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PHASE IV.III, MULTICENTER, OPEN, RANDOMIZED TREATMENT STUDY TO EVALUATE THE EFFICACY OF MAINTENANCE THERAPY WITH CAPECITABINE (X) AFTER STANDARD ADJUVANT CHEMOTHERAPY IN PATIENTS WITH OPERABLE, HORMONE RECEPTOR AND HER2neu NEGATIVE BREAST CANCER. (CIBOMA/2004-01)

COALICIÓN IBEROAMERICANA DE INVESTIGACIÓN EN ONCOLOGÍA MAMARIA (CIBOMA)
CIBOMA/2004-01

STATISTICAL ANALYSIS PLAN

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CIBOMA/2004-01
Quimioterapia vs. Observación

NCT: 00130533

Date: May 2010

STATISTICAL ANALYSIS PLAN CIBOMA 2004-01_v.1

1. STUDY DATA ANALYSIS

1.1.Description of sample characteristics

All the demographic, baseline, histologic and treatment data clinically relevant for the study will be included and analyzed, including frequency and percentages for qualitative variables, and median and range for quantitative variables. When applicable, the associated p-value for data comparison between the treatment arms will be included to verify that both arms are equally balanced for important characteristics that describe the test sample.

1.2.End of Treatment

All the causes for the end of treatment, including the percentage, will be indicated and the situation in both arms will be described.

1.3.Capecitabine: Doses and cycles administered

The number of cycles administered for the capecitabine arm will be described, correlating it with the previous item in order to describe those patients who have not received all cycles and why.

The *cumulative dose received* (CDR) (mg/m^2) for capecitabine will be calculated. This is defined as the sum of all the doses of each cycle of capecitabine divided into the body surface(baseline). The median and the range will be described primarily.

The *dose intensity received* (DIR) (mg/m^2/week) will be calculated. This is defined as the ratio between the total dose received divided into the number of weeks that the treatment lasted. The median and the range will be described primarily.

The *relative dose intensity* (RDI) (%) will be calculated. This is defined as the ratio between the dose intensity received and the expected dose intensity multiplied by 100. The median and the range will be described primarily.

Dose reductions, delays and omission doses in the Xeloda arm will be analyzed at each treatment cycle.

1.4.Adverse Events and/or Toxicity

A description of all adverse events, including the percentage, will be included for both arms by patient. The applicable and clinically relevant events may be compared by treatment arm, using the Chi-Square test or Fisher's test. It will be optional to include the analysis of adverse events by treatment cycle. Toxicity corresponding to those adverse events that are

strictly related to capecitabine should be assessed in the Xeloda arm. The study SAEs should also be analyzed and/or described.

Note: The adverse events by patient are calculated as the maximum degree that the patient has had throughout the treatment (taking all cycles into account) for a certain adverse event.

1.5.Disease-Free Survival

All the events for disease-free survival should be described indicating the frequency and percentage and comparing them by arm, when applicable, using the Chi-Square test or Fisher's test. The description should also include the types of relapse, second primary cancers and causes of death for disease-free survival.

The disease-free survival curves, the associated p-value comparing the curves between both arms, the hazard ratio (taking the control, observation arm as reference) will be included, as well as the 95% confidence interval and the survival median (and its 95% interval), if it is achieved.

The datum of disease-free survival after 5 years will also be included in percentage (probability of continuing without relapse).

1.6.Overall Survival

All the events for overall survival should be described indicating the frequency and percentage and comparing them by arm, when applicable, using the Chi-Square test or Fisher's test. This description should also include the causes of death for overall survival.

The overall survival curves, the associated p-value comparing the curves between both arms, the hazard ratio (taking the control(observation) arm as reference) will be included, as well as the 95% confidence interval and the survival median (and its 95% interval), if it is achieved.

The datum of overall survival after 5 years will also be included in percentage (probability of continuing alive).

1.7.Multivariate Analyses

A Cox's multiple regression analysis will be included for disease-free and overall survival, in order to adjust the comparison of treatment for the primary prognostic factors.

1.8.Study Interim Analyses

The potential interim analyses of the study are at the coordinator's discretion and will include the applicable items of the sections above. These analyses will take into account that the use of the p-value for comparison is very restricted and the set value is stricter.