy ≥ grade 2
4. Severe and relevant comorbidity that would interact with the application of cytotoxic agents or the participation in the study including acute cystitis and ischuria and chronic kidney disease.
5. Prior malignancy with a disease-free survival of < 10 years, except curatively treated basalioma of the skin, pTis of the cervix uteri or ipsilateral ductal carcinoma in-situ (DCISpTis of the breast)
6. Non-operable breast cancer including inflammatory breast cancer
7. Previous or concurrent treatment with cytotoxic agents for any reason after consultation with the sponsor
8. Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational not marketed drug within 30 days prior to study entry
9. Male breast cancer

10. Concurrent pregnancy; patients of childbearing potential must implement a highly effective (less than 1% failure rate) non-hormonal contraceptive measures during the study treatment
11. Breast feeding woman
12. Sequential breast cancer
13. Lack of patient compliance

Additional Exclusion Criteria (Randomisation):
Patients who meet one of the following additional exclusion criteria will not be eligible for the planB trial:

14. Inadequate organ function including:
    - Leucocytes < 3,5 G/l
    - Platelets < 100 G/l
    - Creatinine or bilirubin above normal limits
    - Alkaline phosphatise ≤ 5 ULN
    - ASAT and/or ALAT associated with AP > 2.5 ULN
    - Uncompensated cardiac function
15. Time since axillary dissection (if SLND is performed this date is authoritative for the timeline) > 42 days

9.3.3 Removal of Patients from Therapy or Assessment

Reasons for premature withdrawal or discontinuation criteria include

- Unacceptable Toxicity
- Withdrawn Consent
- Relapse
- Second primary malignancy (with the exception of curatively treated non-melanoma skin cancer or in situ carcinoma of the cervix)
- Death
- Administration of other systemic cancer treatment other than study drug or endocrine therapy as per protocol

The reason and date of chemotherapy discontinuation for all patients will be documented in the case report form (e.g. completed study, adverse event, lost to follow-up, etc.).
The investigator will attempt to complete all discharge procedures at the time a patient is discontinued from the study.
Patients who stop chemotherapy for any reason other than having been administered systemic anticancer therapy for disease relapse or 2nd primary malignancy must be followed in a regular follow-up.

Patients were free to withdraw from the study at any time without giving a reason. Patients were advised that if they requested to withdraw from the study, at any time during the trial, then this would have no negative consequences.

The investigator could also withdraw patients from the trial if they deemed it appropriate for safety or ethical reasons or if it was considered to be to be detrimental to the well-being of the patient.

409 patients could not be randomised (99 violations of inclusion and exclusion criteria, 310 withdrawals of consent form before randomisation). 157 patients withdrew their

consent for the study after randomisation but before treatment of the first cycle of the therapy.

9.4

9.4 TREATMENTS

Not more than 14 days should elapse between the date of randomisation and the start date of the first cycle of adjuvant chemotherapy.
Chemotherapy doses will be calculated according to baseline body surface area (BSA) for all cycles. If there is a 10 % or greater decrease in body weight compared to baseline, the BSA will be recalculated. If the calculated BSA of the patient is > 2.0 m², the dose to be given to the patient will be calculated according to BSA = 2.0 m². No ideal body weight should be used for the calculation of BSA.
Dose adjustments and/or treatment delay and treatment discontinuation are planned for each arm in case of severe hematologic and/or non-hematologic toxicities. In the event of relapse during treatment, unacceptable toxicities, withdrawn consent, treatment shall finish earlier.

9.4.1 Treatments administered

Arm A: Docetaxel-Cyclophosphamide (TC)
TC treatment will consist of 6 cycles of docetaxel and cyclophosphamide.
Docetaxel will be given first:

Dose:	75 mg/m², day 1
Route:	1 hour intravenous infusion. During the first 5 minutes, the infusion must be done drop by drop in order to reduce the incidence of acute hypersensitivity reaction (AHSR).
Schedule:	Every 3 weeks

Followed by cyclophosphamide:

Dose:	600 mg/m², day 1
Route:	5 to 60 minutes intravenous bolus injection (as per hospital policy)
Schedule:	Every 3 weeks

This is called a cycle of treatment and will be given 6 times.
In the event of relapse during treatment, unacceptable toxicities or withdrawn consent, treatment shall finish earlier.

Arm B: EC➔Docetaxel (EC-DOC)
EC Segment:
Epirubicin

Dose:	90 mg/m², day 1
Route:	5 - 15 minute intravenous bolus injection (as per hospital policy)
Schedule:	Every 3 weeks

Followed by cyclophosphamide

Dose:	600 mg/m², day 1
Route:	5 to 60 minutes intravenous bolus injection (as per hospital policy)
Schedule:	Every 3 weeks

This is called a cycle of treatment and is to be given 4 times. Following completion of 4 cycles, the patient will enter the docetaxel segment for this arm of treatment.

Docetaxel Segment:
Three weeks after the last course of EC, docetaxel will be given

Dose:	100 mg/m², day 1
Route:	1 hour intravenous infusion. During the first 5 minutes, the infusion must be done drop by drop in order to reduce the incidence of acute hypersensitivity reaction (AHSR).
Schedule:	Every 3 weeks

This is called a cycle of treatment and is to be given 4 times.
In the event of relapse during treatment, unacceptable toxicities or withdrawn consent, treatment shall finish earlier.

End of Treatment (EOT) Definition
End of treatment (EOT) is defined as 21 days after the last infusion of chemotherapy. Patients will be observed 3 weeks after the last study drug infusion until end of study to document outcome of ongoing side effects.
Reporting of serious adverse events (SAE) will continue for 30 days after last chemotherapy administration.

Prophylactic Premedication Regimen for Docetaxel-related Hypersensitivity Reactions and Fluid Retention
The following premedication regimen must be administered for all patients treated with docetaxel.

Dexamethasone

Day before chemotherapy:	Morning and evening dose of 8 mg p.o.
Day of docetaxel infusion:	Morning dose of 8 mg p.o. 8 mg i.v. prior to infusion of docetaxel Evening dose of 8 mg p.o.
Day after chemotherapy:	Morning and evening dose of 8 mg p.o.

Dexamethasone 8 mg equivalent may be used (Dexamethasone 8 mg = Methylprednisolone 40 mg = Prednisone 50 mg = Prednisolone 50 mg).

Use of Prophylactic Antibiotics
Primary prophylactic use of antibiotics is not allowed in any arm. Prophylactic use of antibiotics will be used in subsequent chemotherapy cycles for those patients who have experienced a serious or life-threatening infection only (see Section 9.2.1).
Prophylactic antibiotics will not be used in subsequent cycles for patients who have had a prior episode of febrile neutropenia.

For patients where a serious or life-threatening infection has occurred, a prophylactic antibiotic is required for all subsequent chemotherapy cycles. Ciprofloxacin is recommended at 500 mg orally twice daily for 10 days starting day 5 of each cycle for remaining chemotherapy cycles. If ciprofloxacin is not available or not tolerated, another oral antibiotic **must** be used. The choice of an antibiotic is at the discretion of the investigator.

Use of Prophylactic G-CSF

The use of G-CSF is permitted only:

- As prophylactic treatment in patients with a prior episode of febrile neutropenia or infection in earlier cycle (see dose modification section 9.2.1.3).
- As prophylactic treatment in patients with risk factors according to figure 4 (page 28).

The aims of use of G-CSF in this trial are to prevent febrile neutropenia to reduce therapy related morbidity and to prevent dose delay or dose reduction in more than 10 % of patients to optimise outcome parameters.

It is highly recommended to use Neulasta® as G-CSF prophylaxis according to table 3. The use of G-CSF biosimilars is not permitted.

Table 2: Dose and Schedule for G-CSF Prophylaxis

	Neulasta®
Dose	6 mg / cycle
Route	Subcutaneous
Schedule	One single injection per cycle on day 2 (24h after chemotherapy).

Neulasta® as primary prophylaxis (i.e. from 1st cycle onwards) is not mandatory but may be used at the discretion of the investigator.

Use of Prophylactic Antiemetics
Antiemetic prophylaxis is mandatory for all patients. Selection of antiemetics is at the discretion of the investigator.

9.4.2 Identity of Investigational Product(s)

All study medication will be commercial ware and not be labelled study specific. Since July 1st 2010 an extension for the marketing authorisation of Taxotere® was given by the EMA for early breast cancer, node negative disease. Therefore since July 20th 2010 Taxotere® will not be free of charge for these patients anymore. For preparation of the chemotherapy solutions and storage, please refer to the summary of product characteristics (SmPCs) of the agents.

Taxotere (Docetaxel): strength: 80 mg, dosage form: concentrate and solvent for production of an infusion solution; application form: i.v.; batch number:

Farmorubicin (Epirubicinhydrochlorid): 10 mg, 20 mg, 50 mg, dosage form: injection solution; application form: i.v.; batch number:

Endoxan (Cyclophosphamid): 100 mg, 200 mg, 500 mg or 1 g, dosage form: powder for the production of an injection solution, application form: i.v.; batch number

9.4.3 Method of Assigning Patients to Treatment Groups

All eligible patients must be randomised by the WSG study coordinator.

A patient who has not been randomised before the first treatment administration will not be accepted for the study at a later date.
The registration forms should be faxed to the coordinators of the study. A registration package outlining the exact process for registering a patient and the registration forms will be forwarded and reviewed to all sites at the initiation site visit by the site CRA.
Registration can be made once eligibility of the patient is checked (including laboratory, HER2 status, ECG/LVEF and radiological results).

The following information was requested:

- Institution name
- Investigator's name
- Patient's identifiers (site number, patient code)
- Patient's birth date (day/month/year)
- Date start of treatment planned

Each eligible patient will be randomised to receive either docetaxel and cyclophosphamide or epirubicin and cyclophosphamide followed by docetaxel.
Investigators will be notified by fax immediately after ALL information has been received from the site as per the registration form. This fax will contain the patient's study number and the randomly allocated treatment group.

All patients registered for the study will have their birth date entered chronologically on the patient log at the initial visit. In the event a patient is excluded from study participation, the reason is to be documented in the space provided on the patient log.
Each patient will be assigned a patient randomisation number on registration, consisting 4 digits for the patient. This number is to be entered on the case report form.

Registration to the planB-trial was made once the patient consented to participate (shipping of tumor block for central pathology review, evaluation of Recurrence Score, participation in chemotherapy question) and the eligibility of the patient was confirmed.
Patients will be registered for screening after signing the informed consent form for participation in planB trial. A patient who does not agree in shipment of tumor material will not be considered to be eligible for the trial.
The registration forms, which were part of the eCRF, had to be completed online, printed, signed by an investigator and faxed to the study coordinator of the Westdeutsche Studiengruppe GmbH. The study participation had to be documented in the patient file.

The following information was requested:

- Institution name
- Investigator's name
- Patient's identifiers (site number, patient screening number)
- Patient's birth date (day/month/year)
- TNM
- Date of signing ICF
- Verification of selected inclusion and exclusion criteria as identified in the patient registration form

The subject identification (ID) number was provided by a service tool implemented in the screening form of the electronic case report form (eCRF). Patients were numbered

consecutively independent from the treatment Arm. Patients were assigned to treatment groups via HER2-status.

9.4.4 Selection of Doses in the Study

Not more than 14 days should elapse between the date of randomisation and the start date of the first cycle of adjuvant chemotherapy.
Chemotherapy doses will be calculated according to baseline body surface area (BSA) for all cycles. If there is a 10 % or greater decrease in body weight compared to baseline, the BSA will be recalculated. If the calculated BSA of the patient is > 2.0 m², the dose to be given to the patient will be calculated according to BSA = 2.0 m². No ideal body weight should be used for the calculation of BSA.
Dose adjustments and/or treatment delay and treatment discontinuation are planned for each arm in case of severe hematologic and/or non-hematologic toxicities.
In the event of relapse during treatment, unacceptable toxicities, withdrawn consent, treatment shall finish earlier.

Arm A: Docetaxel-Cyclophosphamide (TC)
TC treatment will consist of 6 cycles of docetaxel and cyclophosphamide.
Docetaxel will be given first:

Dose:	75 mg/m², day 1
Route:	1 hour intravenous infusion. During the first 5 minutes, the infusion must be done drop by drop in order to reduce the incidence of acute hypersensitivity reaction (AHSR).
Schedule:	Every 3 weeks

Followed by cyclophosphamide:

Dose:	600 mg/m², day 1
Route:	5 to 60 minutes intravenous bolus injection (as per hospital policy)
Schedule:	Every 3 weeks

This is called a cycle of treatment and will be given 6 times.
In the event of relapse during treatment, unacceptable toxicities or withdrawn consent, treatment shall finish earlier.

Arm B: EC➔Docetaxel (EC-DOC)
EC Segment:
Epirubicin

Dose:	90 mg/m², day 1
Route:	5 - 15 minute intravenous bolus injection (as per hospital policy)
Schedule:	Every 3 weeks

Followed by cyclophosphamide

Dose:	600 mg/m², day 1
Route:	5 to 60 minutes intravenous bolus injection (as per hospital policy)
Schedule:	Every 3 weeks

This is called a cycle of treatment and is to be given 4 times. Following completion of 4 cycles, the patient will enter the docetaxel segment for this arm of treatment.

Docetaxel Segment:

Three weeks after the last course of EC, docetaxel will be given

Dose: 100 mg/m², day 1

Route: 1 hour intravenous infusion. During the first 5 minutes, the infusion must be done drop by drop in order to reduce the incidence of acute hypersensitivity reaction (AHSR).

Schedule: Every 3 weeks

This is called a cycle of treatment and is to be given 4 times.

In the event of relapse during treatment, unacceptable toxicities or withdrawn consent, treatment shall finish earlier.

Patients will be treated as per protocol or until disease progression or withdrawal from treatment due to an unacceptable adverse event or treatment consent withdrawal. Prior to each chemotherapy cycle subjects has to be evaluated for evidence of drug-related adverse events.

Toxicities will be graded using the NCI Common Toxicity Criteria (NCI CTC), version 3.0.

Dose reduction is planned for each arm in case of severe hematological and/or non-hematological toxicities. Chemotherapy dose adjustments are to be made according to the organ system showing the greatest degree of toxicity. In case of several toxicities in one patient and conflicting recommendations, the most conservative dose adjustment has to be followed.

Doses which have been reduced for toxicity must not be re-escalated with the exception of liver function tests that improve within ranges given.

Treatment with chemotherapy may be delayed no more than 2 weeks (up to day 35) to allow recovery from acute toxicity.

9.4.5 Selection and Timing of Dose for each Patient

Selection of Timing and Dose was applied as described under 9.4.4.

9.4.6 Blinding

No blinding was performed.

9.4.7 Prior and concomitant therapy

For permitted prophylactic premedications please refer to section 9.4.1 of the report.

Ancillary treatments will be given as medically indicated. They must be specified in the Case Report Form.

The following treatments are not permitted:

Any drugs and anticancer treatments while on study (till relapse or up to 5 years after EOT) without consultation with the sponsor.

Corticosteroids, except as outlined in previous sections as premedication, antiemetics, and acute hypersensitivity reaction during the course of active treatment with chemotherapy and except in cases of chronic treatment at a low dose initiated at least 6 months prior to study entry.

Concomitant treatment with bisphosphonates will not be allowed during the course of active treatment with chemotherapy. Subsequently, bisphosphonates may be used only for non-oncologic indications.

Concomitant treatment with amifostine (Ethyol®) will not be allowed during the course of active treatment with chemotherapy.

Use of dexrazoxane is not permitted.

9.4.8 Treatment Compliance

All study treatment was administered by the study investigator or designated member of staff.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

Table 3: Study evaluations during screening

	INVESTIGATIONS	TIMING within (time) prior to study entry
Patient informed consent	Obtained	prior to registration[1]
History and physical exam	History including: • Diagnosis of breast cancer • Menopausal status • Receptor status at diagnosis • General medical history including cardiac history and allergy • Concurrent illness and existing signs and symptoms • Concomitant medications and their indication used within one month prior to study entry Physical Exam including: • Height • Weight • Karnofsky index for Performance Status/vital signs	21 days prior to registration
Hematology	• Haemoglobin • WBC and neutrophil count • Platelet count	21 days prior to randomisation
Biochemistry	Liver function: • Alkaline phosphatase • ASAT (SGOT) • ALAT (SGPT) • Bilirubin Renal function: • Serum creatinine Electrolyts: • Na^+, K^+ • Cl^-	21 days prior to randomisation Liver function tests are to be repeated within 3 days, if abnormal results.
Urine Analysis	Dipstick	21 days prior to randomisation
ER/PR status	√	Prior to randomisation
HER2 status	√	Prior to randomisation
Pregnancy test	Urine or serum (if applicable)	7 days prior to randomisation

Imaging	Mandatory for all patients: • Contralateral mammography and/or ultrasound (mammogram is preferred), where applicable • Chest-X-Ray (PA and lateral), CT or MRI • Abdominal ultrasound and/or CT scan and/or MRI • Bone scan and bone X-ray in case of hot spots in bone scan Other instrumental examinations as indicated.	3 months prior to randomisation
ECG	ECG	6 weeks prior to randomisation
LVEF	Echocardiography or MUGA scan	6 weeks prior to randomisation

[1]Informed Consent should be obtained prior to any tests specified in this clinical protocol that are not part of the patient's routine care

All patients during the study must be evaluated according to the schedule outlined until they come off chemotherapy.

Table 4: Study evaluations during each cycle of chemotherapy

	INVESTIGATIONS	TIMING
History and physical Exam	Clinical History since previous infusion Physical Exam - including: • Weight • Karnofski index for Performance Status • Clinical tumor assessment	every 3 weeks[1]
Hematology[2]	• Haemoglobin • WBC • Neutrophils • Platelets count	every 3 weeks[1,2]
Biochemistry	• Alkaline phosphatase • ASAT (SGOT) • ALAT (SGPT) • Bilirubin • Serum creatinine • Electrolytes: Na^+, K^+, Cl^-	every 3 weeks[1]
Urine Analysis	Dipstick	every 3 weeks[1]
ECG and LVEF	Echocardiography or MUGA	As clinically indicated
Other Investigations		As clinically indicated

Adverse events including cardiac toxicity	Investigations as indicated	Serious Adverse Events should be reported within 24 hours anytime

[1]Within 3 days prior to chemotherapy.2For the first 100 patients randomised to each treatment arm hematology will be evaluated at days 1, 8, 11 and 14 during every cycle of chemotherapy to evaluate the incidence of febrile neutropenia. For all other patients weekly evaluation of hematology is madatory.

Table 6: Flow Chart of Examination.

Examination	Prior to registration / *randomisation	Prior to each cycle	End of Treatment[9]	Follow-up[10]
	Day - 21 to - 1	Day - 3 to 1	± 3 days	± 14 days[11] ± 28 days[12]
Patient informed consent	✓			
History	✓			
Physical examination Weight Performance Status	✓	✓	✓	✓
Signs and symptoms[1]	✓	✓	✓	
Adverse events, including cardiac		✓	✓	
Concomitant medication[2]	✓	✓	✓	
Hematology • Haemoglobin, WBC, neutrophils, platelets	✓*	✓[8, 13]	✓	
Biochemistry Liver function[3] • ASAT/ ALAT, AP, bilirubin Renal function • Creatinine **Elektrolytes** • **Na^+, K^+, Cl^-**	✓* ✓* ✓* ✓*	✓ ✓ ✓ ✓	✓ ✓ ✓ ✓	
Urine Analysis • **Dipstick**	✓*	✓	✓	
IHC or FISH TEST (negative)[4]	✓			
ER Status / PR Status[4]	✓*			
Pregnancy test (urine or serum)[5]	✓*			
ECG	✓[6]	As clinically indicated, see section 10		
LVEF	✓[6]	As clinically indicated, see section 10		
Imaging: • Mammography and/or ultrasound (mammogram is preferred)	✓[7]	As clinically indicated		

• Chest-X-ray (PA and lateral) and/or chest CT scan and/or chest MRI • Abdominal ultrasound or CT or MRI • Bone scan, bone X-ray in case of hot spots in bone scan		
Other investigations	as clinically indicated	

* Prior to randomisation not registration

[1]Signs and symptoms will be recorded for baseline in the appropriate CRFs and for ALL other visits in the Clinical Adverse Experience CRF.

[2]Concomitant medication will be recorded for baseline on the appropriate CRFs, and will include all medication used within one month prior to registration. For ALL other visits concomitant medication will be captured ONLY if related to adverse events.

[3]Liver function tests are to be repeated within 3 days, if abnormal results.

[4]Result must be known prior to randomisation.

[5]Within 7 days prior to randomisation.

[6]Within 42 days (6 weeks) prior to randomisation.

[7]Within 12 weeks prior to randomisation.

[8]CBC and differential is to be done every three weeks prior to receiving chemotherapy (day –1 or day 1 of each cycle). In case of fever $\geq$ 38.1°C, the CBC and differential must be performed and repeated every 2 days until recovery with temperature < 38.1°C or absolute neutrophil count $\geq$ 1.0

[9]End of Treatment evaluation will be performed 21 days after last dose of chemotherapy (including patients that did not complete all cycles)

[10]To be performed 9, 12, 15, 18, 24, 30, 36, 42, 48, 54 and 60 months after first day of chemotherapy

[11]For FU visits month 9, 12, 15, 18

[12]For FU visits month 24, 30, 42, 48, 54 and 60

[13]For the first 100 patients randomised to each treatment arm hematology will be evaluated at days 1, 8, 11 and 14 during every cycle of chemotherapy to evaluate the incidence of febrile neutropenia. For all other patients weekly evaluation of hematology is mandatory.

9.5.2 Appropriateness of Measurements

In Europe anthracycline-based regimens are standard for the node negative and positive population. Today's guidance for standard anthracycline regimens, as e.g. published by the German AGO, clearly recommend 6 cycles of an anthracycline-based triple chemotherapy with an adequate anthracycline dose of 20 mg/m^2 for doxorubicin and $\geq$ 30 mg/m^2 for epirubicin (Henderson IC et al., 2003). The most frequently used regimens combine fluorouracil, cyclophosphamide and epirubicin.

Henderson et al. showed in their studies superiority of doxorubicin dose of 60 mg/m^2 every 3 weeks vs. lower doses in adjuvant chemotherapy consisting of 4 cycles of EC in node-positive breast cancer. In their second study no additional benefit from dose increasing beyond 60 mg/m^2 could be shown (Henderson IC et al., 2003).

Thus, comparison of disease-free survival in patients treated with either 6 cycles of docetaxel / cyclophosphamide chemotherapy or 4 cycles of EC followed by 4 cycles of docetaxel as adjuvant treatment is a valid study outcome.

9.5.3 Primary Efficacy Variable(s)

The primary efficacy parameter will be 5 year disease-free survival. The disease-free survival is defined as the interval from the date of randomisation to the date of local, regional or metastatic relapse or the date of second primary cancer (with the exception of curatively treated non-melanoma skin cancer or in situ carcinoma of the cervix) or death from any cause whichever occurs first.

Objective Relapse
Any clinical or radiologic evidence of tumor relapse including the central nervous system. Obtain histologic or cytologic proof of failure, if feasible. Detail on flow sheets the appearance of any evidence of malignant disease. Follow-up for survival.

Local relapse
Defined as evidence of tumor in the breast surgical scar, ipsilateral breast (conservative surgery), or evidence of tumor in the ipsilateral anterior chest wall (mastectomy) or skin or soft tissues within the local area.
Histologic or cytologic proof is mandatory.

Regional relapse
Defined as evidence of tumor in the axillary scar, ipsilateral nodal areas (axillary, internal mammary, infraclavicular and supraclavicular) as well as skin or soft tissues within the regional area.
Histologic or cytologic proof is mandatory.

Distant relapse
Defined as evidence of tumor beyond the local-regional level as previously defined.
This includes the following:

1. Lymph nodes not included in the areas defined above (i.e. contralateral axilla, paratracheal, etc.)
2. Skin not included in the areas defined above
3. Liver
4. Lung
5. Bone
6. Central nervous system
7. Contralateral breast
8. Other sites not defined above

Histologic or cytologic proof is preferred especially in solitary lesions.
Elevation of serum markers such as CEA or CA15-3 by themselves will not constitute evidence of relapse without other objective evidence of relapse. These studies are not recommended.

9.5.4 Drug Concentration Measurements

Not applicable.

9.6 DATA QUALITY ASSURANCE

The quality assurance and quality control systems implemented of the following items:

9.6.1 Central Laboratory for Tumour Sample Diagnostics

One paraffin-embedded representative primary tumor block was collected.
For all HR+ patients Recurrence Score was calculated, the evaluation was done by Genomic Health.
The central pathology reviewed local histo-pathological results after evaluation of Recurrence Score for all patients.

9.6.2 Monitoring, Auditing and Inspecting

The study was monitored by regular site visits and telephone calls to the investigator by members of the sponsor or personnel designated by the sponsor WSG. During site visits, the monitor reviewed original patient records and document retention. Additionally, the monitor observed study procedures and discussed any problems with the investigator. The investigator provide direct access to source data/documents for trial related monitoring, audits, IRB/EC review and regulatory inspections.

9.6.3 Study Team Training and Investigator Meetings

Apart from written newsletters and individual training on site level through CRAs, all investigators were regularly (at least once a year) invited to join investigator meetings. These meetings were used to inform all investigators of the study status, present interim data, implement or train on existing processes.

9.6.4 Data Management Activities

All collected data were reviewed by the data management unit of Pallas Healthcare Consulting GmbH according to data management plan (DMP) and data validation plan (DVP).

9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.7.1 Statistical and Analytical Plans

The Kaplan-Meier product limit method will be used to estimate the disease-free survival and the overall survival. The log rank test, stratified for nodal status (N0, N1-3 versus N4+), for hormonal receptor status (estrogen and/or progesterone receptor positive versus negative) and age (<50 / ≥50), will be used to perform all pair wise comparisons between the two treatment arms with respect to disease-free survival and overall survival. Confidence intervals of the median disease-free and overall survival will be calculated using the method of Simon. To test the equivalence of both study treatments, the confidence interval method for the difference in survival probabilities derived from the usual logrank test based upon the observed number of events at each time point and the number expected in the new treatment proposed by PJA Skaff, JA Sloan (1998) will be used. The evaluation will be done by SAS® 9.1 using the algorithms developed for this publication.
Cox's proportional hazards regression analysis will be performed for disease-free survival and overall survival in order to adjust the treatment comparison for the major prognostic factors. These factors include age, menopausal status, type of surgery, histopathological findings, tumor size, pathological markers and molecular markers. Such adjusted analysis,

for instance by nodal status (N0, N1-3 versus N4+) will be reported with appropriate caveat.
In the statistical analysis, a centre will correspond to a participating institution. It is expected to have at the end of the study a large number of centres with few patients per centre. It is consequently not planned to include any centre effect in the analyses. However, should there be centres with a large recruitment, it is planned to compare the consistence of the results between this (these) large centre(s) and the entire study results, in terms of major baseline characteristics and the primary endpoint.

Prospectively planned analyses include analysis of primary endpoint disease-free survival according to topoisomerase II protein (different assay formats), triple negativity (ER -, PR -, HER2 -), etc.

9.7.2 Determination of Sample Size

The sample size determination was done based on the following assumption:

The primary objective of this trial is to show that the treatments under investigation do not differ in terms of disease-free survival.

The following assumptions were made:
Among patients treated with EC➔Doc in the NSABP B27 trial, 71.1 % of patients were disease-free at 5 years. In this study, an accrual period of 3 years and an additionally follow up of 5 years will be planed. The one–sided equivalence test will be done at the significance levels of false positive outcome α = 5 % and false negative outcome β= 20 % i.e. the power of the trial is set to 80 % for the difference of clinical interest. The study treatment will be regarded as equivalent to the reference treatment, if the difference in the 5 years disease-free survival between both study arms will not be greater as 4.4 %.

A total of 2x1224 = 2448 patients are necessary to have sufficient power to show equivalence between EC➔Doc and TC for all randomised patients, assuming an anticipated drop-out rate of 10 %.

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

After including 274 patients, the trial was amended (08/2009) to recommend endocrine therapy (ET) alone for pN0/pN1, locally HR+ patients with RS ≤ 11 (based on an initial RS validation study).

Any modifications to the protocol with impact to the conduct of the study, potential benefit of the patient or patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects required a formal amendment to the protocol. Such amendments were approved by the Ethics Committee prior to implementation and notified to the health authorities in accordance with local regulations.
Administrative changes of the protocol were minor corrections and/or clarifications that had no effect on the way the study is to be conducted. These administrative changes were be documented in a memorandum. The Ethics Committee was notified of administrative changes at the discretion of WSG.

10 STUDY PATIENTS

10.1 DISPOSITION OF PATIENTS

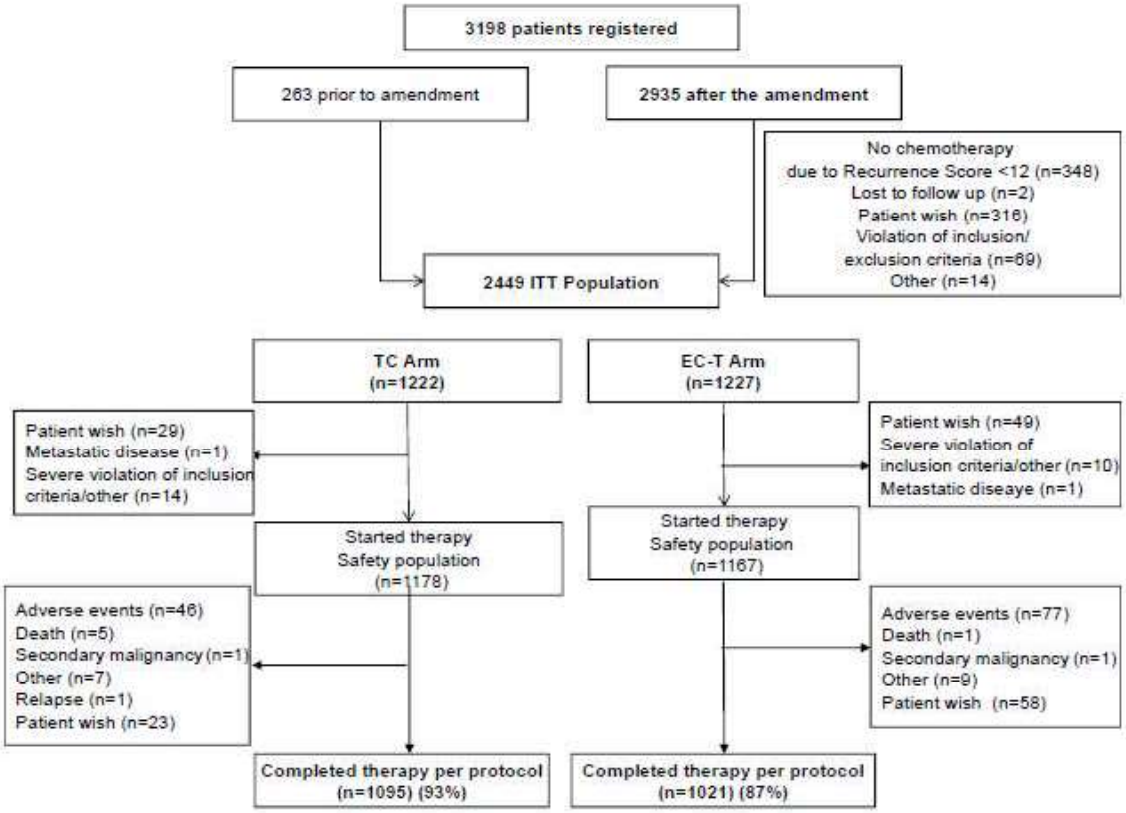

Figure 2: Diagram of PlanB-study.

10.2 PROTOCOL DEVIATIONS

3,198 patients were screened and registered. Of these patients, 2,449 were randomized to 6xTC (N=1,222) and 4xEC-4xT (N=1,227). 263 were randomized prior to the early amendment, which implemented RS testing for HR-positive patients, so 2,186 patients were subsequently tested for RS.

Endocrine therapy (but not chemotherapy) was administered to 348 pN0-1 patients, based on RS≤11; 401 patients were not randomized to chemotherapy for other reasons, including 316 who refused further study participation, particularly in the node-negative group with RS 12-18 (approximately one-third of patients).

1,095 patients of Arm A and 1,021 patients of Arm B completed therapy per protocol (for details please refer to CONSORT diagram).

11

11 EFFICACY EVALUATION

11.1 DATA SETS ANALYSED

The ITT population was determined as described in the CONSORT diagram and included 2,449 randomized patients.

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Between 2/2009 and 12/2011, 3,198 patients were registered and 2,449 were randomized to 6xTC (N=1,222) and 4xEC-4xT (N=1,227). Of these 2,449 randomized patients, 263 were randomized prior to the early amendment, which implemented RS testing for HR-positive patients, 2,186 subsequently. Endocrine therapy (but not chemotherapy) was administered to 348 pN0-1 patients, based on RS≤11; 401 patients were not randomized to chemotherapy for other reasons, including 316 who refused further study participation, particularly in the node-negative group with RS 12-18 (approximately one-third of patients).

Patient characteristics were well-balanced between the study arms. Median age of chemotherapy-treated patients was 55 (range: 25-77) years; approximately 40% had node-positive disease, and about 44% had poorly differentiated tumors (by central assessment).

Table 5: Baseline characteristics

Patient characteristics		**Arm**			
		TC		**EC-T**	
		N	**%**	**N**	**%**
Menopausal status	pre	439	39.2%	429	37.8%
	post	682	60.8%	706	62.2%
Surgery	BCS	995	81.6%	990	80.8%
	Mastectomy	224	18.4%	235	19.2%
pN	pN0	727	59.5%	714	58.2%
	pN1	404	33.1%	428	34.9%
	pN2	72	5.9%	63	5.1%
	pN3	19	1.6%	22	1.8%
pT	pT1	637	52.3%	705	57.6%
	pT2	532	43.6%	471	38.4%
	pT3	41	3.4%	42	3.4%
	pT4	9	0.7%	7	0.6%
HR status (local)	negative	217	17.8%	228	18.6%
	positive	1005	82.2%	999	81.4%
Triple negative (central)	no	917	81.1%	916	81.3%
	yes	214	18.9%	211	18.7%

Ki-67 (central; semi-quantitative)		0-10	364	33.5%	384	35.4%
		15-35	567	52.1%	560	51.6%
		≥40	157	14.4%	141	13.0%
Grade (central)		Central G1-2	659	56.0%	664	56.3%
		Central G3	518	44.0%	516	43.7%
Grade (local)		Local G1-2	782	64.2%	787	64.2%
		Local G3	437	35.8%	438	35.8%
Recurrence (HR+)	**Score**	≤25	703	72.5%	710	73.8%
		>25	266	27.5%	252	26.2%

11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

Neither any measurements of compliance of individual patients with the treatment regimen under study nor any drug concentration measurements in body fluids were performed. The application of any study related treatment was done by the investigator according to study protocol. Drug accountability was documented and monitored.

11.4 EFFICACY RESULTS AND TABULATIONS OF PATIENT DATA

11.4.1 Analysis of efficacy

After a median follow-up of 60 months (in patients alive at time of follow-up), no significant differences in DFS, dDFS, or OS were observed between the study arms. Estimated 5-year DFS was 89.6% (95%-CI, 87.8% to 91.5%) in TC v 89.8% (95%-CI, 87.9% to 91.6%) in EC T, with hazard ratio 1.004 (95%-CI, 0.776 to 1.299). Estimated 5-year dDFS was 94.1% (95%-CI, 92.7% to 95.5%) in TC v 93.4% (95%-CI, 91.9% to 94.9%) in EC T, with hazard ratio 0.875 (95%-CI, 0.625 to 1.225). Estimated 5 year OS was 94.7% (95%-CI, 93.3% to 96.1%) in TC v 94.5% (95%-CI, 93.1% to 95.9%) in EC T, with hazard ratio 0.937 (95%-CI, 0.654 to 1.342). The trial criterion for non-inferiority was achieved, because the upper 90% confidence limit for the DFS hazard ratio (appropriate for the planned one-sided non-inferiority test at alpha=0.05) of 1.246 did not exceed the limiting non-inferiority hazard ratio 1.467, corresponding to the permitted 4.4% margin at the observed 5-year DFS of 89.8% in EC-T. (However, this upper 90% confidence limit 1.246 did exceed the limit of 1.187 derived from the originally assumed 5-year DFS of 71.1% in EC T.)

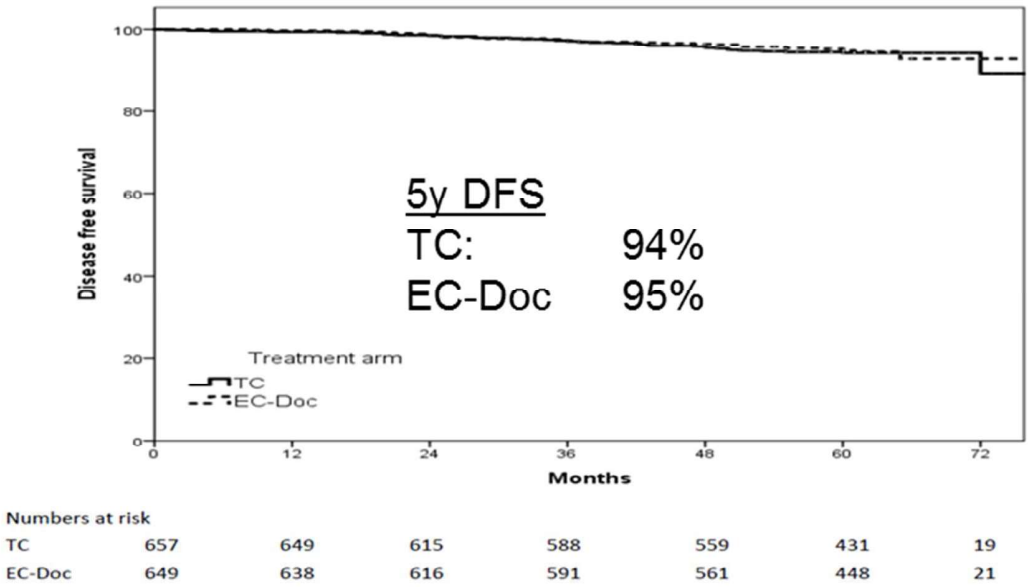

Figure 3: DFS by treatment arm and RS result. The population includes intent-to-treat patients with RS measured (after early amendment). The box under each graph presents the number of patients at risk at each time point. Patients in the ITT population with missing follow-up data (TC:69, EC-Doc:99) are omitted.

Figure 4 presents a forest plot showing efficacy of TC v EC-T (hazard ratio<1 would favor TC) according to several key prognostic factors, RS, nodal status, luminal A-like (Ki-67<15%) v luminal B-like (Ki-67≥15%), local and central grade, and triple-negative (TN) status. Anthracycline-free chemotherapy (TC) was comparable to anthracycline-containing chemotherapy (EC-T) in all evaluated subgroups. There was no significant "predictive" trend for patients with poorer prognosis according to any of these factors to benefit from anthracycline. Particularly, although, as previously reported, 6,7 RS had a substantial prognostic impact in this trial, 5-year DFS, dDFS, and OS were very similar in the study arms within the subgroups RS≤25, RS>25.

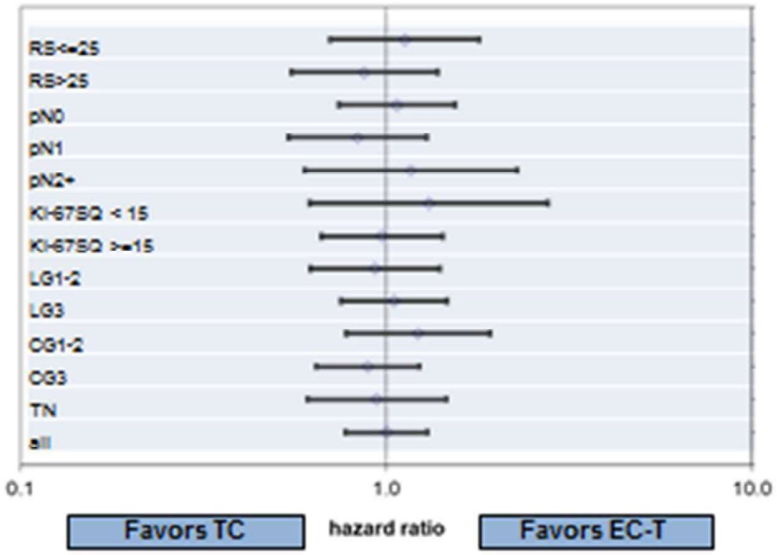

Figure 4: Forest plot of DFS in subgroups, according to chemotherapy arm

Also, 5-year DFS (94.6%; 95%-CI, 92.0% to 97.2%) and dDFS (97.8%; 95%-CI, 96.0% to 99.6%) were excellent in patients not treated with adjuvant chemotherapy, regardless of nodal status (DFS/dDFS: 94.5%/97.7% in node-negative and 94.9%/97.9% in pN1 disease, respectively).

In univariate analysis for DFS, nodal status, tumor size, surgery, local and central grade, continuous RS, progesterone receptor (PR), and Ki-67 were prognostic factors. In a multivariate analysis, only RS and Ki-67 as continuous variables, nodal status, histological grade, and surgery type, were significant and entered the model, whereas study arm, tumor size, ER, and PR were not.

11.4.2 Statistical/Analytical Issues

Please refer to section 9.7.

11.4.2.1 Adjustments for Covariates

Not applicable.

11.4.2.2 Handling of Dropouts or Missing Data

The analysis performed after premature termination of the trial was mainly descriptive. No specific measures were performed to impute missing values.

11.4.2.3 Interim Analyses and Data Monitoring

When the data of the first 100 patients per each treatment arm were completely evaluable for the whole chemotherapy treatment period one safety interim analysis was performed. The results were reviewed by the IDMSC.

11.4.2.4 Multicentre Studies

In total, 98 sites participated in the PlanB study.

11.4.2.5 Multiple Comparison/Multiplicity

Not applicable.

11.4.2.6 Use of an "Efficacy Subset" of Patients

Not applicable.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

Not applicable.

11.4.2.8 Examination of Subgroups

For DFS, dDFS, OS the analyses were done including all patients as well as per clinical subgroup.
In addition, Hazard ratios for TC versus ET-C and CIs were computed in clinically relevant subgroups.

11.4.3 Tabulation of individual response data

Not applicable.

11.4.4 Drug dose, Drug Concentration, and relationships to response

Not applicable.

11.4.5 Drug-drug and Drug-disease interactions

Not applicable.

11.4.6 By-patient displays

Not applicable.

11.4.7 Efficacy conclusions

PlanB is one of four international large randomized trial programs evaluating an anthracycline-free regimen (6xTC) versus a conventional anthracycline-taxane regimen (TaxAC) in HER2-negative EBC. It is unique in that only clinically high-risk (TN, pN2-3) or genomically intermediate/high risk HR-positive/pN0-1 patients were eligible. DFS, dDFS and OS were excellent and virtually identical in patients receiving the anthracycline-containing and anthracycline-free regimens. Subgroups benefiting from the anthracycline-containing regimen were not identified, though a potential benefit in particular (e.g., high-risk) subgroups cannot be ruled out.
Concerning genomic testing, robust retrospective evidence has demonstrated negligible, marginal, and high benefit from administering chemotherapy (in addition to endocrine therapy) in patients with HR-positive tumors and low, intermediate, and high RS, respectively.(Paik et al., 2006, Albain et al., 2010) Prospective evidence from TAILORx for RS<11 pN0 patients confirmed excellent outcomes without adjuvant chemotherapy.(Sparano et al., 2015) Similarly, those 17% of pN0-1 patients with low RS in PlanB who were spared chemotherapy had an excellent 5-year DFS of 94% and dDFS of 98%.(Nitz et al., 2017, Gluz et al., 2017)
In PlanB, the majority of patients with HR-positive tumors underwent RS testing (versus 4% in ABC), so that homogeneously treated, genomically intermediate and high-risk groups were available for analysis. In both RS≤25 and RS>25 patients, the anthracycline-free regimen was non-inferior by exploratory analysis, indicating that RS is not a clinically relevant predictor of anthracycline efficacy, as previously shown for taxanes.(Mamounas et al., 2012, Penault-Llorca et al., 2014)

In WSG PlanB, 5-year DFS and OS for TC and EC-T were equally excellent. Thus, for EBC patients at intermediate risk of recurrence, 6xTC is a safe and effective chemotherapy option

12 SAFETY EVALUATION

12.1 EXTENT OF EXPOSURE

12.2 ADVERSE EVENTS (AEs)

12.2.1 Brief Summary of Adverse Events

The 10 most frequent adverse events by total count of occurrences (% for total number of AE occurrences) were:

(1) Leukopenia	(11,2%)	3446 events
(2) Neutropenia	(10,3%)	3190 patients
(3) Fatigue	(5,2%)	1616 patients
(4) Nausea	(5%)	1548 patients
(5) Leukocyte count decrease	(4%)	1250 patients
(6) Alopecia	(3,7%)	1136 patients
(7) Neutrophil count decrease	(2,9%)	909 patients
(8) Diarrhoea	(2,8%)	855 patients
(9) Bone pain	(2,3%)	720 patients
(10) Mucositis	(2,3%)	703 patients

12.2.2 Display of Adverse Events

Table 6: Number of Adverse Events in total

	n	**%**
All adverse events	**30902**	**(100%)**

DISPLAY OF ADVERSE EVENTS BY TERM
Please refer to 14.3.1

ADVERSE EVENTS BY SYSTEM ORGAN CLASS (SOC)
Table 7: Adverse Events by system organ class

System organ classes		
	n	%
Blood and lymphatic system disorders	7813	25,283
Gastrointestinal disorders	4999	16,177
General disorders and administration site conditions	3571	11,556
Investigations	3049	9,867

Skin and subcutaneous tissue disorders	2606	8,433
Nervous system disorders	2101	6,799
Musculoskeletal and connective tissue disorders	2012	6,511
Infections and infestations	1070	3,463
Respiratory, thoracic and mediastinal disorders	690	2,233
Vascular disorders	650	2,103
Eye disorders	504	1,631
Psychiatric disorders	390	1,262
Cardiac disorders	382	1,236
Metabolism and nutrition disorders	292	0,945
Immune system disorders	153	0,495
Social circumstances	148	0,479
Renal and urinary disorders	131	0,424
Ear and labyrinth disorders	109	0,353
Reproductive system and breast disorders	71	0,230
Injury, poisoning and procedural complications	69	0,223
Surgical and medical procedures	56	0,181
Hepatobiliary disorders	17	0,055
Endocrine disorders	13	0,042
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	0,013
Congenital, familial and genetic disorders	2	0,006

DISPLAY OF ADVERSE EVENTS GRADE >2 IN TOTAL

Table 8: Display of Adverse Events with Grade >2 in total

	TC		**EC-T**		***P* value**
Leukopenia	598	50.8%	671	57.5%	.001
Neutropenia	598	50.8%	676	57.9%	.001
Anemia	4	0.3%	9	0.8%	.18
Febrile neutropenia	63	5.3%	45	3.9%	.09
Infection	82	7.0%	62	5.3%	.1
Nausea	20	1.7%	44	3.8%	.002

Vomiting	5	0.4%	23	2.0%	<.001
(Peripheral) poly-neuropathy	10	0.8%	26	2.2%	.007
Hand-foot syndrome/palmar syndrome	9	0.8%	33	2.8%	<.001
Diarrhea	37	3.1%	39	3.3%	.8
Mucositis/stomatitis	20	1.7%	43	3.7%	.003
Arthralgia/myalgia	18	1.5%	35	3.0%	.02
Pain	37	3.1%	61	5.2%	.01
Cardiac failure	3	0.3%	3	0.3%	1.0
Fatigue	35	3.0%	68	5.8%	.001
Thrombosis	19	1.6%	24	2.1%	.48
Therapy related deaths	5	0.4%	1	0.08%	.2
Cardiac-related deaths*	2	0.1%	2	0.1%	1.0
Acute myeloid leukemia*	0	0	1	0.08%	.3

DISPLAY OF ADVERSE EVENTS GRADE >2 BY TERM
See AE-listing attached

12.2.3 Analysis of Adverse Events

Grade 3-4 leukopenia, neutropenia, nausea, vomiting, (peripheral) polyneuropathy, hand-foot syndrome, mucositis/stomatitis, arthralgia, myalgia, and fatigue were observed in significantly more EC-T than TC-treated patients. Only a non-significant trend towards the higher frequency of grade 3-4 infections and febrile neutropenia under TC were not significant. Use of primary G-CSF during the first cycle of therapy was documented in 14.9% and 4.9% of patients in the TC and EC-T arms, respectively (P<.001). Febrile neutropenia rates were significantly lower in patients with primary prophylaxis during first cycle of therapy in the TC arm (primary prophylaxis *v* not: 1.7% *v* 6.0%; P=.02).

12.2.4 Listing of Adverse Events by Patient

Not applicable.

12.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

12.3.1 Listing of Deaths, other Serious Adverse Events and Other Significant Adverse Events

12.3.1.1 Deaths

Table 9: Display of deaths.

Subject ID	Site ID	Treatment arm	Last cycle number	Date of death	Age of patient	Cause of death	Causal relationship to study medication
0530	046	A	1	11.12.2009	74	Urosepsis	yes
1503	22	A	4	24.10.2010	70	Suspected pulmonary embolism	yes
2812	041	A	2	14.06.2010	63	Streptococcal sepsis, Kreislauf- u. Multiorganversagen	yes
0227	021	A	4	23.11.2009	57	Kardiopulmonales Versagen auf Grund einer Peritonitis	no
1463	055	A	3	07.11.2010	56	Linksventikuläres Herzversagen infolge Staphylokokkus epidermidis Sepsis	yes
2800	096	B	5	06.10.2011	65	Sepsis mit Hypotonie	yes

Other serious adverse events

Not applicable.

Other significant adverse events

Not applicable.

12.3.1.2 Other Serious Adverse Events

Not applicable.

12.3.1.3 Other Significant Adverse Events

Not applicable.

12.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

Not applicable – for discussion of deaths, see below.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

Six treatment-related deaths were observed within the study: Five in the TC arm (0.4%) and one (0.1%) in the EC-T arm (*P*=.2). Five of them were due to infections/septicaemia. The EC-T arm, compared to the TC arm, was characterized by significantly more dose reductions (78 [6.6%] *v* 230 [19.7%]; *P*<.001) and dose delays (>7 days) (78 [6.7%] *v* 47 [4.0%]; *P*=.004). Overall, 87% and 93% of patients in these respective arms completed therapy by protocol.
In further follow-up, four deaths (TC/EC-T: 2/2) were observed due to heart failure and one due to acute myeloid leukemia (EC-T arm).

12.4 CLINICAL LABORATORY EVALUATION

Not applicable.

12.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

Not applicable.

12.6 SAFETY CONCLUSIONS

In terms of acute toxicity WSG-PlanB slightly favors TC. Patients treated with an anthracycline-containing regimen had more nausea and vomiting, whereas those treated with TC had more neutropenia or slightly more febrile neutropenia. Early on, a numerical excess of infection-related deaths was observed in the WSG-PlanB TC arm, but after release of recommendations for particular caution in patients with preexisting gastrointestinal disease (e.g. known diverticulosis), no further deaths occurred. Jones et al. reported a single incident of congestive heart failure for AC (0.2%) and none for TC. In WSG-PlanB, cardiac failure was reported in 0.3% of patients in both arms, consistent with data showing clinically meaningful cardiac longterm toxicity of third-generation regimens containing TaxAC. Overall, WSG PlanB safety results are consistent with those of the ABC trials (specifically, the safety analysis of NSABP B-49) showing no clinically relevant differences in frequencies of severe adverse events in TaxAC versus TC In summary, both regimens are well tolerated, but side effect profiles differ.

13 DISCUSSION AND OVERALL CONCLUSIONS

Please refer to the publications resulting from the PlanB trial

- Nitz U, Glu, O, Clemens M, et al: Prospective WSG Phase III PlanB trial: Adjuvant 4xEC-4xT versus 6xTC in HER2- negative Early Breast Cancer. JCO, *accepted*

- Nitz U, Gluz O, Christgen M, et al: Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomized phase 3 West German Study Group (WSG) PlanB trial. Breast Cancer Res Treat 2017; 165(3): 573-583
- Gluz O, Nitz U, Christgen M, et al: West German Study Group Phase III PlanB Trial: First Prospective Outcome Data for the 21-Gene Recurrence Score Assay and Concordance of Prognostic Markers by Central and Local Pathology Assessment. JCO 2016; 34(20):2341-9

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 DEMOGRAPHIC DATA

Not applicable.

14.2 EFFICACY DATA

Not applicable.

14.3 SAFETY DATA

14.3.1 Displays of Adverse Events

Adverse event term		
	n	%
Leukopenia	3446	11,151
Neutropenia	3190	10,323
Fatigue	1616	5,229
Nausea	1548	5,009
Leukocyte count decreased	1250	4,045
Alopecia	1136	3,676
Neutrophil count decreased	909	2,942
Diarrhoea	855	2,767
Bone pain	720	2,330
Mucositis	703	2,275
Anaemia	542	1,754
Stomatitis	517	1,673
Sensory neuropathy	422	1,366
Vomiting	373	1,207
Nail changes	361	1,168
Constipation	349	1,129
Taste alteration	331	1,071
Headache	318	1,029
Leukocytopenia	311	1,006
Arthralgia	310	1,003
Dyspnoea	288	0,932
Oedema	285	0,922

Obstipation	263	0,851
Fever	256	0,828
Watering eyes	221	0,715
Myalgia	211	0,683
Insomnia	182	0,589
Heartburn	176	0,570
Hot flushes	164	0,531
Haemoglobin decreased	159	0,515
Hand and foot syndrome	158	0,511
Polyneuropathy	152	0,492
Dizziness	152	0,492
Anorexia	139	0,450
Mucositis oral	130	0,421
Rash	123	0,398
Dysgeusia	122	0,395
Cardiac disorder	120	0,388
Febrile neutropenia	118	0,382
Cough	106	0,343
Cold	103	0,333
Non-smoker	102	0,330
Dry skin	101	0,327
Musculoskeletal pain	94	0,304
Cystitis	94	0,304
Hypertension arterial	92	0,298
Back pain	91	0,294
Common cold	89	0,288
Allergic reaction	89	0,288
Paraesthesia	80	0,259
Absolute neutrophil count decreased	80	0,259
Pain	79	0,256
Infection	76	0,246
Joint pain	75	0,243
Tachycardia	73	0,236
Abdominal pain	72	0,233
Taste disturbance	71	0,230
GPT increased	71	0,230
Flushing	71	0,230
Vertigo	69	0,223
Epistaxis	68	0,220
Emesis	68	0,220
Stomach pain	67	0,217

Conjunctivitis	66	0,214
Pain stomach	62	0,201
Hand and foot skin reaction	62	0,201
Pruritis	61	0,197
Haemoglobin low	61	0,197
Urinary tract infection	58	0,188
Hot flush	57	0,184
Thrombocythaemia	53	0,172
Dry mouth	53	0,172
ALT increased	53	0,172
Sleep disorder	52	0,168
Onycholysis	49	0,159
Exanthem	49	0,159
Oedema limbs	48	0,155
Lymphopenia	48	0,155
Pain joint	46	0,149
Unevaluable event	45	0,146
Edema legs	45	0,146
Bronchitis	45	0,146
Muscle pain	44	0,142
AST increased	44	0,142
Depression	42	0,136
Rheumatism	41	0,133
Catheter infection	41	0,133
Appetite lost	41	0,133
Pain bone	39	0,126
Neuropathy	39	0,126
Hysterectomy	39	0,126
Pain in limb	38	0,123
GOT increased	38	0,123
Dry eyes	38	0,123
Hypotension	37	0,120
Dysphagia	37	0,120
LDH increased	36	0,116
Hypertension	36	0,116
Erythema	36	0,116
Diarrhea	36	0,116
Thrombopenia	35	0,113
Sore throat	34	0,110
Pain muscle	32	0,104
Neurotoxicity	31	0,100

Gastritis	31	0,100
Dry eye	31	0,100
Palmar-plantar erythema	30	0,097
Venous thrombosis	29	0,094
Alkaline phosphatase increased	29	0,094
Granulocytopenia	28	0,091
Redness facial	27	0,087
Platelet count decreased	27	0,087
General body pain	27	0,087
Allergy	27	0,087
Pneumonia	26	0,084
Weight loss	25	0,081
Sweaty	25	0,081
Smoker	25	0,081
Skin rash	25	0,081
Mucosal dryness	25	0,081
Chills	25	0,081
Aspartate aminotransferase decreased	25	0,081
Urticaria	24	0,078
Herpes zoster	24	0,078
Amblyopia	24	0,078
Weight gain	22	0,071
Vulval abscess	22	0,071
Thrush	22	0,071
Syncope	22	0,071
Loss of taste	22	0,071
Alanine aminotransferase increased	22	0,071
Palpitation	21	0,068
Pain NOS	21	0,068
Pain legs	21	0,068
Pain in extremity	21	0,068
Oedema legs	21	0,068
Haemorrhoids	21	0,068
Flu like symptoms	21	0,068
Eczema	21	0,068
Dysuria	21	0,068
Coronary heart disease	21	0,068
Stomach ache	20	0,065
Pyrosis	20	0,065
Peripheral sensory neuropathy	20	0,065
Palpitations	20	0,065

Lymphoedema	20	0,065
Hyperglycaemia	20	0,065
Ex-smoker	20	0,065
Thrombosis	19	0,061
Thrombocyte count decreased	19	0,061
Oedema peripheral	19	0,061
Gamma-glutamyltransferase increased	19	0,061
Exanthema	19	0,061
Dry cough	19	0,061
Diabetes	19	0,061
Mood altered	18	0,058
Migraine	18	0,058
Taste changed	17	0,055
Reduced general condition	17	0,055
Neuropathy peripheral	17	0,055
Dyspnoea exertional	17	0,055
Dyspepsia	17	0,055
Thrombophlebitis	16	0,052
Tearing eyes	16	0,052
Smell alteration	16	0,052
Sleep disturbance	16	0,052
Redness	16	0,052
Pain in arm	16	0,052
Neuralgia	16	0,052
Leukocytosis	16	0,052
Facial rash	16	0,052
Edema	16	0,052
Ageusia	16	0,052
Respiratory infection	15	0,049
Herpes labialis	15	0,049
Disorder circulatory system	15	0,049
Tinnitus	14	0,045
Subclavian vein thrombosis	14	0,045
Hypokalaemia	14	0,045
Gamma GT increased	14	0,045
CRP increased	14	0,045
Concentration loss	14	0,045
Breast pain	14	0,045
Wound complication	13	0,042
Thrombosis arm	13	0,042
Sinusitis	13	0,042

Runny nose	13	0,042
Gastric pain	13	0,042
Flatulence	13	0,042
Drug allergy	13	0,042
Blurred vision	13	0,042
Weakness	12	0,039
Upper respiratory tract infection	12	0,039
Tonsillitis	12	0,039
Rhinitis	12	0,039
Pain throat	12	0,039
Nail pain	12	0,039
Nail disorder	12	0,039
Mastitis	12	0,039
Leg pain	12	0,039
Leg edema	12	0,039
GGT decreased	12	0,039
Gastralgia	12	0,039
Creatinine increased	12	0,039
Blood LDH abnormal	12	0,039
Bleeding nose	12	0,039
Arrhythmia	12	0,039
Shoulder pain	11	0,036
Pain in fingers	11	0,036
Eye infection	11	0,036
Erysipelas	11	0,036
Edematous feet	11	0,036
Drug maladministration	11	0,036
Circulatory insufficiency	11	0,036
Cephalgia	11	0,036
Acne	11	0,036
Unspecified circulatory system disorder	10	0,032
Tremor	10	0,032
Sinus tachycardia	10	0,032
SGPT increased	10	0,032
Pain back	10	0,032
Nocturia	10	0,032
Feeling cold	10	0,032
Edema face	10	0,032
Edema arms	10	0,032
Dermatitis	10	0,032
Decreased appetite	10	0,032

Catheter site pain	10	0,032
Cardiac pain	10	0,032
Bronchial infection	10	0,032
Agitation	10	0,032
Abdominal pain upper	10	0,032
Vaginal mycosis	9	0,029
Tooth pain	9	0,029
Thoracic pain	9	0,029
Pulmonary embolism	9	0,029
Pharyngitis	9	0,029
Paraesthesia foot	9	0,029
Pain chest	9	0,029
Nose bleeds	9	0,029
Neck pain	9	0,029
Influenza	9	0,029
Inflammation localised	9	0,029
Herpes simplex	9	0,029
Gingivitis	9	0,029
Edema limbs	9	0,029
Depression aggravated	9	0,029
Catheter related complication	9	0,029
Cardiac arrhythmia	9	0,029
Anxiety	9	0,029
Tooth infection	8	0,026
Swelling arm	8	0,026
Paraesthesia of fingers	8	0,026
Painful feet	8	0,026
Pain head	8	0,026
Pain foot	8	0,026
Oliguria	8	0,026
Nasal irritation	8	0,026
Mycosis	8	0,026
Hoarseness	8	0,026
Hand rash	8	0,026
Flu-like illness	8	0,026
Cardiac failure	8	0,026
Abdominal cramp	8	0,026
Wound healing disturbance of	7	0,023
Vision decreased	7	0,023
Vaginitis	7	0,023
Vaginal infection	7	0,023

Urinary infection	7	0,023
Skin disorder	7	0,023
Sensory disturbance	7	0,023
Restlessness	7	0,023
Redness of face	7	0,023
Redness in breast	7	0,023
Potassium low	7	0,023
Pain knee	7	0,023
Pain kidney	7	0,023
Obstruction	7	0,023
Nasal dryness	7	0,023
Micturition urgency	7	0,023
Lymphocytopenia	7	0,023
Libido decreased	7	0,023
Leg oedema	7	0,023
Itching	7	0,023
Infection urinary tract	7	0,023
Hyperthyroidism	7	0,023
Haemorrhage nasal	7	0,023
Flushed face	7	0,023
Flu	7	0,023
Eye inflammation	7	0,023
Edema hands	7	0,023
Dry eye syndrome	7	0,023
Concentration impaired	7	0,023
Cognitive disturbance	7	0,023
Breast infection	7	0,023
Backache	7	0,023
Atrial fibrillation	7	0,023
Ankle oedema	7	0,023
Abscess	7	0,023
Wound infection	6	0,019
Visual disturbance	6	0,019
Vaginal dryness	6	0,019
Urinary incontinence	6	0,019
Urinary frequency	6	0,019
Stomach pressure sensation of	6	0,019
Stomach cramps	6	0,019
Scar pain	6	0,019
Rhagades	6	0,019
Restless legs	6	0,019

Renal pain	6	0,019
Phlebitis	6	0,019
Pancytopenia	6	0,019
Ocular surface disease	6	0,019
Night sweats	6	0,019
Nail dystrophy	6	0,019
Infection bladder	6	0,019
Inappetence	6	0,019
Hyperuricaemia	6	0,019
Head pain	6	0,019
Gastrointestinal infection	6	0,019
Febrile infection	6	0,019
Facial flushing	6	0,019
Dry nose	6	0,019
Cranial neuropathy	6	0,019
Appetite disorder	6	0,019
Alanine aminotransferase decreased	6	0,019
Xerostomia	5	0,016
Vaginal mucositis	5	0,016
Toothache	5	0,016
Thrombosis venous arm	5	0,016
Thrombosis leg	5	0,016
Thrombocyte count increased	5	0,016
Taste loss	5	0,016
Skin eruption	5	0,016
Sickness	5	0,016
Seroma	5	0,016
Restless leg syndrome	5	0,016
Renal disease	5	0,016
Rash face	5	0,016
Peripheral motor neuropathy	5	0,016
Otitis media	5	0,016
Nycturia	5	0,016
Nasal disorder	5	0,016
Lymphedema	5	0,016
Leucocytopenia	5	0,016
Laryngitis	5	0,016
Itchy skin	5	0,016
Injection site reaction	5	0,016
Hypersensitivity reaction	5	0,016
Hyperbilirubinaemia	5	0,016

Hemorrhage nasal	5	0,016
H1N1 influenza	5	0,016
Eyelid twitching	5	0,016
Eye disorder	5	0,016
Exanthema facial	5	0,016
Esophagitis	5	0,016
Ear pain	5	0,016
Dysaesthesia	5	0,016
Dehydration	5	0,016
Catheter thrombosis	5	0,016
Catheter site erythema	5	0,016
Burning eyes	5	0,016
Body temperature increased	5	0,016
Bladder infection	5	0,016
Appetite absent	5	0,016
Anorectic	5	0,016
Angina tonsillaris	5	0,016
Visual impairment	4	0,013
Varicose vein	4	0,013
Transaminases increased	4	0,013
Tiredness	4	0,013
Throat swelling	4	0,013
Swallowing difficult	4	0,013
Sleeplessness	4	0,013
Skin reaction	4	0,013
Skin infection	4	0,013
Skin erythema	4	0,013
Short of breath	4	0,013
Rash desquamating	4	0,013
Proteinuria	4	0,013
Polyuria	4	0,013
Pollakiuria	4	0,013
Paraesthesia hand	4	0,013
Painful respiration	4	0,013
Pain in hip	4	0,013
Oral pain	4	0,013
Oesophagitis	4	0,013
Oedema hands	4	0,013
Numbness in feet	4	0,013
Neurodermatitis	4	0,013
Musculoskeletal disorder	4	0,013

Muscle weakness	4	0,013
Mood swings	4	0,013
Memory impairment	4	0,013
Leukocyturia	4	0,013
Joint disorder	4	0,013
Infection upper respiratory	4	0,013
Hypothyroidism	4	0,013
Hypercholesterolaemia	4	0,013
Hay fever	4	0,013
Gum bleeding	4	0,013
Extravasation	4	0,013
Epigastric pain	4	0,013
Dorsalgia	4	0,013
Colpitis	4	0,013
Colitis	4	0,013
Coated tongue	4	0,013
Chest pain	4	0,013
Cardialgia	4	0,013
Cardiac ischaemia	4	0,013
Candidiasis	4	0,013
Calf pain	4	0,013
Axillary pain	4	0,013
Atypical pneumonia	4	0,013
Alopecia totalis	4	0,013
Allergic rash	4	0,013
Adhesive tape allergy	4	0,013
Abdominal pain lower	4	0,013
Watery diarrhea	3	0,010
Vulvovaginal mycotic infection	3	0,010
Vulvitis	3	0,010
Vaginal yeast infection	3	0,010
Urinary retention	3	0,010
Upper respiratory infection	3	0,010
Unrest	3	0,010
Trigeminal neuralgia	3	0,010
Tooth abscess	3	0,010
Thorax pain	3	0,010
Taste metallic	3	0,010
Taste diminished	3	0,010
Tachycardia paroxysmal	3	0,010
Swollen tongue	3	0,010

Swelling of legs	3	0,010
Sternal pain	3	0,010
Staphylococcal sepsis	3	0,010
Small intestinal mucositis	3	0,010
Sleep disturbed	3	0,010
Skin irritation	3	0,010
Shivering	3	0,010
Seizure	3	0,010
Scalp pain	3	0,010
Reflux esophagitis	3	0,010
Psoriasis	3	0,010
Potassium decreased	3	0,010
Pericardial effusion	3	0,010
Penicillin allergy	3	0,010
Parotitis	3	0,010
Pancreatitis	3	0,010
Painful R arm	3	0,010
Pain pelvic	3	0,010
Pain of skin	3	0,010
Pain localised	3	0,010
Pain in toe	3	0,010
Pain in spine	3	0,010
Pain breast	3	0,010
Oral thrush	3	0,010
Oedematous feet	3	0,010
Oedema arms	3	0,010
Obesity	3	0,010
Numbness	3	0,010
Neck rash	3	0,010
Nail discolouration	3	0,010
Muscular pain	3	0,010
Mucous membrane disorder	3	0,010
Meteorism	3	0,010
Melalgia	3	0,010
Low back pain	3	0,010
Localised oedema	3	0,010
Localised itching	3	0,010
Liver pain	3	0,010
Jugular vein thrombosis	3	0,010
Irritant cough	3	0,010
Intervertebral disc prolapse	3	0,010

Incontinence	3	0,010
Iatrogenic pneumothorax	3	0,010
Hospitalization for further diagnosis	3	0,010
Herpes NOS	3	0,010
Herpes genitalis	3	0,010
Hearing impaired	3	0,010
Haemorrhoidal bleeding	3	0,010
Growing pains	3	0,010
Glucosuria	3	0,010
Genital infection fungal	3	0,010
Gastrointestinal pain	3	0,010
Foot edema	3	0,010
Folliculitis	3	0,010
Fibromyalgia	3	0,010
Fever of unknown origin	3	0,010
Embolism lung	3	0,010
Ear ache	3	0,010
Drug hypersensitivity	3	0,010
Diverticulitis	3	0,010
Distension NOS	3	0,010
Colic	3	0,010
Cold feet	3	0,010
Coagulopathy	3	0,010
Chest wall pain	3	0,010
Brittle nails	3	0,010
Bladder pain	3	0,010
Axillary vein thrombosis	3	0,010
Asthenia	3	0,010
Arthritis	3	0,010
Ankle edema	3	0,010
Angular cheilitis	3	0,010
Angina pectoris	3	0,010
Anal mucositis	3	0,010
Anal fissure	3	0,010
Allergic exanthema	3	0,010
Abdominal infection	3	0,010
Vulval pruritus	2	0,006
Viral infection	2	0,006
Vaginosis fungal NOS	2	0,006
Vaginal discharge	2	0,006
Vaginal candida	2	0,006

Urticarial rash	2	0,006
Urgency urination	2	0,006
Urge incontinence	2	0,006
Upper aerodigestive tract infection	2	0,006
Tooth extraction	2	0,006
Tonsillar abscess	2	0,006
Tinea pedis	2	0,006
Thrush vaginal	2	0,006
Thrombophlebitis leg	2	0,006
Thrombophlebitis arm	2	0,006
Throat pain	2	0,006
Taste absent	2	0,006
Syncope vasovagal	2	0,006
Syncope convulsive	2	0,006
Swelling of tongue	2	0,006
Swelling of feet	2	0,006
Sweating	2	0,006
Suicide attempt	2	0,006
Stomach discomfort	2	0,006
Spinal disorder	2	0,006
Slipped disc	2	0,006
Skin ulceration	2	0,006
Skin fissure	2	0,006
Sigmoiditis	2	0,006
Shortness of breath	2	0,006
Shingles	2	0,006
Sepsis	2	0,006
Sciatica	2	0,006
Rosacea	2	0,006
Rickets	2	0,006
Rib pain	2	0,006
Respiratory tract infection	2	0,006
Rash pruritic	2	0,006
Rash over arms	2	0,006
Rash on legs & arms	2	0,006
Radius fracture	2	0,006
Pyrexia	2	0,006
Pustule	2	0,006
Purulence	2	0,006
Pruritus generalised	2	0,006
Pruritus breast	2	0,006

Prickling of hand	2	0,006
Pneumothorax	2	0,006
Pneumonitis	2	0,006
Photosensitivity	2	0,006
Phosphatase alkaline increased	2	0,006
Phlebitis arm	2	0,006
Peripheral ischaemia	2	0,006
Perioral dermatitis	2	0,006
Periodontal disease	2	0,006
Perianal abscess	2	0,006
Perforation colon	2	0,006
Paranasal sinus infection	2	0,006
Paraesthesia lower limb	2	0,006
Panic attack	2	0,006
Panaritium	2	0,006
Painful L arm	2	0,006
Painful defaecation	2	0,006
Pain tongue	2	0,006
Pain retrosternal	2	0,006
Pain mucosal	2	0,006
Pain jaw	2	0,006
Pain in eyes	2	0,006
Pain eye	2	0,006
Overactive bladder	2	0,006
Ototoxicity	2	0,006
Otitis	2	0,006
Osteoporosis	2	0,006
Ostealgia	2	0,006
Oral fungal infection	2	0,006
Onychomycosis	2	0,006
Olfactory nerve disorder	2	0,006
Oedema fingers	2	0,006
Numbness mouth	2	0,006
Numbness in toes	2	0,006
Neutrophils reduced	2	0,006
Nephrolithiasis	2	0,006
Necrosis	2	0,006
Nasal mucosal disorder	2	0,006
Nasal bleeding	2	0,006
Myasthenia	2	0,006
Mucosal ulceration	2	0,006

Movements involuntary	2	0,006
Menses irregular	2	0,006
Maculo-papular exanthema	2	0,006
Lymphocele	2	0,006
Lymphangitis	2	0,006
Localised rash	2	0,006
Localised infection	2	0,006
Localised erythema	2	0,006
Left deep vein thrombosis	2	0,006
Larynx pain	2	0,006
Knee pain	2	0,006
Jaw pain	2	0,006
Itchy scalp	2	0,006
Itchy rash	2	0,006
Intermenstrual bleeding	2	0,006
Injection site pain	2	0,006
Infection mycotic	2	0,006
Infected toe	2	0,006
Hypocalcaemia	2	0,006
Hypersensitivity	2	0,006
Hypersensation skin	2	0,006
House dust allergy	2	0,006
Hepatic steatosis	2	0,006
Hemorrhage uterine	2	0,006
Hemoglobin low	2	0,006
Hematoma	2	0,006
Heaviness in extremities	2	0,006
Hearing loss	2	0,006
Hearing decreased	2	0,006
Haemorrhagic cystitis	2	0,006
Haemoglobinuria	2	0,006
Haematuria	2	0,006
Genital itching	2	0,006
Genital herpes	2	0,006
Generalised itching	2	0,006
Gastric mucositis	2	0,006
Gamma glutamyl transpeptidase increased	2	0,006
Gallbladder pain	2	0,006
Furuncle	2	0,006
Fungal foot infection	2	0,006
Flu-like symptoms	2	0,006

Fingernail discoloration	2	0,006
Femoral neck fracture	2	0,006
Eyes tearing	2	0,006
Eyelid disorder	2	0,006
Eye swelling	2	0,006
Erythema multiforme	2	0,006
Erythema facial	2	0,006
Embolism	2	0,006
Efflorescence	2	0,006
Edema extremities	2	0,006
Dyspnea exertional	2	0,006
Dyspnea	2	0,006
Diverticulosis	2	0,006
Desquamation	2	0,006
Depressed mood	2	0,006
Decubitus	2	0,006
Creatinine low	2	0,006
C-reactive protein abnormal	2	0,006
Costal pain	2	0,006
Coprostasis	2	0,006
Coordination disturbance	2	0,006
Climacteric discomfort	2	0,006
Chronic obstructive pulmonary disease	2	0,006
Chest pressure	2	0,006
Catheter site infection	2	0,006
Catheter placement	2	0,006
Carpal tunnel syndrome	2	0,006
Cardiovascular event prophylaxis	2	0,006
Cardiac insufficiency	2	0,006
Burning sensation	2	0,006
Burning micturition	2	0,006
Burning lips	2	0,006
Burning anal	2	0,006
Breathlessness	2	0,006
Bloody stool	2	0,006
Blood pressure low	2	0,006
Blood alkaline phosphatase decreased	2	0,006
Bacteriuria	2	0,006
Bacterial infection	2	0,006
Asthma bronchial	2	0,006
Arthrosis	2	0,006

Arthritic pains	2	0,006
Anxiety disorder	2	0,006
Anal pruritus	2	0,006
Anal fungal infection	2	0,006
ALT decreased	2	0,006
Allergic skin reaction	2	0,006
Adynamia	2	0,006
Adrenal insufficiency	2	0,006
Acroedema	2	0,006
Abscess breast	2	0,006
Abdominal distension	2	0,006
Abdominal abscess	2	0,006
Xerophthalmia	1	0,003
Wound secretion	1	0,003
Wound pain	1	0,003
Wound healing delayed	1	0,003
Wound dehiscence	1	0,003
Wound debridement	1	0,003
Wound	1	0,003
Weight increased	1	0,003
Weakness of limbs	1	0,003
Vulval infection	1	0,003
Vulval candida	1	0,003
Voice alteration	1	0,003
Vocal cord inflammation	1	0,003
Vocal cord disorder	1	0,003
Vitamin D deficiency	1	0,003
Visual acuity decreased	1	0,003
Vision loss	1	0,003
Vision blurred	1	0,003
Vision abnormal	1	0,003
Ventricular tachycardia	1	0,003
Ventricular arrhythmia NOS	1	0,003
Venous thrombophlebitis	1	0,003
Venous stenosis	1	0,003
Vascular disorder	1	0,003
Varicophlebitis	1	0,003
Vaginosis bacterial	1	0,003
Vaginal itching	1	0,003
Vaginal inflammation	1	0,003
Vaginal candidiasis	1	0,003

Vaginal bleeding	1	0,003
Uveitis	1	0,003
Uterine haemorrhage	1	0,003
Uterine bleeding	1	0,003
Urosepsis	1	0,003
Urination pain	1	0,003
Urination frequency of	1	0,003
Urinary urgency	1	0,003
Urinary tract yeast infection	1	0,003
Urinary tract infection NOS	1	0,003
Upper gastrointestinal haemorrhage	1	0,003
Unspecified disorder of knee joint	1	0,003
Ulcus ventriculi	1	0,003
Tympanic membrane perforation	1	0,003
Tympanic membrane disorder	1	0,003
Tremor limb	1	0,003
Tremble	1	0,003
Traumatic hemorrhage	1	0,003
Transfusion reaction	1	0,003
Torticollis	1	0,003
Tooth development disorder	1	0,003
Tongue tip numbness of	1	0,003
Tongue spasm	1	0,003
Tongue pain	1	0,003
Tongue mucositis	1	0,003
Tongue haemorrhage	1	0,003
Tongue disorder	1	0,003
Tongue coated	1	0,003
Tingling	1	0,003
Thyroid function abnormal	1	0,003
Thyroid cold nodule	1	0,003
Thrush oral	1	0,003
Thrombosis venous	1	0,003
Thrombocytosis	1	0,003
Throat infection	1	0,003
Thoracic vertebral fracture T8	1	0,003
Thoracic vertebral fracture T12	1	0,003
Thoracic vertebral fracture	1	0,003
Thirst	1	0,003
Temporal arteritis	1	0,003
Temperature elevation	1	0,003

Taste bitter	1	0,003
Tachyarrhythmia	1	0,003
Swollen wrists	1	0,003
Swollen lips	1	0,003
Swollen eyes	1	0,003
Swollen ankles	1	0,003
Swelling of limb	1	0,003
Swelling of fingers	1	0,003
Swelling of elbows	1	0,003
Sweating attack	1	0,003
Swallowing painful	1	0,003
Suture granuloma	1	0,003
Supraventricular tachycardia	1	0,003
Sulfonamide allergy	1	0,003
Subileus	1	0,003
Sty	1	0,003
Streptococcal sepsis	1	0,003
Streptococcal infection	1	0,003
Strain	1	0,003
Stomatomycosis	1	0,003
Stomatitis aphthous	1	0,003
Stomach ulcer	1	0,003
Stomach flu	1	0,003
Sticky eyes	1	0,003
Sterilisation	1	0,003
Stab wound	1	0,003
Spotting vaginal	1	0,003
Spondylodiscitis	1	0,003
Splitting nails	1	0,003
Spinal root pain	1	0,003
Spinal cord disorder	1	0,003
Speech impairment NOS	1	0,003
Sore eye	1	0,003
Sodium low	1	0,003
Sodium decreased	1	0,003
Sleep apnoea	1	0,003
Skull fracture	1	0,003
Skin red	1	0,003
Skin reaction localised	1	0,003
Skin peeling	1	0,003
Skin necrosis	1	0,003

Skin lesion	1	0,003
Skin laceration	1	0,003
Skin inflammation	1	0,003
Skin candida	1	0,003
SIRS	1	0,003
Sicca syndrome	1	0,003
Shoulder discomfort	1	0,003
Shooting pain	1	0,003
Shaking	1	0,003
SGOT increased	1	0,003
Serum glutamic-oxaloacetic transaminase increased	1	0,003
Serum creatinine increased	1	0,003
Serratia infection	1	0,003
Sensory peripheral neuropathy	1	0,003
Sensation of pressure in eye	1	0,003
Sensation of pressure in ear	1	0,003
Sacral pain	1	0,003
Retinal detachment	1	0,003
Respiratory insufficiency	1	0,003
Renal failure	1	0,003
Reflux oesophagitis	1	0,003
Reflux gastritis	1	0,003
Redness of legs	1	0,003
Redness generalised	1	0,003
Red blood cells urine	1	0,003
Rectal mucositis	1	0,003
Rectal bleeding	1	0,003
Raw tongue	1	0,003
Rash both legs	1	0,003
Rash acneiform	1	0,003
Pulmonary congestion	1	0,003
Psychosis	1	0,003
Psoriasis pustular	1	0,003
Pseudothrombocytopenia	1	0,003
Pseudomonal sepsis	1	0,003
Pseudomembranous colitis	1	0,003
Pruritus cutaneous	1	0,003
Prosthesis related infection	1	0,003
Productive cough	1	0,003
Potassium increased	1	0,003
Postoperative wound complication	1	0,003

Postoperative pain	1	0,003
Postoperative complication	1	0,003
Post procedural site wound infection	1	0,003
Portacath insertion	1	0,003
Poor concentration	1	0,003
Polyarthritis	1	0,003
Pollinosis	1	0,003
Pneumocystis jiroveci infection	1	0,003
Pleural effusion	1	0,003
Platelets increased	1	0,003
Pimple	1	0,003
Photosensitive dermatitis	1	0,003
Phlebothrombosis	1	0,003
Petechia	1	0,003
Peritonitis	1	0,003
Peripheral edema	1	0,003
Periodontitis	1	0,003
Pericarditis	1	0,003
Perianal ulcer	1	0,003
Perianal fistula	1	0,003
Perceptual disturbance	1	0,003
Pelvic pain	1	0,003
Patella fracture	1	0,003
Partial hearing loss	1	0,003
Paronychia	1	0,003
Paraesthesia of limbs	1	0,003
Papilloedema	1	0,003
Pancreatitis recurrent	1	0,003
Painful urination	1	0,003
Pain sacroiliac	1	0,003
Pain rectal	1	0,003
Pain pharynx	1	0,003
Pain of extremities	1	0,003
Pain neck	1	0,003
Pain mouth	1	0,003
Pain in jaw	1	0,003
Pain ear	1	0,003
Pain bladder	1	0,003
Pain abdominal	1	0,003
Ovariectomy	1	0,003
Ovarian haemorrhage	1	0,003

Otitis externa	1	0,003
Otalgia	1	0,003
Osteoneuralgia	1	0,003
Oscillopsia	1	0,003
Oral aphthae	1	0,003
Ophthalmitis	1	0,003
Onychorrhexis	1	0,003
Oesophageal pain	1	0,003
Oesophageal irritation	1	0,003
Oesophageal infection	1	0,003
Oedema face	1	0,003
Oedema eyelid	1	0,003
Odynophagia	1	0,003
Numbness oral	1	0,003
Numbness in fingers	1	0,003
Nosebleed	1	0,003
Noises in head	1	0,003
Nipple infection	1	0,003
Nipple discharge	1	0,003
Neutrophils	1	0,003
Neurogenic pain	1	0,003
Neuralgia trigeminal	1	0,003
Neck tightness	1	0,003
Neck swelling	1	0,003
Nausea prophylaxis	1	0,003
Nausea post chemotherapy	1	0,003
Nail bed tenderness	1	0,003
Nail bed bleeding	1	0,003
Myogelosis	1	0,003
Myocardial infarction	1	0,003
Muscle weakness upper limb	1	0,003
Muscle weakness lower limb	1	0,003
Muscle twitching	1	0,003
Muscle strain	1	0,003
Muscle rupture	1	0,003
Muscle fibrillation	1	0,003
Muscle cramps	1	0,003
Mouth pain	1	0,003
Motor peripheral neuropathy	1	0,003
Motor activity retarded	1	0,003
Mood depression	1	0,003

Mitral valve prolapse	1	0,003
Migraine headache	1	0,003
Middle ear inflammation	1	0,003
Methicillin-resistant staphylococcal aureus infection	1	0,003
Mental disorder	1	0,003
Mental concentration difficult	1	0,003
Menorrhagia	1	0,003
Memory disturbance	1	0,003
Melanoma	1	0,003
Mastopathy	1	0,003
Mallory-Weiss syndrome	1	0,003
Malignant melanoma	1	0,003
Malassezia infection	1	0,003
Maculopapular rash	1	0,003
Lymph nodes enlarged	1	0,003
Lung infection	1	0,003
Lump feeling in throat	1	0,003
Lumbar vertebral fracture	1	0,003
Lumbar pain	1	0,003
Lumbago	1	0,003
Lower extremities weakness of	1	0,003
Low platelets	1	0,003
Loss of weight	1	0,003
Loss of teeth	1	0,003
Loss of smell	1	0,003
Loss of libido	1	0,003
Loose tooth	1	0,003
Localised tingling	1	0,003
Localised skin reaction	1	0,003
Liver disorder	1	0,003
Lipase increased	1	0,003
Lip infection	1	0,003
Leucopenia	1	0,003
Left ventricular ejection fraction decreased	1	0,003
Left ventricular dysfunction	1	0,003
Left sided paralysis	1	0,003
Left heart failure	1	0,003
LDH decreased	1	0,003
Lactate dehydrogenase increased	1	0,003
Lacrimation increased	1	0,003
Lacrimation	1	0,003

Labium majus pudendi ulcer	1	0,003
Ketonuria	1	0,003
Joint stiffness	1	0,003
Joint ankylosis	1	0,003
Itching eyes	1	0,003
Itching both hands	1	0,003
Itching - generalised	1	0,003
Irritative cough	1	0,003
Irritation of eyes	1	0,003
Irritation eye	1	0,003
Irregular menstruation	1	0,003
Intraocular pressure increased	1	0,003
Intracardiac thrombus	1	0,003
Intestinal haemorrhage	1	0,003
Intestinal cramps	1	0,003
Intervertebral disc protrusion	1	0,003
Interstitial pneumonia	1	0,003
Inflammation gum	1	0,003
Infectious colitis	1	0,003
Infection localised	1	0,003
Infection breast	1	0,003
Infected thumb	1	0,003
Infected scar	1	0,003
Indigestion	1	0,003
Incontinence urinary	1	0,003
Impetigo	1	0,003
Ileus paralytic	1	0,003
Ileus	1	0,003
Icterus	1	0,003
Hyposmia	1	0,003
Hyponatraemia	1	0,003
Hypokalemia	1	0,003
Hypoglycaemic coma	1	0,003
Hypogeusia	1	0,003
Hypogastric pain	1	0,003
Hypoaesthesia	1	0,003
Hypervolaemia	1	0,003
Hypertensive crisis	1	0,003
Hypermenorrhoea	1	0,003
Hyperkinesia	1	0,003
Hyperhidrosis	1	0,003

Hyperaesthesia	1	0,003
Hot flushes facial	1	0,003
Hordeolum	1	0,003
Hoarse voice	1	0,003
High pulse rate	1	0,003
Herpes zoster oticus	1	0,003
Herpes on lip	1	0,003
Herpes infection	1	0,003
Herniated disc	1	0,003
Hemorrhage rectum	1	0,003
Hemoglobin decreased	1	0,003
Hebephrenia	1	0,003
Heat sensitivity	1	0,003
Heart valve replacement	1	0,003
Heart rate increased	1	0,003
Heart racing	1	0,003
Heart disorder	1	0,003
Hand swelling	1	0,003
Hallucination	1	0,003
Hair loss	1	0,003
Haemorrhagic diarrhoea	1	0,003
Haemorrhage vaginal	1	0,003
Haemoglobinaemia	1	0,003
Haemoglobin high	1	0,003
Haematoma infection	1	0,003
Haematoma	1	0,003
Haematemesis	1	0,003
Glycosuria	1	0,003
Glutamic-pyruvic transaminase increased	1	0,003
Glucose urine	1	0,003
Glucose high	1	0,003
Glossopharyngeal nerve disorder	1	0,003
Glaucoma	1	0,003
Gingival pain	1	0,003
Gingival bleeding	1	0,003
GI pain	1	0,003
Genitourinary tract infection	1	0,003
Genital ulceration	1	0,003
Genital infection	1	0,003
Genital disorder female	1	0,003
Generalized joint pain	1	0,003

Generalized edema	1	0,003
Generalised oedema	1	0,003
Gastrointestinal infection NOS	1	0,003
Gastrointestinal fungal infection	1	0,003
Gastroesophageal reflux	1	0,003
Gastroenteritis	1	0,003
Gastric ulcer helicobacter	1	0,003
Gallstones removal	1	0,003
Gallbladder enlargement	1	0,003
Fungal infection	1	0,003
Fruit allergy	1	0,003
Foreign body	1	0,003
Foot fracture	1	0,003
Flushed skin	1	0,003
Fingers stiffness	1	0,003
Finger nail removal	1	0,003
Finger cramps	1	0,003
Fibrosis	1	0,003
Feeling sick	1	0,003
Feeling queasy	1	0,003
Fecal incontinence	1	0,003
Faint	1	0,003
Facial paralysis	1	0,003
Face oedema	1	0,003
Eyelid oedema	1	0,003
Eye strain	1	0,003
Eye redness	1	0,003
Eye pain	1	0,003
Eye irritation	1	0,003
Extremities hot feeling of	1	0,003
Extremities burning sensation of	1	0,003
Exsiccosis	1	0,003
Exertional dyspnoea	1	0,003
Exanthema generalised	1	0,003
Epigastralgia	1	0,003
Epidermolysis	1	0,003
Enuresis	1	0,003
Enterocolitis hemorrhagic	1	0,003
Enteritis	1	0,003
Emphysema pulmonary	1	0,003
Elevated liver enzymes	1	0,003

Edema tongue	1	0,003
Edema generalized	1	0,003
Edema eyelid	1	0,003
Earache	1	0,003
Ear injury	1	0,003
Ear infection	1	0,003
Dyssomnia	1	0,003
Dysphonia	1	0,003
Dysmenorrhoea	1	0,003
Dysentery	1	0,003
Dysaesthesia extremity	1	0,003
Drug intoxication	1	0,003
Drug eruption	1	0,003
Dog bite	1	0,003
Diverticulitis intestinal	1	0,003
Disorder sleep	1	0,003
Dislocation of vertebra	1	0,003
Dislocation of elbow	1	0,003
Discomfort in joints	1	0,003
Discolouration nail	1	0,003
Discoloration tongue	1	0,003
Discoloration nail	1	0,003
Disc lesion lumbar	1	0,003
Diplopia	1	0,003
Diminished sense of smell	1	0,003
Difficult digestion	1	0,003
Diarrhoea infectious	1	0,003
Diarrhea hemorrhagic	1	0,003
Diabetes mellitus	1	0,003
Device issue	1	0,003
Dermatosis	1	0,003
Deep vein thrombosis leg	1	0,003
Deep vein thrombosis	1	0,003
Cystitis-like symptom	1	0,003
Cyst breast	1	0,003
Cramps leg	1	0,003
Cramps in the calves	1	0,003
Cramps calf	1	0,003
Cramps	1	0,003
Cramp of limb	1	0,003
Cramp	1	0,003

Coxarthrosis	1	0,003
Coronary arterial stent insertion	1	0,003
COPD	1	0,003
Contusion	1	0,003
Conjunctival xerosis	1	0,003
Conjunctival redness	1	0,003
Confusion	1	0,003
Concentration impairment	1	0,003
Colon perforation	1	0,003
Colitis ulcerative acute episode	1	0,003
Cluster headache	1	0,003
Climacteric symptoms	1	0,003
Claudication	1	0,003
Circulatory collapse	1	0,003
Cholecystolithiasis	1	0,003
Chest tightness	1	0,003
Cervical uterine polyp	1	0,003
Cerebral ischaemia	1	0,003
Central retinal artery occlusion	1	0,003
Catheter site inflammation	1	0,003
Catheter removal	1	0,003
Catheter related infection	1	0,003
Catheter access port issue	1	0,003
Catarrh	1	0,003
Candidal oesophagitis	1	0,003
Candida vaginal	1	0,003
Candida stomatitis	1	0,003
Calcium low	1	0,003
Cachexia	1	0,003
Burning tongue	1	0,003
Burning mouth	1	0,003
Burning feeling vagina	1	0,003
Bronchospasm	1	0,003
Bronchopneumonia	1	0,003
Broken nose	1	0,003
Breast swelling	1	0,003
Breast hematoma	1	0,003
Breast edema	1	0,003
Breast abscess	1	0,003
Bradycardia	1	0,003
Bowel cramps	1	0,003

Blurry vision	1	0,003
Blood pressure fluctuation	1	0,003
Blood in urine	1	0,003
Blood in stool	1	0,003
Blood glucose increased	1	0,003
Blood glucose	1	0,003
Blood albumin decreased	1	0,003
Blisters	1	0,003
Blister	1	0,003
Bleeding gingival	1	0,003
Bleeding gastrointestinal	1	0,003
Bladder disorder	1	0,003
Biliary colic	1	0,003
Belching	1	0,003
Balance impaired NOS	1	0,003
Balance disorder	1	0,003
Axillary abscess	1	0,003
AV block third degree	1	0,003
Attempted suicide	1	0,003
Atrioventricular nodal reentrant tachycardia	1	0,003
Atrial septal defect	1	0,003
Athlete's foot	1	0,003
Ataxia	1	0,003
Asthma	1	0,003
AST decreased	1	0,003
Arterial restenosis	1	0,003
Arrhythmia absoluta	1	0,003
Aphthous stomatitis	1	0,003
Aphtha	1	0,003
Anxiety state	1	0,003
Anxiety depression	1	0,003
Anuria	1	0,003
Ankylosis	1	0,003
Ankle fracture	1	0,003
Anal irritation	1	0,003
Anal infection	1	0,003
Anal haemorrhage	1	0,003
Anal dilatation	1	0,003
Amnesia	1	0,003
Amenorrhoea	1	0,003
Alveolitis allergic	1	0,003

Altered smell sensation	1	0,003
Alopecia areata	1	0,003
Allodynia	1	0,003
Allergy to metals	1	0,003
Allergy multiple	1	0,003
Allergic rhinitis	1	0,003
Allergic contact dermatitis	1	0,003
Agranulocytosis	1	0,003
Agitated depression	1	0,003
Adnexectomy	1	0,003
Acute vascular leak syndrome	1	0,003
Acute periodontitis	1	0,003
Acute pancreatitis	1	0,003
Acute gastroenteritis	1	0,003
Acute dyspnoea	1	0,003
Acute diverticulitis	1	0,003
Acute depression	1	0,003
Activities of daily living impaired	1	0,003
Acid reflux (oesophageal)	1	0,003
Achilles tendon rupture	1	0,003
Achilles tendinitis	1	0,003
Ache	1	0,003
Abscess sweat gland	1	0,003
Abscess oral	1	0,003
Abscess leg	1	0,003
Abscess jaw	1	0,003
Abnormal touch sensation	1	0,003
Abnormal pigmentation	1	0,003
Abnormal faeces	1	0,003
Abdominal wall infection	1	0,003
Abdominal pain NOS	1	0,003
Abdominal fullness	1	0,003
Abdominal discomfort	1	0,003

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

Not applicable.

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Not applicable.

14.3.4 Abnormal Laboratory Value Listing (Each Patient)

Not applicable.

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16 APPENDICES

16.1 STUDY INFORMATION

16.1.1 Protocol and protocol amendments

Prot_Final 1.0_Plan_B_2008090

planB_Protokoll_Version_3.0..pdf

16.1.2 Sample case report form (unique pages only)

PlanB_pCRF_neu.pdf

16.1.3 List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - Representative written information for patient and sample consent forms

Ethics Committees and Patient Informed Consent form

Land	Institut	Abteilung
Baden-Württemberg	Landesärztekammer Baden Württemberg	Ethikkommission
Bayern	Landesärtzekammer Bayern	Ethikkommission
Berlin	Landesamt für Gesundheit und Soziales	Ethikkommission
Brandenburg	Landesärztekammer Brandenburg	Ethikkommission
Hessen	Landesärztekammer Hessen	Ethikkommission
Niedersachsen	Ärztekammer Niedersachsen	Ethikkommission
Rheinland Pfalz	Landesärztekammer Rheinland-Pfalz	Ethikkommission
Saarland	Ärztekammer des Saarlandes	Ethikkommission
Sachsen-Anhalt	Landesamt für Verbraucherschutz	Ethikkommission
Sachsen	Sächsische Landesärztekammer	Ethikkommission
Schleswig-Holstein	Ärztekammer Schleswig-Hostein	Ethikkommission
Thüringen	Landesärztekammer Thüringen	Ethikkommission
Westfalen-Lippe	Ärztekammer Westfalen-Lippe	Ethikkommission
Uni Bonn	Rheinische Friedrich-Wilhelms-Universität	Ethikkommission
Uni Essen	Universitätsklinikum Essen	Ethikkommission
Uni Freiburg	Universität Freiburg	Ethikkommission
Uni Göttingen	Universitätsmedizin Göttingen	Ethikkommission
Uni Greifswald	Universität Greifswald	Ethikkommission
Uni Halle	Martin-Luther-Universität	Ethikkommission
Uni Heidelberg	Med. Fakultät Heidelberg	Ethikkommission
Uni Kiel	Med. Fakultät Kiel	Ethikkommission
Uni Köln	Universität zu Köln	Ethikkommission

Uni Leipzig	Med. Fakultät Leipzig	Ethikkommission
Uni Magdeburg	Otto von Guericke Universität	Ethikkommission
Uni Marburg	Philipps Universität	Ethikkommission
Uni München	Fakultät für Medizin der Universität München	Ethikkommission
Uni Rostock	Med. Fakultät der Universität Rostock	Ethikkommission
Uni Witten	Universität Witten/Herdecke	Ethikkommission
Uni Würztburg	Universität Würzburg	Ethikkommission
Nordrhein	Ärztekammer Nordrhein	Ethikkommission

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