AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA BULGARIA

FINISHED PRODUCT: None
ACTIVE INGREDIENT: None

Study No: NIS-OBG-XXX-2012/1; NCT01715155
A RETROSPECTIVE COHORT STUDY ON THERAPEUTIC MANAGEMENT OF METASTATIC BREAST CANCER IN CLINICAL PRACTICE IN BULGARIA

Developmental Phase: Non-Interventional Study
Study Completion Date: 29/06/2013
Date of Report: 23/06/2014

Study type

The design of this study was a multicentre, national, observational, 18-month retrospective cohort study. The study was conducted through medical chart review of MBC female patients diagnosed between 1st July 2010 and 30st June 2011.

OBJECTIVES:

(a) Primary objective

The primary objective of the study was the estimation of the incidence rate of disease progression in a cohort of patients newly diagnosed with metastatic breast cancer, either De Novo or having progressed from a non-metastatic stage.

(b) Main secondary objectives

1. To estimate the progression free survival (PFS) rates at 12 and 18 months after diagnosis of MBC
2. To estimate time to progression (TTP);
3. To describe clinical and pathological characteristics of newly diagnosed MBC patients, including type and location of metastasis, tumor size, co-morbidities and performance status;
4. To describe socio-demographic and anthropometric characteristics of newly diagnosed MBC patients;
5. To describe diagnostic and clinical management patterns of MBC patients since confirmed diagnosis of metastatic disease;

6. To describe health care utilization associated with the disease in Bulgaria.

METHODS:

Sixteen specialists enrolled 171 patients.

The study was based on the collection of data from electronical or paper-based medical records with available data on patients that fulfil the study-specific eligibility criteria. All required information for the purposes of this study was collected using electronic Case Record Form (e-CRF).

Target subject population

Patients newly diagnosed with breast cancer (according to ICD-10) with confirmed metastasis, regardless of being de novo diagnosed or progressed from a non-metastatic stage. A representative sample of sites according to the MBC management reality in Bulgaria was selected. Representativeness was inferred from available publications and/or a panel of experts from the country.

Diagnosis and Main Criteria for Inclusion:

The subject population that was observed in the research study fulfilled all of the following criteria: the patients enrolled were females aged 18 years with new diagnosis of breast cancer according to ICD-10 with confirmed metastasis, confirmed diagnosis between 1st July 2010 and 30st June 2011. The female patients should be managed for her disease at the same setting where final diagnosis of MBC was performed.

The prescription of the medicinal products is clearly separated from the decision to include the patient in the study.

Evaluations:

The primary variable of the study is the estimation of the disease progression incidence rate expressed as the number of progression events on a per patient-year-basis.

The secondary variables (endpoints) of this study are the following:

- Proportion of patients among study population who have not progressed at 12 and 18 months after they were diagnosed (12- and 18-month PFS rate).
- Median and mean time interval that elapsed between diagnosis and first objective tumor progression (TTP) event and subsequent events;
- Median and mean time from the date of diagnosis to the date of breast cancer progression or death whichever occurred first (PFS time);

- Number of confirmed deaths due to any cause and due to MBC on a per patient-year-basis;

- Patient baseline sociodemographic and anthropometric characteristics including age, body height;

- Menstrual and reproductive history including menopausal status (premenopausal, perimenopausal, postmenopausal) at time of diagnosis of MBC, age at menopause, age at menarche, age at first delivery, number of live births, nursing history, oral contraceptive and hormone replacement therapy use history;

- Clinical and pathological characteristics including: age at primary diagnosis for patients who have progressed from a non metastatic state, information on whether the patient progressed within the first 12 months after adjuvant therapy onset and whether she had undergone surgical resection of the primary tumor (only for those who have progressed from a non metastatic state), age at diagnosis of metastases, estrogen receptor (ER) status, progesterone receptor (PR), HER2 receptor status, histological grade, primary tumor size and type, number, type and location of metastases, dominant metastasis, ECOG performance status, comorbidities, breast and ovarian cancer family history;

- Treatment & management patterns since documented diagnosis including type of therapy (endocrine therapy, chemotherapy, biological therapy, radiotherapy, surgery), setting of treatment (sequencing) as well as supportive care;

- Diagnostic patterns including clinical breast examination, mammography, imaging work-up [plain radiography, ultrasound, computed tomography (CT) scans and magnetic resonance imaging (MRI), DCE-MRI, skeletal scintigraphy, positron emission tomography fused with computed tomography (PET-CT)], tumor markers and circulating tumor cells testing and breast biopsy;

- Rates of inpatient, emergency department, and outpatient visits and other healthcare resources utilisation (i.e., number of hospital admissions and length of stay, number of emergency room visits, number of hospital outpatient visits, number of physician office visits and home healthcare/hospice services) during the follow-up period after diagnosis.

Statistical Methods:

Descriptive statistical analysis was performed for all study data and epidemiological methods were applied. Continuous variables were summarized with the use of descriptive statistical measures [mean value, standard deviation (SD), median and extreme values] and categorical/distinct variables were displayed as frequency tables (N, %). The normality of

distribution of continuous variables was examined using the Kolmogorov-Smirnov test in order to determine whether or not to use parametric methods for the analysis of the sample data.

Incidence rate (IR) of disease progression was calculated per patient-year with the respective 95% CI. Kaplan Meier method was used to estimate Progression Free Survival (PFS), Time to Progression (TTP) while the relevant plots were created. Differences in PFS, and TTP between groups of patients were evaluated with Log-Rank test.

All the aforementioned statistical tests were two-sided and were performed at a 0.05 significance level. The interpretation of all results was performed in a descriptive manner and missing data were not replaced.

RESULTS:

Subject Disposition and Demography:

Data is analyzed for the following populations:

- The **All Subjects population** is defined as all enrolled subjects. The listings include data from all patients.
- The **Full Analysis Set (FAS)** is defined as all enrolled and eligible subjects.
- The **Per-Protocol Population (PP)** is defined as all enrolled and eligible subjects who have non-missing primary variables. The FAS is used for all tables except the primary variables tables where PP is used.

The number of patients involved in the study is 171. Every subject fulfilled the inclusion and exclusion criteria, but only 158 (92.4%) of them are included in the Per-Protocol Population due to uncomplete data.

The age at the date of inclusion in the study - similarly to other continuous variables - is characterized by the number of non-missing values (n), its average value, standard deviation, median and quarters, minimum and maximum values.

The average age of the subjects is 62.99 years with minimum and maximum of 31, 87 years respectively.

Large proportion of the involved subjects lived in city: 129 subjects (75.4%). The average height of the subjects is 163.78 cms with minimum and maximum of 145, 180 cms respectively. The average weight of the subjects is 69.5 kgs with minimum and maximum of 47, 186 kgs respectively.

122 subjects (71.3%) were first diagnosed in non metastatic stage and 49 subjects (28.7%) in De Novo metastatic stage.

Treatment and Dosing:

As neoadjuvant treatment for non –metastatic disease the average duration of chemotherapy was 3.46 months for the 24 involved subjects with minimum and maximum of 1, 5 months respectively. The tables below provide greater details regarding the neoadjuvant treatments.

As main therapy for non-metastic disease the most frequent surgery was curative, radical procedure with 94 subjects (55%). The most frequent radiation therapy was curative, extended field with 70 subjects (40.9%). For the medical therapy for non-metastic disease the average duration of chemotherapy was 5.09 months for the 77 involved subjects with minimum and maximum of 1, 15 months respectively. The average duration of hormonal therapy was 32.87 months for the 75 involved subjects with minimum and maximum of 1, 60 months respectively.

42 subjects (24.6%) had palliative surgery and 47 subjects (27.5%) had radiotherapy for metastatic disease.

27 subjects (15.8%) were treated with other concomitant therapy for breast cancer and 25 subjects (14.6%) were treated with other concomitant therapy for pre-existent comorbidities.

Results:

The primary objective was to calculate the incidence rate of progression of disease in a cohort of patients newly diagnosed with MBC, either De Novo or having progressed from a non-metastatic stage.

The primary objective is analysed in the PP population (N=158).

Progression is defined as a documented progression or death due to any cause after diagnosis of MBC. 95% confidence interval of the incidence rate is calculated based on Byar's confidence limits method.

The incidence rate of disease progression per patient-year is 0.477 with 95% confidence interval of [0.387, 0.582].

Progression Free Survival (PFS) is defined as the length of time after diagnosis of MBC until documented progression or death due to any cause. PFS is calculated in the PP population (N=158) with the Kaplan--Meier method.

92 events were observed (58.2%). The median of Time to Event is 465 days with 95% confidence interval of [391, 578].

The estimated probability (and 95% CI) of PFS is 0.6114 (0.5279, 0.6847) at 360 days (~12 months) after diagnosis of MBC, and 0.4558 (0.3732, 0.5346) at 540 days (~18 months) after diagnosis of MBC.

Time to Progression (TTP) is defined as the length of time after diagnosis of MBC until documented progression or death due to MBC. TTP is calculated in the PP population (N=158) with the Kaplan--Meier method. Note: In case of unknown cause of death, it was counted as death due to MBC.

91 events were observed (57.6%). The median of Time to Event is 483 days with 95% confidence interval of [397, 607].

The estimated probability (and 95% CI) of TTP is 0.6174 (0.5338, 0.6904) at 360 days (~12 months) after diagnosis of MBC, and 0.4603 (0.3773, 0.5393) at 540 days (~18 months) after diagnosis of MBC.

There are 161 subjects with non-missing death status in the study. 60 subjects (37.27%) died due to any cause which implies a death rate of 0.239 per patient-year. 58 subjects (36.02%) died due to MBC which implies a death rate of 0.231 per patient-year. Note: In case of unknown cause of death, it was counted as death due to MBC.

The average age at menopause is 49.88 years with minimum and maximum of 34, 56 years respectively. The average age at first delivery is 22.52 years with minimum and maximum of 18, 42 years respectively. 35 subjects are known to have given birth at least once. The average number of live births is 1.56 with minimum and maximum of 1, 3 respectively. 17 subjects are known to have breast feeding history. The average duration of breast feeding is 6.36 months with minimum and maximum of 2, 12 months respectively.

The average age at primary diagnosis for patients who have progressed from a non metastatic state is 56.2 years with minimum and maximum of 25, 84 years respectively.

The average age at metastatic disease diagnosis is 61.16 years with minimum and maximum of 31, 85 years respectively.

The most frequent TN stage was T2 N1 with 25 subjects (14.6%).

87 subjects (50.9%) had ER positive, 78 subjects (45.6%) had PR positive breast cancer tumor, and in 25 cases (14.6%) the tumor was positive for Her 2 receptor.

From metastasis site 47 subjects (27.5%) had ER positive, 39 subjects (22.8%) had PR positive tumor, and in 15 cases (8.8%) the tumor was positive for Her 2 receptor.

The most frequent location was bone with 86 subjects (50.3%). The most frequent ECOG status at time of metastatic stage diagnosis was ECOG 1 with 71 subjects (41.5%).