# A multicenter, single-arm study to evaluate the safety of eribulin as third-line chemotherapy in patients with locally advanced or metastatic HER2-negative breast cancer previously treated with taxanes and anthracyclines: OnSITE study (OncoSur Analysis of the Treatment in Third Line of ABC with Eribulin)

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| **Name of study drug** | Halaven® |
| **Indication studied** | Locally advanced or metastatic breast cancer with disease progression after at least one chemotherapy regimen for advanced disease |
| **Sponsor's name** | Fundación ONCOSUR |
| **Protocol number** | ONCOSUR 2012-02 |
| **EUDRACT number** | 2013-01416-30 |
| **Phase** | IV |
| **Date of enrollment of first patient and site-patient** | 17-Dec-2013 (patient 04-01) |
| **Date of last completer and site-patient** | 31-Jan-2016 (patients 06-02 and 10-05) |
| **Study Coordinator and Principal Investigator** | Dr. Luis Manuel Manso Sánchez |
| **Document type** | Final report of Protocol ONCOSUR 2012-02 version 01 dated December 7, 2016 |
| **Version** | 1.0 |
| **Release date** | 25-Jan-2017 |
| **Author** | Dr. Manso (Coordinator and Principal Investigator)<br>Rosa Suárez (PM, Experior)<br>Arancha Maciá (Head of the Start-up Unit, Experior<br>Chelo González (Head of the Statistics and Data Management Unit, Experior) |

# SIGNATURE PAGE FOR THE FINAL REPORT

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| **Author** | Dr. Luis Manso Sánchez (Coordinator and Principal Investigator)<br>Rosa Suárez (PM, Experior)<br>Arancha Maciá (Head of the Start-up Unit, Experior<br>Chelo González (Head of the Statistics and Data Management Unit, Experior) |
| **Sponsor contact person:** | Dr. Luis Manso Sánchez |
| **Sponsor, signature and date:** | |
| **Author, signature and date:** | |

# 1. Synopsis

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|---|---|
| **Type of application** | Clinical trial for evaluation of safety and efficacy |
| **Sponsor** | Fundación Oncosur |
| **Title** | A multicenter, single-arm study to evaluate the safety of eribulin as third-line chemotherapy in patients with locally advanced or metastatic HER2-negative breast cancer previously treated with taxanes and anthracyclines: OnSITE study (OncoSur Analysis of the Treatment in Third Line of ABC with Eribulin) |
| **Short title** | OnSITE study |
| **EudraCT number** | 2013-001416-30 |
| **Protocol number** | ONCOSUR 2012-02 |
| **Principal investigator and study coordinator** | Name: Dr. Luis Manuel Manso Sánchez<br>Site: Hospital Universitario 12 de Octubre<br>Telephone: (+34) 913908003<br>E-mail: lmanso.hdoc@salud.madrid.org<br>Position: Specialist Physician in Medical Oncology |
| **Central Ethics Committee** | Regional EC of the Community of Madrid |
| **Name and qualification of the persons in charge of Monitoring** | Experior, S.L.<br>C/ Vicente Galmés 1A<br>46139 La Pobla de Farnals (Valencia)<br>Tel.: 902.105.255; Fax: 96.145.21.91 |
| **Clinical sites where the study is planned to be conducted** | The study was conducted in approximately 15 Spanish hospitals. |
| **Investigational drug: Dose, pharmaceutical form and route of administration, pharmacotherapeutic group** | **Active ingredient: Eribulin**<br>**Brand name:** Halaven®<br>**Laboratory:** Eisai Europe Ltd<br>**Therapeutic group / ATC code:** Other antineoplastic agents / L01XX41<br>**Route of administration:** Short intravenous infusion (2 to 5 minutes).<br>The eribulin dose in the study is 1.23 mg/m$^2$, administered intravenously in bolus injection, 2-5 minutes, on Day 1 and Day 8 of every cycle. One cycle is 21 days.<br>Prior therapy must have included an anthracycline and a taxane, unless these treatments were not suitable for the patients. |
| **Trial phase** | Phase IV |
| **Duration of therapy** | The treatment is given to the patient until:<br>• Appropriately documented disease progression.<br>• Unacceptable toxicity.<br>• Investigator's or patient's decision.<br>• Or major non-compliance with the study protocol. |
| **Objectives** | **Primary objective:** To evaluate the safety of eribulin as single agent in third-line therapy in patients with locally advanced or metastatic HER2-negative breast cancer previously treated with taxanes and anthracyclines in terms of adverse reactions.<br>**Secondary objectives:**<br>• To evaluate the efficacy of eribulin in the study population in terms of 1-year overall survival (OS) and progression-free survival (PFS).<br>• To determine the clinical response rate of the study treatment as clinically indicated.<br>• To determine the objective response rate (ORR) of the study treatment according to the RECIST criteria.<br>• To determine the clinical benefit rate (CBR) of the study treatment according to the RECIST criteria. |

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| | • To evaluate the time to disease progression upon treatment completion in patients without disease progression during treatment.<br>• To evaluate duration of response.<br>• To explore the dynamics of circulating tumor cells (CTCs) during treatment with eribulin, as well as its correlation with prognosis and/or early failure of treatment with eribulin.<br>• To evaluate the presence or absence of visceral disease. |
| **Endpoints** | **Primary endpoints**:<br>• Adverse reactions<br>• Treatment duration<br>• Number of patients treated<br>• Number of patients who complied with the regimen<br>• Drug dose<br>• Concomitant medication<br>• Death<br>**Secondary endpoints:**<br>• The endpoints considered to assess overall survival (OS) are death and time to death; and in cases where the patient has not died, patient observation time.<br>• The endpoints considered to assess progression-free survival (PFS) are progression and time to progression; or in cases where the patient had not progressed, patient observation time.<br>• Clinical response rate, as defined by clinical criteria.<br>• Objective response rate (ORR), defined as: (CR+PR)/total.<br>• Clinical benefit rate (CBR), defined as (CR+PR+SD)/total.<br>• The variables that considered to assess time to progression after treatment are progression after treatment and time to progression after treatment; or in cases where the patient has not progressed, patient observation time after treatment.<br>• Duration of response.<br>• Circulating tumor cell (CTC) count before starting study treatment and after the first cycle.<br>• Presence/absence of visceral disease |
| **Study design** | This is a national, multicenter, single-arm study where all patients receive the same treatment.<br>One cycle is 21 days; treatment is given on Days 1 and 8 of every cycle. |
| **Study population** | Patients with locally advanced or metastatic HER2-negative breast cancer who had previously progressed to taxanes and anthracyclines in third-line chemotherapy for their locally advanced/metastatic disease. |
| **Patient screening** | **INCLUSION CRITERIA**<br>Patients are eligible for inclusion in this study only if they fulfill ALL of the following criteria:<br>1. Patients who have histologically confirmed diagnosis of stage IIIb/IV locally advanced or metastatic HER2-negative breast cancer.<br>2. Patients who are to receive a third line of chemotherapy i.e., patients who have previously received at least two previous chemotherapy lines for metastatic disease.<br>3. Age ≤ 18 years.<br>4. Patients must have previously progressed to a neoadjuvant or adjuvant therapy including taxanes (docetaxel, paclitaxel, nab-paclitaxel) and anthracyclines (doxorubicin, epirubicin, or liposome variants of these) for locally advanced or metastatic disease, unless there is no indication to receive these treatments for clinical purposes (limiting dose of anthracyclines or residual toxicity due to |

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| | taxanes).<br>5. Patients may have received previous additional anti-hormone therapy.<br>6. Written informed consent.<br>7. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.<br>8. Patients must have recovered from all toxicities related to previous treatments, with CTCAE v. 4.0 $\geq$ grade 1, except for sensory neuropathy < grade 2 and/or alopecia.<br>9. Patients must have a measurable or evaluable disease (RECIST 1.1).<br>10. Adequate bone marrow function as shown by: ANC ≤ 1.5 x $10^9$/L, platelets ≤ 100 x $10^9$/L, Hb > 10 g/dL.<br>11. Adequate liver function, as shown by serum bilirubin ≥ 1.5 mg/dL (>26 µmol/L, equivalent in the IS); ALT-GPT and AST-GOT ≥ 3 x ULN (≥ 5 x ULN in patients with liver metastasis).<br>12. Adequate renal function: Serum creatinine ≥ 1.5 mg/dL (>132 micromole/L equivalent in the IS).<br>13. Patients must have a life expectancy above 3 months. |
| **Patient screening** | **EXCLUSION CRITERIA**<br>Patients are NOT eligible for inclusion in this study if they fulfill any of the following criteria:<br>1. Patients who have previously received a single line of chemotherapy or ≤ 3 lines of chemotherapy for metastatic disease.<br>2. Patients who have received prior oncology treatment within the following periods:<br>• Chemotherapy, radiotherapy or hormone therapy within the past 2 weeks.<br>• Other investigational drugs within the past 4 weeks.<br>3. Radiotherapy affecting > 30% of the bone marrow.<br>4. Pulmonary lymphangitis with respiratory dysfunction requiring active treatment, including oxygen therapy.<br>5. Patients who have had major surgery or significant traumatic injury within 4 weeks before start of study treatment, or patients who have not recovered from the side effects of any major surgery (defined as surgery requiring general anesthesia) or patients who may require major surgery during the trial.<br>6. Uncontrolled brain or leptomeningeal metastasis, including patients who continue treatment with glucocorticosteroids for brain or leptomeningeal metastases. Patients with prior history of brain metastases must submit a normal or stable MRI at study entry, and at least three months should have passed from the end of surgery or radiotherapy.<br>7. Patients who have any severe and/or inadequately controlled medical conditions or other alterations that may affect their participation in the study, such as:<br>• Unstable angina, symptomatic congestive heart failure (NYHA III or IV), myocardial infarction within the past 6 months, severe uncontrolled cardiac arrhythmia, congenital long QT syndrome, or any other clinically significant heart diseases<br>• Severe deterioration of lung function<br>• Active (acute or chronic) or uncontrolled severe infection<br>• Liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis<br>• Known history of HIV seropositivity<br>• Active bleeding diathesis |

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| | 8. Other malignancies within the past 3 years, except for: Carcinoma in situ of the cervix, and basal cell carcinoma or squamous cell carcinoma of the skin that have been adequately treated.<br>9. Pregnant or breast-feeding patients or adults of childbearing potential who do not use effective methods of contraception. Female patients of child-bearing potential must have a negative urine or serum pregnancy test within 7 days before start of study treatment. Hormonal methods of contraception are not acceptable as a single method of contraception. If barrier methods of contraception are chosen, these must be continued during the whole study for both sexes.<br>10. Chronic treatment with systemic corticosteroids or any other immunosuppressive agents (except for corticosteroids with a daily dose equivalent to prednisone ≥ 20 mg). If patients receive corticosteroids, there should be a stable dosing regimen for at least 4 weeks before entering the study. Topical and inhaled corticosteroids are allowed.<br>11. Documented active alcohol or drug abuse.<br>12. Patients with a prior history of non-compliance with medical regimens. |
| **Number of expected patients** | Sixty patients with locally advanced or metastatic HER2-negative breast cancer were expected to be enrolled. |
| **Study calendar** | Date of submission to Health Authorities/Ethics Committee: May 2013<br>Start of patient enrollment: December 2013<br>Recruitment: Enrollment period of one year<br>End of patient enrollment: December 2014<br>End of study: Up to December 2015<br>Report: Expected date: First six months of 2016 |

## 2. Table of contents

**Abbreviations**

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|---|---|
| AE | Adverse Event |
| ALT-GPT | Alanine aminotransferase |
| ANC | Absolute Neutrophil Count |
| AST-GOT | Aspartate aminotransferase |
| CBR | Clinical benefit rate |
| CR | Complete Response |
| CRA | Clinical Research Assistant |
| CRO | Contract Research Organization |
| CTC | Circulating Tumor Cells |
| CTCAE | Common Terminology Criteria for Adverse Events |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EMA | European Medicines Agency |
| ESMO | European Society for Medical Oncology |
| GCP | Good Clinical Practice |
| Hb | Hemoglobin |
| ICH | International Conference on Harmonization |
| IS | International System of Units |
| MRI | Magnetic Resonance Imaging |
| NA/A | Neoadjuvant/adjuvant therapy |
| NYHA | New York Heart Association |

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|---|---|
| ORR | Objective Response Rate |
| OS | Overall survival |
| PD | Progressive disease |
| PFS | Progression-free survival |
| P-GP | P-glycoprotein (transporter) |
| PHI | Patient's protected health information |
| PIS | Patient Information Sheet |
| PR | Partial Response |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Stable Disease |
| TEAE | Treatment-emergent adverse event |
| TPC | Treatment of physician’s choice |
| TTP | Time to progression |
| ULN | Upper Limit of Normal |

## 3. Summary of results

Third-line chemotherapy with eribulin for locally advanced or metastatic breast cancer is effective and minimally toxic, manageable and similar to the therapy previously described in pivotal trials. Treatment was effective with a median progression-free survival of 4.03 months and a median overall survival of 13.6 months and it also had a high clinical benefit rate.

**Figure 3-1 Kaplan-Meier curve of progression-free survival**

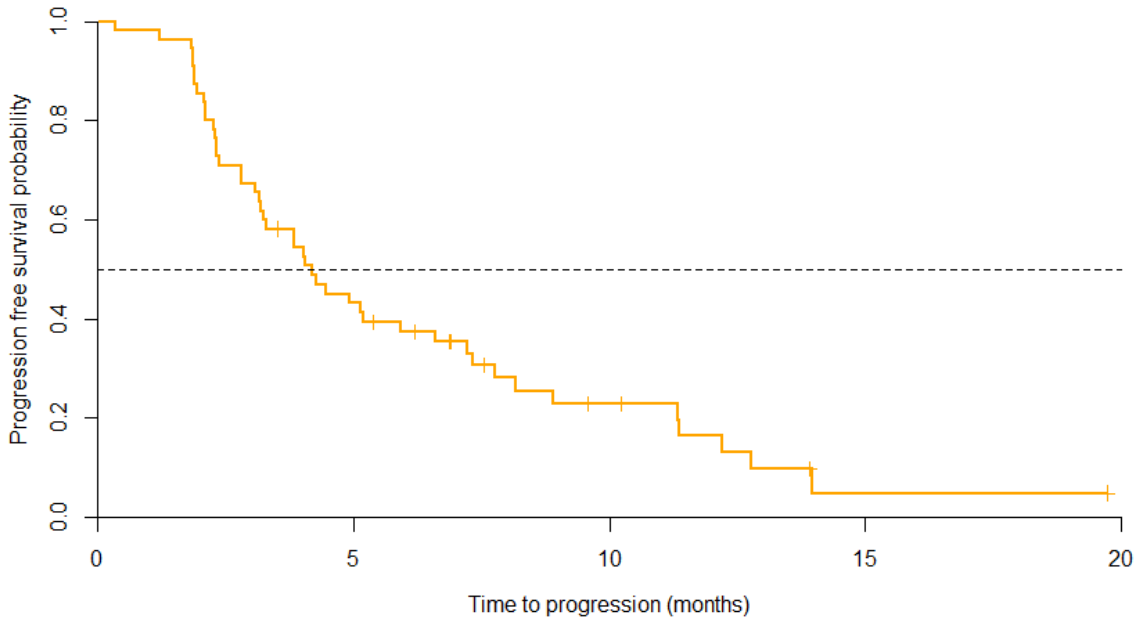
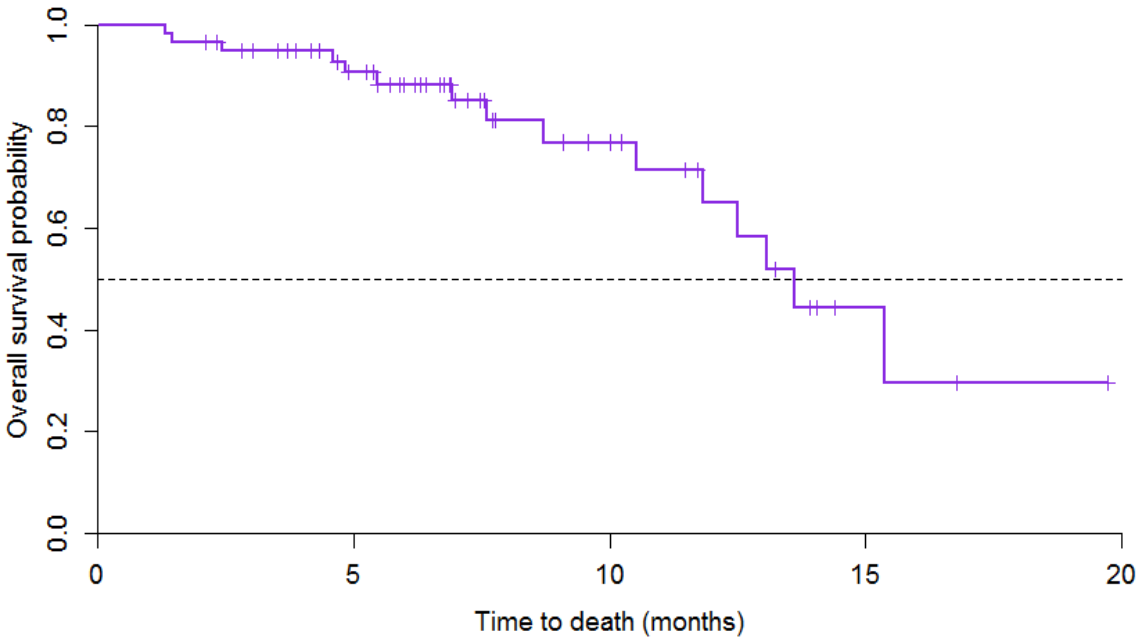



**Figure 3-2 Kaplan-Meier curve of progression-free survival**



# 4. Ethics

## *4.1 Independent Ethics Committee (central EC)*

The study and its amendments were reviewed by the EC of Hospital 12 de Octubre.

## *4.2 Study ethical development*

The study was carried out in accordance with the ethical principles laid down in the Declaration of Helsinki.

## *4.3 Patient Information Sheet and Consent*

Before enrolling any subject and before performing any specific study evaluation or test, the informed consent was explained and obtained. The informed consent should be provided in order to be read by the patient before signing it and to explain the benefits and potential risks of the trial. The consent should be documented by the patient's dated signature. The signature certifies that the consent is based on information which has been understood. A copy of the consent was provided to the patient. The subject must be informed of the right to participate or not in the study and to withdraw consent to participate at any time of the study.

The subjects participating in the study were recruited in the participating investigators' offices based on standard clinical practice. Participants were male and female subjects > 18 years of age who had been previously diagnosed with stage IIIb/IV locally advanced or metastatic HER2-negative breast cancer.

There were two versions of the patient information sheet and informed consent (PIS/IC): The first version v.1.0 dated March 18, 2013 was not used because the central EC required changes to be made, and therefore version 2.0 dated June 18, 2013 was the version used during the study.

# 5. Investigators and Study Administrative Structure

Dr. Luis Manuel Manso was the Study Coordinator and Principal Investigator.

Twelve sites out of the 16 participating sites enrolled patients. See Appendix 5.

The EC of Hospital 12 de Octubre was the central Ethics Committee evaluating the study.

The Sponsor is Fundación Oncosur and they delegated tasks to Experior SL, CRO in charge of Monitoring.

Data handling and subsequent statistical analysis was conducted by Experior SL.

# 6. Background

Many patients with breast cancer who have been treated with neoadjuvant and/or adjuvant (NA/A) chemotherapy presented a relapse in the same location where the original primary tumor was diagnosed (locally advanced stage of the disease) or in a farther location (metastasis). Chemotherapy is the therapy

chosen in such cases. Today there is a wide range of treatment options for patients with locally advanced or metastatic disease, and none of them is clearly better than the others in terms of efficacy. The first-line therapy is not an exception; monotherapy (single agent) schemes and drug combinations are not different in terms of survival. The randomized study (E-1193) of the Eastern Cooperative Oncology Group (ECOG) showed that, although the response rate and time to progression were higher in patients treated with paclitaxel and doxorubicin combinations, survival was the same in both groups (combination or monotherapy) (Sledge et al 2003). Therefore, choosing a therapy is determined by other factors such as disease progression rate or physician/patient opinion, personalizing the therapy administered.

In post-menopausal patients with positive hormone receptors (ER and PR) and recently diagnosed metastatic disease, hormone therapy must be considered to be the initial treatment, especially when metastases are near bones or guts, and the patient has not received adjuvant anti-estrogen treatment or she received it more than one year ago (Mauri et al 2006). Instead, for patients with negative ER tumor or early relapse (e.g., before 6 months), the most appropriate choice seems to be chemotherapy. The combination of taxanes and anthracyclines has generally become the standard first-line therapy in metastatic breast cancer (Friedrich et al 2004).

Today, the most aggressive chemotherapy combinations have been replaced with individualized therapies that optimize dose strength and treatment duration to avoid toxicity excess. Both the sequential schemes and single-agent treatments (monotherapy) have shown a survival comparable to combination chemotherapy, but with less toxicity and, therefore, are considered to be an effective palliative approach. In first-line therapy for metastatic disease, many drugs have been studied in monotherapy, including taxanes, anthracyclines, capecitabine and vinorelbine (Friedrich et al 2004; Gelmon et al 2006; Pronzato and Rondini 2006).

Since achieving disease control for long periods of time is unlikely in this type of patients, it is required to identify new agents able to obtain a good disease control without quality of life impairment. For this reason, eribulin seems to be the optimal choice because this drug has a very favorable toxicity profile; it can improve survival in highly pre-treated patients with metastatic breast cancer (Cortes et al 2010). Furthermore, its mechanism of action and available clinical data suggest that its therapeutic activity is maintained in patients previously treated with taxanes and anthracyclines (Vahdt et al 2009).

## 7. Study objectives

### *7.1 Primary objective*

To evaluate the safety of eribulin as single agent in third-line therapy in patients with locally advanced or metastatic HER2-negative breast cancer previously treated with taxanes and anthracyclines in terms of adverse reactions.

The following variables were considered to evaluate the study primary objective:

- Adverse reactions

- Treatment duration
- Number of patients treated
- Number of patients who complied with the regimen
- Drug dose
- Concomitant medication
- Death

### *7.2 Secondary objectives*

- To evaluate the efficacy of eribulin in the study population in terms of 1-year overall survival (OS) and progression-free survival (PFS).
- To determine the clinical response rate of the study treatment as clinically indicated.
- To determine the objective response rate (ORR) of the study treatment according to the RECIST criteria.
- To determine the clinical benefit rate (CBR) of the study treatment according to the RECIST criteria.
- To evaluate the time to disease progression upon treatment completion in patients without disease progression during treatment.
- To evaluate duration of response.
- To explore the dynamics of circulating tumor cells (CTCs) during treatment with eribulin, as well as its relation to prognosis and/or early failure of treatment with eribulin.
- To evaluate the presence or absence of visceral disease.

## 8. Investigational plan

### *8.1 Study general design and plan description*

Multicenter, single arm, phase IV study in sixty patients with locally advanced or metastatic HER2-negative breast cancer who had previously received two lines of chemotherapy for advanced disease including anthracyclines and taxanes; all patients received the same treatment.

Randomization, blinding and a control group are not required in this design.

Eligible patients with histologically confirmed diagnosis of stage IIIb/IV metastatic HER2-negative breast cancer receive monotherapy with eribulin 1.23 mg/m$^2$, in IV bolus, on Day 1 and Day 8 of each 21-day cycle. Treatment is given to patients until appropriately documented disease progression, unacceptable toxicity, investigator's or patient's decision, or major non-compliance with the study protocol.

If required by the investigator, dose modifications and delays are allowed, provided instructions in Section 5.7.5 of the protocol are followed. In case of clinical signs of disease progression or unacceptable toxicity, drug administration should be discontinued. The choice of the next therapy depends on the clinical judgment of the investigator. After the last dose of eribulin, the patients are followed up for up to 3 months.

**Table 8-1.- Visit schedule**

| | **BASELINE Day -21 (Day 0)** | **EVERY CYCLE Day 1** | **EVERY CYCLE Day 8** | **END OF STUDY AND FOLLOW-UP** |
|---|---|---|---|---|
| **Standard clinical procedures** | | | | |
| Signed informed consent | x | | | |
| Medical history | x | | | |
| Physical exam | x | | | x |
| ECG [4] | x | | | |
| ECOG performance status | x | x | | x |
| Concomitant medication record | x | x | x | x |
| AE/SAE record | | X | X | X |
| Toxicities CTCAE v.4.0 | x | x | x | x |
| RECIST treatment response assessment | x | | | X[1] |
| **Laboratory procedures** | | | | |
| Serum or urine pregnancy test | x | | | |
| Hematology | x | x | x | x |
| Chemistry (hepatic and renal profile) | x | x | x | x |
| CTC (circulating tumor cell) measurement | | X[2] | | |
| **Study medication** | | | | |
| Eribulin dispensation and record | | X[3] | x[3] | |

1 According to the site standard clinical practice, it is recommended every three cycles of treatment with eribulin and at the end of the study, following the RECIST assessment criteria (version 1.1) as described in the RECIST guidelines attached to this protocol.

2 Cycle 1 Day 1 prior to the administration of eribulin and Cycle 2 Day 1 prior to the administration of eribulin

3 Dose as established in the protocol. Administration on Days 1 and 8 of each cycle, whenever possible. If they occur on a holiday or if administration is not possible on Days 1 or 8, drug administration may be scheduled 1 day before or 2 days after the scheduled date (window of -1/+2 days). In case of a long delay due to toxicity, it should be evaluated and approved by the study Sponsor.

4 ECG: Always at baseline and, if applicable due to patient's medical history, in subsequent cycles

### *8.1.1 Circulating peripheral tumor cell isolation and quantification*

For all patients, blood was taken before chemotherapy to determine the number of baseline circulating tumor cells (CTCs) before starting treatment with eribulin on Cycle 1 Day 1 and Cycle 2 Day 1 before eribulin administration. Patients underwent additional follow-up tests not included in the standard protocol of the Department of Medical Oncology.

Each of these blood samples was transferred in 10 mL EDTA Vacutainer tubes. A standard cell preservative was added over them. Blood samples were stored at room temperature and were processed within 96 hours after blood drawing in the Hospital Universitario 12 de Octubre. Once the blood sample was processed, CTCs were extracted using the following technique:

Immunomagnetic separation is performed in 7.5 mL of processed blood using ferrofluids with antibodies directed to epithelial adhesion molecules according to the CellSearch Epithelial Cell Kit system (Veridex LLC, Johnson and Johnson Company). Isolated cells are bound by fluorescence technology with 4′,6-diamidino-2-phenylindole (DAPI nucleotides and monoclonal antibodies which are specific for leukocytes (CD-45-allophycocyanin) and for epithelial cells (cytokeratin 8,18,19-phycoerythrin). They were then analyzed with the CellSpotter Analyzer system (Veridex LLC, Johnson and Johnson Company).

Sample draws are handled and processed by a Laboratory Technician expressly trained in CellSearch System functioning.

## *8.2 Discussion about study design*

This study is aimed to evaluate the safety of eribulin monotherapy as third-line therapy in patients with locally advanced or metastatic HER2-negative breast cancer previously exposed to taxane and anthracycline chemotherapy.

Based on data published to date on the efficacy and safety of eribulin and the evidence that it maintains its therapeutic efficacy in tumor cells, which are refractory/resistant to taxanes and anthracyclines (Kuznetsov et al 2007), it is reasonable to expect that eribulin may constitute a valid therapeutic alternative for this type of patients. In fact, given its efficacy in terms of overall survival increase, it would be expected to be used as soon as possible within its approved clinical indication, i.e. in third-line therapy for the advanced disease. A post hoc analysis of the pivotal study EMBRACE data showed how the therapeutic benefit in terms of overall survival increase was higher in the group of patients treated with third-line eribulin than in those patients who received eribulin in more advanced lines (Blunt, SABCS 2010). However, there are no tolerability data by treatment line. Therefore, for the purposes of optimizing treatment with eribulin, it would be interesting that, besides third-line efficacy data, additional safety data were available.

The presence of tumor cells in peripheral blood in women with metastatic breast cancer treated with chemotherapy may be a predictive factor of response and prognosis, which may be added to the already existing factors.

## *8.3 Study population selection*

Subjects eligible for inclusion in this study must fulfill all of the inclusion criteria and none of the exclusion criteria.

### *8.3.1 Inclusion criteria*

1. Patients who have histologically confirmed diagnosis of stage IIIb/IV locally advanced or metastatic HER2-negative breast cancer.
2. Patients who are to receive a third-line chemotherapy i.e., patients who have previously progressed to two previous lines of chemotherapy for metastatic disease.
3. Age ≤ 18 years.
4. Patients must have previously progressed to a neoadjuvant or adjuvant therapy including taxanes (docetaxel, paclitaxel, nab-paclitaxel) and/or anthracyclines (doxorubicin, epirubicin, or liposome variants of these) for locally advanced or metastatic disease, unless there is no indication to receive these treatments for clinical purposes (limiting dose of anthracyclines or residual toxicity due to taxanes).
5. Patients may have received previous additional anti-hormone therapy.
6. Written informed consent.
7. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.
8. Patients must have recovered from all toxicities related to previous treatments, with CTCAE v. 4.0 ≥ grade 1, except for sensory neuropathy < grade 2 and/or alopecia.
9. Patients must have a measurable or evaluable disease (RECIST 1.1).
10. Adequate bone marrow function as shown by: ANC ≤ 1.5 x $10^9$/L, platelets ≤ 100 x $10^9$/L, Hb > 10 g/dL.
11. Adequate liver function, as shown by serum bilirubin ≥ 1.5 mg/dL (>26 µmol/L, equivalent in the IS); ALT-GPT and AST-GOT ≥ 3 x ULN (≥ 5 x ULN in patients with liver metastases).
12. Adequate renal function: Serum creatinine ≥ 1.5 mg/dL (>132 micromole/L equivalent in the IS).
13. Patients must have a life expectancy above 3 months.

### *8.3.2 Exclusion criteria*

1. Patients who have previously received a single line of chemotherapy or ≤ 3 lines of chemotherapy for metastatic disease.
2. Patients who have received prior oncology treatment within the following periods:
   - Chemotherapy, radiotherapy or hormone therapy within the past 2 weeks.
   - Other investigational drugs within the past 4 weeks.
3. Radiotherapy affecting > 30 % of the bone marrow.
4. Pulmonary lymphangitis with respiratory dysfunction requiring active treatment, including oxygen therapy.
5. Patients who have had major surgery or significant traumatic injury within 4 weeks before start of study treatment, or patients who have not recovered from the side effects of any major surgery (defined as surgery requiring general anesthesia) or patients who may require major surgery during the trial.
6. Uncontrolled brain or leptomeningeal metastasis, including patients who continue treatment with glucocorticosteroids for brain or leptomeningeal metastases. Patients with prior history of brain metastases must submit a normal or stable MRI at study entry, and at least three months should have passed from the end of surgery or radiotherapy.
7. Patients who have any severe and/or inadequately controlled medical conditions or other alterations that may affect their participation in the study, such as:
   - Unstable angina pectoris, symptomatic congestive heart failure (NYHA III or IV), myocardial infarction within the past 6 months, severe uncontrolled cardiac arrhythmia, congenital long QT syndrome, or any other clinically significant heart diseases.
   - Severe deterioration of lung function.
   - Active (acute or chronic) or uncontrolled severe infection.
   - Liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis.
   - Known history of HIV seropositivity.
   - Active bleeding diathesis.
8. Other malignancies within the past 3 years, except for: Carcinoma in situ of the cervix, and basal cell carcinoma or squamous cell carcinoma of the skin that have been adequately treated.
9. Pregnant or breast-feeding patients or adults of childbearing potential who do not use

effective methods of contraception. Female patients of child-bearing potential must have a negative urine or serum pregnancy test within 7 days before start of study treatment. Hormonal methods of contraception are not acceptable as a single method of contraception. If barrier methods of contraception are chosen, these must be continued during the whole study for both sexes.

10. Chronic treatment with systemic corticosteroids or any other immunosuppressive agents (except for corticosteroids with a daily dose equivalent to prednisone ≥ 20 mg). If patients receive corticosteroids, there should be a stable dosing regimen for at least 4 weeks before entering the study. Topical and inhaled corticosteroids are allowed.
11. Documented active alcohol or drug abuse.
12. Patients with a prior history of non-compliance with medical regimens

### *8.3.3 Patient withdrawal from therapy or evaluation*

Patients may discontinue the study:

- If, in the investigators' opinion, discontinuing the study treatment is warranted.
- If, for any circumstance, the patient declares his/her willingness to discontinue the study.
- In case of clinical signs of disease progression or unacceptable toxicities (if clinical monitoring and blood tests after 2 weeks of dose delay (with or without an adjustment) are not normalized, the study treatment must be definitely discontinued).
- In case of major non-compliance with the study protocol, including:
    - Failure to comply with inclusion/exclusion criteria
    - Efficacy criteria
    - Therapeutic failure, at the investigating physician's discretion
    - Adverse events
    - Trial completion

If a patient is considered as screening failure, only available data from baseline visit and the Screening Failure eCRF page are recorded. This patient is not regarded as eligible.

All patients who have received at least one dose of study treatment are eligible.

If a patient interrupts the study treatment permanently, that patient is not be replaced. The reason for treatment interruption is recorded.

## *8.4 Treatments*

### *8.4.1 Treatment administered*

TRADE NAME OF THE INVESTIGATIONAL MEDICINAL PRODUCT: HALAVEN 0.44 mg/mL injectable solution.

### *8.4.2 Qualitative and quantitative composition*

One ml vial contains 0.44 mg eribulin (equivalent to 0.5 mg eribulin mesylate). Each 2 mL vial contains 0.88 mg eribulin (equivalent to 1 g eribulin mesylate).

The study dose of eribulin as a ready-to-take solution is 1.23 mg/m2 (equivalent to 1.4 mg/m2 of eribulin mesylate), which is administered intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day cycle.

### *8.4.3 Methods for assigning patients to treatment groups*

All patients enrolled in the study received the same treatment, there were no different treatment groups.

### *8.4.4 Study dosing selection*

Eribulin dosing was selected based on the Summary of Product Characteristics.

The study dose of eribulin as a ready-to-take solution is 1.23 mg/m2 (equivalent to 1.4 mg/m2 of eribulin mesylate), which is administered intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day cycle.

### *8.4.5 Identity of the investigational medicinal product*

Marketed drugs were not altered; they were only re-labeled as investigational medication. The label indicated that they were “Only to be used for clinical research”, as required by applicable law (Appendix 13 Manufacturing of investigational drugs, AEMPS).

Bioavailability of drugs administered was carefully controlled by checking the expiry date and correct storage according to the manufacturer storage guidelines:

- Unused vials of this medication do not require any special storage conditions.
- If not used immediately, HALAVEN® as the undiluted solution in a syringe should not normally be stored longer than 4 hours at 25°C and ambient light, or 24 hours at 2°C - 8°C.

Storage, transport and distribution of drugs was performed by and from Laboratorium Sanitatis, S.L. to the pharmacy of the sites participating in the study.

Used medication (empty vial after dilution) was destroyed by sites that generated a destruction certificate or returned to Sanitatis that destroyed it upon completion of the trial.

The initial medication stock was 2470 vials. The total number of vials destroyed at the end of the trial was 100. The remaining medication was administered to the patients.

There was no temperature excursion in the sites participating in the study.

Find below the minor deviations due to failure to comply with the treatment.

### *8.4.6 Selection and duration of dosing for each patient*

Patients received monotherapy with 1.23 mg/m$^2$ eribulin in IV bolus on Day 1 and Day 8 of each 21-day cycle.

### *8.4.7 Previous and concomitant therapy*

No type of chemotherapy, hormone therapy or investigational drug was allowed during the trial.

**Table 8-2.-Permitted and prohibited treatments during the trial**

| Prohibited treatments | Permitted treatments |
|---|---|
| No type of chemotherapy, hormone therapy, immune therapy, or investigational drug<br><br>If radiotherapy were required, this results in early study withdrawal, and disease progression should be documented | **Antiemetics**<br><br>**Colony-stimulating factors** (G-CSF and similar drugs) |

There was no case of administration of prohibited treatments.

All concomitant treatments were recorded in the eCRF.

### *8.4.8 Treatment compliance*

Treatment compliance was checked by the study monitor via drug counts as specified using the drug count forms.

#### *8.4.8.1. Dose delays and adjustments allowed during the study*

Before each eribulin dose, the patient must undergo hematology monitoring (complete blood count) and clinical assessment. The requirements for the study treatment administration, as well as potential dose adjustments and delays are detailed below.

#### *8.4.8.2. Requirements to start study treatment administration*

In order to **administer the first dose of the study drug**, the patient must fulfill the following clinical and laboratory requirements:

- ANC ≤ 1.5 x $10^9$/L
- Platelets > 100 x 109/L
- Absence of non-hematological toxicities ≤ grade 2

If these criteria are not fulfilled, clinical and laboratory monitoring are repeated one week later. If the above requirements are fulfilled in the next monitoring, treatment is started with the established full dose. Otherwise, the investigator considers the possibility of delaying the start of treatment one more week, after which clinical and laboratory monitoring is performed again to confirm that the patient fulfills all established requirements. Otherwise, or if the investigator finds it suitable, the patient is considered to be ineligible and is not enrolled in the study, the patient receives an alternative treatment. In these cases where the patient does not fulfill the initial criteria required to receive the experimental therapy, the patient is considered to be ineligible (screening failure) and is replaced with a new patient.

**Table 8-3.-Summary of delays of the study starting dose**

| **Adverse reaction** | **Resolution** |
|---|---|
| | **Delay eribulin administration until:** |
| ANC < 1 x $10^9$/L | ANC ≤ 1.5 x $10^9$/L |
| Platelets < 75 x $10^9$/L | Platelets > 100 x $10^9$/L |
| Non-hematological toxicities grade 3 or 4 | Absence of non-hematological toxicities or resolution to ≥ grade 2 |

#### *8.4.8.3. Requirements to give consecutive doses of study treatment*

Before administration of each eribulin dose (i.e., second dose in Cycle 1 and subsequent doses), the patient must undergo hematology monitoring within 24 hours.

The study drug may be given at the same dose than the last dose applied, if the following requirements are fulfilled:

- ANC < 1 x $10^9$/L
- Platelets < 75 x $10^9$/L

- Non-hematological toxicities ≥ grade 3

If any of these requirements is not fulfilled, dose administration may be delayed one week, provided that clinical and laboratory monitoring performed then confirms the recovery of clinical and laboratory deviations, i.e. all requirements established in Table 8-3 are fulfilled.

If in this second monitoring, which is performed one week after the planned start date of dose administration, clinical and laboratory abnormalities are still present, treatment administration may be delayed one more week, if monitoring is adequate then. If the delayed dose is the second dose in a cycle, this cycle is considered to have only one dose. When the drug is given again, the new dose is counted as if it were the dose of Day 1 of the next treatment cycle.

If drug administration is delayed 2 weeks, the dose is adjusted according to the pattern indicated below (Table 8-4). When a dose adjustment (reduction) is performed, re-increasing the dose is not permitted, even if the patient's clinical condition and laboratory monitoring are normalized.

**Table 8-4.-Summary of adjustments of the study dose**

| **Adverse reaction** | **Resolution** |
|---|---|
| **HEMATOLOGICAL** | |
| ANC < 0.5 x $10^9$/L lasting more than 7 days | **Administer 0.97 mg/m² (20% reduction of study dose)** |
| Neutropenia with ANC < 1 x $10^9$/L complicated by fever or infection | |
| Thrombocytopenia with platelets < 25 x $10^9$/L | |
| Thrombocytopenia with platelets < 50 x $10^9$/L complicated by hemorrhage or requiring blood or platelet transfusion | |
| **NON-HEMATOLOGIC: Including peripheral neuropathy, cardiac toxicity, hepatic failure due to metastasis, renal failure** | |
| Any grade 3 or 4 in the previous cycle | |
| Re-occurrence of any adverse reaction as specified above<br>Despite reduction to 0.97 mg/m² | **Administer 0.62 mg/m²** |

| Adverse reaction | Resolution |
|---|---|
| Re-occurrence of any adverse reaction as specified above<br>Despite reduction to 0.62 mg/m$^2$ | **Treatment discontinuation** |

If after 2 weeks of dose delay (with or without an adjustment) clinical and laboratory monitoring are not normalized, the study treatment must definitely be discontinued (i.e., unacceptable toxicity).

## *8.5 Safety and efficacy variables*

### *8.5.1 Primary study objective*

The primary study objective was to evaluate the safety of eribulin as single agent in third-line therapy in patients with locally advanced or metastatic HER2-negative breast cancer previously treated with taxanes and anthracyclines in terms of adverse reactions.

### *8.5.2 Secondary study objectives*

- To evaluate the efficacy of eribulin in the study population in terms of 1-year overall survival (OS) and progression-free survival (PFS).
- To determine the clinical response rate of the study treatment as clinically indicated.
- To determine the objective response rate (ORR) of the study treatment according to the RECIST criteria.
- To determine the clinical benefit rate (CBR) of the study treatment according to the RECIST criteria.
- To evaluate the time to disease progression upon treatment completion in patients without disease progression during treatment.
- To evaluate duration of response.
- To explore the dynamics of circulating tumor cells (CTCs) during treatment with eribulin, as well as its relation to prognosis and/or early failure of treatment with eribulin.
- To evaluate the presence or absence of visceral disease.

### *8.5.3 Study endpoints*

#### *8.5.3.1. Primary endpoint*

The following variables were considered to evaluate the study primary objective:

- Adverse reactions
- Treatment duration
- Number of patients treated
- Number of patients who complied with the regimen
- Drug dose
- Concomitant medication
- Death

#### *8.5.3.2. Secondary endpoints*

- The endpoints to be considered to assess overall survival (OS) are death and time to death; and in cases where the patient has not died, patient observation time.
- The variables to be considered to assess PFS are progression and time to progression; or in cases where the patient has not progressed, patient observation time.
- Clinical response rate, as defined by clinical criteria.
- Objective response rate (ORR), defined as: (CR+PR)/total.
- Clinical benefit rate (CBR) defined as (CR+PR+SD)/total.
- The variables that considered to assess time to progression after treatment are progression after treatment and time to progression after treatment; or in cases where the patient has not progressed, patient observation time after treatment.
- Duration of response.
- Circulating tumor cell (CTC) count before starting study treatment and after the first cycle.
- Presence/absence of visceral disease

### *8.5.4 Descriptive analysis*

Study information, as well as tumor data, were summarized using descriptive statistics and statistical figures. Categorical variables were summarized by the number of missing values, frequency, percentages and 95% confidence interval (as required). Continuous variables

were summarized by the number of valid observations, mean, standard deviation, median, minimum, maximum and 95% confidence interval (as required). Survival variables were summarized by confidence rates and intervals (as required) and survival median times.

#### *8.5.4.1. Missing data analysis procedures*

No imputation procedures for missing values are planned. The analysis is performed with all available data. Only data obtained up to the end of clinical follow-up period of patients established in the protocol were considered for all statistical analyses.

#### *8.5.4.2. Analytical statistical procedures*

Trend analyses were conducted by means of the repeated measures ANOVA. The estimate of survival medians and percentages was performed by means of the Kaplan-Meyer method. In order to analyze potential predictive factors of clinical response to treatment (hormone receptor status and presence of visceral disease) and its tolerability, Cox regression models were used. For secondary analyses, a p-value ≥ 0.05 was considered to be statistically significant.

#### *8.5.4.3. Analysis of baseline characteristics*

Patient baseline characteristics were analyzed with descriptive methods.

#### *8.5.4.4. Primary analysis*

The safety analysis for all patients treated with eribulin was assessed in 3 levels:

- Firstly, exposure duration was examined to determine the grade in which safety may be assessed in this study. Treatment duration, number of treated patients, number of patients complying with treatment regimen and drug dose were described.
- Secondly, AEs recorded during the study (indicating grade, relationship, body system, action taken and result) and concomitant medications given to the patient were described.
- Finally, SAEs and deaths resulting in treatment interruption were described.

#### *8.5.4.5. Secondary analyses*

The analysis of overall survival time was performed by means of the Kaplan-Meyer estimate of median OS time with 95% confidence interval and 25th and 75th percentiles. The analysis of time to progression was performed by means of the Kaplan-Meyer estimate of median PFS with 95% confidence interval and 25th and 75th percentiles.

The clinical response rate (complete response, partial response, objective response, stable disease and clinical benefit rate (CBR)) of treatment and the objective response rate (ORR) according to the RECIST criteria (Table 8-5) is summarized with the number of missing values, frequencies and percentages.

**Table 8-5.-Summary of response assessment according to the RECIST criteria**

| Target lesions | Non-target lesions | New lesions | Overall response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Without CR / Without PD | No | PR |
| CR | Not all of them were evaluated | No | PR |
| PR | Without PD / Not all of them were evaluated | No | PR |
| SD | Without PD / Not all of them were evaluated | No | ED |
| Not all of them were evaluated | Without PD | No | NE |
| PD | Any | Any | PD |
| Any | PD | Any | PD |
| Any | Any | Yes | PD |
| Non-target | CR | No | CR |
| Non-target | Without CR / Without PD | No | Without CR / Without PD |
| Non-target | Not all of them were evaluated | No | NE |
| Non-target | Unequivocal PD | Any | PD |
| Non-target | Any | Yes | PD |

The analysis of time to progression after treatment was performed by means of the Kaplan-Meyer estimate of median time to progression after treatment with 95% confidence interval.

Duration of response is defined as the period when the patient's response started until the patient's remission. It is studied for complete, partial and stable responses, and clinical benefit. The duration of response analysis is performed by means of the Kaplan-Meyer median estimate, and 25th and 75th percentiles with confidence interval (95%).

The dynamics of CTCs and its relation to prognosis and/or early failure were explored by means of repeated measures ANOVA.

The presence or absence of visceral disease was described by the number of missing values, frequencies and percentages.

### *8.5.5 Statistical Methods*

The statistical analysis plan (SAP) was completed prior to database lock. The SAP followed the internal procedures of Fundación ONCOSUR. Primary and secondary objectives, efficacy and safety analysis, analysis responsibilities, and a complete and detailed description of the statistical methodology are developed in this document.

The statistical analysis was performed using the R software.

## *8.6 Data Quality Assurance*

All clinical trials where the Sponsor delegates tasks in Experior are subject to quality control and data quality safety measures as determined by the Quality Department and by Experior Standard Operating Procedures (SOPs), thus guaranteeing data quality assurance and compliance with Good Clinical Practice (GCP).

All quality control activities are intrinsic to all trials where Experior acts as CRO and they were performed by the persons in charge involved in the trial. These activities include but are not limited to, site monitoring, SAE reporting, review of medical histories of the patients, and review of the regulatory documents.

During the study, the monitor visited the site regularly (the first monitoring visit was scheduled as soon as possible after the enrollment of the first patient and the frequency of the following monitoring visits was based on the site needs) to control data accuracy, protocol adherence and the Guidelines for GCP. The monitoring SOPs of Experior require checking that the informed consent has been obtained and that no study procedure has been performed before obtaining it, to check the progress summaries (source document), to comply with all the inclusion criteria and none of the exclusion criteria, and to document serious adverse events and report them within 24 hours of learning of its occurrence.

All clinical trial data (recorded in the eCRF) were monitored at the investigator site. Queries were generated by the CRA during the monitoring visits; and the eCRF was programmed with internal rules to generate self-queries. Moreover, when all data had been monitored, the Data Management Department reviewed data and generated queries, as necessary.

Samples were processed centrally to standardize their analysis.
No internal or external audits were performed.

### *8.7 Sample size calculation*

The primary objective was to describe the safety of eribulin as single agent in third-line therapy in patients with locally advanced or metastatic HER2-negative breast cancer previously treated with taxanes and anthracyclines. Since it is a descriptive study, and based on the SAE incidence of pivotal study EMBRACE, it was expected that the most common (10%- >1%) SAEs could be detected with 60 patients.

#### *8.7.1 Power for analysis of key secondary variables*

Not applicable.

#### *8.7.2 Changes in the study conduct or the planned analyses*

N was the N indicated in the protocol.

On March 5, 2015, the enrollment period was closed and the trial was closed on January 31, 2016.

Medication was initially planned for a mean of 12 cycles per patient, even though some patients continued for much longer than initially expected. The study completion was expected for July 2015, but considering the clinical benefit shown in some cases it was extended to December 2015.

The clinical trial was not completed as planned in the protocol (last patient last visit for December 2015), as at the end of the study there were still 2 active patients.

In January 2016, the Sponsor evaluated the study state, and even though there were still two active patients (Hospital Severo Ochoa, Patient 06-02; Hospital San Pedro Alcántara; Patient 10-05), the Sponsor decided to close the study due to lack of medication stock and lack of funding.

## 9. Study patients

The total number of patients enrolled was 66, 7 out of which were screening failures.

Fifty-nine patients received monotherapy with eribulin (1.23 mg/m$^2$ in IV bolus) on Day 1 and Day 8 of each 21-day cycle. Treatment was administered until disease progression.

Thirteen patients, out of the 59 patients treated, discontinued the study for the following reasons:

- Investigator's decision: 1 patient (discontinued treatment due to surgery)
- Adverse event: 4 patients
- Volunteer's wish (consent withdrawal): 5 patients
- Treatment failure 1 patient

- Trial close-out: 2 patients

Only one analysis population is defined. This population consists of any patients screened and receiving at least one treatment dose.

### *9.1 Patient disposition*

Only one analysis population was defined. This population consisted of any patients screened and receiving at least one treatment dose. All analyses were performed in this population.

Categorical variables were described by absolute frequency (AF) and relative frequency (RF) in percentage (see Table 9-1).

Comparisons between the frequency of the two categorical variables were performed using the Chi-square test; and if the required hypotheses were not proved to be true, the Fisher's exact test was used.

Continuous variables were described by number of valid values, number of missing values, mean, standard deviation (SD), median, first quartile (Q1), and third quartile (Q3).

Comparisons between continuous variables of two groups were performed using the Student's t-test; and if the required hypotheses were not proved to be true, the Wilcoxon's exact test was used.

The analysis of survival time was performed by means of the Kaplan-Meyer estimate of median survival time with 95% confidence interval.

The Mantel-Haenszel test, also known as log-rank test, was used to compare the survival curves of two groups, as long as the proportional hazard hypothesis was proved to be true. Otherwise, the Peto's test was used.

The frequency of the patients treated is provided below; out of 66 screened patients 60 received study treatment. Out of these, 59 patients were considered valid and 1 patient was not considered valid due to failure to comply with the eligibility criteria (inclusion/exclusion criteria).

**Table 9-1.-Absolute and relative (%) frequencies for patients treated**

| | AF | RF (%) |
|---|---|---|
| Valid patients (n = 59) | 59 | 100.00 |
| All patients (n = 66) | 60 | 90.91 |

The number of enrolled patients is provided below by patient for each of the sites participating in the study.

**Figure 9-1 Enrollment of subjects by site**

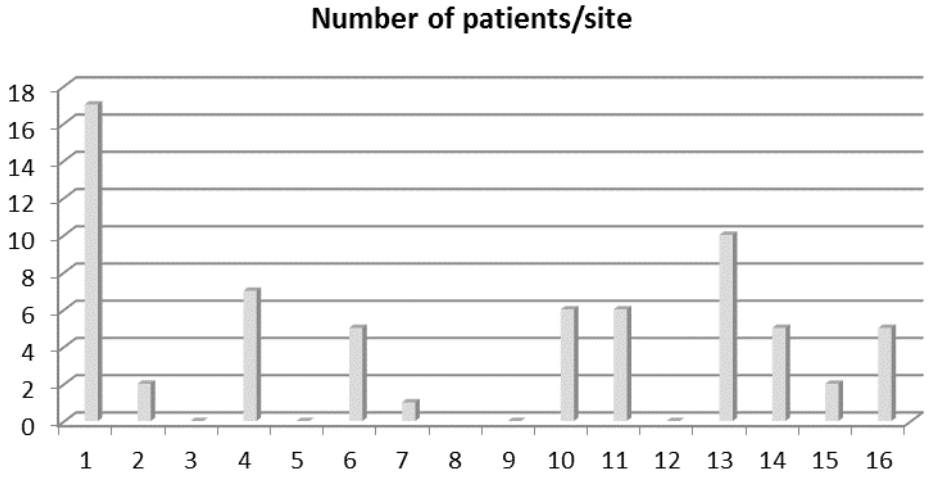



**Table 9-2.-Enrolled subjects, screening failures and discontinued patients by site**

| Site | Site No. | Patient | Screening failure | Withdrawn patients |
|---|---|---|---|---|
| H 12 de Octubre | **1** | **17** | **1** | **5** |
| H Fundación Alcorcón | **2** | **2** | **1** | |
| H U Getafe | **3** | **0** | | |
| H Jimenez Díaz | **4** | **7** | | **1** |
| H Infanta Cristina de Parla | **5** | **0** | | |
| H Severo Ochoa | **6** | **5** | | **1** |
| H Virgen de la Salud de Toledo | **7** | **1** | **1** | |
| H U de Guadalajara | **8** | | | |
| H U de Torrejón | **9** | **0** | | **0** |
| H San Pedro de Alcántara | **10** | **6** | **1** | **2** |
| H Infanta Cristina de Badajoz | **11** | **6** | **2** | **1** |
| H Virgen de la Luz de Cuenca | **12** | **0** | | **0** |
| H Clínico San Carlos | **13** | **10** | | **1** |
| H Ramón y Cajal | **14** | **5** | **1** | **1** |
| H La Princesa | **15** | **2** | | |
| H de Leon | **16** | **5** | | **1** |
| Total | | **66** | **7** | **13** |

### *9.2 Protocol deviations*

During the study, there were several major and minor protocol deviations. They are detailed in the following table:

**Table 9-3.-Protocol deviations**

| Date when it becomes known | Site | Patient | Description of the deviation | Action taken | Category | Major (MD) or minor (md) deviation? |
|---|---|---|---|---|---|---|
| 28-Feb-2014 | 04 | 0401<br>0402 | The handwriting in the patient information sheet of both patients is different; the patient's handwriting and the PI's handwriting. | The investigator staff is trained in how to obtain the informed consent appropriately and in GCP. | Informed consent | Major deviation |
| 26-MAR-2014 | 11 | 1101 | The dose for C2D1 for patient 11-01 is given by mistake with three vials of eribulin that correspond to another clinical trial, specifically the Meribel study. | The investigator staff is trained in how to administer medication appropriately and in GCP. | Investigational drug | Major deviation |
| 15-APR-2014 | 01 | 0101,<br>0102 and<br>0105 | Patients 01-01 and 01-02:<br>Non-compliance regarding dates for C2D1;<br>Patient 0105:<br>Non-compliance regarding dates for C3D8 | The investigator staff is trained in the protocol and GCP. | Investigational drug | Minor deviation |
| 30-APR-2014 | 01 | 0101<br>0105 | The dose of eribulin is administered on 30-APR-2014 since 01-MAY-2014 is a holiday. | The investigator staff is trained in the protocol and GCP. | Investigational drug | Minor deviation |
| 16-MAY-2014 | 16 | 16-01 | The patient does not comply with the exclusion criterion number 2, since the patient completed the palliative radiotherapy for the hip ten days before the administration of the first cycle of eribulin. | The Sponsor is notified immediately and after discussing it with the PI they decide that the patients should continue in the study and receive the first dos as soon as possible. | Selection criteria | Major deviation |
| 15-JUN-2014 | 01 | 01-07 | Non-compliance regarding dates for C2D1 and C3D8 (2 days), and C1D8, C2D8 and C3D1 (1 day). | The investigator staff is trained in the protocol and GCP. | Investigational drug | Minor deviation |
| 09-SEP-2014 | 02 | 02-01 | There is a one-week delay in the start of cycle 6 for patient 02-01 because of a mistake in the hospital appointment. | The investigator staff is trained in the protocol, in how to administer the study | Investigational drug | Minor deviation |

| Date when it becomes known | Site | Patient | Description of the deviation | Action taken | Category | Major (MD) or minor (md) deviation? |
|---|---|---|---|---|---|---|
| | | | | medication appropriately, and in GCP. | | |
| 10-SEP-2014 | 11 | 11-02<br>11-03 | Non-compliance regarding dates for C4D1 for patient 11-02 (14 days), and for C4D8 and C5D1 for patient 11-03 (2 days). | The investigator staff is trained in the protocol and GCP. | Investigational drug | Minor deviation |
| 30-SEP-2014 | 04 | 04-01<br>04-02<br>04-03 | The start of C3D8 is delayed 5 days for patient 04-03 due to the holidays of the long weekend in May. Non-compliance regarding dates for C1D8, C2D1 and C2D8 for patient 04-01, for C2D1 and C2D8 for patient 04-02, and for C2D1 and C2D8 for patient 04-03 (1 day). | The investigator staff is trained in the protocol and GCP. | Investigational drug | Minor deviation |
| 30-SEP-2014 | 15 | 15-01 | Non-compliance regarding dates for C2D1, C2D8 and C6D1 for patient 15-01. | The investigator staff is trained in the protocol and GCP. | Investigational drug | Minor deviation |
| 07-OCT-2014 | 01 | 01-07 | The administration of the study medication is delayed for patient 01-07 on C13D8 as there are doubts as to whether there was progression until all tests are performed. | The investigator staff is trained in the protocol and GCP. | Investigational drug | Minor deviation |
| 14-OCT-2014 | 16 | 16-01<br>16-05 | Non-compliance regarding dates for C1D8 for patient 16-01 (1 day) and for C2D1 for patient 16-05 (7 days). | The investigator staff is trained in the protocol and GCP. | Investigational drug | Minor deviation |
| 28-OCT-2014 | 13 | 13-08 | Non-compliance regarding procedures for collection of biological samples. The CTC sample was not collected for patient 13-08 on C2D1 by mistake. | | Other | Minor deviation |
| 01-DEC-2014 | 13 | 13-02<br>13-03<br>13-06<br>13-07 | Non-compliance regarding dates for C4D8 for patient 13-02 (2 days), for C3D1 for patient 13-03 (8 days), for C2D1 for patient 13-06 (5 days), and for C2D1 for patient 13-07 (1 day). | The investigator staff is trained in the protocol and GCP. | Investigational drug | Minor deviation |
| 11-DEC-2014 | 10 | 10-02<br>10-03<br>10-04 | Non-compliance regarding dates for C6D1 for patient 10-02 (2 days), for C5D8 (5 days) and C5D1 (3 days) for patient 10-03, and for C2D1 and C2D8 for patient 10-04 (1 day). | The investigator staff is trained in the protocol and GCP. | Investigational drug | Minor deviation |
| 12-DEC-2014 | 10 | 10-01 | The PI performs an ECG at the start of the | The investigator staff is | Safety | Major |

| Date when it becomes known | Site | Patient | Description of the deviation | Action taken | Category | Major (MD) or minor (md) deviation? |
|---|---|---|---|---|---|---|
| | | | study for patient 10-01. Despite this patient has a cardiovascular history and although it is stipulated in the protocol (CARDIAC TOXICITY: Patients should be monitored for QT prolongation. ECG monitoring is recommended if treatment is started in patients with congestive heart failure, bradyarrhythmias, medication known to prolong the QT interval, including class Ia and III antiarrhythmics, and electrolyte abnormalities), the ECG is not repeated before administering eribulin in subsequent cycles. | trained again in the study protocol and GCP. | | deviation |
| 18-DEC-2014 | 01 | 01-12 | The patient did not receive study medication as there are doubts as to whether there was progression until all tests were performed. | The investigator staff is trained in the protocol and GCP. | Investigational drug | Minor deviation |
| 25-DEC-2014 | 01 | 01-11 | The patient did not receive study medications because she did not attend the visit. She was on holiday. | The investigator staff is trained in the protocol and GCP. | Investigational drug | Minor deviation |
| 19-JAN-2015 | 14 | 14-02 and 14-03 | Non-compliance regarding dates for C2D1 and C2D8 for patients 14-02 and 14-03 (1 day). | The investigator staff is trained in the protocol and GCP. | Investigational drug | Minor deviation |
| 20150217 | 01 | 01-16 | The patient did not attend the visit on 17-FEB-2015 and did not receive medication for C2D8. | The investigator staff is trained in the protocol and GCP. | Investigational drug | Minor deviation |
| 20150330 | 06 | 06-02, 06-03 and 06-05 | Non-compliance regarding dates for C11D1 and C11D8 for patient 06-02 (1 day), for C7D1 and C7D8 for patient 06-03 (1 day) and for C4D1 and C4D8 for patient 06-05 (5 days). | The investigator staff is trained in the protocol and GCP. | Investigational drug | Minor deviation |
| 20150506 | 14 | 14-05 | The patient did not attend the visit on 13-MAR-2015 and did not receive medication for C3D8. | The investigator staff is trained in the protocol and GCP. | Investigational drug | Minor deviation |
| 20150618 | 10 | 10-04 | The patient received eribulin (study treatment) in fourth-line instead of in third-line therapy. | The investigator staff is trained in the protocol and GCP. | Investigational drug | Major deviation |

| Date when it becomes known | Site | Patient | Description of the deviation | Action taken | Category | Major (MD) or minor (md) deviation? |
|---|---|---|---|---|---|---|
| 20150618 | 10 | 10-05 | There is a medication delay due to personal problems of the patient. The patient received medication for C7D8 on 20-MAY-2015, but medication for C8D1 was not started until 23-JUN-2015. | The investigator staff is trained in the protocol, in how to administer the study medication appropriately, and in GCP. | Investigational drug | Minor deviation |
| 20140811 | 11 | 11-03 | There is a delay of study medication of two weeks for patient 11-03 on C6D1 due to cellulites. | The investigator staff is trained in the protocol and GCP. | Investigational drug | Minor deviation |
| 20160225 | 06 | 06-03 | Non-compliance regarding dates for C11D1 (1 day after) and C11D8 (1 day before). There is a delay for C12D1 (1 day) and for C17D1 (1 week). | The investigator staff is trained in the protocol and GCP. | Investigational drug | Minor deviation |
| 20160208 | 06 | 06-01 | Non-compliance regarding the date of CTC sample draw on Day 8 instead of Day 1 of Cycle 1. | The investigator staff is trained in the protocol. | | Minor deviation |
| 20160422 | 06 | 06-02 | Non-compliance regarding dates for C20D1 (1-week delay). | The investigator staff is trained in the protocol and GCP. | Investigational drug | Minor deviation |
| 20151118 | 13 | 13-03 | Non-compliance regarding the blood test previous to the medication dose of C3D8. | The investigator staff is trained in the protocol and GCP. | Other | Minor deviation |
| 20160126 | 13 | 13-05 | Non-compliance regarding study procedures. No ECG is performed at baseline visit. | | Other | Minor deviation |
| 20160125 | 13 | 13-06 | Non-compliance regarding the blood test previous to the medication dose of C2D8 and C3D8. | | Other | Minor deviation |
| 20160225 | 15 | 15-02 | The patient received marketed drug for C13D1 despite being participating in the study. | The investigator staff is trained in the protocol and GCP. | Investigational drug | Major deviation |
| 20160323 | 06 | 06-01 | The patient receives an incorrect dose of eribulin (1.23) on C10D8; this dose had been previously decreased to 0.97. | Training in protocol and GCP. | Investigational drug | Major deviation |
| 20160323 | 06 | 06-01 and 06-02 | 06-01: The follow-up visit and the death are not recorded in the medical history. For 06-02 there is no information in the medical history | | | Minor deviation |

| Date when it becomes known | Site | Patient | Description of the deviation | Action taken | Category | Major (MD) or minor (md) deviation? |
|---|---|---|---|---|---|---|
| | | | regarding the ECOG performance status on D1 for cycles 6, 10, 11, 13, 14, 16, 22, and 29. | | | |
| 20161013 | 01 | NA | The Collaborating Investigator, Dr. César Mendiola, was not finally trained in the study. | A Note to File is written | | Minor deviation |
| 20160711 | 01 | All site patients | The site only signs those blood tests with clinically assessable values. | A Note to File is written | | Minor deviation |
| 20160628 | 06 | All site patients | The site only signs those blood tests with clinically assessable values. | A Note to File is written | | Minor deviation |
| 20160627 | 04 | All site patients | The site only signs those blood tests with clinically assessable values. | A Note to File is written | | Minor deviation |
| 20160623 | 13 | All site patients | The site only signs those blood tests with clinically assessable values. | A Note to File is written | | Minor deviation |
| 20160726 | 14 | All site patients | The site only signs those blood tests with clinically assessable values. | A Note to File is written | | Minor deviation |
| 20160727 | 01 | NA | The number of the vial dispensed is not available in the dispensation logs of certain patients. | A Note to File is written | | Minor deviation |
| 20160628 | 06 | NA | The vial number not available, it has not been recorded in the internal dispensation logs of the Pharmacy Department. | A Note to File is written | | Minor deviation |

## 10. Evaluation of the primary variables

The primary objective was based on incidence, severity, frequency and cumulative nature of treatment-emergent adverse events (TEAE). TEAEs are defined as AEs appearing or deteriorating or becoming serious during the study period and its relationship to the study medication.

CTCAE version 4.0 is used in this study to classify AEs.

Blood test, vital signs and 12-lead ECG abnormalities are recorded as AEs only if they are clinically significant, i.e. ≤ grade 3, symptomatic or lasting over 7 days, causing discontinuation, delay or reduction, or meeting a severity criterion.

### *10.1 Data sets analyzed*

Populations were not differentiated for the analysis.

### *10.2 Demographic and other baseline characteristics*

#### *10.2.1 Demographic data*

Fifty-nine women (100%) were enrolled. The mean age was 57.71 years with a standard deviation of 12.81 years.

**Table 10-1.-Absolute and relative (%) frequencies for distribution by sex**

| Sex | AF | % (n=59) | Valid % (n=59) |
|---|---|---|---|
| **Male** | 0 | 0.00 | 0.00 |
| **Female** | 59 | 100.00 | 100.00 |
| **N** | 59 | 100.00 | 100.00 |
| **NA** | 0 | 0.00 | |

##### *10.2.1.1. Age at treatment start*

**Table 10-2.-Descriptive statistics for age at treatment start**

| N | NA | Mean | SD | Median | Q1 | Q3 |
|---|---|---|---|---|---|---|
| 59 | 0 | 57.71 | 12.81 | 56 | 48 | 66.5 |

#### *10.2.1.2. Sex*

**Table 10-3.-Absolute and relative (%) frequencies for distribution by sex**

| Sex | AF | % (n=59) | Valid % (n=59) |
|---|---|---|---|
| **Male** | 0 | 0.00 | 0.00 |
| **Female** | 59 | 100.00 | 100.00 |
| **N** | 59 | 100.00 | 100.00 |
| **NA** | 0 | 0.00 | |

### *10.2.2 Number of patients treated*

The table with a total of 59 patients considered to be valid for the analysis is included below.

**Table 10-4.-Absolute and relative (%) frequencies for patients treated**

| | Absolute frequency | RF (%) |
|---|---|---|
| Valid patients (n = 59) | 59 | 100.00 |
| All patients (n = 66) | 60 | 90.91 |

## *10.3 Compliance with treatment regimen*

Regarding treatment compliance approximately half of the patients treated complied with the treatment regimen indicated in the protocol (47.46%), as shown in Table 10-5.

**Table 10-5.-Absolute and relative (%) frequencies for compliance with treatment regimen**

| Compliance with treatment regimen | AF | RF % (n = 59) | Valid % (n=59) |
|---|---|---|---|
| **Yes** | 28 | 47.46 | 47.46 |
| **No** | 31 | 52.54 | 52.54 |
| **N** | 59 | 100.00 | 100.00 |
| **NA** | 0 | 0.00 | |

### *10.3.1 Delays*

The following table provides the total number of delays in the administration of the treatment dose. There was a total of 53 delays for a total of 404 cycles administered.

**Table 10-6.-Total dose delays**

| N | Total no. of cycles administered | Total no. of delays | No. of patients with delay |
|---|---|---|---|
| 59 | 404 | 53 | 30 |

**Table 10-7.-Absolute and relative (%) frequencies for dose delays by treatment cycle**

| Cycle | N | No. of delays by cycle | No. of patients with delay | % (N) |
|---|---|---|---|---|
| **1** | 59 | 4 | 4 | 6.78 |
| **2** | 56 | 9 | 9 | 16.07 |
| **3** | 53 | 5 | 4 | 7.55 |
| **4** | 41 | 9 | 9 | 21.95 |
| **5** | 33 | 4 | 4 | 12.12 |
| **6** | 29 | 6 | 5 | 17.24 |
| **7** | 20 | 1 | 1 | 5.00 |
| **8** | 18 | 2 | 2 | 11.11 |
| **9** | 17 | 3 | 2 | 11.76 |
| **10** | 12 | 1 | 1 | 8.33 |
| **11** | 10 | 0 | 0 | 0.00 |
| **12** | 9 | 3 | 3 | 33.33 |
| **13** | 7 | 1 | 1 | 14.29 |
| **14** | 7 | 1 | 1 | 14.29 |
| **15** | 7 | 1 | 1 | 14.29 |
| **16** | 6 | 1 | 1 | 16.67 |
| **17** | 5 | 1 | 1 | 20.00 |
| **18** | 3 | 0 | 0 | 0.00 |
| **19** | 2 | 0 | 0 | 0.00 |
| **20** | 2 | 1 | 1 | 50.00 |
| **21** | 1 | 0 | 0 | 0.00 |
| **22** | 1 | 0 | 0 | 0.00 |
| **23** | 1 | 0 | 0 | 0.00 |
| **24** | 1 | 0 | 0 | 0.00 |
| **25** | 1 | 0 | 0 | 0.00 |

| | | | | |
|---|---|---|---|---|
| **26** | 1 | 0 | 0 | 0.00 |
| **27** | 1 | 0 | 0 | 0.00 |
| **28** | 1 | 0 | 0 | 0.00 |
| **29** | 0 | 0 | 0 | --- |
| **30** | 0 | 0 | 0 | --- |

Cycle 4 had the highest number of absolute delays (9).

**Table 10-8.-Absolute and relative (%) frequencies for cycles with the first dose delay**

| Cycle with first delay | AF | % (n=59) |
|---|---|---|
| **No delay** | 29 | 49.15 |
| **1** | 4 | 6.78 |
| **2** | 8 | 13.56 |
| **3** | 2 | 3.39 |
| **4** | 6 | 10.17 |
| **5** | 2 | 3.39 |
| **6** | 3 | 5.08 |
| **7** | 1 | 1.69 |
| **8** | 1 | 1.69 |
| **9** | 0 | 0.00 |
| **10** | 1 | 1.69 |
| **11** | 0 | 0.00 |
| **12** | 1 | 1.69 |
| **13** | 0 | 0.00 |
| **14** | 0 | 0.00 |
| **15** | 0 | 0.00 |
| **16** | 0 | 0.00 |
| **17** | 0 | 0.00 |
| **18** | 0 | 0.00 |
| **19** | 0 | 0.00 |
| **20** | 1 | 1.69 |
| **21** | 0 | 0.00 |
| **22** | 0 | 0.00 |
| **23** | 0 | 0.00 |
| **24** | 0 | 0.00 |
| **25** | 0 | 0.00 |
| **26** | 0 | 0.00 |
| **27** | 0 | 0.00 |
| **28** | 0 | 0.00 |
| **29** | 0 | 0.00 |

| Cycle with first delay | AF | % (n=59) |
|---|---|---|
| **30** | 0 | 0.00 |
| **N** | 59 | 100.00 |
| **NA** | 0 | 0.00 |

Cycles where the first dose delay occurred more times were cycle 2 (13.56%) and cycle 4 (10.17%).

### *10.3.2 Adjustments*

**Table 10-9.- Total dose adjustments**

| N | Total no. of cycles administered | Total no. of adjustments | No. of patients with adjustment |
|---|---|---|---|
| 59 | 404 | 15 | 10 |

There were 15 dose adjustments in a total of 10 patients.

**Table 10-10.- Absolute and relative (%) frequencies for dose adjustments by treatment cycle**

| Cycle | N | No. of adjustments by cycle | No. of patients with adjustment | % (N) |
|---|---|---|---|---|
| **1** | 59 | 0 | 0 | 0.00 |
| **2** | 56 | 1 | 1 | 1.79 |
| **3** | 53 | 4 | 2 | 3.77 |
| **4** | 41 | 4 | 3 | 7.32 |
| **5** | 33 | 1 | 1 | 3.03 |
| **6** | 29 | 2 | 2 | 6.90 |
| **7** | 20 | 1 | 1 | 5.00 |
| **8** | 18 | 1 | 1 | 5.56 |
| **9** | 17 | 0 | 0 | 0.00 |
| **10** | 12 | 0 | 0 | 0.00 |
| **11** | 10 | 0 | 0 | 0.00 |
| **12** | 9 | 0 | 0 | 0.00 |
| **13** | 7 | 0 | 0 | 0.00 |
| **14** | 7 | 1 | 1 | 14.29 |
| **15** | 7 | 0 | 0 | 0.00 |
| **16** | 6 | 0 | 0 | 0.00 |
| **17** | 5 | 0 | 0 | 0.00 |
| **18** | 3 | 0 | 0 | 0.00 |
| **19** | 2 | 0 | 0 | 0.00 |
| **20** | 2 | 0 | 0 | 0.00 |
| **21** | 1 | 0 | 0 | 0.00 |

| Cycle | N | No. of adjustments by cycle | No. of patients with adjustment | % (N) |
|---|---|---|---|---|
| **22** | 1 | 0 | 0 | 0.00 |
| **23** | 1 | 0 | 0 | 0.00 |
| **24** | 1 | 0 | 0 | 0.00 |
| **25** | 1 | 0 | 0 | 0.00 |
| **26** | 1 | 0 | 0 | 0.00 |
| **27** | 1 | 0 | 0 | 0.00 |
| **28** | 1 | 0 | 0 | 0.00 |
| **29** | 0 | 0 | 0 | --- |
| **30** | 0 | 0 | 0 | --- |

The cycles with the highest number of dose adjustments were cycles 3 and 4.

**Table 10-11.- Absolute and relative (%) frequencies for cycles with the first dose adjustments**

| Cycle with first adjustment | AF | % (n=59) |
|---|---|---|
| **No adjustment** | 49 | 83.05 |
| **1** | 0 | 0.00 |
| **2** | 1 | 1.69 |
| **3** | 2 | 3.39 |
| **4** | 2 | 3.39 |
| **5** | 0 | 0.00 |
| **6** | 2 | 3.39 |
| **7** | 1 | 1.69 |
| **8** | 1 | 1.69 |
| **9** | 0 | 0.00 |
| **10** | 0 | 0.00 |
| **11** | 0 | 0.00 |
| **12** | 0 | 0.00 |
| **13** | 0 | 0.00 |
| **14** | 1 | 1.69 |
| **15** | 0 | 0.00 |
| **16** | 0 | 0.00 |
| **17** | 0 | 0.00 |
| **18** | 0 | 0.00 |
| **19** | 0 | 0.00 |
| **20** | 0 | 0.00 |
| **21** | 0 | 0.00 |
| **22** | 0 | 0.00 |
| **23** | 0 | 0.00 |
| **24** | 0 | 0.00 |
| **25** | 0 | 0.00 |
| **26** | 0 | 0.00 |
| **27** | 0 | 0.00 |
| **28** | 0 | 0.00 |
| **29** | 0 | 0.00 |
| **30** | 0 | 0.00 |
| **N** | 59 | 100.00 |
| **NA** | 0 | 0.00 |

The cycles where the first dose adjustment occurred more times were cycles 3, 4 and 6.

### *10.3.3 Concomitant medication*

**Table 10-12.- Absolute and relative (%) frequencies for concomitant medication classified by ATC code**

| ATC code | AF | % (n=615) | Valid % (n=614) |
|---|---|---|---|
| **A** | 163 | 26.50 | 26.55 |
| **B** | 24 | 3.90 | 3.91 |
| **C** | 48 | 7.80 | 7.82 |
| **D** | 9 | 1.46 | 1.47 |
| **G** | 1 | 0.16 | 0.16 |
| **H** | 78 | 12.68 | 12.70 |
| **J** | 37 | 6.02 | 6.03 |
| **L** | 39 | 6.34 | 6.35 |
| **M** | 42 | 6.83 | 6.84 |
| **N** | 146 | 23.74 | 23.78 |
| **R** | 12 | 1.95 | 1.95 |
| **S** | 4 | 0.65 | 0.65 |
| **V** | 11 | 1.79 | 1.79 |
| **N** | 614 | 99.84 | 100.00 |
| **NA** | 1 | 0.16 | |

## *10.4 Drug dose*

### *10.4.1 Dose strength*

**Table 10-13.- Strength of the dose administered in the study**

| N | Total no. of cycles administered | Total actual dose (mg/m²) | Total target dose (mg/m²) | Dose strength |
|---|---|---|---|---|
| 59 | 404 | 964.78 | 993.84 | 0.97 |

Dose strength was 0.97.

**Table 10-14.- Descriptive statistics of dose strength by patient**

| N | NA | Mean | SD | P25 | P50 | P75 |
|---|---|---|---|---|---|---|
| 59 | 0 | 3.11 | 1.80 | 1.92 | 2.76 | 3.87 |

### *10.4.2 Starting dose*

**Table 10-15.- Absolute and relative (%) frequencies for starting dose**

| Starting dose | AF | % (n=59) |
|---|---|---|
| **1.23 mg/m² (full dose)** | 59 | 100.00 |
| **0.97 mg/m²** | 0 | 0.00 |
| **0.62 mg/m²** | 0 | 0.00 |
| **N** | 59 | 100.00 |
| **NA** | 0 | 0.00 |

All patients started the trial with a full dose (1.23 mg/m²) as starting dose.

## 11. Primary objective assessment: Safety (adverse reactions)

### *11.1 Exposure scope*

The scope of exposure to the investigational medicinal product is shown below with the number of patients exposed, exposure duration and dose they were exposed to (already detailed in the previous section).

### *11.1.1 Number of patients treated*

**Table 11-1.- Absolute and relative (%) frequencies for patients treated**

| | AF | RF (%) |
|---|---|---|
| Valid patients (n = 59) | 59 | 100.00 |
| All patients (n = 66) | 60 | 90.91 |

### *11.1.2 Treatment duration*

Descriptive statistics of treatment duration in months and number of treatment cycles are provided in the following tables.

The mean duration of treatment was 4.53 months while the mean of the cycles administered was 6.85.

**Table 11-2.- Descriptive statistics for duration of treatment (months)**

| N | NA | Mean | SD | Median | Q1 | Q3 |
|---|---|---|---|---|---|---|
| 59 | 0 | 4.53 | 3.91 | 3.20 | 1.80 | 5.93 |

**Table 11-3.- Descriptive statistics for number of cycles administered**

| N | NA | Mean | SD | Median | Q1 | Q3 |
|---|---|---|---|---|---|---|
| 59 | 0 | 6.85 | 5.34 | 5.00 | 3.00 | 9.00 |

## *11.2 Adverse Events*

### *11.2.1 Brief summary of adverse events*

From the total of 598 adverse events recorded, 22 (affecting 17 patients) were classified as serious.

Based on the system organ class, the blood and lymphatic system disorders were most affected by adverse events (6).

The most common adverse events (AF > o = 10%) were alopecia (27), anemia (13), decreased appetite (15), arthralgia (10), asthenia (58), headache (12), diarrhea (14), dyspnea (15), back pain (10), constipation (24), mucosal inflammation (13), leukopenia (16), nausea (14), peripheral neuropathy (23), neutropenia (20), paresthesia (11), pyrexia (20), and vomiting (10). The most common serious adverse event was febrile neutropenia with 3 cases.

The study ONSITE confirms the previous data from randomized Phase 3 clinical trials with eribulin in a third-line therapy for advanced or metastatic HER2-negative disease. Toxicity with eribulin may be considered mild and it can be expected and managed as described in previous pivotal studies.

**Table 11-4.- Total adverse reactions**

| N | Total no. of AEs | No. of patients with any AE |
|---|---|---|
| 59 | 598 | 58 |

There were 598 adverse events that affected 58 patients.

### *11.2.2 Sample of adverse events and serious adverse events*

The absolute and relative frequencies for serious and non-serious adverse events are provided in Table 11-5.

**Table 11-5.- Absolute and relative (%) frequencies for serious and non-serious adverse reactions**

| Serious | No. of AEs | No. of patients with any AE |
|---|---|---|
| **Yes** | 22 | 17 |
| **No** | 576 | 41 |
| **Total** | 598 | 58 |

**Table 11-6.- Absolute and relative (%) frequencies for AEs and SAEs by PT**

| | Serious | | | | | |
|---|---|---|---|---|---|---|
| | Yes | | | No | | |
| AE | AF | RF (%) | Total % N (59) | AF | RF (%) | Total % N (59) |
| Gingival abscess | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Hot flush | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Aerophagia | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Alanine aminotransferase increased | 0 | 0.00 | 0.00 | 5 | 0.87 | 8.47 |
| House dust allergy | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Alopecia | 0 | 0.00 | 0.00 | 27 | 4.69 | 45.76 |
| Gait disturbance | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Anemia | 0 | 0.00 | 0.00 | 13 | 2.26 | 22.03 |
| Anxiety | 0 | 0.00 | 0.00 | 2 | 0.35 | 3.39 |
| Decreased appetite | 0 | 0.00 | 0.00 | 15 | 2.60 | 25.42 |
| Areflexia | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Arthralgia | 0 | 0.00 | 0.00 | 10 | 1.74 | 16.95 |
| Aspartate aminotransferase increased | 0 | 0.00 | 0.00 | 5 | 0.87 | 8.47 |
| Asthenia | 2 | 9.09 | 3.39 | 58 | 10.07 | 98.31 |
| Astigmatism | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Dry mouth | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Discoloration nail | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Cataract | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |

| | Serious | | | | | |
|---|---|---|---|---|---|---|
| | Yes | | | No | | |
| AE | AF | RF (%) | Total % N (59) | AF | RF (%) | Total % N (59) |
| Catarrh | 0 | 0.00 | 0.00 | 8 | 1.39 | 13.56 |
| Headache | 0 | 0.00 | 0.00 | 12 | 2.08 | 20.34 |
| Cellulitis | 1 | 4.55 | 1.69 | 1 | 0.17 | 1.69 |
| Cervicalgia | 0 | 0.00 | 0.00 | 3 | 0.52 | 5.08 |
| Spinal cord compression | 1 | 4.55 | 1.69 | 0 | 0.00 | 0.00 |
| Conjunctivitis | 0 | 0.00 | 0.00 | 2 | 0.35 | 3.39 |
| Contusion | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Depression | 0 | 0.00 | 0.00 | 4 | 0.69 | 6.78 |
| Pleural effusion | 0 | 0.00 | 0.00 | 4 | 0.69 | 6.78 |
| Diabetes mellitus | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Diarrhea | 0 | 0.00 | 0.00 | 14 | 2.43 | 23.73 |
| Diastasis recti abdominis | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Dysphagia | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Dysgeusia | 0 | 0.00 | 0.00 | 7 | 1.22 | 11.86 |
| Dyslipidemia | 0 | 0.00 | 0.00 | 2 | 0.35 | 3.39 |
| Dyspnea | 0 | 0.00 | 0.00 | 15 | 2.60 | 25.42 |
| Exertional dyspnea | 0 | 0.00 | 0.00 | 2 | 0.35 | 3.39 |
| Dyspepsia | 0 | 0.00 | 0.00 | 4 | 0.69 | 6.78 |
| Pain | 1 | 4.55 | 1.69 | 1 | 0.17 | 1.69 |
| Abdominal pain | 0 | 0.00 | 0.00 | 5 | 0.87 | 8.47 |
| Back pain | 0 | 0.00 | 0.00 | 10 | 1.74 | 16.95 |
| Catheter site pain | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Pain in the upper abdomen | 0 | 0.00 | 0.00 | 3 | 0.52 | 5.08 |
| Limb pain | 0 | 0.00 | 0.00 | 6 | 1.04 | 10.17 |
| Groin pain | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Musculoskeletal pain | 0 | 0.00 | 0.00 | 2 | 0.35 | 3.39 |
| Oropharyngeal pain | 0 | 0.00 | 0.00 | 2 | 0.35 | 3.39 |
| Bone pain | 0 | 0.00 | 0.00 | 6 | 1.04 | 10.17 |
| Pleuritic pain | 0 | 0.00 | 0.00 | 2 | 0.35 | 3.39 |
| Chest pain | 0 | 0.00 | 0.00 | 6 | 1.04 | 10.17 |
| Musculoskeletal chest pain | 0 | 0.00 | 0.00 | 5 | 0.87 | 8.47 |
| Edema | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Peripheral edema | 0 | 0.00 | 0.00 | 4 | 0.69 | 6.78 |

| | Serious | | | | | |
|---|---|---|---|---|---|---|
| | Yes | | | No | | |
| AE | AF | RF (%) | Total % N (59) | AF | RF (%) | Total % N (59) |
| Hepatic enzyme increased | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Epistaxis | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Erythema | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Rash | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Rash maculo-papular | 1 | 4.55 | 1.69 | 0 | 0.00 | 0.00 |
| Chills | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Muscle spams | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Constipation | 2 | 9.09 | 3.39 | 24 | 4.17 | 40.68 |
| Tooth extraction | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Atrial fibrillation | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Blood alkaline phosphatase increased | 0 | 0.00 | 0.00 | 2 | 0.35 | 3.39 |
| Hip fracture | 1 | 4.55 | 1.69 | 0 | 0.00 | 0.00 |
| Femur fracture | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Lumbar vertebral fracture | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Gamma glutamiltransferase increased | 0 | 0.00 | 0.00 | 7 | 1.22 | 11.86 |
| Hematoma | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Hematotoxicity | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Hemiparesis | 1 | 4.55 | 1.69 | 0 | 0.00 | 0.00 |
| Hepatomegaly | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Hepatotoxicity | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Hypercholesterolemia | 0 | 0.00 | 0.00 | 3 | 0.52 | 5.08 |
| Hyperglycemia | 1 | 4.55 | 1.69 | 6 | 1.04 | 10.17 |
| Hyperhidrosis | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Hypertension | 0 | 0.00 | 0.00 | 4 | 0.69 | 6.78 |
| Pulmonary hypertension | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Hypertransaminasemia | 0 | 0.00 | 0.00 | 3 | 0.52 | 5.08 |
| Ventricular hypertrophy | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Hyponatremia | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Hypotension | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Hypothyroidism | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Ischemic stroke | 1 | 4.55 | 1.69 | 0 | 0.00 | 0.00 |
| Respiratory tract | 0 | 0.00 | 0.00 | 5 | 0.87 | 8.47 |

| | Serious | | | | | |
|---|---|---|---|---|---|---|
| | Yes | | | No | | |
| AE | AF | RF (%) | Total % N (59) | AF | RF (%) | Total % N (59) |
| infection | | | | | | |
| Upper respiratory tract infection | 0 | 0.00 | 0.00 | 2 | 0.35 | 3.39 |
| Urinary tract infection | 0 | 0.00 | 0.00 | 3 | 0.52 | 5.08 |
| Catheter site infection | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Lung infection | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Mucosal inflammation | 0 | 0.00 | 0.00 | 13 | 2.26 | 22.03 |
| Influenza | 0 | 0.00 | 0.00 | 5 | 0.87 | 8.47 |
| Insomnia | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Respiratory failure | 2 | 9.09 | 3.39 | 0 | 0.00 | 0.00 |
| Blood lactate dehydrogenase increased | 0 | 0.00 | 0.00 | 9 | 1.56 | 15.25 |
| Lacrimation increased | 0 | 0.00 | 0.00 | 3 | 0.52 | 5.08 |
| Geographic tongue | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Skin lesion | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Leukocytosis | 0 | 0.00 | 0.00 | 2 | 0.35 | 3.39 |
| Leukopenia | 0 | 0.00 | 0.00 | 16 | 2.78 | 27.12 |
| Lymphedema | 0 | 0.00 | 0.00 | 2 | 0.35 | 3.39 |
| Lymphopenia | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Malaise | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Dizziness | 0 | 0.00 | 0.00 | 3 | 0.52 | 5.08 |
| Myalgia | 0 | 0.00 | 0.00 | 3 | 0.52 | 5.08 |
| Nasopharyngitis | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Nausea | 0 | 0.00 | 0.00 | 14 | 2.43 | 23.73 |
| Pneumonia | 1 | 4.55 | 1.69 | 0 | 0.00 | 0.00 |
| Neuralgia | 0 | 0.00 | 0.00 | 2 | 0.35 | 3.39 |
| Peripheral neuropathy | 0 | 0.00 | 0.00 | 23 | 3.99 | 38.98 |
| Peripheral sensory neuropathy | 0 | 0.00 | 0.00 | 2 | 0.35 | 3.39 |
| Neurotoxicity | 0 | 0.00 | 0.00 | 5 | 0.87 | 8.47 |
| Neutropenia | 2 | 9.09 | 3.39 | 20 | 3.47 | 33.90 |
| Febrile neutropenia | 3 | 13.64 | 5.08 | 0 | 0.00 | 0.00 |
| Odynophagia | 0 | 0.00 | 0.00 | 2 | 0.35 | 3.39 |
| Onycholysis | 0 | 0.00 | 0.00 | 6 | 1.04 | 10.17 |
| Osteoporosis | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Pancytopenia | 1 | 4.55 | 1.69 | 0 | 0.00 | 0.00 |

| | Serious | | | | | |
|---|---|---|---|---|---|---|
| | Yes | | | No | | |
| AE | AF | RF (%) | Total % N (59) | AF | RF (%) | Total % N (59) |
| Paresthesia | 0 | 0.00 | 0.00 | 11 | 1.91 | 18.64 |
| Muscular weakness | 0 | 0.00 | 0.00 | 3 | 0.52 | 5.08 |
| Weight decreased | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Pyelonephritis | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Pyrexia | 0 | 0.00 | 0.00 | 20 | 3.47 | 33.90 |
| Lumbosacral plexopathy | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Polyneuropathy | 0 | 0.00 | 0.00 | 6 | 1.04 | 10.17 |
| Pruritus | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Eye pruritus | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Vulvovaginal pruritus | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Psoriasis | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Eyelid ptosis | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Vaginal cyst | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Breast reconstruction | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Rhinitis | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Burning sensation | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Syncope | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Palmar-plantar erythrodysesthesia syndrome | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Cough | 1 | 4.55 | 1.69 | 4 | 0.69 | 6.78 |
| Skin toxicity | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Thrombocytopenia | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Venous thrombosis | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Deep vein thrombosis | 0 | 0.00 | 0.00 | 2 | 0.35 | 3.39 |
| Vertigo | 0 | 0.00 | 0.00 | 3 | 0.52 | 5.08 |
| Vomiting | 0 | 0.00 | 0.00 | 10 | 1.74 | 16.95 |
| Total | 22 | 100.00 | | 576 | 99.79 | |

**Table 11-7.- Absolute and relative (%) frequencies for serious and non-serious adverse reactions by SOC**

| | Serious | | | | | |
|---|---|---|---|---|---|---|
| | Yes | | | No | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Investigations | 0 | 0.00 | 0.00 | 30 | 5.21 | 50.85 |
| Infections and infestations | 2 | 9.09 | 3.39 | 23 | 3.99 | 38.98 |
| Injury, poisoning and procedural complications | 1 | 4.55 | 1.69 | 3 | 0.52 | 5.08 |
| Surgical and medical procedures | 0 | 0.00 | 0.00 | 2 | 0.35 | 3.39 |
| Cardiac disorders | 0 | 0.00 | 0.00 | 2 | 0.35 | 3.39 |
| Skin and subcutaneous tissue disorders | 1 | 4.55 | 1.69 | 42 | 7.29 | 71.19 |
| Blood and lymphatic system disorders | 6 | 27.27 | 10.17 | 54 | 9.38 | 91.53 |
| Reproductive system and breast disorders | 0 | 0.00 | 0.00 | 2 | 0.35 | 3.39 |
| Metabolism and nutrition disorders | 1 | 4.55 | 1.69 | 28 | 4.86 | 47.46 |
| Ear and labyrinth disorders | 0 | 0.00 | 0.00 | 3 | 0.52 | 5.08 |
| Immune system disorders | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Nervous system disorders | 3 | 13.64 | 5.08 | 75 | 13.02 | 127.12 |
| Endocrine disorders | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Gastrointestinal disorders | 2 | 9.09 | 3.39 | 80 | 13.89 | 135.59 |
| General disorders and administration site conditions | 3 | 13.64 | 5.08 | 107 | 18.58 | 181.36 |
| Hepatobiliary disorders | 0 | 0.00 | 0.00 | 5 | 0.87 | 8.47 |
| Musculoskeletal and connective tissue disorders | 0 | 0.00 | 0.00 | 52 | 9.03 | 88.14 |
| Eye disorders | 0 | 0.00 | 0.00 | 7 | 1.22 | 11.86 |
| Psychiatric disorders | 0 | 0.00 | 0.00 | 7 | 1.22 | 11.86 |
| Renal and urinary disorders | 0 | 0.00 | 0.00 | 1 | 0.17 | 1.69 |
| Respiratory, thoracic and mediastinal disorders | 3 | 13.64 | 5.08 | 38 | 6.60 | 64.41 |

| | Serious | | | | | |
|---|---|---|---|---|---|---|
| | Yes | | | No | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Vascular disorders | 0 | 0.00 | 0.00 | 13 | 2.26 | 22.03 |
| Total | 22 | 100.00 | | 576 | 100.00 | |

The most common serious adverse events were blood and lymphatic system disorders (6).

#### *11.2.2.1. Adverse reactions by grade*

##### *11.2.2.1.1. Adverse reactions by PT*

The most common adverse events for each grade were asthenia (37) for grade 1; asthenia (21) for grade 2; neutropenia (9) for grade 3; alopecia, femur fracture, neutropenia (1) and febrile neutropenia (1) for grade 4, and pyrexia (7) for grade 5.

**Table 11-8.- Absolute and relative (%) frequencies for grade of adverse reactions by PT**

| | Grade | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | | 2 | | | 3 | | | 4 | | | 5 | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Gingival abscess | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 2.56 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hot flush | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Aerophagia | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Alanine aminotransferase increased | 4 | 0.91 | 6.78 | 1 | 0.93 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| House dust allergy | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Alopecia | 13 | 2.96 | 22.03 | 11 | 10.19 | 18.64 | 2 | 5.13 | 3.39 | 1 | 20.00 | 1.69 | 0 | 0.00 | 0.00 |
| Gait disturbance | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Anemia | 12 | 2.73 | 20.34 | 1 | 0.93 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Anxiety | 2 | 0.46 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Decreased appetite | 13 | 2.96 | 22.03 | 2 | 1.85 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Areflexia | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Arthralgia | 9 | 2.05 | 15.25 | 1 | 0.93 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Aspartato | 4 | 0.91 | 6.78 | 1 | 0.93 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Grade | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | | 2 | | | 3 | | | 4 | | | 5 | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| aminotransferase increased | | | | | | | | | | | | | | | |
| Asthenia | 37 | 8.43 | 62.71 | 21 | 19.44 | 35.59 | 2 | 5.13 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Astigmatism | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Dry mouth | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Discoloration nail | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Cataract | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Catarrh | 5 | 1.14 | 8.47 | 3 | 2.78 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Headache | 12 | 2.73 | 20.34 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Cellulitis | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 1 | 2.56 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Cervicalgia | 3 | 0.68 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Spinal cord compression | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 2.56 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Conjunctivitis | 2 | 0.46 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Contusion | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Depression | 4 | 0.91 | 6.78 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pleural effusion | 2 | 0.46 | 3.39 | 2 | 1.85 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Diabetes mellitus | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Diarrhea | 10 | 2.28 | 16.95 | 4 | 3.70 | 6.78 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Diastasis recti abdominis | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Grade | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | | 2 | | | 3 | | | 4 | | | 5 | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Dysphagia | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Dysgeusia | 7 | 1.59 | 11.86 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Dyslipidemia | 2 | 0.46 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Dyspnea | 10 | 2.28 | 16.95 | 5 | 4.63 | 8.47 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Exertional dyspnea | 2 | 0.46 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Dyspepsia | 4 | 0.91 | 6.78 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pain | 2 | 0.46 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Abdominal pain | 4 | 0.91 | 6.78 | 1 | 0.93 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Back pain | 9 | 2.05 | 15.25 | 1 | 0.93 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Catheter site pain | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pain in the upper abdomen | 3 | 0.68 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Limb pain | 6 | 1.37 | 10.17 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Groin pain | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Musculoskeletal pain | 1 | 0.23 | 1.69 | 1 | 0.93 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Oropharyngeal pain | 2 | 0.46 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Bone pain | 6 | 1.37 | 10.17 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pleuritic pain | 2 | 0.46 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Chest pain | 2 | 0.46 | 3.39 | 3 | 2.78 | 5.08 | 1 | 2.56 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Musculoskeletal chest pain | 4 | 0.91 | 6.78 | 1 | 0.93 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Grade | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | | 2 | | | 3 | | | 4 | | | 5 | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Edema | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Peripheral edema | 4 | 0.91 | 6.78 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hepatic enzyme increased | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Epistaxis | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Erythema | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Rash | 0 | 0.00 | 0.00 | 1 | 0.93 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Rash maculo-papular | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Chills | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Muscle spams | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Constipation | 23 | 5.24 | 38.98 | 3 | 2.78 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Tooth extraction | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Atrial fibrillation | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Blood alkaline phosphatase increased | 1 | 0.23 | 1.69 | 1 | 0.93 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hip fracture | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 2.56 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Femur fracture | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 20.00 | 1.69 | 0 | 0.00 | 0.00 |
| Lumbar vertebral fracture | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Gamma glutamiltransferase increased | 2 | 0.46 | 3.39 | 2 | 1.85 | 3.39 | 2 | 5.13 | 3.39 | 1 | 20.00 | 1.69 | 0 | 0.00 | 0.00 |

| | Grade | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | | 2 | | | 3 | | | 4 | | | 5 | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Hematoma | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hematotoxicity | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 2.56 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hemiparesis | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 2.56 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hepatomegaly | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hepatotoxicity | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hypercholesterolemia | 3 | 0.68 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hyperglycemia | 6 | 1.37 | 10.17 | 0 | 0.00 | 0.00 | 1 | 2.56 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hyperhidrosis | 0 | 0.00 | 0.00 | 1 | 0.93 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hypertension | 3 | 0.68 | 5.08 | 1 | 0.93 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pulmonary hypertension | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hypertransaminasemia | 3 | 0.68 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Ventricular hypertrophy | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hyponatremia | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hypotension | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hypothyroidism | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Ischemic stroke | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 2.56 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Respiratory tract infection | 1 | 0.23 | 1.69 | 3 | 2.78 | 5.08 | 1 | 2.56 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Upper respiratory tract infection | 0 | 0.00 | 0.00 | 2 | 1.85 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Grade | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | | 2 | | | 3 | | | 4 | | | 5 | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Urinary tract infection | 3 | 0.68 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Catheter site infection | 0 | 0.00 | 0.00 | 1 | 0.93 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Lung infection | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Mucosal inflammation | 8 | 1.82 | 13.56 | 4 | 3.70 | 6.78 | 1 | 2.56 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Influenza | 5 | 1.14 | 8.47 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Insomnia | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Respiratory failure | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 2 | 5.13 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Blood lactate dehydrogenase increased | 8 | 1.82 | 13.56 | 0 | 0.00 | 0.00 | 1 | 2.56 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Lacrimation increased | 3 | 0.68 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Geographic tongue | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Skin lesion | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Leukocytosis | 2 | 0.46 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Leukopenia | 11 | 2.51 | 18.64 | 2 | 1.85 | 3.39 | 3 | 7.69 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Lymphedema | 2 | 0.46 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Lymphopenia | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Malaise | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Dizziness | 3 | 0.68 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Myalgia | 3 | 0.68 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Nasopharyngitis | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Grade | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | | 2 | | | 3 | | | 4 | | | 5 | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Nausea | 12 | 2.73 | 20.34 | 2 | 1.85 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pneumonia | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 2.56 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Neuralgia | 2 | 0.46 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Peripheral neuropathy | 14 | 3.19 | 23.73 | 8 | 7.41 | 13.56 | 1 | 2.56 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Peripheral sensory neuropathy | 2 | 0.46 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Neurotoxicity | 3 | 0.68 | 5.08 | 1 | 0.93 | 1.69 | 1 | 2.56 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Neutropenia | 7 | 1.59 | 11.86 | 5 | 4.63 | 8.47 | 9 | 23.08 | 15.25 | 1 | 20.00 | 1.69 | 0 | 0.00 | 0.00 |
| Febrile neutropenia | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 2 | 5.13 | 3.39 | 1 | 20.00 | 1.69 | 0 | 0.00 | 0.00 |
| Odynophagia | 2 | 0.46 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Onycholysis | 4 | 0.91 | 6.78 | 2 | 1.85 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Osteoporosis | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pancytopenia | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 2.56 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Paresthesia | 10 | 2.28 | 16.95 | 1 | 0.93 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Muscular weakness | 3 | 0.68 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Weight decreased | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pyelonephritis | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pyrexia | 13 | 2.96 | 22.03 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 7 | 100.00 | 11.86 |
| Lumbosacral plexopathy | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Polyneuropathy | 4 | 0.91 | 6.78 | 1 | 0.93 | 1.69 | 1 | 2.56 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Grade | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | | 2 | | | 3 | | | 4 | | | 5 | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Pruritus | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Eye pruritus | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Vulvovaginal pruritus | 0 | 0.00 | 0.00 | 1 | 0.93 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Psoriasis | 0 | 0.00 | 0.00 | 1 | 0.93 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Eyelid ptosis | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Vaginal cyst | 0 | 0.00 | 0.00 | 1 | 0.93 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Breast reconstruction | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Rhinitis | 0 | 0.00 | 0.00 | 1 | 0.93 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Burning sensation | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Syncope | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Palmar-plantar erythrodysesthesia syndrome | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Cough | 5 | 1.14 | 8.47 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Skin toxicity | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Thrombocytopenia | 0 | 0.00 | 0.00 | 1 | 0.93 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Venous thrombosis | 0 | 0.00 | 0.00 | 1 | 0.93 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Deep vein thrombosis | 2 | 0.46 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Vertigo | 3 | 0.68 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Vomiting | 8 | 1.82 | 13.56 | 2 | 1.85 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Total | 439 | 100.00 | | 108 | 100.00 | | 39 | 100.00 | | 5 | 100.00 | | 7 | 100.00 | |

#### *11.2.2.1.2. Adverse reactions by SOC*

The analysis of adverse reactions by SOC showed that the most common reactions for each grade were: Blood and lymphatic system disorders (71) for grade 1, general disorders and administration site conditions (28) for grade 2, blood and lymphatic system disorders (16) for grade 3, blood and lymphatic system disorders (2) for grade 4, and general disorders and administration site conditions (7) for grade 5.

**Table 11-9.- Absolute and relative (%) frequencies for grade of adverse reactions by SOC**

| | Grade | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | | 2 | | | 3 | | | 4 | | | 5 | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Investigations | 21 | 4.78 | 35.59 | 5 | 4.63 | 8.47 | 3 | 7.69 | 5.08 | 1 | 20.00 | 1.69 | 0 | 0.00 | 0.00 |
| Infections and infestations | 14 | 3.19 | 23.73 | 7 | 6.48 | 11.86 | 4 | 10.26 | 6.78 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Injury, poisoning and procedural complications | 2 | 0.46 | 3.39 | 0 | 0.00 | 0.00 | 1 | 2.56 | 1.69 | 1 | 20.00 | 1.69 | 0 | 0.00 | 0.00 |
| Surgical and medical procedures | 2 | 0.46 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Cardiac disorders | 2 | 0.46 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Skin and subcutaneous tissue disorders | 24 | 5.47 | 40.68 | 16 | 14.81 | 27.12 | 2 | 5.13 | 3.39 | 1 | 20.00 | 1.69 | 0 | 0.00 | 0.00 |
| Blood and lymphatic system disorders | 33 | 7.52 | 55.93 | 9 | 8.33 | 15.25 | 16 | 41.03 | 27.12 | 2 | 40.00 | 3.39 | 0 | 0.00 | 0.00 |
| Reproductive system and breast disorders | 0 | 0.00 | 0.00 | 2 | 1.85 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Metabolism and nutrition disorders | 26 | 5.92 | 44.07 | 2 | 1.85 | 3.39 | 1 | 2.56 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Ear and labyrinth disorders | 3 | 0.68 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Grade | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | | 2 | | | 3 | | | 4 | | | 5 | | |
| **AE** | **AF** | **RF (%)** | **% Total N (59)** | **AF** | **RF (%)** | **% Total N (59)** | **AF** | **RF (%)** | **% Total N (59)** | **AF** | **RF (%)** | **% Total N (59)** | **AF** | **RF (%)** | **% Total N (59)** |
| Immune system disorders | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Nervous system disorders | 61 | 13.90 | 103.39 | 11 | 10.19 | 18.64 | 6 | 15.38 | 10.17 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Endocrine disorders | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Gastrointestinal disorders | 70 | 15.95 | 118.64 | 12 | 11.11 | 20.34 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| General disorders and administration site conditions | 71 | 16.17 | 120.34 | 28 | 25.93 | 47.46 | 4 | 10.26 | 6.78 | 0 | 0.00 | 0.00 | 7 | 100.00 | 11.86 |
| Hepatobiliary disorders | 5 | 1.14 | 8.47 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Musculoskeletal and connective tissue disorders | 48 | 10.93 | 81.36 | 4 | 3.70 | 6.78 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Eye disorders | 7 | 1.59 | 11.86 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Psychiatric disorders | 7 | 1.59 | 11.86 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Renal and urinary disorders | 1 | 0.23 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Respiratory, thoracic and mediastinal disorders | 29 | 6.61 | 49.15 | 10 | 9.26 | 16.95 | 2 | 5.13 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Total | 439 | 100.00 | | 108 | 100.00 | | 39 | 100.00 | | 5 | 100.00 | | 7 | 100.00 | |

#### *11.2.2.2. Adverse reactions by relationship to medication*

##### *11.2.2.2.1. Adverse reactions by relationship to medication and PT*

Adverse reactions classified as definitely related to the medication were: Aerophagia, alopecia, anemia, decreased appetite, asthenia, headache, diarrhea, dysgeusia, dyspepsia, edema, rash, constipation, hematotoxicity, hypertransaminasemia, mucosal inflammation, leukopenia, myalgia, nausea, peripheral neuropathy, sensory peripheral neuropathy, neutropenia, febrile neutropenia, odynophagia, paresthesia, cough, vomiting.

**Table 11-10.- Absolute and relative (%) frequencies for relationship of adverse reactions to medication by PT**

| | Relationship to medication | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Not related | | | Unlikely | | | Possible | | | Probable | | | Definite | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Gingival abscess | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hot flush | 0 | 0.00 | 0.00 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Aerophagia | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 0.96 | 1.69 |
| Alanine aminotransferase increased | 5 | 1.91 | 8.47 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| House dust allergy | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Alopecia | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 13 | 12.26 | 22.03 | 13 | 12.50 | 22.03 |
| Gait disturbance | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Anemia | 6 | 2.29 | 10.17 | 3 | 5.56 | 5.08 | 1 | 1.39 | 1.69 | 1 | 0.94 | 1.69 | 2 | 1.92 | 3.39 |
| Anxiety | 2 | 0.76 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Decreased appetite | 1 | 0.38 | 1.69 | 1 | 1.85 | 1.69 | 6 | 8.33 | 10.17 | 3 | 2.83 | 5.08 | 4 | 3.85 | 6.78 |
| Areflexia | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Arthralgia | 9 | 3.44 | 15.25 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Relationship to medication | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Not related | | | Unlikely | | | Possible | | | Probable | | | Definite | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Aspartato aminotransferase increased | 5 | 1.91 | 8.47 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Asthenia | 14 | 5.34 | 23.73 | 2 | 3.70 | 3.39 | 15 | 20.83 | 25.42 | 11 | 10.38 | 18.64 | 18 | 17.31 | 30.51 |
| Astigmatism | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Dry mouth | 0 | 0.00 | 0.00 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Discoloration nail | 0 | 0.00 | 0.00 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Cataract | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Catarrh | 8 | 3.05 | 13.56 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Headache | 4 | 1.53 | 6.78 | 1 | 1.85 | 1.69 | 4 | 5.56 | 6.78 | 1 | 0.94 | 1.69 | 2 | 1.92 | 3.39 |
| Cellulitis | 2 | 0.76 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Cervicalgia | 2 | 0.76 | 3.39 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Spinal cord compression | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Conjunctivitis | 2 | 0.76 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Contusion | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Depression | 3 | 1.15 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 0.94 | 1.69 | 0 | 0.00 | 0.00 |
| Pleural effusion | 2 | 0.76 | 3.39 | 1 | 1.85 | 1.69 | 1 | 1.39 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Diabetes mellitus | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Diarrhea | 1 | 0.38 | 1.69 | 1 | 1.85 | 1.69 | 3 | 4.17 | 5.08 | 7 | 6.60 | 11.86 | 2 | 1.92 | 3.39 |
| Diastasis recti abdominis | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Relationship to medication | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Not related | | | Unlikely | | | Possible | | | Probable | | | Definite | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Dysphagia | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 1.39 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Dysgeusia | 1 | 0.38 | 1.69 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 2 | 1.89 | 3.39 | 3 | 2.88 | 5.08 |
| Dyslipidemia | 2 | 0.76 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Dyspnea | 10 | 3.82 | 16.95 | 2 | 3.70 | 3.39 | 0 | 0.00 | 0.00 | 3 | 2.83 | 5.08 | 0 | 0.00 | 0.00 |
| Exertional dyspnea | 2 | 0.76 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Dyspepsia | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 0.94 | 1.69 | 3 | 2.88 | 5.08 |
| Pain | 1 | 0.38 | 1.69 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Abdominal pain | 3 | 1.15 | 5.08 | 0 | 0.00 | 0.00 | 1 | 1.39 | 1.69 | 1 | 0.94 | 1.69 | 0 | 0.00 | 0.00 |
| Back pain | 9 | 3.44 | 15.25 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Catheter site pain | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pain in the upper abdomen | 1 | 0.38 | 1.69 | 1 | 1.85 | 1.69 | 1 | 1.39 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Limb pain | 6 | 2.29 | 10.17 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Groin pain | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Musculoskeletal pain | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 2 | 2.78 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Oropharyngeal pain | 2 | 0.76 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Bone pain | 6 | 2.29 | 10.17 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pleuritic pain | 2 | 0.76 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Chest pain | 6 | 2.29 | 10.17 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Musculoskeletal chest pain | 5 | 1.91 | 8.47 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Relationship to medication | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Not related | | | Unlikely | | | Possible | | | Probable | | | Definite | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Edema | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 0.96 | 1.69 |
| Peripheral edema | 3 | 1.15 | 5.08 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hepatic enzyme increased | 0 | 0.00 | 0.00 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Epistaxis | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 0.94 | 1.69 | 0 | 0.00 | 0.00 |
| Erythema | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Rash | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 0.96 | 1.69 |
| Rash maculo-papular | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Chills | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Muscle spams | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 1.39 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Constipation | 9 | 3.44 | 15.25 | 2 | 3.70 | 3.39 | 3 | 4.17 | 5.08 | 8 | 7.55 | 13.56 | 4 | 3.85 | 6.78 |
| Tooth extraction | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Atrial fibrillation | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Blood alkaline phosphatase increased | 2 | 0.76 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hip fracture | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Femur fracture | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Lumbar vertebral fracture | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Gamma glutamiltransferase increased | 3 | 1.15 | 5.08 | 1 | 1.85 | 1.69 | 3 | 4.17 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hematoma | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Relationship to medication | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Not related | | | Unlikely | | | Possible | | | Probable | | | Definite | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Hematotoxicity | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 0.96 | 1.69 |
| Hemiparesis | 0 | 0.00 | 0.00 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hepatomegaly | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hepatotoxicity | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 0.94 | 1.69 | 0 | 0.00 | 0.00 |
| Hypercholesterolemia | 3 | 1.15 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hyperglycemia | 6 | 2.29 | 10.17 | 0 | 0.00 | 0.00 | 1 | 1.39 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hyperhidrosis | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hypertension | 4 | 1.53 | 6.78 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pulmonary hypertension | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hypertransaminasemia | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 1 | 1.39 | 1.69 | 0 | 0.00 | 0.00 | 1 | 0.96 | 1.69 |
| Ventricular hypertrophy | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hyponatremia | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hypotension | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hypothyroidism | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Ischemic stroke | 0 | 0.00 | 0.00 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Respiratory tract infection | 4 | 1.53 | 6.78 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 0.94 | 1.69 | 0 | 0.00 | 0.00 |
| Upper respiratory tract infection | 2 | 0.76 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Urinary tract infection | 3 | 1.15 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Catheter site infection | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 0.94 | 1.69 | 0 | 0.00 | 0.00 |

| | Relationship to medication | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Not related | | | Unlikely | | | Possible | | | Probable | | | Definite | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Lung infection | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Mucosal inflammation | 0 | 0.00 | 0.00 | 1 | 1.85 | 1.69 | 2 | 2.78 | 3.39 | 2 | 1.89 | 3.39 | 8 | 7.69 | 13.56 |
| Influenza | 5 | 1.91 | 8.47 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Insomnia | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Respiratory failure | 2 | 0.76 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Blood lactate dehydrogenase increased | 2 | 0.76 | 3.39 | 6 | 11.11 | 10.17 | 1 | 1.39 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Lacrimation increased | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 1 | 1.39 | 1.69 | 0 | 0.00 | 0.00 | 1 | 0.96 | 1.69 |
| Geographic tongue | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 1.39 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Skin lesion | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Leukocytosis | 1 | 0.38 | 1.69 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Leukopenia | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 7 | 9.72 | 11.86 | 6 | 5.66 | 10.17 | 3 | 2.88 | 5.08 |
| Lymphedema | 2 | 0.76 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Lymphopenia | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 0.94 | 1.69 | 0 | 0.00 | 0.00 |
| Malaise | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 1.39 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Dizziness | 2 | 0.76 | 3.39 | 0 | 0.00 | 0.00 | 1 | 1.39 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Myalgia | 0 | 0.00 | 0.00 | 1 | 1.85 | 1.69 | 1 | 1.39 | 1.69 | 0 | 0.00 | 0.00 | 1 | 0.96 | 1.69 |
| Nasopharyngitis | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Nausea | 4 | 1.53 | 6.78 | 0 | 0.00 | 0.00 | 1 | 1.39 | 1.69 | 6 | 5.66 | 10.17 | 3 | 2.88 | 5.08 |

| | Relationship to medication | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Not related | | | Unlikely | | | Possible | | | Probable | | | Definite | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Pneumonia | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Neuralgia | 2 | 0.76 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Peripheral neuropathy | 5 | 1.91 | 8.47 | 1 | 1.85 | 1.69 | 3 | 4.17 | 5.08 | 6 | 5.66 | 10.17 | 8 | 7.69 | 13.56 |
| Peripheral sensory neuropathy | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 0.94 | 1.69 | 1 | 0.96 | 1.69 |
| Neurotoxicity | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 1 | 1.39 | 1.69 | 3 | 2.83 | 5.08 | 0 | 0.00 | 0.00 |
| Neutropenia | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 1.39 | 1.69 | 5 | 4.72 | 8.47 | 16 | 15.38 | 27.12 |
| Febrile neutropenia | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 2 | 1.89 | 3.39 | 1 | 0.96 | 1.69 |
| Odynophagia | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 1.39 | 1.69 | 0 | 0.00 | 0.00 | 1 | 0.96 | 1.69 |
| Onycholysis | 2 | 0.76 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 4 | 3.77 | 6.78 | 0 | 0.00 | 0.00 |
| Osteoporosis | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pancytopenia | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Paresthesia | 2 | 0.76 | 3.39 | 0 | 0.00 | 0.00 | 1 | 1.39 | 1.69 | 7 | 6.60 | 11.86 | 1 | 0.96 | 1.69 |
| Muscular weakness | 3 | 1.15 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Weight decreased | 0 | 0.00 | 0.00 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pyelonephritis | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pyrexia | 6 | 2.29 | 10.17 | 11 | 20.37 | 18.64 | 1 | 1.39 | 1.69 | 2 | 1.89 | 3.39 | 0 | 0.00 | 0.00 |
| Lumbosacral plexopathy | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Polyneuropathy | 2 | 0.76 | 3.39 | 0 | 0.00 | 0.00 | 2 | 2.78 | 3.39 | 2 | 1.89 | 3.39 | 0 | 0.00 | 0.00 |
| Pruritus | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Relationship to medication | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Not related | | | Unlikely | | | Possible | | | Probable | | | Definite | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Eye pruritus | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Vulvovaginal pruritus | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Psoriasis | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Eyelid ptosis | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Vaginal cyst | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Breast reconstruction | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Rhinitis | 0 | 0.00 | 0.00 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Burning sensation | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Syncope | 0 | 0.00 | 0.00 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Palmar-plantar erythrodysesthesia syndrome | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 0.94 | 1.69 | 0 | 0.00 | 0.00 |
| Cough | 4 | 1.53 | 6.78 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 0.96 | 1.69 |
| Skin toxicity | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Thrombocytopenia | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 1.39 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Venous thrombosis | 0 | 0.00 | 0.00 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Deep vein thrombosis | 1 | 0.38 | 1.69 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Vertigo | 2 | 0.76 | 3.39 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Vomiting | 4 | 1.53 | 6.78 | 0 | 0.00 | 0.00 | 1 | 1.39 | 1.69 | 2 | 1.89 | 3.39 | 3 | 2.88 | 5.08 |
| Total | 262 | 100.00 | | 54 | 100.00 | | 72 | 100.00 | | 106 | 100.00 | | 104 | 100.00 | |

#### *11.2.2.2.2. Adverse reactions by relationship to medication and SOC*

The results of the analysis by SOC of the adverse reactions classified as definitely related to the medication was as follows: Skin and subcutaneous tissue disorders, blood and lymphatic system disorders, metabolism and nutrition disorders, nervous system disorders, gastrointestinal disorders, general and administration site disorders, hepatobiliary disorders, musculoskeletal and connective tissue disorders, eye disorders and respiratory, thoracic and mediastinal disorders.

**Table 11-11.- Absolute and relative (%) frequencies for relationship of adverse reactions to medication by SOC**

| | Relationship to medication | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Not related | | | Unlikely | | | Possible | | | Probable | | | Definite | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Investigations | 17 | 6.49 | 28.81 | 9 | 16.67 | 15.25 | 4 | 5.56 | 6.78 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Infections and infestations | 22 | 8.40 | 37.29 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 2 | 1.89 | 3.39 | 0 | 0.00 | 0.00 |
| Injury, poisoning and procedural complications | 4 | 1.53 | 6.78 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Surgical and medical procedures | 2 | 0.76 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Cardiac disorders | 2 | 0.76 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Skin and subcutaneous tissue disorders | 10 | 3.82 | 16.95 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 18 | 16.98 | 30.51 | 14 | 13.46 | 23.73 |
| Blood and lymphatic system disorders | 8 | 3.05 | 13.56 | 4 | 7.41 | 6.78 | 10 | 13.89 | 16.95 | 15 | 14.15 | 25.42 | 23 | 22.12 | 38.98 |
| Reproductive system and breast disorders | 2 | 0.76 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Metabolism and nutrition disorders | 14 | 5.34 | 23.73 | 1 | 1.85 | 1.69 | 7 | 9.72 | 11.86 | 3 | 2.83 | 5.08 | 4 | 3.85 | 6.78 |
| Ear and labyrinth disorders | 2 | 0.76 | 3.39 | 1 | 1.85 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Relationship to medication | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Not related | | | Unlikely | | | Possible | | | Probable | | | Definite | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Immune system disorders | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Nervous system disorders | 23 | 8.78 | 38.98 | 6 | 11.11 | 10.17 | 12 | 16.67 | 20.34 | 22 | 20.75 | 37.29 | 15 | 14.42 | 25.42 |
| Endocrine disorders | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Gastrointestinal disorders | 22 | 8.40 | 37.29 | 5 | 9.26 | 8.47 | 13 | 18.06 | 22.03 | 25 | 23.58 | 42.37 | 17 | 16.35 | 28.81 |
| General disorders and administration site conditions | 33 | 12.60 | 55.93 | 16 | 29.63 | 27.12 | 19 | 26.39 | 32.20 | 15 | 14.15 | 25.42 | 27 | 25.96 | 45.76 |
| Hepatobiliary disorders | 2 | 0.76 | 3.39 | 0 | 0.00 | 0.00 | 1 | 1.39 | 1.69 | 1 | 0.94 | 1.69 | 1 | 0.96 | 1.69 |
| Musculoskeletal and connective tissue disorders | 43 | 16.41 | 72.88 | 4 | 7.41 | 6.78 | 4 | 5.56 | 6.78 | 0 | 0.00 | 0.00 | 1 | 0.96 | 1.69 |
| Eye disorders | 5 | 1.91 | 8.47 | 0 | 0.00 | 0.00 | 1 | 1.39 | 1.69 | 0 | 0.00 | 0.00 | 1 | 0.96 | 1.69 |
| Psychiatric disorders | 6 | 2.29 | 10.17 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 0.94 | 1.69 | 0 | 0.00 | 0.00 |
| Renal and urinary disorders | 1 | 0.38 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Respiratory, thoracic and mediastinal disorders | 32 | 12.21 | 54.24 | 3 | 5.56 | 5.08 | 1 | 1.39 | 1.69 | 4 | 3.77 | 6.78 | 1 | 0.96 | 1.69 |
| Vascular disorders | 10 | 3.82 | 16.95 | 3 | 5.56 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Total | 262 | 100.00 | | 54 | 100.00 | | 72 | 100.00 | | 106 | 100.00 | | 104 | 100.00 | |

#### *11.2.2.3. Adverse reactions by action taken*

##### *11.2.2.3.1. Adverse reactions by action taken (by PT)*

The analysis of adverse reactions based on actions taken is provided in Table 11-12. Reactions leading to treatment discontinuation or withdrawal were: Decreased appetite (1 discontinuation), hip fracture (1 interruption), hemiparesis (1 discontinuation), leukopenia (1 interruption), neutropenia (1 discontinuation y 3 interruptions), febrile neutropenia (2 interruptions).

**Table 11-12.- Absolute and relative (%) frequencies for action taken for adverse reactions by PT**

| | Action taken | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | None | | | Discontinuation | | | Interruption | | | Perfusion delay | | | Dose reduction | | | Delay and reduction | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Gingival abscess | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 4.17 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hot flush | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Aerophagia | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Alanine aminotransferase increased | 5 | 0.89 | 8.47 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| House dust allergy | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Alopecia | 27 | 4.83 | 45.76 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Gait disturbance | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Anemia | 13 | 2.33 | 22.03 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Anxiety | 2 | 0.36 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Decreased appetite | 14 | 2.50 | 23.73 | 1 | 25.00 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Areflexia | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Arthralgia | 10 | 1.79 | 16.95 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Action taken | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | None | | | Discontinuation | | | Interruption | | | Perfusion delay | | | Dose reduction | | | Delay and reduction | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Aspartato aminotransferase increased | 5 | 0.89 | 8.47 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Asthenia | 59 | 10.55 | 100.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 4.17 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Astigmatism | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Dry mouth | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Discoloration nail | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Cataract | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Catarrh | 8 | 1.43 | 13.56 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Headache | 12 | 2.15 | 20.34 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Cellulitis | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 2 | 8.33 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Cervicalgia | 3 | 0.54 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Spinal cord compression | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Conjunctivitis | 2 | 0.36 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Contusion | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Depression | 4 | 0.72 | 6.78 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pleural effusion | 4 | 0.72 | 6.78 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Diabetes mellitus | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Diarrhea | 14 | 2.50 | 23.73 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Diastasis recti | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Action taken | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | None | | | Discontinuation | | | Interruption | | | Perfusion delay | | | Dose reduction | | | Delay and reduction | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| abdominis | | | | | | | | | | | | | | | | | | |
| Dysphagia | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Dysgeusia | 7 | 1.25 | 11.86 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Dyslipidemia | 2 | 0.36 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Dyspnea | 14 | 2.50 | 23.73 | 1 | 25.00 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Exertional dyspnea | 2 | 0.36 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Dyspepsia | 4 | 0.72 | 6.78 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pain | 2 | 0.36 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Abdominal pain | 5 | 0.89 | 8.47 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Back pain | 10 | 1.79 | 16.95 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Catheter site pain | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pain in the upper abdomen | 3 | 0.54 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Limb pain | 6 | 1.07 | 10.17 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Groin pain | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Musculoskeletal pain | 2 | 0.36 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Oropharyngeal pain | 2 | 0.36 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Bone pain | 6 | 1.07 | 10.17 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pleuritic pain | 2 | 0.36 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Chest pain | 5 | 0.89 | 8.47 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 4.17 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Action taken | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | None | | | Discontinuation | | | Interruption | | | Perfusion delay | | | Dose reduction | | | Delay and reduction | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Musculoskeletal chest pain | 5 | 0.89 | 8.47 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Edema | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Peripheral edema | 4 | 0.72 | 6.78 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hepatic enzyme increased | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Epistaxis | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Erythema | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Rash | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Rash maculo-papular | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Chills | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Muscle spams | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Constipation | 26 | 4.65 | 44.07 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Tooth extraction | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Atrial fibrillation | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Blood alkaline phosphatase increased | 2 | 0.36 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hip fracture | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 14.29 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Femur fracture | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 4.17 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Lumbar vertebral fracture | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Action taken | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | None | | | Discontinuation | | | Interruption | | | Perfusion delay | | | Dose reduction | | | Delay and reduction | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Gamma glutamiltransferase increased | 6 | 1.07 | 10.17 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 4.17 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hematoma | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hematotoxicity | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 25.00 | 1.69 | 0 | 0.00 | 0.00 |
| Hemiparesis | 0 | 0.00 | 0.00 | 1 | 25.00 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hepatomegaly | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hepatotoxicity | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hypercholesterolemia | 3 | 0.54 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hyperglycemia | 6 | 1.07 | 10.17 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 4.17 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hyperhidrosis | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hypertension | 4 | 0.72 | 6.78 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pulmonary hypertension | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hypertransaminasemia | 3 | 0.54 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Ventricular hypertrophy | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hyponatremia | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hypotension | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Hypothyroidism | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Ischemic stroke | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Action taken | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | None | | | Discontinuation | | | Interruption | | | Perfusion delay | | | Dose reduction | | | Delay and reduction | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Respiratory tract infection | 3 | 0.54 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 2 | 8.33 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Upper respiratory tract infection | 2 | 0.36 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Urinary tract infection | 3 | 0.54 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Catheter site infection | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Lung infection | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Mucosal inflammation | 12 | 2.15 | 20.34 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 25.00 | 1.69 | 0 | 0.00 | 0.00 |
| Influenza | 4 | 0.72 | 6.78 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 4.17 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Insomnia | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Respiratory failure | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 4.17 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Blood lactate dehydrogenase increased | 9 | 1.61 | 15.25 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Lacrimation increased | 3 | 0.54 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Geographic tongue | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Skin lesion | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Leukocytosis | 2 | 0.36 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Leukopenia | 13 | 2.33 | 22.03 | 0 | 0.00 | 0.00 | 1 | 14.29 | 1.69 | 2 | 8.33 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Lymphedema | 2 | 0.36 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Lymphopenia | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Action taken | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | None | | | Discontinuation | | | Interruption | | | Perfusion delay | | | Dose reduction | | | Delay and reduction | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Malaise | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Dizziness | 3 | 0.54 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Myalgia | 3 | 0.54 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Nasopharyngitis | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Nausea | 14 | 2.50 | 23.73 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pneumonia | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 4.17 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Neuralgia | 2 | 0.36 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Peripheral neuropathy | 22 | 3.94 | 37.29 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 25.00 | 1.69 | 0 | 0.00 | 0.00 |
| Peripheral sensory neuropathy | 2 | 0.36 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Neurotoxicity | 5 | 0.89 | 8.47 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Neutropenia | 12 | 2.15 | 20.34 | 1 | 25.00 | 1.69 | 3 | 42.86 | 5.08 | 6 | 25.00 | 10.17 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Febrile neutropenia | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 2 | 28.57 | 3.39 | 1 | 4.17 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Odynophagia | 2 | 0.36 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Onycholysis | 6 | 1.07 | 10.17 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Osteoporosis | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pancytopenia | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Paresthesia | 10 | 1.79 | 16.95 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 25.00 | 1.69 | 0 | 0.00 | 0.00 |
| Muscular weakness | 3 | 0.54 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Weight decreased | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Action taken | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | None | | | Discontinuation | | | Interruption | | | Perfusion delay | | | Dose reduction | | | Delay and reduction | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Pyelonephritis | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pyrexia | 20 | 3.58 | 33.90 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Lumbosacral plexopathy | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Polyneuropathy | 6 | 1.07 | 10.17 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Pruritus | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Eye pruritus | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Vulvovaginal pruritus | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Psoriasis | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Eyelid ptosis | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Vaginal cyst | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Breast reconstruction | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Rhinitis | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Burning sensation | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Syncope | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Palmar-plantar erythrodysesthesia syndrome | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Cough | 5 | 0.89 | 8.47 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Skin toxicity | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Thrombocytopenia | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 4.17 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Action taken | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | None | | | Discontinuation | | | Interruption | | | Perfusion delay | | | Dose reduction | | | Delay and reduction | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Venous thrombosis | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Deep vein thrombosis | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 4.17 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Vertigo | 3 | 0.54 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Vomiting | 10 | 1.79 | 16.95 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Total | 559 | 100.00 | | 4 | 100.00 | | 7 | 100.00 | | 24 | 100.00 | | 4 | 100.00 | | 0 | 0.00 | |

#### *11.2.2.3.2. Adverse reactions by action taken (by SOC)*

The analysis of adverse reactions by SOC based on actions taken is provided in Table 11-13. Reactions leading to treatment discontinuation or interruption were: Injury, poisoning and procedural complications (1 interruption), blood and lymphatic system disorders (1 discontinuation, 6 interruptions), metabolism and nutrition disorders (1 discontinuation), nervous system disorders (1 discontinuation), respiratory, thoracic and mediastinal disorders (1 discontinuation).

**Table 11-13.- Absolute and relative (%) frequencies for action taken for adverse reactions by SOC**

| | Action taken | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | None | | | Discontinuation | | | Interruption | | | Perfusion delay | | | Dose reduction | | | Delay and reduction | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Investigations | 29 | 5.19 | 49.15 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 4.17 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Infections and infestations | 18 | 3.22 | 30.51 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 7 | 29.17 | 11.86 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Injury, poisoning and procedural complications | 2 | 0.36 | 3.39 | 0 | 0.00 | 0.00 | 1 | 14.29 | 1.69 | 1 | 4.17 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Surgical and medical procedures | 2 | 0.36 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Cardiac disorders | 2 | 0.36 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Skin and subcutaneous tissue disorders | 43 | 7.69 | 72.88 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Blood and lymphatic system disorders | 42 | 7.51 | 71.19 | 1 | 25.00 | 1.69 | 6 | 85.71 | ### | 10 | 41.67 | 16.95 | 1 | 25.00 | 1.69 | 0 | 0.00 | 0.00 |
| Reproductive system and breast disorders | 2 | 0.36 | 3.39 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Metabolism and nutrition disorders | 27 | 4.83 | 45.76 | 1 | 25.00 | 1.69 | 0 | 0.00 | 0.00 | 1 | 4.17 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Ear and labyrinth disorders | 3 | 0.54 | 5.08 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |

| | Action taken | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | None | | | Discontinuation | | | Interruption | | | Perfusion delay | | | Dose reduction | | | Delay and reduction | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Immune system disorders | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Nervous system disorders | 75 | 13.42 | 127.12 | 1 | 25.00 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 2 | 50.00 | 3.39 | 0 | 0.00 | 0.00 |
| Endocrine disorders | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Gastrointestinal disorders | 82 | 14.67 | 138.98 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| General disorders and administration site conditions | 107 | 19.14 | 181.36 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 2 | 8.33 | 3.39 | 1 | 25.00 | 1.69 | 0 | 0.00 | 0.00 |
| Hepatobiliary disorders | 5 | 0.89 | 8.47 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Musculoskeletal and connective tissue disorders | 52 | 9.30 | 88.14 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Eye disorders | 7 | 1.25 | 11.86 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Psychiatric disorders | 7 | 1.25 | 11.86 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Renal and urinary disorders | 1 | 0.18 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Respiratory, thoracic and mediastinal disorders | 39 | 6.98 | 66.10 | 1 | 25.00 | 1.69 | 0 | 0.00 | 0.00 | 1 | 4.17 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Vascular disorders | 12 | 2.15 | 20.34 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 1 | 4.17 | 1.69 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 |
| Total | 559 | 100.00 | | 4 | 100.00 | | 7 | 100.00 | | 24 | 100.00 | | 4 | 100.00 | | 0 | 0.00 | |

The analysis of adverse reactions by SOC based on actions taken is provided in Table 11-13. Reactions leading to treatment discontinuation or interruption were: Injury, poisoning and procedural complications (1 interruption), blood and lymphatic system disorders (1 discontinuation, 6 interruptions), metabolism and nutrition disorders (1 discontinuation), nervous system disorders (1 discontinuation), respiratory, thoracic and mediastinal disorders (1 discontinuation).

#### *11.2.2.4. Adverse reactions by outcome*

##### *11.2.2.4.1. Adverse reactions by outcome (PT level)*

The analysis of the adverse reactions by outcome (recovery or ongoing) is shown in Table 11-14.

**Table 11-14.- Absolute and relative (%) frequencies for outcome of adverse reactions by PT**

| | Result | | | | | |
|---|---|---|---|---|---|---|
| | Resolved | | | Ongoing | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Gingival abscess | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Hot flush | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Aerophagia | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Alanine aminotransferase increased | 5 | 1.23 | 8.47 | 0 | 0.00 | 0.00 |
| House dust allergy | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Alopecia | 9 | 2.21 | 15.25 | 18 | 9.42 | 30.51 |
| Gait disturbance | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Anemia | 7 | 1.72 | 11.86 | 6 | 3.14 | 10.17 |
| Anxiety | 0 | 0.00 | 0.00 | 2 | 1.05 | 3.39 |
| Decreased appetite | 10 | 2.46 | 16.95 | 5 | 2.62 | 8.47 |
| Areflexia | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Arthralgia | 6 | 1.47 | 10.17 | 4 | 2.09 | 6.78 |
| Aspartato aminotransferase increased | 5 | 1.23 | 8.47 | 0 | 0.00 | 0.00 |
| Asthenia | 44 | 10.81 | 74.58 | 16 | 8.38 | 27.12 |
| Astigmatism | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Dry mouth | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Discoloration nail | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Cataract | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Catarrh | 8 | 1.97 | 13.56 | 0 | 0.00 | 0.00 |
| Headache | 11 | 2.70 | 18.64 | 1 | 0.52 | 1.69 |
| Cellulitis | 2 | 0.49 | 3.39 | 0 | 0.00 | 0.00 |
| Cervicalgia | 3 | 0.74 | 5.08 | 0 | 0.00 | 0.00 |
| Spinal cord compression | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Conjunctivitis | 1 | 0.25 | 1.69 | 1 | 0.52 | 1.69 |
| Contusion | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Depression | 1 | 0.25 | 1.69 | 3 | 1.57 | 5.08 |
| Pleural effusion | 1 | 0.25 | 1.69 | 3 | 1.57 | 5.08 |
| Diabetes mellitus | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |

| | Result | | | | | |
|---|---|---|---|---|---|---|
| | Resolved | | | Ongoing | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Diarrhea | 12 | 2.95 | 20.34 | 2 | 1.05 | 3.39 |
| Diastasis recti abdominis | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Dysphagia | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Dysgeusia | 4 | 0.98 | 6.78 | 3 | 1.57 | 5.08 |
| Dyslipidemia | 0 | 0.00 | 0.00 | 2 | 1.05 | 3.39 |
| Dyspnea | 10 | 2.46 | 16.95 | 5 | 2.62 | 8.47 |
| Exertional dyspnea | 1 | 0.25 | 1.69 | 1 | 0.52 | 1.69 |
| Dyspepsia | 3 | 0.74 | 5.08 | 1 | 0.52 | 1.69 |
| Pain | 1 | 0.25 | 1.69 | 1 | 0.52 | 1.69 |
| Abdominal pain | 2 | 0.49 | 3.39 | 3 | 1.57 | 5.08 |
| Back pain | 4 | 0.98 | 6.78 | 6 | 3.14 | 10.17 |
| Catheter site pain | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Pain in the upper abdomen | 3 | 0.74 | 5.08 | 0 | 0.00 | 0.00 |
| Limb pain | 4 | 0.98 | 6.78 | 2 | 1.05 | 3.39 |
| Groin pain | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Musculoskeletal pain | 1 | 0.25 | 1.69 | 1 | 0.52 | 1.69 |
| Oropharyngeal pain | 1 | 0.25 | 1.69 | 1 | 0.52 | 1.69 |
| Bone pain | 4 | 0.98 | 6.78 | 2 | 1.05 | 3.39 |
| Pleuritic pain | 2 | 0.49 | 3.39 | 0 | 0.00 | 0.00 |
| Chest pain | 4 | 0.98 | 6.78 | 2 | 1.05 | 3.39 |
| Musculoskeletal chest pain | 4 | 0.98 | 6.78 | 1 | 0.52 | 1.69 |
| Edema | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Peripheral edema | 3 | 0.74 | 5.08 | 1 | 0.52 | 1.69 |
| Hepatic enzyme increased | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Epistaxis | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Erythema | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Rash | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Rash maculo-papular | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Chills | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Muscle spams | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Constipation | 23 | 5.65 | 38.98 | 3 | 1.57 | 5.08 |
| Tooth extraction | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Atrial fibrillation | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Blood alkaline phosphatase increased | 1 | 0.25 | 1.69 | 1 | 0.52 | 1.69 |

| | Result | | | | | |
|---|---|---|---|---|---|---|
| | Resolved | | | Ongoing | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Hip fracture | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Femur fracture | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Lumbar vertebral fracture | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Gamma glutamiltransferase increased | 2 | 0.49 | 3.39 | 5 | 2.62 | 8.47 |
| Hematoma | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Hematotoxicity | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Hemiparesis | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Hepatomegaly | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Hepatotoxicity | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Hypercholesterolemia | 1 | 0.25 | 1.69 | 2 | 1.05 | 3.39 |
| Hyperglycemia | 6 | 1.47 | 10.17 | 1 | 0.52 | 1.69 |
| Hyperhidrosis | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Hypertension | 0 | 0.00 | 0.00 | 4 | 2.09 | 6.78 |
| Pulmonary hypertension | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Hypertransaminasemia | 2 | 0.49 | 3.39 | 1 | 0.52 | 1.69 |
| Ventricular hypertrophy | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Hyponatremia | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Hypotension | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Hypothyroidism | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Ischemic stroke | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Respiratory tract infection | 5 | 1.23 | 8.47 | 0 | 0.00 | 0.00 |
| Upper respiratory tract infection | 2 | 0.49 | 3.39 | 0 | 0.00 | 0.00 |
| Urinary tract infection | 2 | 0.49 | 3.39 | 1 | 0.52 | 1.69 |
| Catheter site infection | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Lung infection | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Mucosal inflammation | 13 | 3.19 | 22.03 | 0 | 0.00 | 0.00 |
| Influenza | 5 | 1.23 | 8.47 | 0 | 0.00 | 0.00 |
| Insomnia | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Respiratory failure | 1 | 0.25 | 1.69 | 1 | 0.52 | 1.69 |
| Blood lactate dehydrogenase increased | 7 | 1.72 | 11.86 | 2 | 1.05 | 3.39 |
| Lacrimation increased | 3 | 0.74 | 5.08 | 0 | 0.00 | 0.00 |
| Geographic tongue | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Skin lesion | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Leukocytosis | 2 | 0.49 | 3.39 | 0 | 0.00 | 0.00 |

| | Result | | | | | |
|---|---|---|---|---|---|---|
| | Resolved | | | Ongoing | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Leukopenia | 15 | 3.69 | 25.42 | 1 | 0.52 | 1.69 |
| Lymphedema | 0 | 0.00 | 0.00 | 2 | 1.05 | 3.39 |
| Lymphopenia | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Malaise | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Dizziness | 3 | 0.74 | 5.08 | 0 | 0.00 | 0.00 |
| Myalgia | 2 | 0.49 | 3.39 | 1 | 0.52 | 1.69 |
| Nasopharyngitis | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Nausea | 13 | 3.19 | 22.03 | 1 | 0.52 | 1.69 |
| Pneumonia | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Neuralgia | 1 | 0.25 | 1.69 | 1 | 0.52 | 1.69 |
| Peripheral neuropathy | 11 | 2.70 | 18.64 | 12 | 6.28 | 20.34 |
| Peripheral sensory neuropathy | 0 | 0.00 | 0.00 | 2 | 1.05 | 3.39 |
| Neurotoxicity | 2 | 0.49 | 3.39 | 3 | 1.57 | 5.08 |
| Neutropenia | 20 | 4.91 | 33.90 | 2 | 1.05 | 3.39 |
| Febrile neutropenia | 2 | 0.49 | 3.39 | 1 | 0.52 | 1.69 |
| Odynophagia | 2 | 0.49 | 3.39 | 0 | 0.00 | 0.00 |
| Onycholysis | 4 | 0.98 | 6.78 | 2 | 1.05 | 3.39 |
| Osteoporosis | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Pancytopenia | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Paresthesia | 2 | 0.49 | 3.39 | 9 | 4.71 | 15.25 |
| Muscular weakness | 3 | 0.74 | 5.08 | 0 | 0.00 | 0.00 |
| Weight decreased | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Pyelonephritis | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Pyrexia | 20 | 4.91 | 33.90 | 0 | 0.00 | 0.00 |
| Lumbosacral plexopathy | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Polyneuropathy | 3 | 0.74 | 5.08 | 3 | 1.57 | 5.08 |
| Pruritus | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Eye pruritus | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Vulvovaginal pruritus | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Psoriasis | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Eyelid ptosis | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Vaginal cyst | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Breast reconstruction | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Rhinitis | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |

| | Result | | | | | |
|---|---|---|---|---|---|---|
| | Resolved | | | Ongoing | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Burning sensation | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Syncope | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Palmar-plantar erythrodysesthesia syndrome | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Cough | 4 | 0.98 | 6.78 | 1 | 0.52 | 1.69 |
| Skin toxicity | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Thrombocytopenia | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Venous thrombosis | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Deep vein thrombosis | 1 | 0.25 | 1.69 | 1 | 0.52 | 1.69 |
| Vertigo | 3 | 0.74 | 5.08 | 0 | 0.00 | 0.00 |
| Vomiting | 7 | 1.72 | 11.86 | 3 | 1.57 | 5.08 |
| Total | 407 | 100.00 | | 191 | 100.00 | |

#### *11.2.2.4.2. Adverse reactions by outcome (SOC level)*

**Table 11-15.- Absolute and relative (%) frequencies for outcome of adverse reactions by SOC**

| | Result | | | | | |
|---|---|---|---|---|---|---|
| | Resolved | | | Ongoing | | |
| AE | AF | RF (%) | % Total N (59) | AF | RF (%) | % Total N (59) |
| Investigations | 20 | 4.91 | 33.90 | 10 | 5.24 | 16.95 |
| Infections and infestations | 22 | 5.41 | 37.29 | 3 | 1.57 | 5.08 |
| Injury, poisoning and procedural complications | 3 | 0.74 | 5.08 | 1 | 0.52 | 1.69 |
| Surgical and medical procedures | 2 | 0.49 | 3.39 | 0 | 0.00 | 0.00 |
| Cardiac disorders | 0 | 0.00 | 0.00 | 2 | 1.05 | 3.39 |
| Skin and subcutaneous tissue disorders | 19 | 4.67 | 32.20 | 24 | 12.57 | 40.68 |
| Blood and lymphatic system disorders | 49 | 12.04 | 83.05 | 11 | 5.76 | 18.64 |
| Reproductive system and breast disorders | 2 | 0.49 | 3.39 | 0 | 0.00 | 0.00 |
| Metabolism and nutrition disorders | 18 | 4.42 | 30.51 | 11 | 5.76 | 18.64 |
| Ear and labyrinth disorders | 3 | 0.74 | 5.08 | 0 | 0.00 | 0.00 |
| Immune system disorders | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Nervous system disorders | 40 | 9.83 | 67.80 | 38 | 19.90 | 64.41 |
| Endocrine disorders | 0 | 0.00 | 0.00 | 1 | 0.52 | 1.69 |
| Gastrointestinal disorders | 69 | 16.95 | 116.95 | 13 | 6.81 | 22.03 |
| General disorders and administration site conditions | 86 | 21.13 | 145.76 | 24 | 12.57 | 40.68 |
| Hepatobiliary disorders | 3 | 0.74 | 5.08 | 2 | 1.05 | 3.39 |
| Musculoskeletal and connective tissue disorders | 32 | 7.86 | 54.24 | 20 | 10.47 | 33.90 |
| Eye disorders | 4 | 0.98 | 6.78 | 3 | 1.57 | 5.08 |
| Psychiatric disorders | 2 | 0.49 | 3.39 | 5 | 2.62 | 8.47 |
| Renal and urinary disorders | 1 | 0.25 | 1.69 | 0 | 0.00 | 0.00 |
| Respiratory, thoracic and mediastinal disorders | 29 | 7.13 | 49.15 | 12 | 6.28 | 20.34 |
| Vascular disorders | 3 | 0.74 | 5.08 | 10 | 5.24 | 16.95 |
| Total | 407 | 100.00 | | 191 | 100.00 | |

### *11.2.3 Analysis of adverse events*

There was no comparative study of adverse events, since all patients considered as valid in the study received the same treatment.

Regarding safety, the most common side effects grade 3/4 were as expected in previous bibliography, being the hematological toxicities neutropenia (17%), febrile neutropenia (5%) or

leukopenia (5%) the most common ones. The most common non-hematological disorders grade 3/4 were alopecia (5%) and asthenia (3%). 1.69% of patients had peripheral neuropathy.

#### *11.2.4 List of adverse events by patient*

See Appendix 16 for details.

#### *11.2.5 Adverse events leading to treatment interruption*

The adverse reactions leading to treatment interruption were hip fracture, leukopenia, neutropenia and febrile neutropenia. When analyzed by SOC results are classified in: Injury, poisoning and procedural complications and blood and lymphatic system disorders. For more details, see section 11.2.2.3.

### *11.3 Deaths, other serious adverse events (SAE) and other significant adverse events*

#### *11.3.1 Frequency of deaths*

**Table 11-16.- Absolute and relative frequencies (%) for deaths**

| Death | AF | % (n=59) | Valid % (n=58) |
|---|---|---|---|
| **Yes** | 15 | 25.42 | 25.86 |
| **No** | 43 | 72.88 | 74.14 |
| **N** | 58 | 98.31 | 100.00 |
| **NA** | 1 | 1.69 | |

There was a 25.42% of deaths in the study (25.86% of valid ones).

**Table 11-17.- List of patients with death**

| Patient |
|---|
| 01-01 |
| 02-01 |
| 04-03 |
| 04-05 |
| 04-07 |
| 06-01 |
| 11-01 |
| 11-02 |
| 11-06 |
| 13-05 |
| 13-10 |
| 14-02 |
| 14-05 |
| 16-01 |
| 16-05 |

### *11.3.2 Analysis and discussion of deaths, other serious adverse events and other significant adverse events*

There was no death related to the drug. All deaths were due to disease progression.

### *11.4 Conclusions regarding safety*

Since the study started there have been 22 serious adverse events (19 events not related to the investigational medicinal product and 3 events related to the investigational medicinal product, two of them were considered as suspected unexpected serious adverse reaction (SUSAR).

The Sponsor required reporting of two SUSARs to the Health Authorities, as they were considered as adverse events possibly related to the study medication, they were not included in the reference study information and were therefore unexpected.

The Sponsor required reporting of the following events to the Health Authorities as SUSAR:

- **Patient 01-06: Febrile neutropenia plus left hemiparesis and inflammatory myopathy.** The patient suffered from febrile neutropenia together with left hemiparesis and inflammatory myopathy**.**
  Left hemiparesis was considered as possibly related to the study medication and unexpected as it was not described in the reference information of the study medication.
  Inflammatory myopathy was considered as unlikely and it was not described in the reference information; therefore, adverse events were reported as unexpected serious adverse reactions and the requirements of expedited reporting to the authorities were complied with.
- **Patient 13-10: Respiratory infection + respiratory failure + acute renal failure.** Since the adverse event was considered as unlikely related to the study medication. Despite being unlikely related, a possible relationship to the study medication is not ruled out, and as it was not included in the reference information it was considered as unexpected and was immediately reported to the Health Authorities.

Third-line chemotherapy with eribulin for locally advanced or metastatic breast cancer was minimally toxic, manageable and similar to the therapy previously described in pivotal trials.

## 12. Efficacy assessment: Secondary objectives

This study includes 8 secondary objectives related to the efficacy of treatments:

- To evaluate the efficacy of eribulin in the study population in terms of 1-year overall survival (OS) and progression-free survival (PFS).
- To determine the clinical response rate of the study treatment as clinically indicated.
- To determine the objective response rate (ORR) of the study treatment according to the RECIST criteria.

- To determine the clinical benefit rate (CBR) of the study treatment according to the RECIST criteria.
- To evaluate the time to disease progression upon treatment completion in patients without disease progression during treatment.
- To evaluate duration of response.
- To explore the dynamics of circulating tumor cells (CTCs) during treatment with eribulin, as well as its relation to prognosis and/or early failure of treatment with eribulin.
- To evaluate the presence or absence of visceral disease.

## *12.1 Analysis of the efficacy of eribulin regarding OS and PFS*

The frequency of deaths, Kaplan Meier estimates of overall survival and estimates of overall survival at 1 year are provided below.

### *12.1.1 Overall survival rates*

**Table 12-1.- Absolute and relative frequencies (%) for deaths**

| Death | AF | % (n=59) | Valid % (n=58) |
|---|---|---|---|
| **Yes** | 15 | 25.42 | 25.86 |
| **No** | 43 | 72.88 | 74.14 |
| **N** | 58 | 98.31 | 100.00 |
| **NA** | 1 | 1.69 | |

**Table 12-2.- Kaplan-Meier estimate of overall survival**

| | | | 95% CI | |
|---|---|---|---|---|
| **N** | **Events** | **Median** | **LL** | **UL** |
| 58 | 15 | 13.60 | 11.80 | --- |

**Figure 12-1 Kaplan-Meier curve of overall survival**

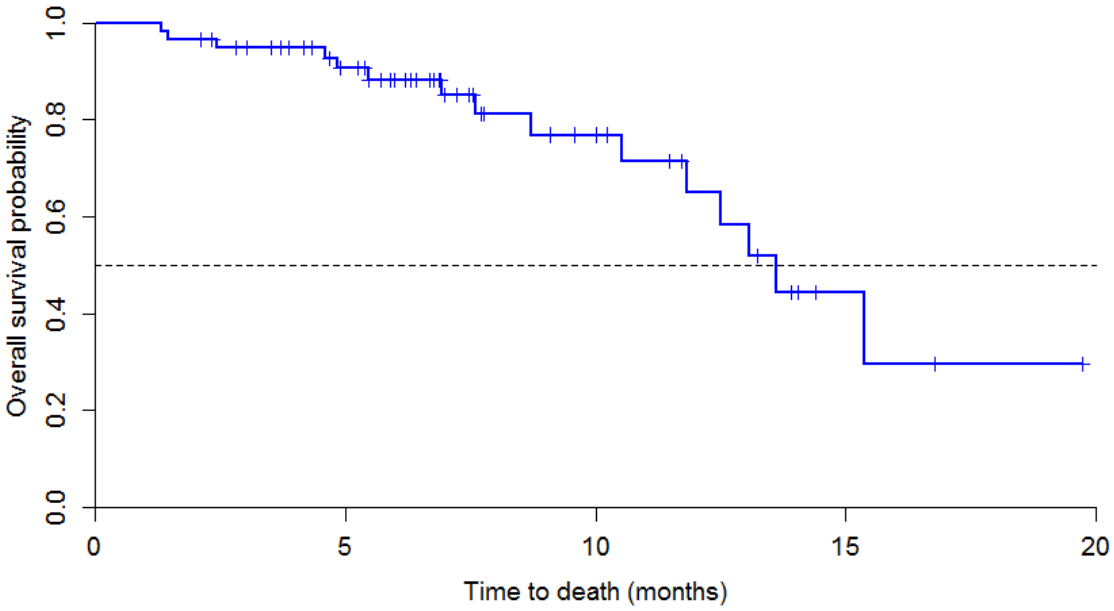
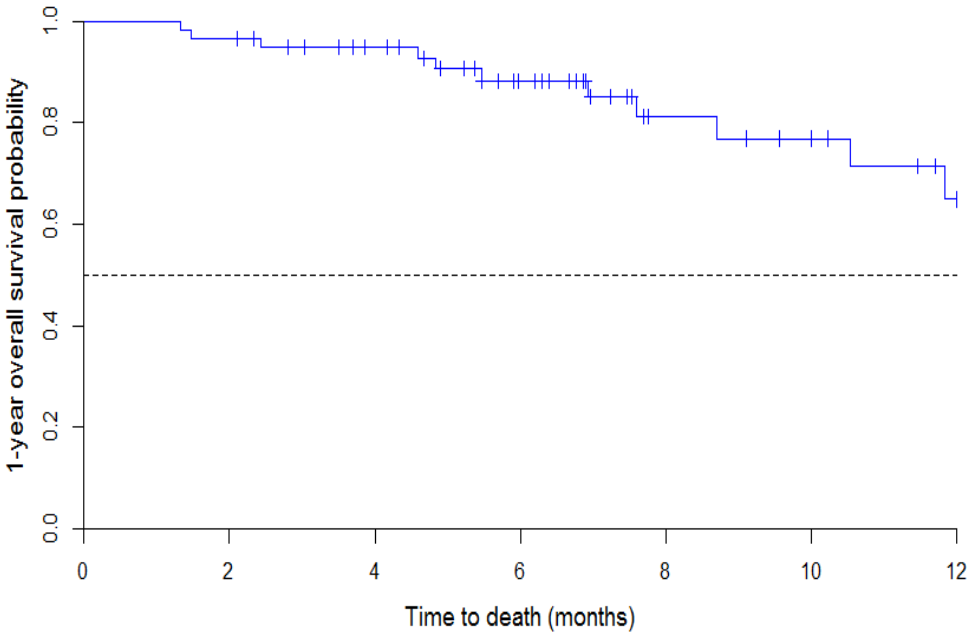



**Table 12-3.- Kaplan-Meier estimate of 1-year overall survival**

| | | | 95% CI | |
|---|---|---|---|---|
| **N** | **Events** | **Median** | **LL** | **UL** |
| 58 | 11 | ---[1] | 11.80 | --- |

[1] The median survival cannot be estimated as probability of survival during the first year is > 0.5 at all times.

**Figure 12-2 Kaplan-Meier curve of 1-year overall survival**




### *12.1.2 Progression-free survival*

**Table 12-4.- Kaplan-Meier estimate of progression-free survival**

| | | | 95% CI | |
|---|---|---|---|---|
| **N** | **Events** | **Median** | **LL** | **UL** |
| 55 | 45 | 4.03 | 3.07 | 5.93 |

**Figure 12-3 Kaplan-Meier curve of progression-free survival curve**

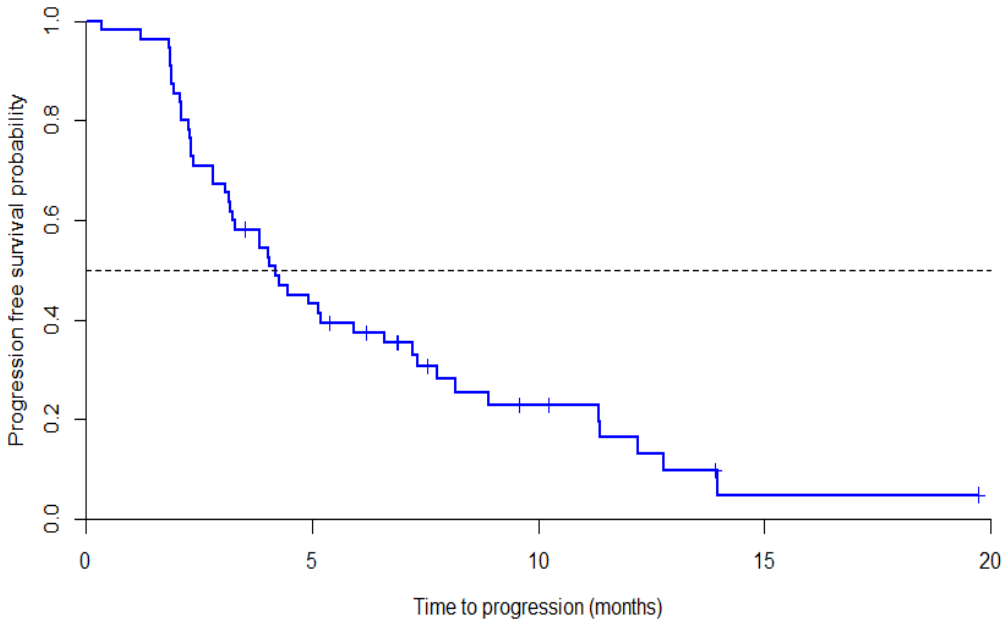
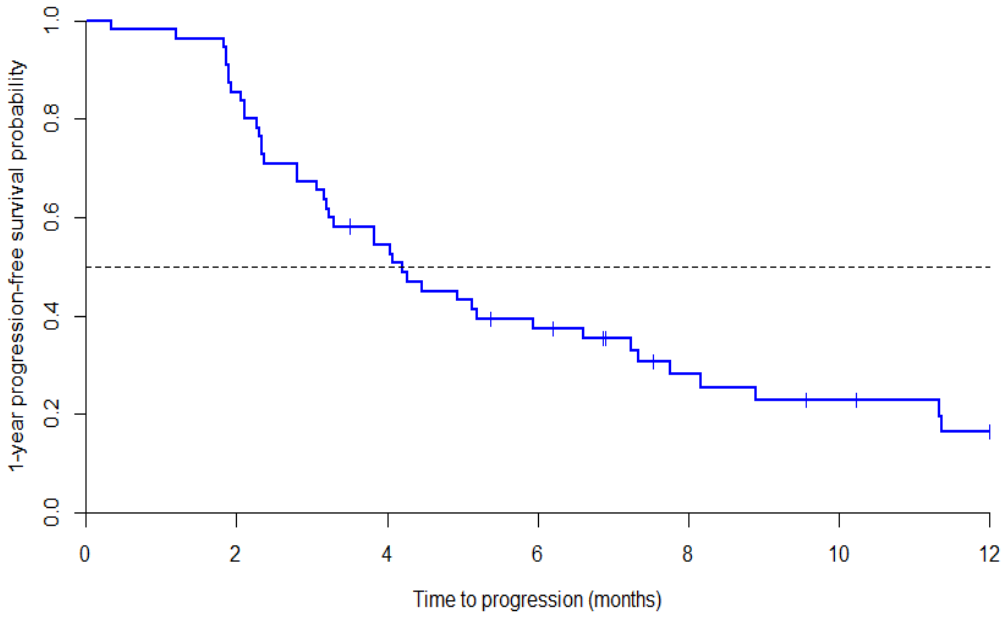



**Table 12-5.- Kaplan-Meier estimate of 1-year progression-free survival**

| | | | 95% CI | |
|---|---|---|---|---|
| **N** | **Events** | **Median** | **LL** | **UL** |
| 55 | 42 | 4.03 | 3.07 | 5.93 |

**Figure 12-4 Kaplan-Meier curve of 1-year progression-free survival**



### *12.2 Determination of the clinical response rate of the study treatment as clinically indicated*

The frequency of the clinical response rate was calculated based on the best response obtained:

**Table 12-6.- Absolute and relative (%) frequencies for best clinical response**

| Best response | AF | % (n=59) | Valid % (n=54) |
|---|---|---|---|
| **CR** | 0 | 0.00 | 0.00 |
| **PR** | 10 | 16.95 | 18.52 |
| **SD** | 23 | 38.98 | 42.59 |
| **DP** | 21 | 35.59 | 38.89 |
| **NE** | 0 | 0.00 | 0.00 |
| **N** | 54 | 91.53 | 100.00 |
| **NA** | 5 | 8.47 | |

### *12.3 Determination of the objective response rate (ORR) of the study treatment according to the RECIST criteria*

**Table 12-7.- Absolute and relative (%) frequencies for objective response**

| Objective response | AF | % (n=59) | Valid % (n=54) |
|---|---|---|---|
| **Yes** | 10 | 16.95 | 18.52 |
| **No** | 44 | 74.58 | 81.48 |
| **N** | 54 | 91.53 | 100.00 |
| **NA** | 5 | 8.47 | |

### *12.4 Determination of the clinical benefit rate (CBR) of the study treatment according to the RECIST criteria*

The frequency of clinical benefit was calculated based on the RECIST criteria as shown below:

**Table 12-8.- Absolute and relative (%) frequencies for clinical benefit**

| Clinical benefit | AF | % (n=59) | Valid % (n=54) |
|---|---|---|---|
| **Yes** | 33 | 55.93 | 61.11 |
| **No** | 21 | 35.59 | 38.89 |
| **N** | 54 | 91.53 | 100.00 |
| **NA** | 5 | 8.47 | |

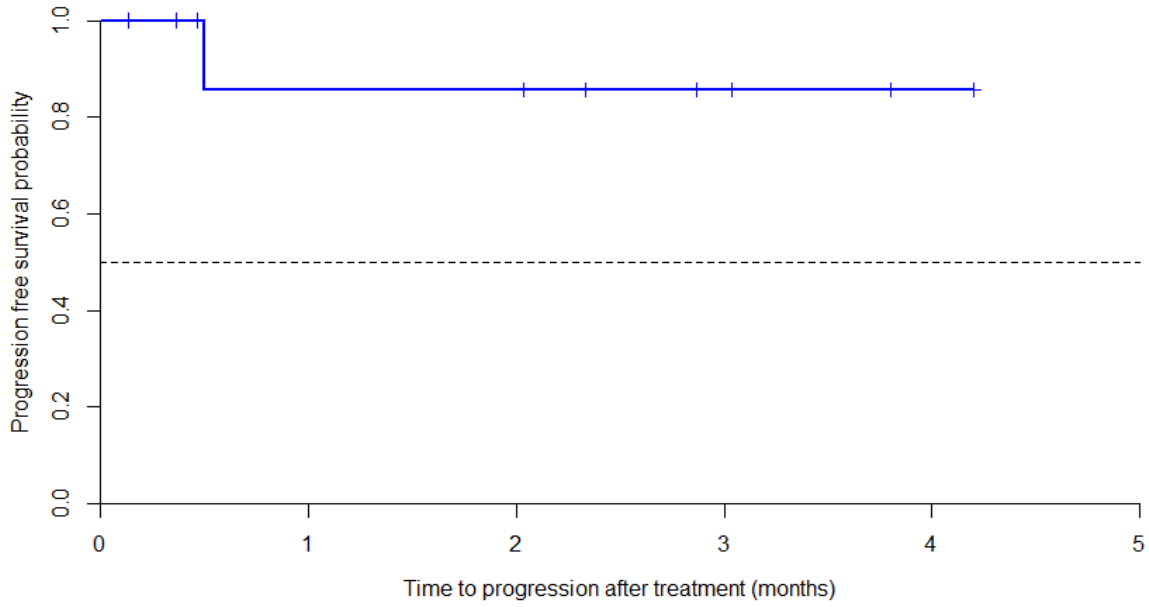
### *12.5 Time to progression after treatment*

The time to disease progression upon treatment completion was calculated for patients who had not completed the study due to disease progression.

**Table 12-9.- Kaplan-Meier estimate of progression-free survival after treatment**

| | | | 95% CI | |
|---|---|---|---|---|
| **N** | **Events** | **Median** | **LL** | **UL** |
| 11 | 1 | ---[2] | --- | --- |

**Figure 12-5 Kaplan-Meier curve of progression-free survival after treatment**




## *12.6 Duration of response*

Duration of response was calculated for patients with objective response who had a subsequent progression.

**Table 12-10.- Descriptive statistics for duration of response**

| **N** | **NA** | **Mean** | **SD** | **P25** | **P50** | **P75** |
|---|---|---|---|---|---|---|
| 7 | 0 | 3.56 | 3.49 | 2.13 | 2.90 | 3.08 |

## *12.7 Circulating Tumor Cells (CTCs)*

### *12.7.1 Dynamics of circulating tumor cells (CTCs)*

The dynamics of circulating tumor cells (CTCs) during treatment with eribulin, as well as its relation to prognosis and/or early failure of treatment with eribulin are described below.

[2] The median survival cannot be estimated as probability of survival after treatment is > 0.5 at all times. In any case, it should be considered that the number of available observations is very low and results might not be reliable.

**Table 12-11.- Descriptive statistics for CTCs at baseline and cycle 2**

| Timepoint | N | NA[1] | Mean | SD | Median | Q1 | Q3 | p-value |
|---|---|---|---|---|---|---|---|---|
| **Baseline** | 49 | 10 | 16.84 | 26.26 | 3.00 | 0.00 | 21.00 | <0.001 |
| **Cycle 2** | 48 | 11 | 5.40 | 10.29 | 1.00 | 0.00 | 8.50 | |

[1]. Patient 16-05 had a count of 5000 CTCs at baseline and 664 CTCs in cycle 2. Since values are very extreme, they are ignored in the calculation of descriptive statistics in order to avoid data distortion.

**Table 12-12.- Absolute and relative (%) frequencies for count of CTCs classified as "< 5" and "≤ 5" at baseline**

| CTCs at baseline | AF[1] | % (n=59) | Valid % (n=50) |
|---|---|---|---|
| **< 5** | 26 | 44.07 | 52.00 |
| **≤ 5** | 24 | 40.68 | 48.00 |
| **N** | 50 | 84.75 | 100.00 |
| **NA** | 9 | 15.25 | |

[1]. Data of patient 16-05 is considered in the calculation of absolute frequencies since when recoding the count of CTCs as "<5"and "≤5", results are not distorted.

**Table 12-13.- Absolute and relative (%) frequencies for count of CTCs classified as "< 5" and "≤ 5" in cycle 2**

| CTCs in cycle 2 | AF | % (n=59) | Valid % (n=49) |
|---|---|---|---|
| **< 5** | 34 | 57.63 | 69.39 |
| **≤ 5** | 15 | 25.42 | 30.61 |
| **N** | 49 | 83.05 | 100.00 |
| **NA** | 10 | 16.95 | |

[1]. Data of patient 16-05 is considered in the calculation of absolute frequencies since when recoding the count of CTCs as "<5"and "≤5", results are not distorted.

**Table 12-14.- Absolute and relative (%) frequencies for count of CTCs classified as "< 5" and "≤ 5" at baseline compared to the count of CTCs in cycle 2**

| CTCs at baseline | CTCs in cycle 2 | | | Fisher's test |
|---|---|---|---|---|
| | <5 | ≤ 5 | Total | p-value |
| **<5** | 18 (62.07%) | 3 (23.08%) | **21** | 0.043 |
| **≤ 5** | 11 (37.93%) | 10 (76.92%) | **21** | |
| **Total** | **29 (100.00%)** | **13 (100.00%)** | **42** | |

**Table 12-15.- Absolute and relative (%) frequencies for count of CTCs classified as "< 5" and "≤ 5" in cycle 2 compared to the count of CTCs at baseline**

| CTCs at baseline | CTCs in cycle 2 | | | Fisher's test |
|---|---|---|---|---|
| | <5 | ≤ 5 | Total | p-value |
| **<5** | 18 (85.71%) | 3 (14.29%) | **21 (100.00%)** | 0.043 |
| **≤ 5** | 11 (52.38%) | 10 (47.62%) | **21 (100.00%)** | |
| **Total** | **29** | **13** | **42** | |

### *12.7.2 CTCs and progression-free survival*

Estimates of progression-free survival based on the level of baseline CTCs are described below:

**Table 12-16.- Kaplan-Meier estimate of progression-free survival based on whether the level of baseline CTCs is < 5 or ≤ 5**

| | | | | 95% CI | | p-value |
|---|---|---|---|---|---|---|
| CTCs at baseline | N | Events | Median | LL | UL | |
| **<5** | 25 | 18 | 4.27 | 2.80 | --- | 0.375 |
| **≤ 5** | 21 | 20 | 3.23 | 2.27 | 7.77 | |

**Figure 12-6 Kaplan-Meier curve of progression-free survival based on whether the level of baseline CTCs is < 5 or ≤ 5**

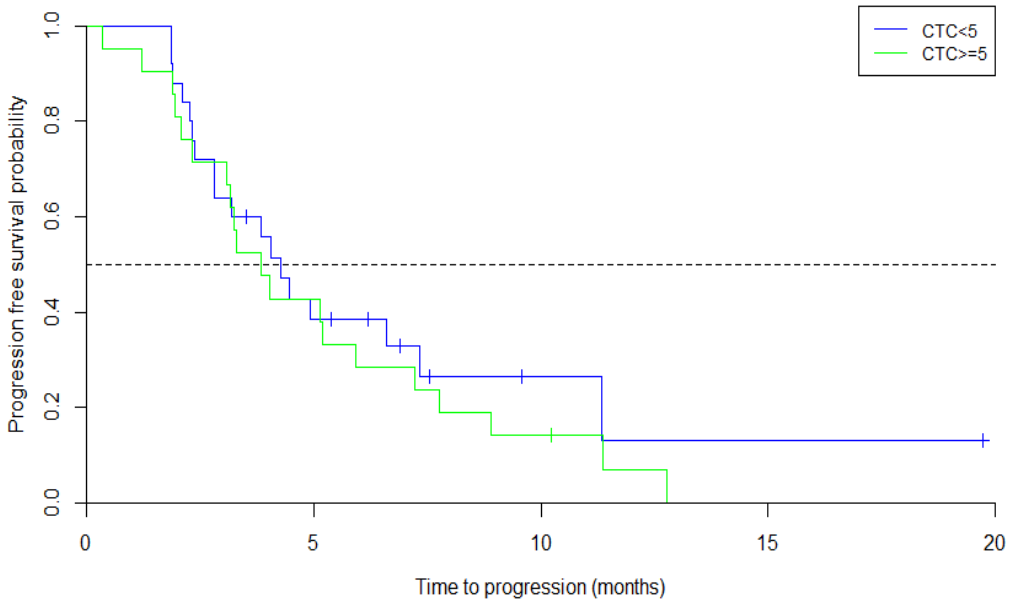



**Table 12-17.- Cox regression analysis for progression-free survival based on the level of baseline CTCs**

| Covariable | Coef | Exp (coef) | SE (coef.) | z | p-value |
|---|---|---|---|---|---|
| Baseline CTCs | 0.0003 | 1.0003 | 0.0002 | 1.584 | 0.113 |

**Table 12-18.- Kaplan-Meier estimate of progression-free survival based on whether the level of CTCs in cycle 2 is < 5 or ≤ 5**

| | | | | 95% CI | | p-value |
|---|---|---|---|---|---|---|
| CTCs in cycle 2 | N | Events | Median | LL | UL | |
| **<5** | 32 | 25 | 3.83 | 2.80 | 8.90 | 0.563 |
| **≤ 5** | 14 | 13 | 3.60 | 2.07 | 12.80 | |

**Figure 12-7 Kaplan-Meier curve of progression-free survival based on whether the level of CTCs in cycle 2 is < 5 or ≤ 5**

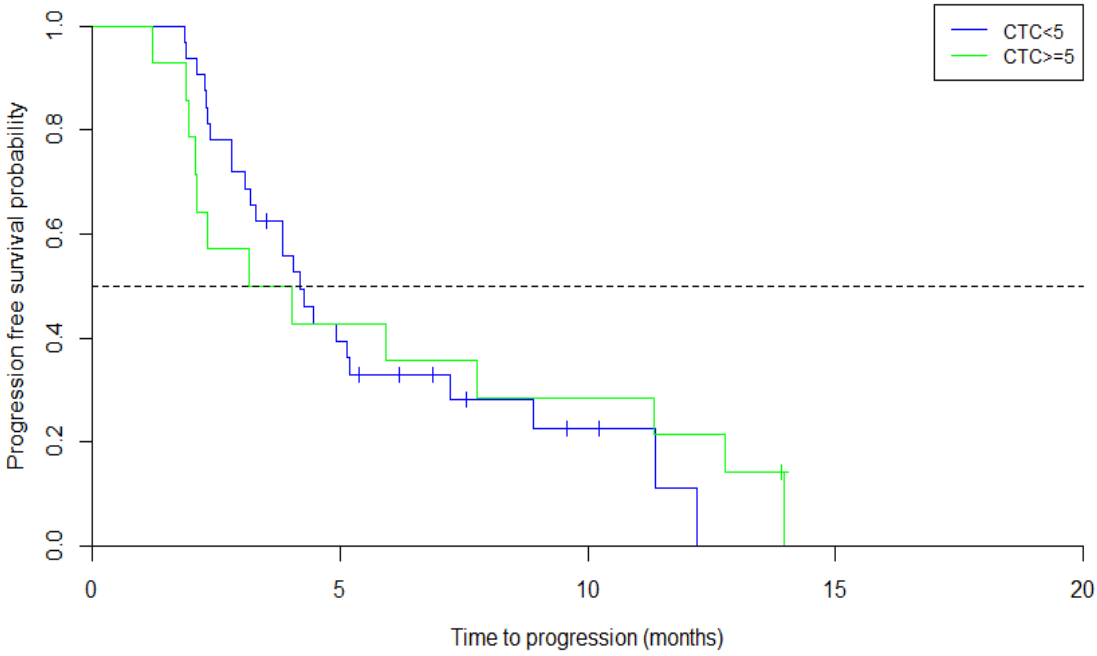



**Table 12-19.- Cox regression analysis for progression-free survival based on the level of CTCs in cycle 2**

| Covariable | Coef | Exp (coef) | SE (coef.) | z | p-value |
|---|---|---|---|---|---|
| CTCs in cycle 2 | 0.0027 | 1.0027 | 0.0016 | 1.709 | 0.0875 |

### *12.7.3 CTCs and objective response*

**Table 12-20.- Absolute and relative (%) frequencies for objective response regarding the count of CTCs at baseline (<5, ≤5)**

| Objective response | Baseline CTCs | | | Fisher's test |
|---|---|---|---|---|
| | <5 | ≤ 5 | Total | p-value |
| **Yes** | 3 (12.50%) | 5 (23.81%) | **8** | 0.443 |
| **No** | 21 (87.50%) | 16 (76.19%) | **37** | |
| **Total** | **24 (100.00%)** | **21 (100.00%)** | **45** | |

**Table 12-21.- Absolute and relative (%) frequencies for count of CTCs at baseline (<5, ≤5) regarding the objective response**

| Objective response | Baseline CTCs | | | Fisher's test |
|---|---|---|---|---|
| | <5 | ≤ 5 | Total | p-value |
| **Yes** | 3 (37.50%) | 5 (62.50%) | **8 (100.00%)** | 0.443 |
| **No** | 21 (56.76%) | 16 (43.24%) | **37 (100.00%)** | |
| **Total** | **24** | **21** | **45** | |

**Table 12-22.- Absolute and relative (%) frequencies for objective response regarding the count of CTCs in cycle 2 (<5, ≤5)**

| Objective response | CTCs in cycle 2 | | | Fisher's test |
|---|---|---|---|---|
| | <5 | ≤ 5 | Total | p-value |
| **Yes** | 7 (21.88%) | 3 (23.08%) | **10** | 1.000 |
| **No** | 25 (78.12%) | 10 (76.92%) | **35** | |
| **Total** | **32 (100.00%)** | **13 (100.00%)** | **45** | |

**Table 12-23.- Absolute and relative (%) frequencies for count of CTCs in cycle 2 (<5, ≤5) regarding the objective response**

| Objective response | CTCs in cycle 2 | | | Fisher's test |
|---|---|---|---|---|
| | <5 | ≤ 5 | Total | p-value |
| **Yes** | 7 (70.00 %) | 3 (30.00 %) | **10 (100.00%)** | 1.000 |
| **No** | 25 (71.43 %) | 10 (28.57 %) | **35 (100.00%)** | |
| **Total** | **32** | **13** | **45** | |

### *12.7.4 CTCs and overall survival*

**Table 12-24.- Kaplan-Meier estimate of overall survival based on whether the level of baseline CTCs is < 5 or ≤ 5**

| CTCs at baseline | N | Events | Median | 95% CI | | p-value |
|---|---|---|---|---|---|---|
| | | | | LL | UL | |
| **<5** | 26 | 3 | 13.10 | 11.80 | --- | 0.045 |
| **≤ 5** | 23 | 10 | 12.50 | 7.60 | --- | |

**Figure 12-8 Kaplan-Meier curve of overall survival based on whether the level of baseline CTCs is < 5 or ≤ 5**

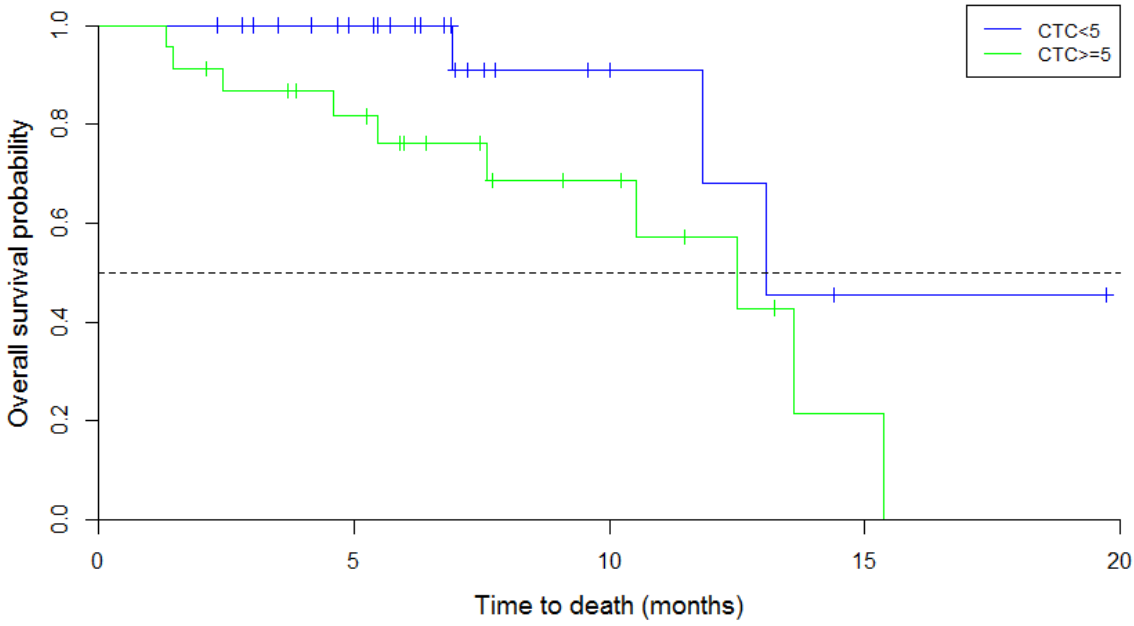



**Table 12-25.- Cox regression analysis for overall survival based on the level of baseline CTCs**

| Covariable | Coef | Exp (coef) | SE (coef) | z | p-value |
|---|---|---|---|---|---|
| Baseline CTCs | 0.0006 | 1.0006 | 0.0002 | 2.641 | 0.0083 |

**Table 12-26.- Kaplan-Meier estimate of overall survival based on whether the level of CTCs in cycle 2 is < 5 or ≤ 5**

| CTCs in cycle 2 | N | Events | Median | 95% CI | | p-value |
|---|---|---|---|---|---|---|
| | | | | LL | UL | |
| **<5** | 34 | 7 | 12.50 | 10.50 | --- | 0.748 |
| **≤ 5** | 15 | 5 | 15.40 | 13.60 | --- | |

**Figure 12-9 Kaplan-Meier curve of overall survival based on whether the level of CTCs in cycle 2 is < 5 or ≤ 5**

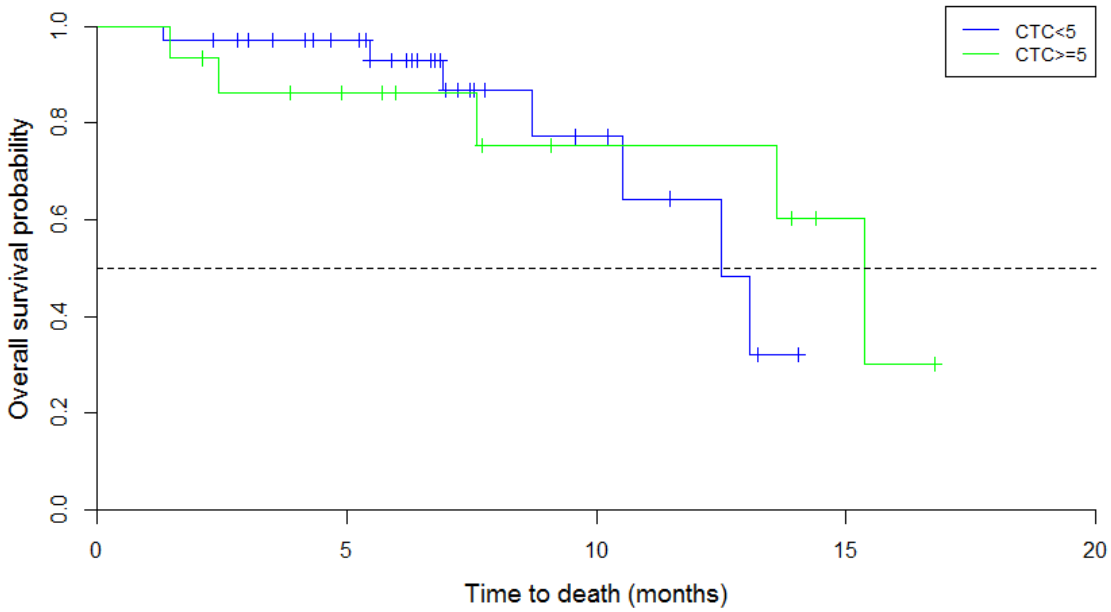



**Table 12-27.- Cox regression analysis for overall survival based on the level of CTCs in cycle 2**

| Covariable | Coef | Exp (coef) | SE (coef) | z | p-value |
|---|---|---|---|---|---|
| CTCs in cycle 2 | 0.0047 | 1.0047 | 0.0019 | 2.488 | 0.0129 |

To sum up, 52.4% of the patients with CTCs ≤ 5 at baseline had decreased levels of CTCs < 5 before cycle 2 (p=0.043). There were no significant differences (p=0.066) in PFS based on the CTCs measured at baseline, despite being classified as <5 or ≤5 cells/mL. However, there were statistically significant differences for OS at baseline (p=0.045). During cycle 2 there was a positive relationship between the levels of CTCs and OS that was statistically significant (p=0.0129) when analyzed without a cut-off point. There were no significant differences between the levels of CTCs and the objective response at baseline or in cycle 2.

Our study suggests that there is a significant correlation between the levels of CTCs and the disease prognosis. Monotherapy with eribulin was related to a significant reduction of the CTCs count.

### *12.8 Evaluation of the presence or absence of visceral disease*

**Table 12-28.- Absolute and relative (%) frequencies for visceral disease**

| Visceral disease | AF | % (n=59) | Valid % (n=59) |
|---|---|---|---|
| **Yes** | 50 | 84.75 | 84.75 |
| **No** | 9 | 15.25 | 15.25 |
| **N** | 59 | 100.00 | 100.00 |
| **NA** | 0 | 0.00 | |

### *12.9 Statistical/analytical issues*

#### *12.9.1 Adjustment by covariants*

There were no adjustments by covariants.

#### *12.9.2 Management of discontinuations or missing data*

No missing values were imputed. The analysis was performed with all available data.

#### *12.9.3 Interim analysis and data monitoring*

An interim analysis was performed in January 2015 to submit an abstract for the IMPAKT 2015 Breast Cancer Conference. Before performing this analysis, an interim cut-off was performed to clean the data to be analyzed for that abstract.

This analysis included descriptive statistics for sex, age, prior treatments and hormone receptors to characterize the patients. Additionally, descriptive statistics for CTCs were provided and the levels of CTCs at baseline and in cycle 2 were compared. The relationship between the level of CTCs and response based on RECIST was also analyzed.

Adjustments at a significance level were not performed in the final analysis. Dynamics of CTCs was evaluated using the same type of analysis as the interim analysis, but other additional analyses were also performed in order to confirm the conclusions obtained.

#### *12.9.4 Multicenter studies*

No separate analyses for each site were performed.

#### *12.9.5 Multiple comparisons/Multiplicity*

No multiple comparisons were performed.

#### *12.9.6 Use of an Efficacy Subgroup of patients*

No efficacy subgroup was considered.

### *12.9.7 Active-control studies to show equivalence*

This was not an active-control study to show equivalence.

### *12.10 Conclusions regarding efficacy*

Regarding the secondary objectives of the ONSITE study, the median progression-free survival was 4.03 months (95% CI: 3.07-5.93) and the median overall survival was 13.6 months (11.8-not achieved). At the follow-up visit, 75% of the patients were still alive. 17% of the patients had a partial disease response, 39% of the patients were stable and 35% of the patients had disease progression. 56% of the patients had a clinical benefit from the third-line therapy with eribulin.

## 13. Comments and general conclusions

Third-line chemotherapy with eribulin for locally advanced or metastatic breast cancer was minimally toxic, manageable and similar to the therapy previously described in pivotal trials.

This study suggests that there is a significant correlation between the levels of CTCs and the disease prognosis. Monotherapy with eribulin was related to a significant reduction of the number of CTCs.

## 14. Appendixes

### *14.1 Study information*

### *14.1.1 Protocol and protocol amendments*

Appendix 1.- Protocol v.4.0 dated June 18, 2013

Appendix 2.- Protocol v.5.0 dated February 28, 2014

Appendix 3.- Protocol v.6.0 dated March 2, 2015

### *14.2 Model for case report form (only pages that are not repeated) and monitoring manual*

Appendix 4.- Blank CRF

### *14.3 Lists of ECs or IRBs (incorporate the name of the chair of the committee, if required by the regulatory authorities) — model patient information and informed consent*

Appendix 5.- List of ECs, sites and Principal Investigators

### *14.4 List and description of the investigators and other important study participants, including a brief CV (1 page) or equivalent summaries of training and relevant experience to participate in the clinical study*

CVs of the participants are not sent, but they are available in the Trial Master File, if required.

Appendix 5 includes a list of the sites, ethics committees and investigators participating in the study.

### *14.5 Signatures of the Principal Investigator and coordinator or doctor of the Sponsor based on the requirements of the regulatory authorities*

Appendix 6.- Protocol signature page of the Sponsor v.3.0

Appendix 7.- Protocol signature page of the Sponsor v.4.0

Appendix 8.- Protocol signature page of the Sponsor v.4.0

### *14.6 Randomization code and list*

Not applicable, since all patients received the same medication.

### *14.7 Audit certificate*

During this study, there were no audits.

### *14.8 Statistical method documentation*

Appendix 10.- Statistical Analysis Plan

### *14.9 Central Laboratory*

The central laboratory for this study was the **Laboratory of Hospital 12 de Octubre**. All CTC measurements were performed there.

### *14.10 Publications based on the study*

Appendix 11.- An interim analysis was performed to submit an abstract for the IMPAKT 2015 Breast Cancer Conference, organized by the European Society for Medical Oncology (ESMO). The abstract was accepted and a poster was submitted.

Appendix 12.- Following the final analysis an abstract was submitted for the conference of the European Society for Medical Oncology (ESMO) 2016.

Appendix 13.- Another abstract was submitted for the conference of the San Antonio Breast Cancer Symposium 2016. Both abstracts were accepted and posters were submitted for the conference.

### *14.11 Discontinued patients*

Appendix 14.- List of discontinued patients and reasons for discontinuation.

### *14.12 Protocol deviations*

Appendix 15.- List of protocol deviations.

### *14.13 Patients excluded from the efficacy analyses*

Patients excluded from the efficacy analysis were screening failures. See section 9.1

### *14.14 Demographic data*

They have already been included in the final report. See section 10.2.1

### *14.15 Data of compliance and/or drug strength*

They have already been included in the final report.

### *14.16 Data of individual efficacy response*

**Table 14-1.- Data of individual efficacy response**

| Patient | OS time (months) | Death | PFS time (months) | Progression | Best response | PFS time after treatment (months) | Progression after treatment | Duration of response (months) | Baseline CTCs | CTCs in cycle 2 |
|---|---|---|---|---|---|---|---|---|---|---|
| 01-01 | 15.37 | Yes | 12.77 | Yes | PR | | | 11.17 | 65 | 8 |
| 01-02 | 6.40 | No | 3.30 | Yes | SD | | | | 21 | 2 |
| 01-04 | 9.57 | No | 9.57 | No | SD | 3.03 | No | | 0 | 0 |
| 01-05 | 14.40 | No | 11.33 | Yes | SD | | | | 2 | 10 |
| 01-06 | 5.97 | No | | | | | | | 10 | 11 |
| 01-07 | 5.47 | No | 2.37 | Yes | DP | | | | 0 | 0 |
| 01-08 | 6.87 | No | 6.87 | No | PR | 2.87 | No | | | 0 |
| 01-09 | 9.10 | No | 5.93 | Yes | PR | | | 2.90 | 32 | 12 |
| 01-10 | | | | | | | | | 41 | |
| 01-11 | 6.20 | No | 6.20 | No | PR | 0.47 | No | | 0 | 0 |
| 01-12 | 4.90 | No | 2.10 | Yes | | | | | 2 | 10 |
| 01-13 | 4.17 | No | 2.27 | Yes | DP | | | | 0 | 0 |
| 01-14 | 3.03 | No | 2.80 | Yes | DP | | | | 0 | 0 |
| 01-15 | 3.70 | No | 3.23 | Yes | DP | | | | 73 | |
| 01-16 | 2.33 | No | | | | | | | 3 | 0 |
| 01-17 | 2.10 | No | 2.07 | Yes | DP | | | | 5 | 12 |
| 02-01 | 12.50 | Yes | 7.23 | Yes | SD | | | | 18 | 2 |
| 04-01 | 4.90 | No | 1.87 | Yes | DP | | | | 0 | |
| 04-02 | 7.23 | No | 4.27 | Yes | DP | | | | 2 | 1 |
| 04-03 | 6.93 | Yes | 3.20 | Yes | DP | | | | 3 | 4 |

| Patient | OS time (months) | Death | PFS time (months) | Progression | Best response | PFS time after treatment (months) | Progression after treatment | Duration of response (months) | Baseline CTCs | CTCs in cycle 2 |
|---|---|---|---|---|---|---|---|---|---|---|
| 04-04 | 6.77 | No | 3.83 | Yes | SD | | | | 0 | 0 |
| 04-05 | 4.60 | Yes | 0.33 | Yes | DP | | | | 69 | |
| 04-06 | 6.90 | No | 6.90 | No | SD | 2.03 | No | | 0 | |
| 04-07 | 4.83 | Yes | 1.83 | Yes | DP | | | | | |
| 06-01 | 13.60 | Yes | 7.77 | Yes | SD | | | | 45 | 23 |
| 06-02 | 19.73 | No | 19.73 | No | SD | 0.37 | No | | 3 | |
| 06-03 | 16.77 | No | 13.97 | Yes | PR | | | 12.10 | | 48 |
| 06-04 | 3.50 | No | 3.50 | No | SD | 0.47 | No | | 0 | 1 |
| 06-05 | 6.67 | No | 2.30 | Yes | DP | | | | | 1 |
| 10-01 | 7.53 | No | 7.53 | No | SD | 3.80 | No | | 0 | 0 |
| 10-02 | 7.70 | No | 4.03 | Yes | SD | | | | 22 | 10 |
| 10-03 | 5.23 | No | 3.83 | Yes | SD | | | | 5 | 1 |
| 10-05 | 13.90 | No | 13.90 | No | SD | 0.13 | No | | | 10 |
| 10-06 | 2.80 | No | 4.07 | Yes | PR | | | 1.90 | 3 | 2 |
| 11-01 | 13.07 | Yes | 2.33 | Yes | DP | 0.50 | Yes | | 0 | 2 |
| 11-02 | 11.83 | Yes | 7.33 | Yes | SD | | | | 0 | |
| 11-03 | 14.03 | No | 12.20 | Yes | SD | | | | | 0 |
| 11-06 | 7.60 | Yes | 3.17 | Yes | SD | | | | 107 | 48 |
| 13-01 | 5.37 | No | 5.37 | No | SD | 2.33 | No | | 1 | 0 |
| 13-02 | 7.77 | No | 4.47 | Yes | SD | | | | 2 | 0 |
| 13-03 | 6.30 | No | 2.80 | Yes | DP | | | | 2 | 0 |
| 13-04 | 11.70 | No | 8.17 | Yes | SD | | | | | |
| 13-05 | 5.47 | Yes | 1.90 | Yes | DP | | | | 17 | 2 |

| Patient | OS time (months) | Death | PFS time (months) | Progression | Best response | PFS time after treatment (months) | Progression after treatment | Duration of response (months) | Baseline CTCs | CTCs in cycle 2 |
|---|---|---|---|---|---|---|---|---|---|---|
| 13-06 | 3.87 | No | 2.33 | Yes | DP | | | | 16 | 6 |
| 13-07 | 5.70 | No | 1.90 | Yes | DP | | | | 2 | 12 |
| 13-08 | 10.00 | No | 6.60 | Yes | SD | | | | 0 | |
| 13-09 | 5.90 | No | 3.07 | Yes | DP | | | | 7 | 1 |
| 13-10 | 1.33 | Yes | | | | | | | 8 | 0 |
| 14-02 | 1.47 | Yes | 1.20 | Yes | DP | | | | 97 | 11 |
| 14-03 | 4.67 | No | 1.87 | Yes | DP | | | | 1 | 0 |
| 14-04 | 10.23 | No | 10.23 | No | PR | 4.20 | No | | 13 | 1 |
| 14-05 | 10.53 | Yes | 5.13 | Yes | DP | | | | 35 | 1 |
| 15-01 | 7.47 | No | 5.20 | Yes | PR | | | 2.97 | 52 | 2 |
| 15-02 | 11.47 | No | 8.90 | Yes | SD | | | | 17 | 0 |
| 16-01 | 8.70 | Yes | 4.20 | Yes | SD | | | | | 2 |
| 16-02 | 4.33 | No | 2.10 | Yes | SD | | | | | 0 |
| 16-03 | 13.23 | No | 11.37 | Yes | PR | | | 9.50 | 24 | 3 |
| 16-04 | 6.97 | No | 4.93 | Yes | PR | | | 2.60 | 0 | 0 |
| 16-05 | 2.43 | Yes | 1.93 | Yes | DP | | | | 5000 | 664 |

### *14.17 Lists of adverse events (by patient)*

Appendix 16.- List of adverse events (by patient).

### *14.18 CRF*

Appendix 17.- All data collected from all patients during the study are attached electronically.