Statistical Report

Version 1.0

AstraZeneca Brazil

RETROSPECTIVE BRAZILIAN STUDY OF FULVESTRANT IN ADVANCED BREAST CANCER

Study Code

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1. STUDY OUTLINE AND OBJECTIVES

The objectives of this retrospective study were to characterize the demographic and clinical features and to estimate the efficacy and tolerability among postmenopausal patients with advanced breast cancer treated with fulvestrant in Brazil. The primary variable of interest in the study was the time to tumour progression (TTP) in the evaluable subgroup, defined as those patients with at least one pre-treatment and two post-treatment radiographic scans for analysis. Unfortunately, the collection of scans was not possible for the vast majority of patients, thus precluding the analysis of TTP. The first among the secondary variables of interest was the duration of treatment with fulvestrant. Given the retrospective nature of the study, the collection of data on adverse events was not standardized according to validated instruments.

2. VARIABLES AND STATISTICAL METHODS

The following variables were analyzed in this study:

- Age;
- Sex;
- Ethnicity;
- Body mass index;
- Diagnostic method;
- Tumour histology;
- Hormone-receptors status (estrogen and progesterone receptors);
- HER-2 status;
- Metastatic sites;
- Types of therapy used before, during, and after fulvestrant administration;
- Durantion of treatment with fulvestrant;
- Number of fulvestrant cicles;
- Survival information, including disease status at last followup;
- Frequency of adverse events.

These variables were summarized using tables and graphs as appropriate. The Kaplan-Meier method was used for survival analysis, and comparisons between survival curves were done using the logrank test. All statistical analyses were performed using MedCalc software (Mariakerke, Belgium, v. 11.0.0.0).

3. RESULTS

Baseline characteristics

Data from 80 adult Brazilian patients with advanced breast cancer and failure of at least one previous therapy before treatment with fulvestrant 250 mg monthly by intramuscular injection were analyzed.

As shown in Table 1, the mean age (± standard deviation [SD]) of the patients was 62 (± 11) years, and patients were predominantly white (78.8%). Diagnosis was made chiefly using histologic samples (92.5%). All patients had invasive carcinomas, mostly ductal (73.7%), lobular (10.0%), or mixed ductal and lobular (8.7%) histology. Only one patient had mucinous carcinoma, and for the remaining five patients the histological subtype was unknown. Of all patients, 96.2% and 73.7% had estrogen- and progesterone-receptor positive tumours, respectively, and most patients had HER-2-negative or unknown disease. The main sites of metastases are also summarized in Table 1, considering more than one site of metastases per patient.

Table 1. Baseline demographic and clinical characteristics of the patients.

Variable	Value or N (%)
Mean age (± SD), years	**62 (± 11)**
Median age (interquartile range), years	**60 (54-69)**
Race	
White	**63 (78.8)**
Mixed	**5 (6.2)**
Black	**2 (2.5)**
Asian	**1 (1.2)**
Unknown	**9 (11.2)**
Method of diagnosis	
Histology	**74 (92.5)**
Citology	**2 (2.5)**
Unknown	**4 (5.0)**
Tumor histology	
Ductal carcinoma	**59 (73.8)**
Lobular carcinoma	**8 (10.0)**
Ductal and locular carcinoma	**7 (8.8)**
Mucinous carcinoma	**1 (1.2)**

Variable	Value or N (%)
Unknown	5 (6.2)
Hormone receptor status	
Estrogen positive	77 (96.2)
Estrogen negative	3 (3.8)
Progesterone positive	59 (73.8)
Progesterone negative	20 (25.0)
Unknown progesterone status	1 (1.2)
HER-2 status	
0	33 (41.2)
+1	10 (12.5)
+2	13 (16.2)
+3	5 (6.2)
Unknown	19 (23.8)
Metastatic sites	
Bones	65 (81.2)
Skin and soft tissues	25 (31.2)
Lungs	25 (31.2)
Non-regional lymph nodes	18 (22.5)
Liver	17 (21.2)
Pleura	12 (15.0)
Other	14 (17.5)

Table 2 summarizes therapies for early and advanced disease used before and after treatment with fulvestrant. None of the patients has used any antineoplastic agent other than fulvestrant during fulvestrant administration, since this was an exclusion criterion.

Table 2. Therapies used before, concurrently, or after fulvestrant treatment.

Treatment	N (%)
Adjuvant treatments for early disease	
Any treatment	55 (68.8)
Hormone therapy	45 (81.8)
Chemotherapy	39 (70.9)
Treatments for advanced disease before fulvestrant administration	

Treatment	N (%)
Any treatment	68 (85.0)
Hormone therapy	56 (82.4)
Chemotherapy	46 (67.6)
Monoclonal antibody with or without chemotherapy	2 (2.9)
Treatments for advanced disease after fulvestrant administration	
Any treatment	63 (78.8)
Chemotherapy	60 (95.2)
Hormone therapy	25 (39.7)
Monoclonal antibody with or without chemotherapy	7 (11.1)

Many patients had also received radiation therapy before and concurrently with the administration of fulvestrant. Table 3 shows data about irradiation sites.

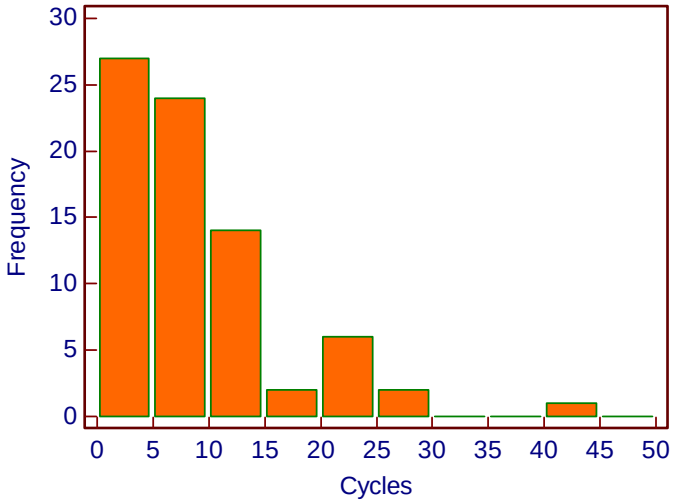
Table 3. Irradiation sites on patients who received radiation therapy.

Treatment	N (%)
Irradiation before fulvestrant administration	
Any site	63 (78.8)
Breast	37 (58.7)
Bones, joints, or spine	29 (46.0)
Supraclavicular fossa	16 (25.4)
Surgical bed	15 (23.8)
Axillae	9 (14.3)
Other sites	12 (19.0)
Unknown	6 (9.5)
Irradiation concurrent to fulvestrant administration	
Any site	14 (17.5)
Bones, joints, and spine	13 (92.9)
Other sites	4 (28.6)

Treatment disposition

Patients received between one and 44 cycles of therapy with fulvestrant, with a median of five cycles (Figure 1). In four patients, the number of cycles was unknown. Treatment was discontinued due to disease progression in 63 patients (78.8%). Other reasons for treatment discontinuation were lack of compliance (N=5), death from disease progression (N=4), adverse event (N=2), and miscelaneous causes (N=6).

Figure 1. Distribution of number of cycles.



Safety analisys

Adverse events

Safety analysis was done with reported adverse events occuring during administration of fulvestrant, considering as the denominator the total number of individual citations of adverse events. The most common adverse event was pain (27.1% of cited events), followed by fatigue/exhaustion (3.5%), dyspnea (2.1%), and nausea (2.1%). See Table 4 for more adverse events. Two patients had to discontinue fulvestrant due to an adverse event. Those events were neurotoxicity and arthralgia/myalgia.

Table 4. Frequency of cited adverse events during administration of fulvestrant.

Adverse event	%
Pain	**27.1**
Fatigue/exhaustion	**3.5**
Dyspnea	**2.1**
Nausea	**2.1**
Coughing	**1.9**
Dizziness/vertigo	**1.9**

Adverse event	%
Hypertensive peak	**1.6**
Diarrhea	**1.4**
Vomit	**1.2**
Anxiety	**1.2**
Weight loss	**1.2**
Weight gain	**1.2**
Others*	**53.9**

* Includes adverse events with frequency <1.0%.

Severe adverse events

Severe adverse events (SAE) were reported in 14 patients (17.5%). Nine patients (64.3%) experienced only one SAE, three patients (21.4%) experienced two SAE, and two patients (14.3%) experienced three SAE. The classification of SAE and the proportion of patients experiencing such events are shown in Table 5. Only one SAE was attributed to fulvestrant (head trauma), and the event resulting in death was chronic renal failure. None of the reported SAEs led to fulvestrant discontinuation.

Table 5. Number and proportion of patients according to SAE classification.*

Classification of SAE	N (%)
Event requiring in-patient hospitalization or prolongation of existing hospitalization	**11 (78.6)**
Event causing persistent or significant disability or incapacity	**3 (21.4)**
Immediately life-threatening event	**1 (7.1)**
Event resulting in death	**1 (7.1)**
Other medically important event	**6 (42.9)**
Unknown	**1 (7.1)**

* Patients may have experienced more than one SAE.

Efficacy analisys

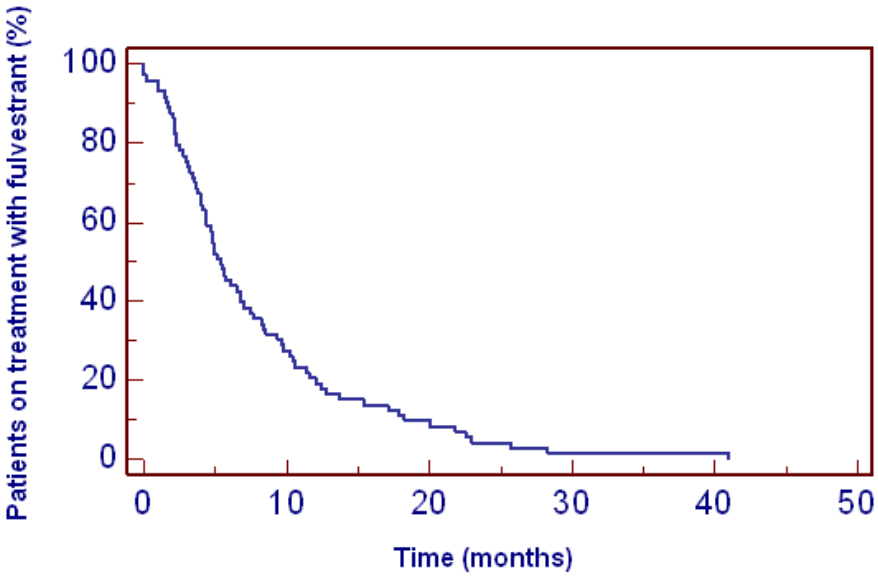
Treatment duration

The duration of treatment with fulvestrant was defined as the time elapsed between treatment initiation and treatment discontinuation due to any reason. Dates were not available for analysis for seven patients, who were therefore excluded from the

analysis of treatment duration. In addition, the exact day of the month was not available either for treatment initiation or treatment discontinuation in 11 patients; in these cases, the 15th day of the month was used to substitute for the missing value.

The duration of treatment ranged from 1 to 41 months. The median duration of treatment estimated with the Kaplan-Meier method was 5.4 months (Figure 2).

Figure 2. Treatment duration for the 73 patients with data available for analyis.

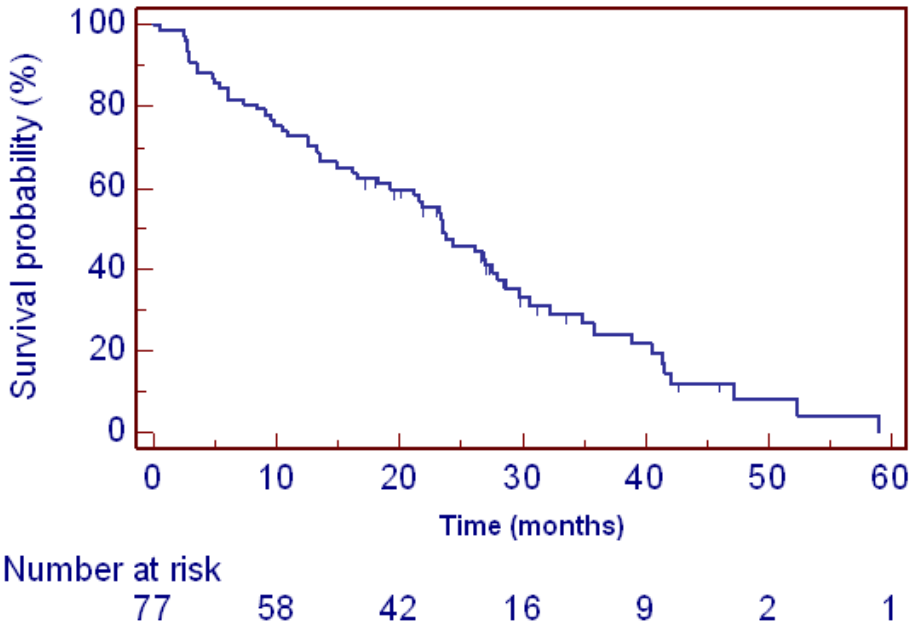


Overall survival

Overall survival was defined as the time elapsed between treatment initiation and death from any cause, with censoring of patients who were alive on last follow up. Sixty-two patients were already deceased on the occasion of the analysis. Dates were not available for analysis for three patients, who were therefore excluded from the analysis of overall survival. In addition, the exact day of the month was not available either for treatment initiation or treatment discontinuation in 12 patients; in these cases, the 15th day of the month was used to substitute for the missing value.

The duration of overall survival ranged from 0.5 to 59 months. The median overall survival estimated with the Kaplan-Meier method was 23.5 months (Figure 3).

Figure 3. Overall survival for the 77 patients with data available for analyis (tick marks represent censoring).

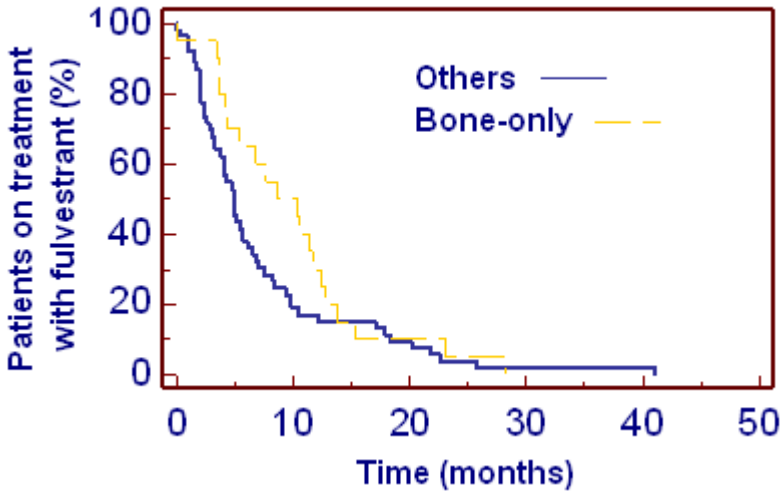


Exploratory analyses

Treatment duration according to the presence of bone-only metastases

The duration of treatment with fulvestrant was compared between patients with bone-only metastases (N=19) versus patients with metastases involving other organs (N=52) who were eligible for this analysis. As shown in Figure 4, the median treatment duration was longer among patients with bone-only disease (8.6 months) than in those with other lesions (4.8 months), but this difference did not reach statistical significance (P=0.15; hazard ratio[HR]=1.43, 95% confidence interval [CI] 0.88 – 2.34).

Figure 4. Treatment duration according to the presence or absence of bone-only disease.



Overall survival according to the presence of bone-only metastases

The duration of overall survival was compared between patients with bone-only metastases (N=19) versus patients with metastases involving other organs (N=58) who were eligible for this analysis. As shown in Figure 5, the overall survival was longer among patients with bone-only disease (median of 32.3 months) than in those with other lesions (median of 21.9 months), but this difference did not reach statistical significance (P=0.16; HR=1.51, 95% CI 0.86 – 2.68).

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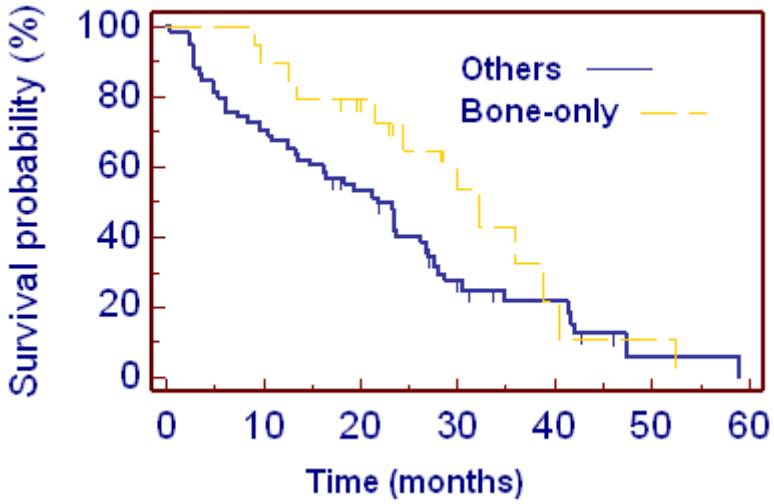
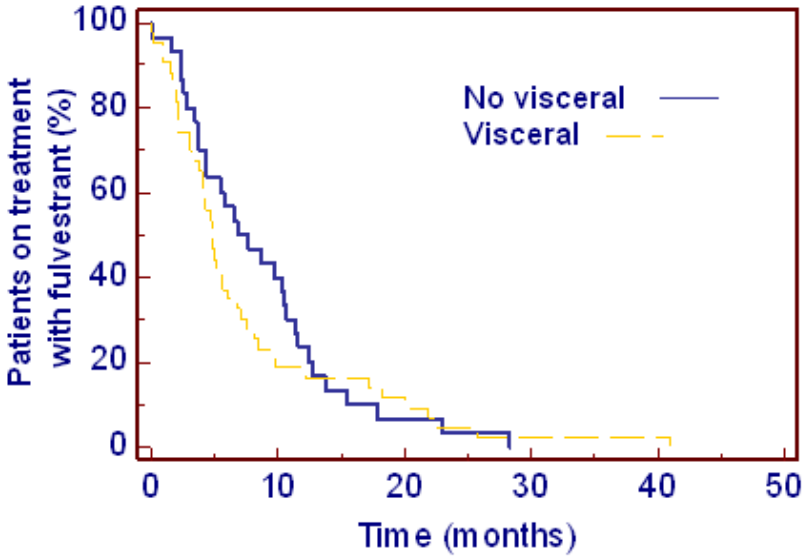
Figure 5. Overall survival according to the presence or absence of bone-only disease (tick marks represent censoring).



Treatment duration according to the presence of visceral metastases

The duration of treatment with fulvestrant was compared between patients with visceral metastases, defined as those with at least one lesion in the lungs, pleura, liver, ovary or brain (N=43) versus patients with no visceral metastases (N=30) who were eligible for this analysis. As shown in Figure 6, the median treatment duration was longer among patients with no visceral metastases (7.7 months) than in those with visceral metastases (4.8 months), but this difference did not reach statistical significance (P=0.43; HR=1.21, 95% confidence interval [CI] 0.75 – 1.93).

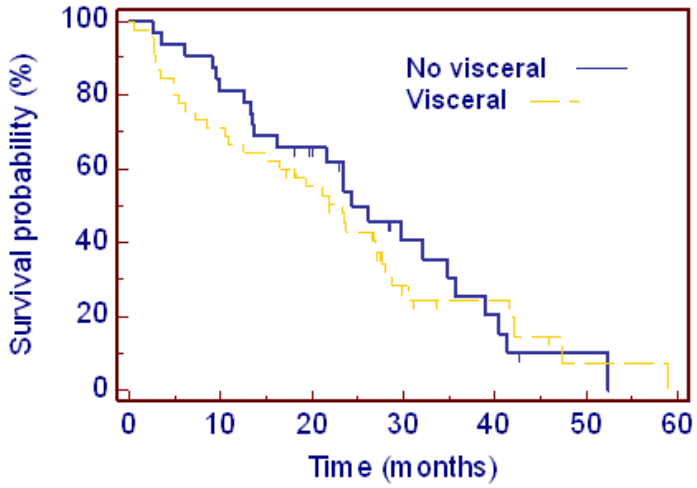
Figure 6. Treatment duration according to the presence or absence of visceral metastases.



Overall survival according to the presence of visceral metastases

Overall survival was compared between patients with visceral metastases, defined as those with at least one lesion in the lungs, pleura, liver, ovary or brain (N=45) versus patients with no visceral metastases (N=32) who were eligible for this analysis. As shown in Figure 7, the median overall survival was approximately equal among patients with no visceral metastases (24.4 months) and in those with visceral metastases (23.3 months) (P=0.61; HR=1.15, 95% confidence interval [CI] 0.61 – 1.93).

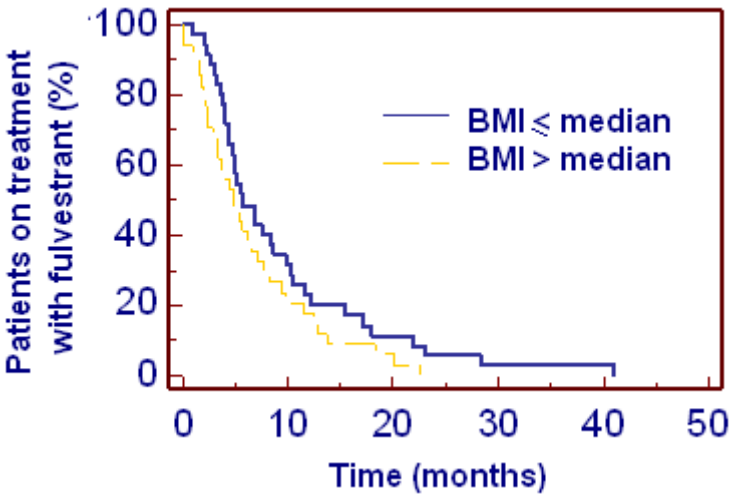
Figure 7. Overall survival according to the presence or absence of visceral metastases (tick marks represent censoring).



Treatment duration according to the body mass index

Body mass index (BMI), defined as the weight in kilograms divided by the square of the height in meters, ranged from 19.28 to 36.41 kg/m^2, with a median of 25.97 kg/m^2. Eligible patients for this analysis (N=69) were categorized according to having a BMI above or equal to/below the median, and the duration of treatment with fulvestrant was compared between the two groups. As shown in Figure 8, there were no significant differences between treatment duration when patients with a higher BMI (median of 4.8 months) where compared with those with lower BMI (5.6 months; P=0.13; HR=0.68, 95% CI 0.42 – 1.11).

Figure 8. Treatment duration according to BMI.



Overall survival according to the use of fulvestrant in first or subsequent lines

Overall survival was compared between patients receiving fulvestrant as a first-line therapy for metastatic disease (N=11) versus patients receiving the agent as second- or subsequent-line therapy (N=66) who were eligible for this analysis. As shown in Figure 9, the median overall survival was longer in the former group (38.9 months) than in the latter (23.4 months), but this analysis should be interpreted with caution, given the inherent bias resulting from the comparison of patients in different phases of their disease (P=0.046; HR=0.51, 95% confidence interval [CI] 0.26 – 0.99).

Figure 9. Overall survival according to the line in which fulvestrant was used (tick marks represent censoring).