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ABCSG 28 / POSYTIVE

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

Statistical Analysis Plan version 1.0 (2017-01-11)

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Statistical Analysis Plan

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Glossary of abbreviations

ABCSG	Austrian Breast & Colorectal Cancer Study Group
SAP	Statistical Analysis Plan
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ER	Estrogen receptor
PGR	Progesterone receptor
EOS	End of study
EOT	End of treatment
FPI	First patient in
HER	Human epithelial growth factor receptor
IHC test	Immunohistochemistry test
FISH test	Fluorescence In Situ Hybridization test
LPLV	Last patient last visit
ITT	Intention to treat
TTPd	Time to distant progression
TTPl	Time to local progression
CEA	Carcinoembryonic antigen
CA 15-3	Carcinoma antigen 15-3
QoL	Quality of Life

1. Introduction

This Statistical Analysis Plan (SAP) is based on the Clinical Study Protocol for the ABCSG study 28 in version 4.0 from Sep 06, 2011 and provides a detailed description of all statistical analyses planned to be conducted within this trial at predefined time points.
All analyses described herein are performed in accordance to the guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

2. Study details

This study is a prospective, randomized, multicentre, study concerning the influence of local treatment on the patients with synchronous metastasized breast cancer. Patients are stratified at inclusion according to the centre, the hormone-receptor status (ER-/PR-/not determinable; any PR and/or Er+),the HER-2 status (positive vs. negative/not determinable), the grading (G1/G2 vs. G3/not determinable), location of metastases (visceral ± vs bone only), and use of first line chemotherapy (anthracyclin-based ± any other, except taxan, vs. taxan-based ± any other vs. other therapies, e.g. antihormonal therapy alone).

The aim of the study is to evaluate the median survival (primary objective) of patients with synchronous metastasized breast cancer and the primary tumor in place comparing arm A with local therapy (lumpectomy or mastectomy + axillary surgery /± radiotherapy) to the primary tumor versus arm B without local therapy (surgery on demand). Systemic therapy is administered at the centers policy.

2.1. Study design

2.1.1. Study duration

4 years recruitment period and maximum study duration of 9 years

2.1.2. End of study

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

2.2. Study objectives

2.2.1. Primary objective

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

2.2.2. Secondary objectives

The secondary study objectives are

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

2.2.3. Safety objectives

The safety objective for this study is to evaluate the safety of surgical therapy and local therapy versus no surgery (surgery on demand) and local therapy.
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2.3. Randomization and stratification criteria

The randomization system used is the software 'Randomizer' which was developed and is maintained by the Institute of Medical Statistics and Informatics at the Medical University of Vienna. In accordance to the inclusion and exclusion criteria, patients are randomized to one of the following arms:

A: Surgical Therapy
B: Surgery on Demand

Patients were stratified with respect to following stratification factors:

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

2.4. Number of subjects - sample size estimation

A sample of 254 patients will be enrolled in this trial (127 in each group) including a drop out rate of 5%. This assumes that there will be a 48-month accrual period. The maximum study duration should be 9 years.

The sample size is estimated for the primary endpoint. The median survival of patients with local therapy to the primary tumor should be increased by 50% in comparison to patients without local therapy to have 80% power to detect a hazard ratio of 0.666 with a two-sided significance level of 0.05. The recruitment period is assumed with 4 years

3. Statistical methods

3.1. Data handling conventions

3.1.1. Data entry errors and potential outliers

Patients may have potential outliers for particular observations. Observations will be checked for correctness by the study team before data freeze and at the time point of data freeze all data should be correct. Values found to be incorrect due to data entry error after data freeze will be excluded from all analyses as missing values. Incidence of incorrect values and potential outliers will be listed and summarized by treatment arm.

3.1.2. Missing data

Subjects may have missing specific data points for a variety of causes. In general, data may be missing due to a missed visit, non-evaluability of a specific clinical measurement at its planned clinical visit or a subject's early withdrawal from study. The general procedures outlined below describe what will be done when a data point is missing.

3.1.2.1. Imputations of missing data

Generally, only evaluable measurements are considered for the analyses. No values are imputed for missed or non-evaluable visits. In case of primary and secondary efficacy endpoints possible specific requirements are stated in the according analysis sections.

3.1.2.2. Partial Dates

Partially incomplete dates (day or day/month missing) will be imputed for dates of progression as well as for therapy begin and/or end dates. Completely missing dates and missing years will not be imputed.

Imputation Rules for Partial Progression Dates

	Missing	Impute	Exception
Event Date	Day	01	Default to Day 1 of the study if an event started the same year and month as Day 1
	Day /Month	01JAN	Default to Day 1 of the study if an event started the same year as Day 1

Imputation Rules for Partial Therapy Start and Stop Dates

	Missing	Impute	Exception
Start date	Day	01	Default to Day 1 of the study if a therapy started the same year and month as Day 1
	Day /Month	01JAN	Default to Day 1 of the study if a therapy started the same year as Day 1
Stop date	Day	Last day of the month	Default to the EOS date if the imputed therapy stop date is after the EOS date
	Day/Month	31Dec	

3.1.3. Stratification errors

Stratification errors are defined as different values in the stratification factors compared between the randomization system and actual patient values from the electronic case report forms (eCRF).

Stratified analyses that are intended to evaluate the treatment effect will be based on the randomized stratum. If stratification error for a factor includes more than 10% of value, actual value instead of randomized stratum will be used in analysis.

Covariate analyses where will be based on subject's actual values.

3.2. Types and time points of analyses

3.2.1. Primary analysis

Primary analysis will be performed after last patient, last visit (LPLV) and subsequent data cleaning.

3.3. Definition of populations for analyses

3.3.1. Intention-to-Treat (ITT) population

Primary and secondary analyses will be based on the Intention-to-Treat (ITT) population; that is, all patients who were included in the randomization. All subjects will be analyzed according to the therapy arm to which they have been randomized. Subjects who terminate the study before their scheduled final study visits will be censored.

3.3.2. QoL population

Data from QoL questionnaires will be analyzed for all the patients which filled baseline or at least on after baseline questionnaire.

3.3.3. Per-Protocol (PP) population

No analysis on Per-Protocol (PP) population will be preformed

3.4. Study population

3.4.1. Patient status

Absolute and relative frequencies of patient status will be tabulated for both therapy arms in terms of patient randomized, patient undergone surgery, end-of-study reasons and cause of deaths.

3.4.2. Protocol deviations

Important protocol deviations were defined with respect of violations of against the inclusion/exclusion criteria, stratification errors and all deviations from protocol of the study, eg. Local therapy, surgery and/or radiotherapy in arm B or surgery of metastases in both arms.

Summaries of IPDs will be presented per treatment arm and in total. Additionally, patient listings will be given.

3.4.3. Baseline demographic and disease characteristics

Demographic and tumour characteristics data at baseline will be summarized descriptively per treatment arm and in total. Demographic and anamnestic data at baseline include age, height, weight, menopausal status, tumour stage, nodal status, tumour grade, HER2-status and hormone receptor status (estragon and progesterone).

3.4.4. Treatment and study information

Exposure during study will be given for local (surgery and/or radiation) as well for systematic therapies. Systematic therapies will be listed per patient.

Surgery type and tumour classification after surgery will be summarized descriptively.

Information on treatment violations will be presented descriptively per treatment arm and in total.

3.5. Primary endpoint evaluation

3.5.1. Primary endpoint

Median survival time will be compared through overall survival. Overall survival (OS) is determined by the time from randomization to death including breast cancer-related deaths and deaths from any other cause. If the patient is alive at the of the observation period, the patient will be censored.

The null and alternative hypotheses for the primary endpoint are as follows:

- H0: Overall survival is equal in patients receiving local therapy (surgery) compared to patients receiving no local therapy (surgery on demand)
- H1: Overall survival differs between patients receiving local therapy (surgery) compared to patients receiving no local therapy (surgery on demand)
-

3.5.2. Data set for primary endpoint

Data analysis for the primary endpoint will be based on the ITT-population. Subjects who terminate the study before their scheduled final study visits will be censored at the time of their last contact.

3.5.3. Efficacy analysis for primary endpoint

For the primary endpoint, a *2-sided log-rank* test (unstratified) will be used to test for differences between local therapy versus no local therapy at an overall alpha level of 0.05.

3.5.4. Sensitivity analyses for primary endpoint

A stratified version of the 2-sided log-rank test will be performed with the stratification factors used for randomization except geographic region. Kaplan-Meier curves and estimates will be provided for each treatment group. Potential confounding effects of the impact of other variables (grading, age, her2-neu expression and so on) will be assessed with the *multiple Cox-Regression analysis*.

3.6. Secondary endpoint evaluation

3.6.1. Secondary endpoints

- Time to distant progression (TTPd)
- Time to local progression (TTPl)

- data from QoL questionnaires
- Reduction of growth factors, circulating tumor cells, stem cells in pre-selected centers

Time to distant progression (TTPd) is defined by the time from randomization to first distant progression. Progression event is defined as a detection of "new" lesions (i.e., newly detected metastases, in a new or pre-existing metastatic site) or progression of existing metastases (i.e., those present at baseline). Distant progression is a progression in location different then breast (localization mamma, chest wall or axilla). Local progression before distant occurrence will be ignored.

Time to local progression (TTPl) is defined by the time from randomization to first local recurrence. Local recurrence is defined as recurrence in breast with localization mamma, chest wall or axilla.

Data from QoL will be assessed using the EORTC QLQ-C30 and the modified QLQ-BR23. Hence, this endpoints are the scores (of the base questionnaire and of the supplementary breast cancer module) described in the scoring procedures.

3.6.2. Data set for secondary endpoints

Data analysis for the secondary endpoint time to distant progression and time to local progression will be based on the ITT-population.

Data from QoL questionnaires will be analyzed for all the patients which filled baseline or at least on after baseline questionnaire.

Reduction of growth factors, circulating tumor cells, stem cells will be analyzed on all evaluable data from pre-selected centers.

3.6.3. Efficacy analyses for secondary endpoints

Difference in time to distant progression and time to local progression between local therapy versus no local therapy will be estimated through 2-sided log-rank

With respect to analysis of QoL endpoints the mean change of the linear transformed scores from baseline (and 95% CI using the normal approximation) will also be assessed. Line charts depicting the mean changes (and standard errors) of items and subscales over time will be provided for each treatment arm from the baseline assessment.

Completion and compliance rates will be summarized at each time point by treatment arm with reasons for missing data.

Reduction of growth factors, circulating tumor cells, stem cells in pre-selected centers will be defined in later version of SAP in an efficient amount of data will be available.

3.7. Safety evaluation

Frequencies of side effects will be summarized descriptively per treatment arm and in total. Patient listings will be given.

3.8. Subgroups

The primary endpoint overall survival will be analyzed in an exploratory way in subgroups defined by strata and other factors assessed at the screening phase:

- Tumor Subtype: Luminal A, Luminal B, Her2 and Basal
- Grading: G1/G2/GX and G3
- HER 2: FISH amplif./IHC+++, Her2 Negative
- Hormone receptor status: any positive, 0/0
- First Line Therapy: Chemotherapy vs Others
- Location of metastases: bone only, visceral +/- bone

Subtypes were defined as follows:
Luminal A = HR+, Her2-, G1/2/X
Luminal B: HR+, Her2-, G3
Her2: Her2+
Basal: HR-, Her2-
Subgroups other than stratification variables will be re-examined for appropriateness.

3.9. Covariates

To adjust for the possible effect of demographic or prognostic factors multivariate analyses will be performed. To avoid multi-collinearity between the covariates, prior correlation analyses will be performed. Depending on the statistical results and the clinical relevance, highly correlated covariates may be excluded from multivariate analyses. Binary dependent variables will be analyzed using logistic regression models. Metric dependent variables will be analyzed using general linear models or a non-parametric equivalent if appropriate. Forest plots will be given where appropriate.

The following variables are candidates for covariates which will be used for analyses to explore the relationship to the primary and secondary endpoints:

- Age group*
- T-stage
- N-stage
- Histologic grade
- Hormone Receptor status*
- HER2 status*
- Tumor Subtype

- Endocrine therapy
- Chemotherapy
- Immunotherapy
- Location of metastases

*Based on patient's actual value (eCRF)

3.10. Software

All analyses will be done using SAS version 9.3 or higher.

4. List of Planned Tables, Figures and Listings

4.1. Baseline demographic and disease characteristics

1. Demographic data of patients, stratification factors and disease characteristic variables in total and by treatment arm
2. Surgery and tumor classification after surgery
3. Patient status summarized in total and by treatment arm

4.2. Primary endpoint

4. Deaths in total and by treatment arm (randomized patients)
5. Result of Log-rank test for OS with treatment arm as covariate without stratification
6. Result of Log-rank test for OS with treatment arm as covariate with randomization stratification
7. Result of multivariable Cox proportional hazard model for OS with treatment arm, and stratification factors* as additional covariates
8. Result of multivariable Cox proportional hazard model for OS with treatment arm and prognostic factors as additional covariates

*actual values (eCRF)

4.3. Secondary endpoints

9. Result of Log-rank test for Time to distant progression with treatment arm as covariate
10. Result of Log-rank test for Time to local progression with treatment arm as covariate
11. Result of Log-rank test for TTPd with treatment arm as covariate with randomization stratification
12. Result of Log-rank test for TTPl with treatment arm as covariate with randomization stratification

13. Result of multivariable Cox proportional hazard model for TTPd with treatment arm, as well as stratification factors and prognostic factors as additional covariates
14. Result of multivariable Cox proportional hazard model for TTPl with treatment arm, as well as stratification factors and prognostic factors as additional covariates

4.4. Exploratory endpoints

15. Forest Plot of Hazard Ratios by Patient Subgroups

4.5. Safety evaluation

16. Side Effects by SOC in total and by treatment arm

4.6. Other Tables

17. Summary of important protocol deviations in total and by treatment arm
18. Patient status in total and by treatment arm
19. Patient exposure to local systematic therapies
20. Laboratory Values: CEA and CA 15-3 summary per visit
21. List of randomization stratification errors

5. Changes of analysis compared to study protocol

Patients were stratified with in Randomiser respect to center (option “Consider center as a factor”) instead of “Geographic region” as stated in protocol. All stratified tests will be performed without “Geographic region” as the stratification factors .