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# GIDO 1201 study

## *"Phase II study of geriatric evaluation as a selection criterion and predictive factor of safety in elderly patients (≥ 70 years) with non-small cell lung cancer and candidates for treatment with bevacizumab, carboplatin and paclitaxel"*

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## *Final statistical analysis*

## *Version 0.2: December 2017*

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## GLOSSARY

| | |
|---|---|
| AUC | Area Under the Curve |
| BMI | Body Mass Index |
| BSA | Body surface area |
| BVZ | Bevacizumab |
| CR | Complete response |
| CRC | Colorectal Cancer |
| CRF | Case Report Form |
| DBP | Diastolic Blood Pressure |
| DP | Disease Progression |
| GS | Global Survival |
| ITT | Intention-to-Treat |
| N | Number of patients |
| NSCLC | Non-small-cell Lung Cancer |
| PFS | Progression-free survival |
| PP | Per-protocol |
| PR | Partial response |
| Q1 | First quartile |
| Q3 | Third quartile |
| SBP | Systolic Blood Pressure |
| SD | Stable disease |
| SD* | Standard deviation |
| S.E | Standard error |
| SIOG | International Society of Geriatric Oncology |

# 1 INTRODUCTION

Despite the high frequency of NSCLC in the elderly population (≥ 70 years), it is difficult to obtain recommendations based on clinical evidence for this patient group as this age group is excluded from the majority of clinical trials. Almost all clinical trials conducted in NSCLC, including older subjects, only use performance status and age as selection criteria for patients eligible to receive chemotherapy. Nevertheless, performance status predicts survival, but is not sufficiently sensitive to predict severe toxicity.

Given that the ageing process is a very individual phenomenon, the SIOG recommends applying chemotherapy treatment schedules adapted to the population group based on biological age and not chronological age. Currently, the most widely used scale is the Comprehensive Geriatric Assessment (CGA), as it includes multiple dimensions including function, co morbidities, depression, cognitive state, and can therefore predict mortality and morbidity in older oncology patients.

Due to the above, a phase II clinical trial was planned with the objective to evaluate the toxicity of treatment based on the combination bevacizumab-carboplatin-paclitaxel, defined as a decrease in grade 3/4 haematologic toxicity in elderly patients (≥ 70 years) with advanced NSCLC that have been selected using a geriatric evaluation.

# 2 OBJECTIVE AND DESIGN

## 2.1 Principal study objective

- To evaluate the toxicity of treatment with bevacizumab, carboplatin and paclitaxel in elderly patients (≥ 70 years) with non-small-cell lung cancer that meet the inclusion criteria for bevacizumab and have been selected based on a geriatric evaluation.

## 2.2 Secondary objectives

The secondary objectives are:

- Determine the predictive factors of toxicity in an elderly population (>70 years).
- Determine the rate of objective response.
- Determine the rate of disease control.
- Determine progression-free survival.
- Determine global survival.

- Determine the safety profile of the combination.

### 2.3 Study design

Phase II clinical trial, open, uncontrolled, multi-centre, national and prospective, to evaluate the toxicity of treatment with bevacizumab, carboplatin and paclitaxel in elderly patients (≥ 70 years) with non-small-cell lung cancer that meet the criteria for the inclusion of bevacizumab and have been selected based on a geriatric evaluation.

### 2.4 Study population

Study population: Elderly patients (≥70 years) diagnosed with advanced non-squamous non-small-cell lung cancer.

**Total number of patients:** Approximately 50-55 patients were expected to be included. **Twenty-seven patients** were finally included.

### 2.5 Inclusion criteria

- Patients that have provided written informed consent in which it states that they understand the purpose of the study and the required procedures and that they agree to participate in the study.
- Able to fulfil the study protocol.
- Patients of both sexes ≥70 years old.
- Patients diagnosed with non-squamous cell non-small cell lung cancer confirmed cytologically and histologically, with negative EGFR mutation or unable to be determined.
- Patients with stage IV disease.
- Patients that have not received first line treatment.
  Patients with a score of 0-1 in the ECOG performance status scale.
- Patients with adequate marrow function, defined as:
  - Absolute neutrophil count (ANC) ≥1.500/mm3 or ≥1,5x109/L;
  - Haemoglobin ≥9 g/dL;
  - Platelets ≥100.000/mm3
- Patients with adequate renal function, defined as:
  - Creatinine clearance ≥40 ml/min, according to the MDRD equation.

- Proteinuria <2+ (dipstick). If proteinuria <2+ (dipstick).the patient should collect, within a 24 hour period, the urine of 24 hours and, in this, the proteins should be less than 1g.

- Fertile males should use adequate contraception methods (failure rate per year <1%) such as sexual abstinence during the trial and for up to 6 months after the final trial treatment administration, have had previous vasectomy and/or have their partner use one of the following methods: implants, injectables, combined oral contraceptives and/or intrauterine device (only hormonal).

### 2.6 Exclusion criteria

- Previous chemotherapy for advanced non-small cell lung cancer.
- History of haemoptysis grade ≥ 2 (defined as bright red blood and at least 2.5mL) in the 3 months prior to inclusion.
- Surgery (including open biopsy), significant traumatic lesion in the 28 days prior to inclusion, or anticipate the need for major surgery during the treatment period.
- Minor surgery, including the insertion of a permanent catheter, in the 24 hours prior to the infusion of bevacizumab.
- Patients with untreated cerebral metastases. Patients with CNS metastases treated with radiotherapy or surgery may be included if there is no evidence of disease progression following treatment.
- Radiological evidence of a tumour that invades or is adjacent to a major blood vessel (for example, pulmonary artery or superior vena cava).
- Radiotherapy, in any location and for any reason, in the 28 days prior to inclusion. Palliative radiotherapy is permitted in the 14 days prior to inclusion in the case of bony lesions.
- Treatment with aspirin (>325 mg/day) or clopidogrel (>75 mg/day) in the 10 days prior to the first dose of bevacizumab. Oral or parenteral administration of anticoagulants or thrombolytic agents at therapeutic doses. The administration of prophylactic anticoagulants is permitted.
- Uncontrolled hypertension (SBP>140 mmHg ad/or DBP>90 mmHg) in the 28 days prior to inclusion or a history of hypertensive crisis or hypertensive encephalopathy.
- Clinically significant cardiovascular disease (for example, cerebrovascular accident or myocardial infarction in the 6 months prior to inclusion, unstable angina, congestive heart

failure NYHA ≥ II, left ventricular ejection fraction (LVEF) <50%, or serious cardiac arrhythmia), that does not respond to treatment or may interfere with the administration of the trial drugs.

- Unhealed wound, active peptic ulcer or untreated bone fracture.
- Hypersensitivity to any of the active drugs of the study (bevacizumab, carboplatin and paclitaxel) or any of their excipients.
- Severe cognitive deterioration that impedes the ability to understand and respond to the questionnaires of the study.
- Psychological, family, social or geographic problems that impede the implementation of monitoring according to protocol.
- Patients with an ADL score <5 in the initial baseline visit.
- Patients with dementia: 9-12 points in the Folstein MMS at the baseline visit.
- Patients that met the Balducci Frailty criteria in the initial visit.
    - Age ≥ 85 years
    - Dependence in 1 or more ADLs
    - >3 co morbidities
    - >1 geriatric syndrome

### 2.7 Treatment Plan

Patients included in the trial received 4-6 cycles (as per the researcher's assessment) of 21 days each of the initial treatment of the bevacizumab-carboplatin-paclitaxel combination with the dose schedule as detailed below:

- Intravenous bevacizumab. 7.5 mg/kg day 1 of each 21 day cycle during 4-6 cycles.
- Intravenous carboplatin. AUC target will be 4mg/min/ml day 1 of each 21 day cycle during 4-6 cycles.
- Intravenous paclitaxel. 175mg/$m^2$ day 1 of each 21 day cycle during 4-6 cycles.

Patients that, after receiving 4-6 cycles (as determined by the researcher) of the initial combination (bevacizumab-carboplatin-paclitaxel) treatment, and in the absence of disease progression or unacceptable toxicity, received maintenance treatment with bevacizumab monotherapy day 1 of each 21 day cycle until clinical disease progression, unacceptable toxicity or death.

# 3 STATISTICAL ANALYSIS METHODS

Detailed below are the statistical analysis methods used to meet the study objectives as well as those used for the descriptive analysis of the variables.

Quantitative variables have been described using measures of central tendency and dispersion (mean, median, SD* (standard deviation), Q1 (first quartile), Q3 (third quartile), minimum and maximum). Qualitative variables have been described using absolute and relative frequencies.

In the descriptive analysis of qualitative variables, two columns of percentages are presented: the total percentage (%) and the valid (% valid), that is the percentage of the sum of the valid responses plus the missing values and the percentage of the total valid responses.

Where necessary 95% confidence intervals were calculated for the results associated with the principal objective and the secondary objectives

The survival analysis was conducted using the Kaplan Meier method, estimating the median, mean, 95% confidence intervals, as well as the number of events and number of censored cases.

Data were analysed using SPSS v18.0 or later.

# 4 STUDY POPULATION

The population analysed is defined below:

- **Population by Intention-to-Treat (ITT):** Includes the patients treated; that is, those that received at least one dose of any of the study drugs.

At the time of the database cut-off (29-09-2017) 27 recruited patients were available, of which one was a screening failure for not meeting the selection criteria and did not receive treatment.

Therefore, the final number of patient analysed and that formed part of the ITT population was **26 patients.**

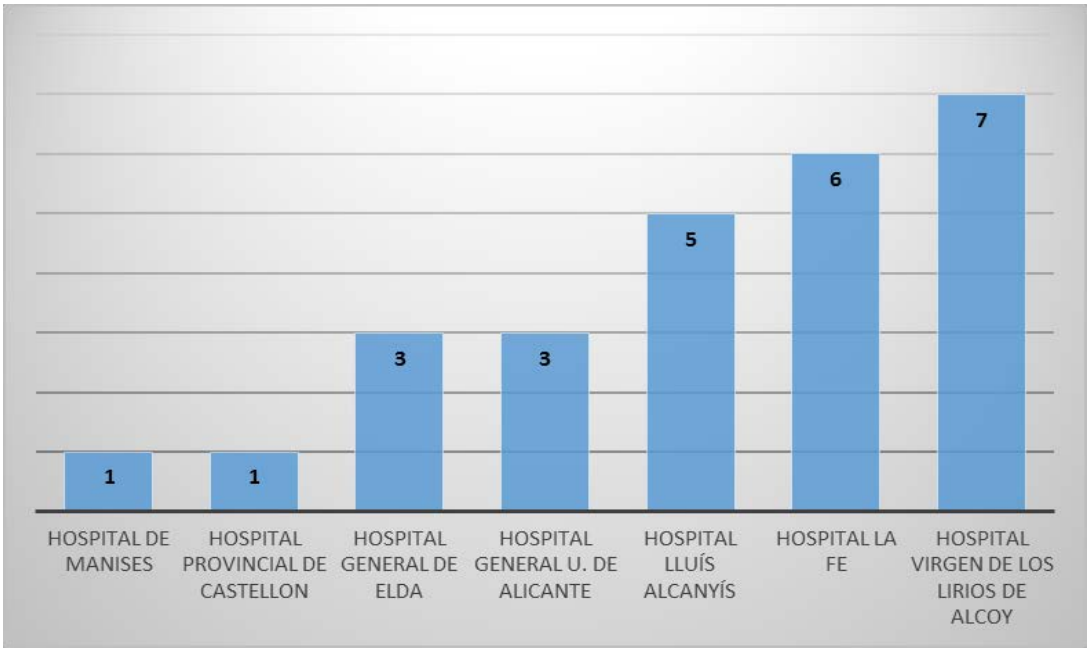
# 5 BASELINE DESCRIPTIVE ANALYSIS

## 5.1 Recruitment period

The patients included in the study between **28-8-2013** and **30-06-2015**.

### 5.2 Figure of recruited patients

| Centre | N | % |
|---|---|---|
| Manises Hospital | 1 | 3.8 |
| Castellon Provincial Hospital | 1 | 3.8 |
| Elda General Hospital | 3 | 11.5 |
| General University Hospital of Alicante | 3 | 11.5 |
| Lluís Alcanyís Hospital | 5 | 19.2 |
| La Fe Hospital | 6 | 23.1 |
| Hospital Virgen de los Lirios de Alcoy | 7 | 26.9 |
| Total | 26 | 100.0 |



### 5.3 Demographic and anthropometric data

| | Mean | SD | Median | Minimum | Maximum | Q1 | Q3 | N |
|---|---|---|---|---|---|---|---|---|
| **Age** | 76.7 | 4.2 | 77.0 | 70.0 | 84.0 | 73.0 | 80.0 | 26 |

| | Mean | SD | Median | Minimum | Maximum | Q1 | Q3 | N |
|---|---|---|---|---|---|---|---|---|
| **Weight (kg)** | 69.5 | 10.4 | 71.0 | 50.0 | 90.0 | 62.0 | 75.8 | 26 |
| **Height (cm)** | 162.5 | 9.0 | 162.5 | 146.0 | 180.0 | 157.5 | 169.5 | 26 |
| **Body surface area ($m^2$)** | 1.7 | 0.2 | 1.7 | 1.5 | 2.1 | 1.6 | 1.9 | 26 |
| **BMI** | 26.4 | 3.7 | 26.6 | 18.4 | 34.2 | 23.5 | 28.5 | 26 |

| | Mean | SD | Median | Minimum | Maximum | Q1 | Q3 | N |
|---|---|---|---|---|---|---|---|---|
| **SBP (mmHg)** | 128.2 | 12.1 | 130.0 | 100.0 | 150.0 | 123.3 | 135.0 | 24 |
| **DBP (mmHg)** | 71.4 | 10.2 | 71.5 | 46.0 | 90.0 | 63.5 | 79.3 | 24 |
| **Heart rate (bpm)** | 80.5 | 13.3 | 80.0 | 62.0 | 107.0 | 67.5 | 90.5 | 25 |

| | | N | % | % valid |
|---|---|---|---|---|
| **Sex** | **Male** | 20 | 76.9 | 76.9 |
| | **Female** | 6 | 23.1 | 23.1 |
| | **Total** | 26 | 100.0 | 100.0 |

| | | N | % | % valid |
|---|---|---|---|---|
| **Smoking habit** | **Smoker** | 6 | 23.1 | 23.1 |
| | **Non-smoker** | 7 | 26.9 | 26.9 |
| | **Ex-smoker** | 13 | 50.0 | 50.0 |
| | **Total** | 26 | 100.0 | 100.0 |

For patients who are smokers, the number of years smoking and the number of packets per week are shown.

| | Mean | SD | Median | Minimum | Maximum | Q1 | Q3 | N |
|---|---|---|---|---|---|---|---|---|
| **No. of years smoking** | 50.2 | 14.7 | 53.0 | 25.0 | 63.0 | 39.0 | 60.0 | 5 |

| | Mean | SD | Median | Minimum | Maximum | Q1 | Q3 | N |
|---|---|---|---|---|---|---|---|---|
| **No. of packets/week** | 9.8 | 5.6 | 7.0 | 7.0 | 21.0 | 7.0 | 12.8 | 6 |

| | | N | % | % valid |
|---|---|---|---|---|
| **ECOG** | **ECOG 0** | 6 | 23.1 | 23.1 |
| | **ECOG 1** | 20 | 76.9 | 76.9 |
| | **Total** | 26 | 100.0 | 100.0 |

### 5.4 Relevant clinical history

The number of patients that have indicated an abnormality in the following systems are described:

| | | N | % |
|---|---|---|---|
| **Relevant clinical history: Abnormal** | **Cardiovascular system** | 19 | 73.1 |
| | **Metabolic and Endocrine system** | 17 | 65.4 |
| | **Other abnormal pathology** | 11 | 42.3 |
| | **CNS and sensory organs** | 10 | 38.5 |
| | **Digestive system** | 10 | 38.5 |
| | **Genitourinary system** | 10 | 38.5 |
| | **Neoplasms** | 8 | 30.8 |
| | **Respiratory system** | 7 | 26.9 |
| | **Musculoskeletal system** | 7 | 26.9 |
| | **Skin, skin appendages and subcutaneous tissue** | 4 | 15.4 |
| | **Haematologic system** | 3 | 11.5 |
| | **Psychiatric** | 1 | 3.8 |

The percentages do not need to add to 100%, as the patients may present with an abnormality in more than one system.
Percentages calculated from the total number of patients analysed (N=26)

In those patients that have indicated an abnormality the pathology is described as ongoing or not ongoing:

| | | N | % |
|---|---|---|---|
| Relevant clinical history: Abnormal (ongoing) | Cardiovascular system | 18 | 94.7 |
| | Metabolic and Endocrine system | 15 | 88.2 |
| | Respiratory system | 7 | 100.0 |
| | Genitourinary system | 7 | 70.0 |
| | Musculoskeletal system | 7 | 100.0 |
| | CNS and sensory organs | 6 | 60.0 |
| | Digestive system | 5 | 50.0 |
| | Haematologic system | 2 | 66.7 |
| | Skin, skin appendages and subcutaneous tissue | 1 | 25.0 |
| | Psychiatric | 1 | 100.0 |
| | Neoplasms | 0 | 0.0 |

Percentages calculated from the total patients that presented abnormality in each of the pathologies.

### 5.5 Clinical history of cancer

Tumour disease

Time from the diagnosis of NSCLC, defined as the time passed, in months, from the diagnosis of NSCLC till the date informed consent was signed.

| | Mean | SD | Median | Minimum | Maximum | Q1 | Q3 | N |
|---|---|---|---|---|---|---|---|---|
| **Time between diagnosis of NSCLC and the date of informed consent (months)** | 4.1 | 9.3 | 0.9 | 0.2 | 41.9 | 0.5 | 1.8 | 26 |

| | | N | % |
|---|---|---|---|
| **Confirmed diagnosis of advanced/metastatic NSCLC** | **Histology (Biopsy)** | 21 | 80.8 |
| | **Cytology (PAAF)** | 8 | 30.8 |

The percentages do not need to add to 100%, as the patients may have with more than one diagnostic confirmation
Percentages calculated from the total number of patients analysed (N=26)

| | | N | % | % valid |
|---|---|---|---|---|
| **Surgical resection** | **No** | 23 | 88.5 | 88.5 |
| | **Yes** | 3 | 11.5 | 11.5 |
| | **Total** | 26 | 100.0 | 100.0 |

| | | N | % | % valid |
|---|---|---|---|---|
| **Radiotherapy** | **No** | 25 | 96.2 | 96.2 |
| | **Yes** | 1 | 3.8 | 3.8 |
| | **Total** | 26 | 100.0 | 100.0 |

Metastatic disease

Time from the diagnosis of metastatic disease, defined as the time passed, in months, from the diagnosis of metastatic disease till the date informed consent was signed.

| | Mean | SD | Median | Minimum | Maximum | Q1 | Q3 | N |
|---|---|---|---|---|---|---|---|---|
| **Time between diagnosis of metastatic disease and the date of informed consent (months)** | 1.7 | 2.5 | 1.0 | 0.1 | 12.4 | 0.5 | 1.8 | 26 |

| | | N | % |
|---|---|---|---|
| **Location** | **Local/regional** | 10 | 38.5 |
| | **Bone** | 8 | 30.8 |
| | **Liver** | 6 | 23.1 |
| | **Pleura** | 6 | 23.1 |
| | **Other[1]** | 5 | 19.2 |
| | **Cerebral** | 4 | 15.4 |
| | **Adrenal** | 4 | 15.4 |
| | **Not available** | 2 | 7.7 |

The percentages do not need to add to 100%, as the patients may present with more than one location. Percentages calculated from the total number of patients analysed (N=26)

[1]The “other locations” indicated are described below:

| | | N | % |
|---|---|---|---|
| **Other location** | **Adenopathy right axilla** | 1 | 3.8 |
| | **Abdominal adenopathy** | 1 | 3.8 |
| | **Hilar and mediastinal adenopathy** | 1 | 3.8 |
| | **Mediastinal adenopathy** | 1 | 3.8 |
| | **Submandibular** | 1 | 3.8 |

### 5.6 Current disease stage

| | | N | % | % valid |
|---|---|---|---|---|
| Primary tumour (T) | Tx | 4 | 15.4 | 16.7 |
| | T1 | 4 | 15.4 | 16.7 |
| | T2 | 7 | 26.9 | 29.2 |
| | T3 | 3 | 11.5 | 12.5 |
| | T4 | 6 | 23.1 | 25.0 |
| | Total | 24 | 92.3 | 100.0 |
| Not available | | 2 | 7.7 | |
| Total | | 26 | 100.0 | |

| | | N | % | % valid |
|---|---|---|---|---|
| Positive lymph nodes (N) | Nx | 2 | 7.7 | 8.3 |
| | N0 | 6 | 23.1 | 25.0 |
| | N1 | 2 | 7.7 | 8.3 |
| | N2 | 8 | 30.8 | 33.3 |
| | N3 | 6 | 23.1 | 25.0 |
| | Total | 24 | 92.3 | 100.0 |
| Not available | | 2 | 7.7 | |
| Total | | 26 | 100.0 | |

| | | N | % | % valid |
|---|---|---|---|---|
| Distant metastases (M) | M1 | 24 | 92.3 | 100.0 |
| | Total | 24 | 92.3 | 100.0 |
| Not available | | 2 | 7.7 | |
| Total | | 26 | 100.0 | |

### 5.7 Target lesions and non-target lesions baseline

A joint analysis of target and non-target lesions will be done during the baseline visit.

If a patient presents with more than one lesion in the same organ, they are considered as one location.

| | | N | % |
|---|---|---|---|
| Location (organ) | Lung | 26 | 100 |
| | Lymphatic system | 19 | 73.1 |
| | Bone | 9 | 34.6 |
| | Liver | 8 | 30.8 |
| | Adrenal | 4 | 15.4 |
| | Kidney | 3 | 11.5 |
| | Spleen | 2 | 7.7 |
| | Myxoma | 1 | 3.8 |
| | Others | 1 | 3.8 |
| | Parietal | 1 | 3.8 |
| | Peritoneum | 1 | 3.8 |

Percentages calculated from the total number of patients analysed (N=26)
The percentages do not need to add to 100%, as the patients may present with more than one location.

| | | N | % | % valid |
|---|---|---|---|---|
| Number of organs | 1 organ | 2 | 7.7 | 7.7 |
| | 2 organs | 10 | 38.5 | 38.5 |
| | 3 organs | 8 | 30.8 | 30.8 |
| | 4 organs | 3 | 11.5 | 11.5 |
| | 5 organs | 1 | 3.8 | 3.8 |
| | 6 organs | 2 | 7.7 | 7.7 |
| Total | | 26 | 100.0 | 100.0 |
| | Mean (SD) | 2.9 (1.3) | | |
| | Median | 3.0 | | |

The total number of lesions that patients presented with, independent from if pertaining to the same organ, are shown below:

| | | N | % | % valid |
|---|---|---|---|---|
| Number of lesions | 2 lesions | 1 | 3.8 | 3.8 |
| | 3 lesions | 3 | 11.5 | 11.5 |
| | 4 lesions | 5 | 19.2 | 19.2 |
| | 5 lesions | 5 | 19.2 | 19.2 |
| | 6 lesions | 3 | 11.5 | 11.5 |
| | 7 lesions | 3 | 11.5 | 11.5 |
| | 8 lesions | 2 | 7.7 | 7.7 |
| | 9 lesions | 2 | 7.7 | 7.7 |
| | 11 lesions | 1 | 3.8 | 3.8 |
| | 12 lesions | 1 | 3.8 | 3.8 |
| Total | | 26 | 100.0 | 100.0 |
| Mean (SD) | | 5.9 (2.5) | | |
| Median | | 5.0 | | |

# 6 TREATMENT

## 6.1 Time in treatment (initial treatment + maintenance treatment)

Total time in treatment, defined as the time, in months, between the dates of the first and last administered treatment cycle for each patient.

| | Mean | SD | Median | Minimum | Maximum | Q1 | Q3 | N |
|---|---|---|---|---|---|---|---|---|
| **Time in treatment (months)** | 7.3 | 5.4 | 6.1 | 1.4 | 25.2 | 3.3 | 9.1 | 26 |

## 6.2 Cycles administered (initial treatment + maintenance treatment)

The following shows the number of cycles received in the initial treatment by the patients independent of the drug received, that is, it was considered a cycle received at the moment when the patient received at least one of the three study drugs.

| | | N | % | % valid |
|---|---|---|---|---|
| **Number of cycles administered in initial treatment** | **2 cycles** | 1 | 3.8 | 3.8 |
| | **3 cycles** | 3 | 11.5 | 11.5 |
| | **4 cycles** | 16 | 61.5 | 61.5 |
| | **5 cycles** | 3 | 11.5 | 11.5 |
| | **6 cycles** | 3 | 11.5 | 11.5 |
| **Total** | | 26 | 100.0 | 100.0 |
| **Mean (SD)** | | **4.2 (0.9)** | | |
| **Median** | | **4.0** | | |
| **Minimum-Maximum** | | **2.0-6.0** | | |
| **Q1-Q3** | | **4.0-4.3** | | |
| **Number of cycles administered** | | **108** | | |

One patient did not receive a dose of bevacizumab during one cycle due to haematuria.

The following shows the number of cycles received during maintenance treatment with bevacizumab.

A total of **17 (65.5%) patients** received maintenance treatment with bevacizumab.

| | | N | % | % valid |
|---|---|---|---|---|
| **Number of cycles administered in maintenance treatment with bevacizumab** | **2 cycles** | 2 | 11.8 | 11.8 |
| | **3 cycles** | 1 | 5.9 | 5.9 |
| | **4 cycles** | 1 | 5.9 | 5.9 |
| | **5 cycles** | 3 | 17.6 | 17.6 |
| | **6 cycles** | 1 | 5.9 | 5.9 |
| | **7 cycles** | 1 | 5.9 | 5.9 |
| | **8 cycles** | 3 | 17.6 | 17.6 |
| | **11 cycles** | 2 | 11.8 | 11.8 |
| | **18 cycles** | 1 | 5.9 | 5.9 |
| | **19 cycles** | 1 | 5.9 | 5.9 |
| | **32 cycles** | 1 | 5.9 | 5.9 |
| **Total** | | 17 | 100.0 | 100.0 |
| **Mean (SD)** | | **9.1 (7.7)** | | |
| **Median** | | **7.0** | | |
| **Minimum-Maximum** | | **2.0-32.0** | | |
| **Q1-Q3** | | **4.5-11.0** | | |
| **Number of cycles administered** | | **154** | | |

The following shows the number of cycles received during the initial treatment plus the number of cycles of maintenance treatment with bevacizumab:

| | | N | % | % valid |
|---|---|---|---|---|
| Number of cycles administered in initial treatment and in maintenance treatment with bevacizumab | 2 cycles | 1 | 3.8 | 3.8 |
| | 3 cycles | 3 | 11.5 | 11.5 |
| | 4 cycles | 2 | 7.7 | 7.7 |
| | 5 cycles | 3 | 11.5 | 11.5 |
| | 6 cycles | 1 | 3.8 | 3.8 |
| | 7 cycles | 1 | 3.8 | 3.8 |
| | 8 cycles | 2 | 7.7 | 7.7 |
| | 9 cycles | 3 | 11.5 | 11.5 |
| | 11 cycles | 1 | 3.8 | 3.8 |
| | 12 cycles | 3 | 11.5 | 11.5 |
| | 14 cycles | 1 | 3.8 | 3.8 |
| | 15 cycles | 2 | 7.7 | 7.7 |
| | 22 cycles | 1 | 3.8 | 3.8 |
| | 23 cycles | 1 | 3.8 | 3.8 |
| | 36 cycles | 1 | 3.8 | 3.8 |
| Total | | 26 | 100.0 | 100.0 |
| Number of cycles administered | | 262 | | |
| Mean (SD) | | 10.1 (7.6) | | |
| Median | | 8.5 | | |
| Minimum-Maximum | | 2.0-36.0 | | |
| Q1-Q3 | | 4.8-12.5 | | |

### 6.3 Delays in treatment (initial treatment + maintenance treatment)

A total of **13 patients** (50%) delayed a cycle of treatment at some point.

| | | N | % | % valid |
|---|---|---|---|---|
| **Number of cycles delayed** | **0 cycles** | 13 | 50.0 | 50.0 |
| | **1 cycles** | 10 | 38.5 | 38.5 |
| | **2 cycles** | 3 | 11.5 | 11.5 |
| | **Total** | 26 | 100.0 | 100.0 |
| **Number of cycles delayed** | | **16** | | |
| **Mean (SD)** | | **0.6 (0.7)** | | |
| **Median** | | **0.5** | | |
| **Minimum-Maximum** | | **0.0-2.0** | | |
| **Q1-Q3** | | **0.0-1.0** | | |

The reasons for delay in the 16 delayed cycles are shown below:

| | | N | % |
|---|---|---|---|
| **Reasons for delay** | **Adverse event** | 1 | 6.3 |
| | **Asthenia** | 1 | 6.3 |
| | **Asthenia and anaemia** | 1 | 6.3 |
| | **Abscess** | 1 | 6.3 |
| | **Fracture** | 1 | 6.3 |
| | **Neutropaenia** | 1 | 6.3 |
| | **Haematologic toxicity** | 1 | 6.3 |
| | **Pulmonary thromboembolism** | 1 | 6.3 |
| | **Vomiting** | 1 | 6.3 |
| | **Hypertension** | 2 | 12.5 |
| | **Proteinuria** | 2 | 12.5 |
| | **Pain** | 1 | 6.3 |
| | **Respiratory tract infection** | 1 | 6.3 |
| | **Administrative reasons** | 1 | 6.3 |
| **Total** | | 16 | 100.0 |

### 6.4 Reduction/Interruption of dose (initial treatment + maintenance treatment)

**Bevacizumab**

A total of **1 patient** (3.8%) reduced a cycle of bevacizumab on any occasion.

| | | N | % | % valid |
|---|---|---|---|---|
| **Number of reduced cycles of bevacizumab** | **0** | 25 | 96.2 | 96.2 |
| | **1** | 1 | 3.8 | 3.8 |
| | **Total** | 26 | 100.0 | 100.0 |
| **Number of reduced cycles** | | **1** | | |
| **Mean (SD)** | | **0.0 (0.2)** | | |
| **Median** | | **0.0** | | |
| **Minimum-Maximum** | | **0.0-1.0** | | |
| **Q1-Q3** | | **0.0-0.0** | | |

The reason for cycle reduction was vomiting. This was patient 08-01 that had a SAE of grade 3 vomiting and for this reason had a dose reduction of bevacizumab.

A total of **1 patient** (3.8%) has interrupted a cycle of bevacizumab during any occasion.

| | | N | % | % valid |
|---|---|---|---|---|
| **Number of interrupted cycles of bevacizumab** | **0** | 25 | 96.2 | 96.2 |
| | **1** | 1 | 3.8 | 3.8 |
| | **Total** | 26 | 100.0 | 100.0 |
| **Total number of interrupted cycles** | | **1** | | |
| **Mean (SD)** | | **0.0 (0.2)** | | |
| **Median** | | **0.0** | | |
| **Minimum-Maximum** | | **0.0-1.0** | | |
| **Q1-Q3** | | **0.0-0.0** | | |

The reasons for the reduction of the cycle were haematuria/proteinuria/hypertension in the patient.

## Carboplatin

A total of **6 patients** (23.1%) had a reduced cycle of carboplatin on any occasion.

| | | N | % | % valid |
|---|---|---|---|---|
| **Number of reduced cycles of Carboplatin** | **0** | 20 | 76.9 | 76.9 |
| | **1** | 5 | 19.2 | 19.2 |
| | **2** | 1 | 3.8 | 3.8 |
| | **Total** | 26 | 100.0 | 100.0 |
| **Number of reduced cycles** | | **7** | | |
| **Mean (SD)** | | **0.3 (0.5)** | | |
| **Median** | | **0.0** | | |
| **Minimum-Maximum** | | **0.0-2.0** | | |
| **Q1-Q3** | | **0.0-0.3** | | |

Below the reasons for reduction of the 7 cycles are shown:

| | | N | % |
|---|---|---|---|
| **Reasons for reduced Carboplatin** | **Renal toxicity** | 1 | 14.3 |
| | **Haematologic toxicity** | 1 | 14.3 |
| | **Nausea/vomiting** | 3 | 42.9 |
| | **Asthenia/anaemia** | 1 | 14.3 |
| | **Elevated creatinine** | 1 | 14.3 |
| **Total** | | 7 | 100.0 |

There were no **interruptions** of treatment with carboplatin.

**Paclitaxel**

A total of **6 patients** (23.1%) had a reduced a cycle of paclitaxel on any occasion.

| | | N | % | % valid |
|---|---|---|---|---|
| **Number of reduced cycles of paclitaxel** | **0** | 20 | 76.9 | 76.9 |
| | **1** | 5 | 19.2 | 19.2 |
| | **2** | 1 | 3.8 | 3.8 |
| | **Total** | 26 | 100.0 | 100.0 |
| **Number of reduced cycles** | | **7** | | |
| **Mean (SD)** | | **0.3 (0.5)** | | |
| **Median** | | **0.0** | | |
| **Minimum-Maximum** | | **0.0-2.0** | | |
| **Q1-Q3** | | **0.0-0.3** | | |

Below the reasons for reduction of the 7 cycles are shown:

| | | N | % |
|---|---|---|---|
| **Reasons for reduction of paclitaxel** | **Haematologic toxicity** | 1 | 14.3 |
| | **Nausea/vomiting** | 3 | 42.9 |
| | **Diarrhoea** | 1 | 14.3 |
| | **Asthenia/anaemia** | 1 | 14.3 |
| | **Poor treatment tolerance** | 1 | 14.3 |
| **Total** | | 7 | 100.0 |

There were no **interruptions** of treatment with paclitaxel.

### 6.5 Dose intensity

**The absolute dose intensity** is defined as the amount of the drug received by the patient over the course of treatment.

For paclitaxel, it was calculated as the sum of all doses administered in mg/m$^2$ divided by the total time on paclitaxel treatment (in weeks).

For bevacizumab, it was calculated as the sum of all doses administered in mg/kg divided by the total time in treatment with bevacizumab (in weeks).

**Relative dose intensity** is defined as the amount of drug the patient received in relation to the amount of drug he should receive according to protocol.

| Absolute intensity | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | Minimum | Maximum | Q1 | Q3 | N |
| **Bevacizumab** | 2.4 | 0.2 | 2.4 | 1.8 | 2.8 | 2.2 | 2.5 | 26 |
| **Paclitaxel** | 53.7 | 6.6 | 57.0 | 37.1 | 59.5 | 48.7 | 58.7 | 26 |

| Relative intensity | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | Minimum | Maximum | Q1 | Q3 | N |
| **Bevacizumab** | 0.9 | 0.1 | 1.0 | 0.7 | 1.1 | 0.9 | 1.0 | 26 |
| **Paclitaxel** | 0.9 | 0.1 | 1.0 | 0.6 | 1.0 | 0.8 | 1.0 | 26 |

### 6.6 Carboplatin dose

| Carboplatin dose (mg) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | Minimum | Maximum | Q1 | Q3 | N |
| **Cycle 1** | 369.3 | 92.9 | 359.8 | 220.0 | 540.0 | 288.5 | 450.9 | 26 |
| **Cycle 2** | 368.5 | 85.1 | 359.8 | 252.7 | 540.0 | 297.5 | 433.9 | 26 |
| **Cycle 3** | 358.1 | 80.5 | 359.7 | 228.9 | 540.0 | 295.0 | 415.0 | 25 |
| **Cycle 4** | 352.7 | 82.1 | 331.3 | 240.0 | 540.0 | 284.7 | 407.9 | 22 |
| **Cycle 5** | 351.5 | 49.2 | 344.8 | 300.0 | 410.0 | 301.8 | 407.9 | 6 |
| **Cycle 6** | 336.5 | 61.2 | 302.4 | 300.0 | 407.2 | 300.0 | - | 3 |

# 7 RESPONSE

- A table is provided in which has been included:
  - Centre no.
  - Patient no.
  - Clinical response experienced by the patients in each of the cycles until the end of the treatment in which the response has been evaluated.
  - Best response achieved by the patients during treatment (RECIST 1.1).
  - Best response achieved by patients CONFIRMED in a subsequent evaluation, following RECIST criteria.
  - Number of cycles administered in combination and as monotherapy.
  - Reasons for ending the study.

In the event that the patient leaves the study without having been evaluated and presents with: Progression of disease or early death due to the disease, before evaluating response, was considered PROGRESSION OF DISEASE as the best response to treatment.

## GIDO1201 study

| Centre | Patient no. | 1st evaluation | 2nd evaluation | 3rd evaluation | 4th evaluation | 5th evaluation | 6th evaluation | Best response | Confirmed response | Number of cycles in initial treatment | Number of cycles in maintenance treatment | Total number of cycles | Reason end of treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 001 | 001 | Stable disease | Partial response | Partial response | Progression | | | PR | PR | 4 | 8 | 12 | Disease progression |
| 001 | 002 | Partial response | | | | | | PR | PR[1] | 5 | | 5 | Toxicity |
| 001 | 003 | Partial response | Partial response | | | | | PR | PR | 5 | | 5 | Adverse event unrelated to the study treatment |
| 001 | 004 | Partial response | Partial response | Partial response | Partial response | Progression | | PR | PR | 4 | 11 | 15 | Disease progression |
| 001 | 005 | Stable disease | | | | | | SD | SD | 4 | | 4 | Lost to follow-up |
| 001 | 006 | Stable disease | Partial response | Progression | | | | PR | SD | 6 | 2 | 8 | Disease progression |
| 002 | 001 | Stable disease | Stable disease | Stable disease | Progression | | | SD | SD | 6 | 8 | 14 | Disease progression |
| 002 | 002 | Partial response | Stable disease | Partial response | Progression | | | PR | SD | 6 | 6 | 12 | Disease progression |
| 002 | 003 | Partial response | | | | | | PR | SD | 2 | | 2 | Consent withdrawn by the patient |
| 002 | 004 | Partial response | | | | | | PR | SD | 4 | 18 | 22 | Disease progression |
| 002 | 005 | | | | | | | DP | DP | 3 | | 3 | Death |
| 004 | 001 | Progression | | | | | | DP | DP | 4 | | 4 | Disease progression |
| 005 | 001 | Partial response | Progression | | | | | PR | SD | 4 | 2 | 6 | Disease progression |
| 006 | 001 | Stable disease | Stable disease | Stable disease | Stable disease | | | SD | SD | 4 | 8 | 12 | Toxicity |
| 006 | 002 | Partial response | Partial response | Progression | | | | PR | PR | 4 | 5 | 9 | Disease progression |

## GIDO1201 study

| Centre | Patient no. | 1st evaluation | 2nd evaluation | 3rd evaluation | 4th evaluation | 5th evaluation | 6th evaluation | Best response | Confirmed response | Number of cycles in initial treatment | Number of cycles in maintenance treatment | Total number of cycles | Reason end of treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 006 | 003 | Partial response | Partial response | Progression | | | | PR | PR | 4 | 5 | 9 | Disease progression |
| 006 | 004 | Stable disease | Partial response | Partial response | Partial response | Partial response | Stable disease | PR | PR | 4 | 11 | 15 | Disease progression |
| 006 | 005 | Partial response | Partial response | Partial response | Partial response | Partial response | Partial response | PR | PR | 4 | 32 | 36 | Death |
| 006 | 006 | Partial response | Stable disease | Stable disease | | | | PR | SD | 4 | 5 | 9 | Toxicity |
| 006 | 007 | Stable disease | Partial response | Partial response | | | | PR | PR | 4 | 7 | 11 | Adverse event unrelated to the study treatment |
| 008 | 001 | Stable disease | Stable disease | | | | | SD | SD | 4 | 4 | 8 | Researcher's decision |
| 008 | 002 | Stable disease | Progression | | | | | SD | SD | 4 | 3 | 7 | Disease progression |
| 008 | 003 | Progression | | | | | | DP | DP | 3 | | 3 | Disease progression |
| 013 | 001 | Stable disease | Stable disease | Stable disease | Stable disease | | | SD | SD | 3 | | 3 | Toxicity |
| 013 | 002 | Stable disease | Stable disease | Stable disease | Stable disease | Progression | | SD | SD | 4 | 19 | 23 | Disease progression |
| 013 | 003 | Partial response | Progression | | | | | PR | SD | 5 | | 5 | Disease progression |

[1] Response confirmed in follow-up

### 7.1 Best response to treatment (RECIST)

| | | N | % | % valid |
|---|---|---|---|---|
| **Best response** | **PR** | 16 | 61.5 | 61.5 |
| | **SD** | 7 | 26.9 | 26.9 |
| | **DP** | 3 | 11.5 | 11.5 |
| | **Total** | 26 | 100.0 | 100.0 |

This was calculated based on the best response, the objective response rate (Complete Response + Partial Response) and the tumour control rate (Complete Response + Partial Response + Stable Disease).

| | N | % | 95% CI |
|---|---|---|---|
| **Rate of objective response** | 16 | 61.5 | 40.7-79.1 |
| **Rate of tumour control** | 23 | 88.5 | 68.7-97.0 |

Percentages calculated from the total number of patients analysed (N=26)

### 7.2 Best CONFIRMED response to treatment (RECIST)

| | | N | % | % valid |
|---|---|---|---|---|
| **Best confirmed response** | **PR** | 9 | 34.6 | 34.6 |
| | **SD** | 14 | 53.8 | 53.8 |
| | **DP** | 3 | 11.5 | 11.5 |
| | **Total** | 26 | 100.0 | 100.0 |

This was calculated based on the best confirmed response, the objective response rate (Complete Response + Partial Response) and the tumour control rate (Complete Response + Partial Response + Stable Disease).

| | N | % | 95% CI |
|---|---|---|---|
| **Rate of confirmed objective response** | 9 | 34.6 | 17.9 - 55.6 |
| **Rate of confirmed tumour control** | 23 | 88.5 | 68.7 - 97.0 |

Percentages calculated from the total number of patients analysed (N=26)

# 8 DEATHS

| | | N | % | % valid |
|---|---|---|---|---|
| Deaths | Alive | 2 | 7.7 | 7.7 |
| | Deceased | 24 | 92.3 | 92.3 |
| | Total | 26 | 100.0 | 100.0 |

| | | N | % valid |
|---|---|---|---|
| Cause of death | Disease progression | 23 | 95.8 |
| | Sepsis | 1 | 4.2 |
| | Total | 24 | 100.0 |

# 9 PATIENT DISCONTINUATION IN STUDY

## 9.1 Reasons for discontinuation

| | | N | % | % valid |
|---|---|---|---|---|
| Reason for discontinuation | Toxicity | 4 | 15.4 | 15.4 |
| | Adverse event unrelated to the study treatment | 2 | 7.7 | 7.7 |
| | Lost to follow-up | 1 | 3.8 | 3.8 |
| | Consent withdrawn by the patient | 1 | 3.8 | 3.8 |
| | Researcher's decision | 1 | 3.8 | 3.8 |
| | Disease progression | 15 | 57.7 | 57.7 |
| | Death | 2 | 7.7 | 7.7 |
| Total | | 26 | 100.0 | 100.0 |

For the 4 cases that stopped treatment due to toxicity, a list will be presented with the toxicity experienced and its relationship with the drugs under study.

| Centre | Pac | Toxicity | Relationship with Bevacizumab | Relationship with Carboplatin | Relationship with Paclitaxel |
|---|---|---|---|---|---|
| 001 | 002 | Cerebral intraparenchimal haemorrhage | Yes | No | No |
| 006 | 001 | Rectal ulcer | Yes | No | No |
| 006 | 006 | Ischaemic colitis | Yes | No | No |
| 013 | 001 | Diarrhoea | Yes | Yes | Yes |

# 10 SURVIVAL

## 10.1 Length of follow-up

Follow-up time is defined as the time elapsed between the start of treatment and the date of the last available follow-up.

| | Mean | SD | Median | Minimum | Maximum | Q1 | Q3 | N |
|---|---|---|---|---|---|---|---|---|
| **Time (months)** | 12.5 | 7.5 | 11.5 | 2.0 | 25.2 | 6.5 | 18.8 | 26 |

### 10.2 Progression-free survival

Progression-free survival was defined as the time from the start of treatment until the patient progresses or dies from any cause.

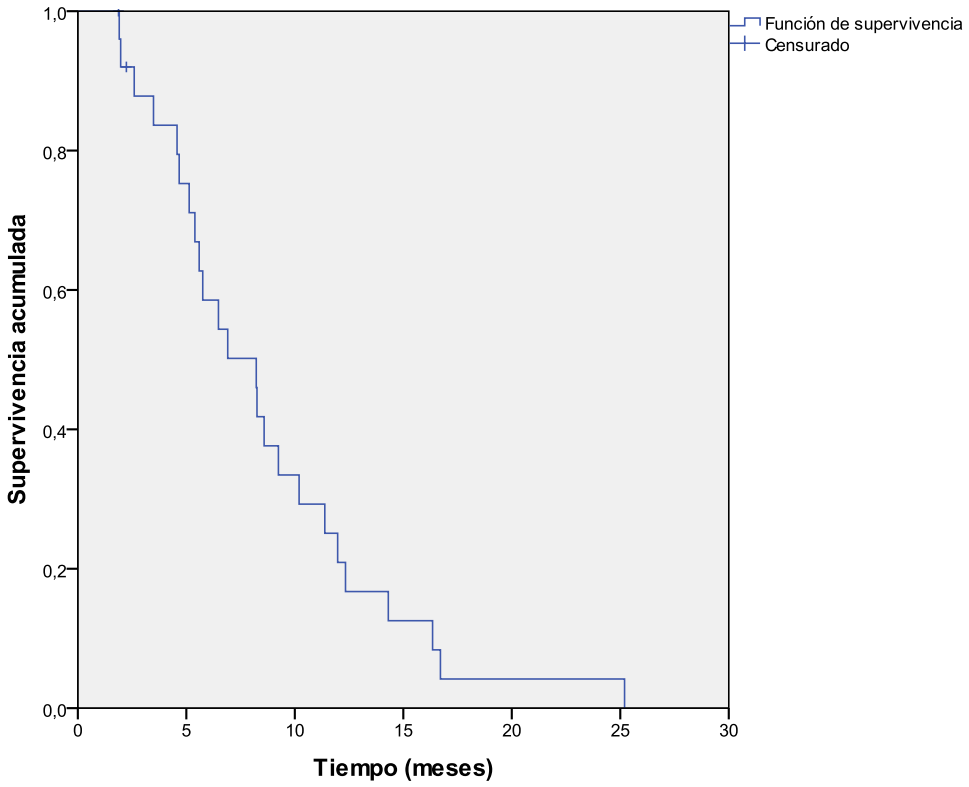
The cases in which the patients have not continued with the study treatment and have initiated a new anti-tumour treatment were considered censored cases at the time of starting the new treatment.

Patients who did not manifest disease progression, did not die, or receive other anti-tumour treatment have been censored on the date of the last available CT scan without evidence of progression.

| Total No. | No. of events | Censored | |
|---|---|---|---|
| | | No. | Percent |
| 26 | 24 | 2 | 7.7 |

| Mean | | | | Median | | | |
|---|---|---|---|---|---|---|---|
| Estimate | Standard error | 95% confidence interval | | Estimate | Standard error | 95% confidence interval | |
| | | Inferior limit | Superior limit | | | Inferior limit | Superior limit |
| 8.659 | 1.123 | 6.458 | 10.861 | 8.224 | 1.521 | 5.243 | 11.204 |

## GIDO1201 study

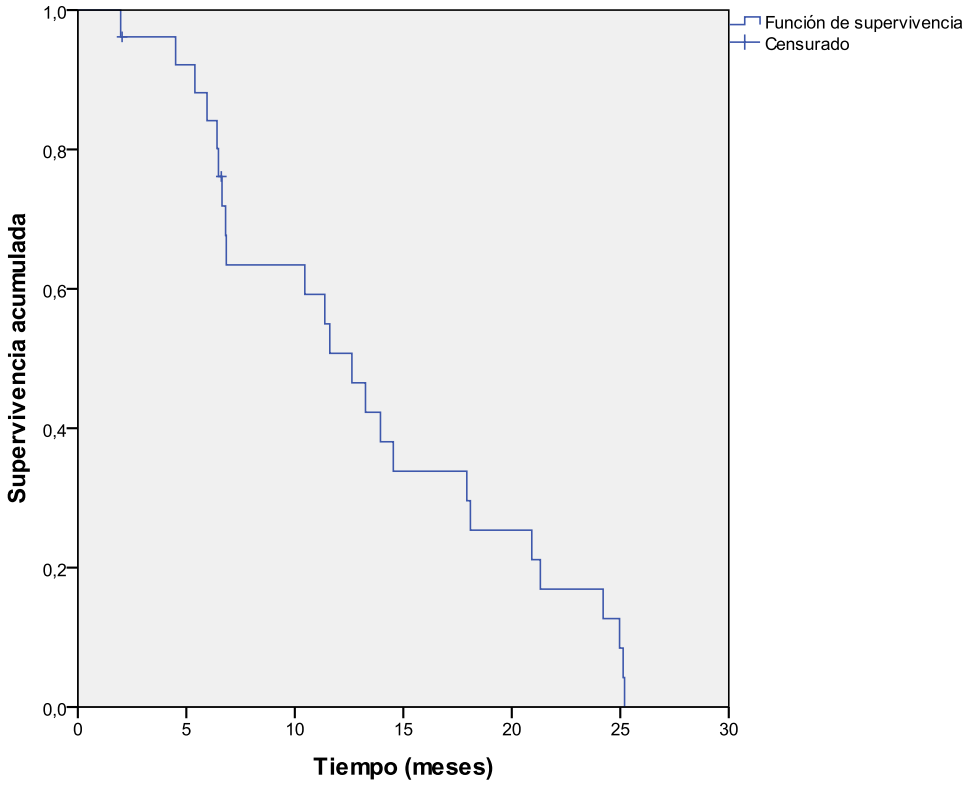


### 10.3 Global Survival

Global survival was defined as the time elapsed from the start of treatment until the patient dies. In the remaining patients, the last available follow-up was taken as the last control.

| Total No. | No. of events | Censored | |
|---|---|---|---|
| | | No. | Percent |
| 26 | 24 | 2 | 7.7 |

| Mean | | | | Median | | | |
|---|---|---|---|---|---|---|---|
| Estimate | Standard error | 95% confidence interval | | Estimate | Standard error | 95% confidence interval | |
| | | Inferior limit | Superior limit | | | Inferior limit | Superior limit |
| 13.318 | 1.500 | 10.377 | 16.259 | 12.632 | 1.682 | 9.335 | 15.928 |



# 11 ADVERSE EVENTS

## 11.1 Toxicity

All adverse events associated in a "related / suspected" way with any of the drugs under treatment were considered as toxicities.

The toxicity analysis is provided per patient. To obtain the toxicity per patient, the maximum grade was calculated for each of the toxicities collected during all the treatment cycles of each patient.

| | N | % | 95% CI |
|---|---|---|---|
| **Patients with at least one toxicity** | 25 | 96.2 | 78.4 - 99.8 |
| **Patients with at least one G3/4 toxicity** | 13 | 50.0 | 30.4 - 69.6 |
| **Patients with at least one haematological G3/4 toxicity** | 5 | 19.2 | 7.3 - 40.0 |
| **Patients with at least one non-haematological G3/4 toxicity** | 10 | 38.5 | 20.9 - 59.3 |
| **Patients with at least one G3/4 neutropaenic toxicity (Febrile neutropaenia)** | 1 | 3.8 | 0.2 - 21.6 |

Percentages calculated from the total number of patients analysed (N=26)

| | Grade 1 | | Grade 2 | | Grade 3 | | Total | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| **Alopecia** | 2 | 7.7 | 10 | 38.5 | 0 | 0.0 | 12 | 46.2 |
| **Anaemia** | 1 | 3.8 | 0 | 0.0 | 4 | 15.4 | 5 | 19.2 |
| **Anorexia** | 1 | 3.8 | 2 | 7.7 | 0 | 0.0 | 3 | 11.5 |
| **Asthenia** | 8 | 30.8 | 7 | 26.9 | 2 | 7.7 | 17 | 65.4 |
| **Lethargy** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Ischaemic colitis** | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 | 1 | 3.8 |
| **Deterioration of renal function** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Diarrhoea** | 3 | 11.5 | 2 | 7.7 | 2 | 7.7 | 7 | 26.9 |
| **Dysphonia** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Dysgeusia** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Dyspnoea** | 2 | 7.7 | 0 | 0.0 | 0 | 0.0 | 2 | 7.7 |
| **Abdominal pain** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Leg pain** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Oedema** | 2 | 7.7 | 1 | 3.8 | 0 | 0.0 | 3 | 11.5 |
| **Epistaxis** | 4 | 15.4 | 2 | 7.7 | 1 | 3.8 | 7 | 26.9 |
| **Constipation** | 3 | 11.5 | 1 | 3.8 | 0 | 0.0 | 4 | 15.4 |

| | Grade 1 | | Grade 2 | | Grade 3 | | Total | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| **Fever** | 2 | 7.7 | 0 | 0.0 | 0 | 0.0 | 2 | 7.7 |
| **Haematuria** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Haemoptysis** | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| **Cerebral intraparenchimal haemorrhage** | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 | 1 | 3.8 |
| **Hypertension** | 0 | 0.0 | 1 | 3.8 | 4 | 15.4 | 5 | 19.2 |
| **Hypothyroidism** | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| **Oral infection** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Dizziness** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Mucositis** | 2 | 7.7 | 2 | 7.7 | 0 | 0.0 | 4 | 15.4 |
| **Thrush** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Nausea** | 2 | 7.7 | 1 | 3.8 | 0 | 0.0 | 3 | 11.5 |
| **Neurotoxicity** | 6 | 23.1 | 5 | 19.2 | 0 | 0.0 | 11 | 42.3 |
| **Neutropaenia** | 0 | 0.0 | 2 | 7.7 | 0 | 0.0 | 2 | 7.7 |
| **Febrile neutropaenia** | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 | 1 | 3.8 |
| **Odynophagia** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Paresthaesias** | 2 | 7.7 | 0 | 0.0 | 0 | 0.0 | 2 | 7.7 |
| **Dry skin** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Polyarthralgia** | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| **Polyneuropathy** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Proteinuria** | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| **Infusion reaction** | 0 | 0.0 | 2 | 7.7 | 0 | 0.0 | 2 | 7.7 |
| **Nasal cavity bleed** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Cutaneous dryness** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Intestinal sub-occlusion secondary to ischaemic colitis** | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 | 1 | 3.8 |
| **Tremor** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Cough** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Pulmonary thromboembolism** | 1 | 3.8 | 1 | 3.8 | 0 | 0.0 | 2 | 7.7 |
| **Rectal ulcer** | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| **Vomiting** | 3 | 11.5 | 1 | 3.8 | 2 | 7.7 | 6 | 23.1 |

Percentages calculated from the total number of patients analysed (N=26)

### 11.2 Adverse events

All adverse events presented by patients throughout the study have been included in this analysis. To obtain the adverse events per patient, the maximum of the grades was calculated for each of the adverse events collected throughout all the treatment cycles of each patient.

| | N | % |
|---|---|---|
| **Patients with at least one adverse event** | 26 | 100.0 |

Percentages calculated from the total number of patients analysed (N=26)

| | Grade 1 | | Grade 2 | | Grade 3 | | Total | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| **Psychomotor agitation** | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| **Alopecia** | 2 | 7.7 | 10 | 38.5 | 0 | 0.0 | 12 | 46.2 |
| **Amnesia** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Anaemia** | 3 | 11.5 | 3 | 11.5 | 4 | 15.4 | 10 | 38.5 |
| **Anorexia** | 8 | 30.8 | 2 | 7.7 | 0 | 0.0 | 10 | 38.5 |
| **Anxiety** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Anuria** | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| **Asthenia** | 9 | 34.6 | 7 | 26.9 | 4 | 15.4 | 20 | 76.9 |
| **Pulmonary atelectasis** | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| **Oral candidiasis** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Lethargy** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Nose cold** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Headache** | 2 | 7.7 | 0 | 0.0 | 0 | 0.0 | 2 | 7.7 |
| **Neck pain** | 2 | 7.7 | 0 | 0.0 | 0 | 0.0 | 2 | 7.7 |
| **Cholelithiasis** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Ischaemic colitis** | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 | 1 | 3.8 |
| **Conjunctivitis** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Coxalgia** | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| **Weakness** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Malaise** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Disorientation** | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| **Deterioration of overall condition** | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| **Deterioration of renal function** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Deterioration of level of consciousness** | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 | 1 | 3.8 |
| **Diarrhoea** | 5 | 19.2 | 2 | 7.7 | 2 | 7.7 | 9 | 34.6 |
| **Dyplopia** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |

| | Grade 1 | | Grade 2 | | Grade 3 | | Total | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| Dysarthria | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Dysphonia | 4 | 15.4 | 0 | 0.0 | 0 | 0.0 | 4 | 15.4 |
| Dysgeusia | 4 | 15.4 | 0 | 0.0 | 0 | 0.0 | 4 | 15.4 |
| Dyspnoea | 6 | 23.1 | 0 | 0.0 | 0 | 0.0 | 6 | 23.1 |
| Acute respiratory distress | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| Abdominal pain | 2 | 7.7 | 1 | 3.8 | 0 | 0.0 | 3 | 11.5 |
| Axilla pain | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 | 1 | 3.8 |
| Arm pain | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| Flank pain | 0 | 0.0 | 2 | 7.7 | 0 | 0.0 | 2 | 7.7 |
| Back pain | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Hemithorax pain | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| Lumbar pain | 4 | 15.4 | 2 | 7.7 | 0 | 0.0 | 6 | 23.1 |
| Leg pain | 3 | 11.5 | 0 | 0.0 | 0 | 0.0 | 3 | 11.5 |
| Bone pain | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| Knee pain | 0 | 0.0 | 2 | 7.7 | 0 | 0.0 | 2 | 7.7 |
| Ankle pain | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| Oedema | 5 | 19.2 | 2 | 7.7 | 0 | 0.0 | 7 | 26.9 |
| Epigastralgia | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Epistaxis | 4 | 15.4 | 2 | 7.7 | 1 | 3.8 | 7 | 26.9 |
| Constipation | 6 | 23.1 | 1 | 3.8 | 0 | 0.0 | 7 | 26.9 |
| Acute pharyngitis | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| Fatigue | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Low grade fever | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Fever | 3 | 11.5 | 2 | 7.7 | 0 | 0.0 | 5 | 19.2 |
| Rectal fistula | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| Photopsia | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Femur fracture | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 | 1 | 3.8 |
| Flu | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Haematochezia | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Haematuria | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Haemoptysis | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| Cerebral intraparenchimal haemorrhage | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 | 1 | 3.8 |
| Haemorrhoids | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Herpes zoster | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Periorbital swelling | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Hyperglycaemia | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| Hypertension | 0 | 0.0 | 1 | 3.8 | 4 | 15.4 | 5 | 19.2 |
| Hypotension | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |

| | Grade 1 | | Grade 2 | | Grade 3 | | Total | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| Hypocalcaemia | 2 | 7.7 | 0 | 0.0 | 0 | 0.0 | 2 | 7.7 |
| Hyponatraemia | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 | 1 | 3.8 |
| Hypothyroidism | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| Cutaneous infection | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Urinary tract infection | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 | 2 | 7.7 |
| Oral infection | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Respiratory infection | 0 | 0.0 | 0 | 0.0 | 2 | 7.7 | 2 | 7.7 |
| Insomnia | 2 | 7.7 | 1 | 3.8 | 0 | 0.0 | 3 | 11.5 |
| Dizziness | 3 | 11.5 | 0 | 0.0 | 0 | 0.0 | 3 | 11.5 |
| Postural dizziness | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Mucosity | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Mucositis | 3 | 11.5 | 2 | 7.7 | 0 | 0.0 | 5 | 19.2 |
| Thrush | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Nausea | 2 | 7.7 | 2 | 7.7 | 0 | 0.0 | 4 | 15.4 |
| Agitation | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Pneumothorax | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| Neurotoxicity | 6 | 23.1 | 5 | 19.2 | 0 | 0.0 | 11 | 42.3 |
| Neutropaenia | 0 | 0.0 | 2 | 7.7 | 0 | 0.0 | 2 | 7.7 |
| Febrile neutropaenia | 0 | 0.0 | 0 | 0.0 | 2 | 7.7 | 2 | 7.7 |
| Odynophagia | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Abduction paralysis | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Paresthaesias | 2 | 7.7 | 0 | 0.0 | 0 | 0.0 | 2 | 7.7 |
| Weight loss | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Dry skin | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Acute pyelonephritis | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Urinary frequency | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Polyarthralgia | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| Polyneuropathy | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Proctitis | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Proteinuria | 1 | 3.8 | 1 | 3.8 | 0 | 0.0 | 2 | 7.7 |
| Disc protrusion | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| Pruritus | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Palpebral ptosis | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Rash | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Infusion reaction | 0 | 0.0 | 2 | 7.7 | 0 | 0.0 | 2 | 7.7 |
| Cold | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Fluid retention | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| Urinary retention | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| Rhinorrhoea | 2 | 7.7 | 0 | 0.0 | 0 | 0.0 | 2 | 7.7 |

| | Grade 1 | | Grade 2 | | Grade 3 | | Total | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| **Nasal cavity bleed** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Sarcopaenia** | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| **Cutaneous dryness** | 2 | 7.7 | 0 | 0.0 | 0 | 0.0 | 2 | 7.7 |
| **Respiratory sepsis** | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 | 1 | 3.8 |
| **Voiding dysfunction** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Toxic syndrome** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Intestinal sub-occlusion secondary to ischaemic colitis** | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 | 1 | 3.8 |
| **Tremor** | 2 | 7.7 | 0 | 0.0 | 0 | 0.0 | 2 | 7.7 |
| **Cough** | 7 | 26.9 | 0 | 0.0 | 0 | 0.0 | 7 | 26.9 |
| **Conduct disorder** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Reactive depression** | 1 | 3.8 | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 |
| **Pulmonary thromboembolism** | 1 | 3.8 | 1 | 3.8 | 0 | 0.0 | 2 | 7.7 |
| **Rectal ulcer** | 0 | 0.0 | 1 | 3.8 | 0 | 0.0 | 1 | 3.8 |
| **Vomiting** | 3 | 11.5 | 1 | 3.8 | 2 | 7.7 | 6 | 23.1 |

Percentages calculated from the total number of patients analysed (N=26)

### 11.3 Serious adverse events

The number of patients with at least one serious adverse event is reported, along with a list of the different serious adverse events experienced by the patients.

14 (53.8%) patients presented with at least one serious adverse event (a total of 19 events).

| Centre | Patient no. | Adverse event | Start date | End date | Intensity | Associated with Bevacizumab | Associated with Carboplatin | Associated with Paclitaxel | Temporary adjustment/interruption of the study medication dose | Permanent discontinuation of the study drug due to this AE | Administration of concomitant medication | Administration of non-pharmacologic therapy | Hospitalisation/prolongation of hospitalisation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 001 | 001 | Respiratory infection | 17-Oct-2013 | 06-Nov-2013 | Grade 3 | Unrelated / Not suspected | Unrelated / Not suspected | Unrelated / Not suspected | | | Yes | | Yes |
| 001 | 002 | Cerebral intraparenchimal haemorrhage | 26-mar-2014 | 01-Apr-2014 | Grade 3 | Related / Suspected | Unrelated / Not suspected | Unrelated / Not suspected | | Yes | Yes | | Yes |
| 001 | 003 | Febrile neutropaenia | 08-Nov-2014 | 15-Nov-2014 | Grade 3 | Related / Suspected | Related / Suspected | Related / Suspected | | | Yes | | . |
| 002 | 003 | Fever | 28-Aug-2014 | 22-Sept-2014 | Grade 2 | Unrelated / Not suspected | Unrelated / Not suspected | Unrelated / Not suspected | | | | | Yes |

## GIDO1201 study

| Centre | Patient no. | Adverse event | Start date | End date | Intensity | Associated with Bevacizumab | Associated with Carboplatin | Associated with Paclitaxel | Temporary adjustment/interruption of the study medication dose | Permanent discontinuation of the study drug due to this AE | Administration of concomitant medication | Administration of non-pharmacologic therapy | Hospitalisation/prolongation of hospitalisation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 002 | 004 | Fever | 18-may-2015 | 20-may-2015 | Grade 2 | Unrelated / Not suspected | Unrelated / Not suspected | Unrelated / Not suspected | | | Yes | | |
| 002 | 005 | Acute respiratory distress | 11-mar-2015 | 11-mar-2015 | Grade 2 | Unrelated / Not suspected | Unrelated / Not suspected | Unrelated / Not suspected | Yes | | Yes | | |
| 004 | 001 | Diarrhoea | 01-July-2014 | 04-July-2014 | Grade 3 | Unrelated / Not suspected | Unrelated / Not suspected | Related / Suspected | | | Yes | Yes | Yes |
| 006 | 003 | Urinary tract infection | 24-mar-2014 | 27-mar-2014 | Grade 3 | Unrelated / Not suspected | Unrelated / Not suspected | Unrelated / Not suspected | | | Yes | | Yes |
| 006 | 006 | Ischaemic colitis | 22-Nov-2015 | 27-Nov-2015 | Grade 3 | Related / Suspected | Unrelated / Not suspected | Unrelated / Not suspected | | | Yes | | Yes |
| 006 | 006 | Intestinal sub-occlusion secondary to ischaemic colitis | 04-Dec-2015 | 16-Dec-2015 | Grade 3 | Related / Suspected | Unrelated / Not suspected | Unrelated / Not suspected | | Yes | Yes | | Yes |

## GIDO1201 study

| Centre | Patient no. | Adverse event | Start date | End date | Intensity | Associated with Bevacizumab | Associated with Carboplatin | Associated with Paclitaxel | Temporary adjustment/interruption of the study medication dose | Permanent discontinuation of the study drug due to this AE | Administration of concomitant medication | Administration of non-pharmacologic therapy | Hospitalisation/prolongation of hospitalisation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 008 | 001 | Respiratory infection | 22-mar-2014 | 26-mar-2014 | Grade 2 | Unrelated / Not suspected | Unrelated / Not suspected | Unrelated / Not suspected | Yes | | Yes | | Yes |
| 008 | 001 | Respiratory infection | 09-Apr-2014 | 19-Apr-2014 | Grade 3 | Unrelated / Not suspected | Unrelated / Not suspected | Unrelated / Not suspected | | | Yes | | Yes |
| 008 | 001 | Vomiting | 26-Oct-2013 | 30-Oct-2013 | Grade 3 | Unrelated / Not suspected | Related / Suspected | Related / Suspected | | | Yes | | Yes |
| 008 | 002 | Deterioration of level of consciousness | 05-may-2014 | 07-may-2014 | Grade 3 | Unrelated / Not suspected | Unrelated / Not suspected | Unrelated / Not suspected | | | Yes | | Yes |
| 008 | 003 | Epistaxis | 18-Nov-2014 | 24-Nov-2014 | Grade 3 | Related / Suspected | Unrelated / Not suspected | Unrelated / Not suspected | | | Yes | Yes | Yes |
| 008 | 003 | Femur fracture | 05-sept-2014 | 16-sept-2014 | Grade 3 | Unrelated / Not suspected | Unrelated / Not suspected | Unrelated / Not suspected | Yes | | Yes | | Yes |
| 013 | 001 | Diarrhoea | 20-may-2015 | 25-may-2015 | Grade 3 | Related / Suspected | Related / Suspected | Related / Suspected | | Yes | Yes | | Yes |

## GIDO1201 study

| Centre | Patient no. | Adverse event | Start date | End date | Intensity | Associated with Bevacizumab | Associated with Carboplatin | Associated with Paclitaxel | Temporary adjustment/interruption of the study medication dose | Permanent discontinuation of the study drug due to this AE | Administration of concomitant medication | Administration of non-pharmacologic therapy | Hospitalisation/prolongation of hospitalisation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 013 | 001 | Vomiting | 25-mar-2015 | 27-mar-2015 | Grade 2 | Related / Suspected | Related / Suspected | Related / Suspected | | | Yes | | Yes |
| 013 | 003 | Respiratory sepsis | 24-Dec-2015 | 28-Dec-2015 | Grade 3 | Unrelated / Not suspected | Unrelated / Not suspected | Unrelated / Not suspected | | | | | |

# 12 BASELINE GERIATRIC EVALUATION

## 12.1 Function: ECOG

| Baseline visit | | N | % | % valid |
|---|---|---|---|---|
| Baseline ECOG | 0 | 5 | 19.2 | 19.2 |
| | 1 | 20 | 76.9 | 76.9 |
| | Not available | 1 | 3.8 | 3.8 |
| | Total | 26 | 100.0 | 100.0 |

## 12.2 Function: KATZ Index

The total score for this index was calculated as the sum of all the basic activities that the patient was able to do.

| Baseline visit | | N | % | % valid |
|---|---|---|---|---|
| Total score KATZ index | 5 | 2 | 7.7 | 7.7 |
| | 6 | 24 | 92.3 | 92.3 |
| | Total | 26 | 100.0 | 100.0 |

## 12.3 Function: Simplified Lawton scale

The total score for this scale was calculated as the sum of all the Lawton instrumental activities that the patient was able to do.

| Baseline visit | | N | % | % valid |
|---|---|---|---|---|
| Total Lawton scale score | 3 | 1 | 3.8 | 3.8 |
| | 4 | 2 | 7.7 | 7.7 |
| | 5 | 8 | 30.8 | 30.8 |
| | 6 | 15 | 57.7 | 57.7 |
| | Total | 26 | 100.0 | 100.0 |

### 12.4 Comorbidity: Charlson Comorbidity Index

The total score for this scale was calculated according to the allocated scores in the following table:

| Condition | X | Score assigned |
|---|---|---|
| Myocardial infarction | | 1 |
| Congestive heart failure | | 1 |
| Peripheral vascular disease | | 1 |
| Cerebrovascular disease | | 1 |
| Dementia | | 1 |
| Chronic lung disease | | 1 |
| Rheumatological disease | | 1 |
| Gastroduodenal ulcer | | 1 |
| Mild liver disease | | 1 |
| Diabetes without complications | | 1 |
| Hemiplegia | | 2 |
| Moderate or severe renal disease | | 2 |
| Diabetes with complications | | 2 |
| Neoplasia | | 2 |
| Leukaemia | | 2 |
| Malignant lymphoma | | 2 |
| Moderate or severe liver disease | | 3 |
| Metastatic solid tumour | | 6 |
| HIV+ | | 6 |
| **Total score:** | | |

| Baseline visit | | N | % |
|---|---|---|---|
| Pathology: Charlson Index | Peripheral vascular disease | 8 | 30.8 |
| | Neoplasia | 8 | 30.8 |
| | Chronic lung disease | 6 | 23.1 |
| | Congestive heart failure | 3 | 11.5 |
| | Diabetes without complications | 3 | 11.5 |
| | Myocardial infarction | 2 | 7.7 |
| | Moderate or severe renal disease | 2 | 7.7 |
| | Rheumatological disease | 1 | 3.8 |
| | Cerebrovascular disease | 0 | 0.0 |
| | Dementia | 0 | 0.0 |
| | Gastroduodenal ulcer | 0 | 0.0 |
| | Mild liver disease | 0 | 0.0 |
| | Hemiplegia | 0 | 0.0 |
| | Diabetes with complications | 0 | 0.0 |
| | Leukaemia | 0 | 0.0 |
| | Malignant lymphoma | 0 | 0.0 |
| | Liver disease (moderate or severe) | 0 | 0.0 |
| | Metastatic solid tumour | 0 | 0.0 |
| | HIV+ | 0 | 0.0 |

Percentages calculated from the total number of patients analysed (N=26)

| Baseline visit | | N | % | % valid |
|---|---|---|---|---|
| Charlson Index | 0 | 5 | 19.2 | 19.2 |
| | 1 | 6 | 23.1 | 23.1 |
| | 2 | 8 | 30.8 | 30.8 |
| | 3 | 7 | 26.9 | 26.9 |
| | Total | 26 | 100.0 | 100.0 |

## 12.1 Comorbidity: Comorbidity index

The total score for this scale was calculated according to the allocated scores in the following table:

| Condition | X | Score assigned |
|---|---|---|
| Tobacco use | | 7 |
| Diabetes mellitus | | 5 |
| Renal failure | | 4 |
| COPD | | 1 |
| Neoplasia (non-pulmonary neoplasia) | | 1 |
| Cardiovascular | | 1 |
| Alcoholism | | 1 |
| **TOTAL:** | | |

| | Baseline visit | N | % |
|---|---|---|---|
| **Co morbidities:** | **Tobacco use** | 19 | 73.1 |
| | **Cardiovascular** | 13 | 50.0 |
| | **Neoplasia** | 8 | 30.8 |
| | **COPD** | 6 | 23.1 |
| | **Diabetes mellitus** | 4 | 15.4 |
| | **Renal failure** | 2 | 7.7 |
| | **Alcoholism** | 0 | 0.0 |

Percentages calculated from the total number of patients analysed (N=26)

| Baseline visit | Mean | SD | Median | Minimum | Maximum | Q1 | Q3 | N |
|---|---|---|---|---|---|---|---|---|
| **Comorbidity index** | 7.5 | 4.5 | 8.0 | 0.0 | 18.0 | 4.5 | 9.0 | 25[1] |

[1]In one patient the application of this questionnaire was indicated to be “not applicable”.

### 12.2 Comorbidity: Medication-Polypharmacy

| Baseline visit | Mean | SD | Median | Minimum | Maximum | Q1 | Q3 | N |
|---|---|---|---|---|---|---|---|---|
| **Number of medications** | 6.1 | 3.6 | 6.0 | 0.0 | 14.0 | 3.0 | 8.0 | 25[1] |

[1]One patient did not complete this questionnaire.

Below are presented the correlation coefficients between the Charlson Index and the number of medications (Polypharmacy) and between the comorbidity index and the number of medications (Polypharmacy).

| *Baseline visit* | Charlson Index | | |
|---|---|---|---|
| | N | Correlation coefficient* | p value |
| **No. of medications** | 25 | 0.406 | **0.044** |

*Spearman

| *Baseline visit* | Comorbidity index | | |
|---|---|---|---|
| | N | Correlation coefficient* | p value |
| **No. of medications** | 24 | 0.355 | 0.089 |

*Spearman

### 12.3 Cognitive level: Dementia FOLSTEIN Mini-Mental

The total score for this scale was calculated according to the maximum score in the following table:

A positive point (i.e. 1) is assigned if the patient is able to perform the activity, with a maximum of 35 points, which means that he is able to answer all the questions.

| | **0 points : Error<br>1 point :<br>Correct/ Able to perform activity** | **Score Maximum** |
|---|---|---|
| **1. Orientation:** | | |
| Day | | **5** |
| Date | | |
| Month | | |
| Season | | |
| Year | | |
| 2. **Where are we?** | | |
| Hospital | | **5** |
| Floor | | |
| City | | |
| Province | | |
| Country | | |
| 3. **Concentration** | | |
| Repeat: Peseta-horse-apple<br>Number of tries: _____ | | **3** |
| 4. **Attention and calculation** | | |
| If you have 30cm and you give them away in groups of 3, how many are left? | | **5** |
| Repeat 5-9-2 (until learned) Now backwards | | **3** |
| 5. **Memory:** | | |
| Repeat the three words from before | | **3** |
| 6. **Language and construction:** | | |
| What is this? (Show a pen) | | **2** |
| Repeat: “In a wheat field were 5 dogs” | | **1** |
| Pear and apples are fruit<br>What is red and green? Dog and cat? | | **2** |
| Action: Fold a paper in half and place it on the floor | | **3** |
| Do what it says: close your eyes | | **1** |
| Write a sentence:_____ | | **1** |
| DRAWING Copy the picture: | | **1** |
| **TOTAL:** | | |

| Baseline visit | Mean | SD | Median | Minimum | Maximum | Q1 | Q3 | N |
|---|---|---|---|---|---|---|---|---|
| **Dementia: Folstein Mini-Mental** | 31.0 | 4.1 | 31.5 | 22.0 | 35.0 | 28.0 | 35.0 | 26 |

### 12.4 Emotional level: Geriatric depression scale

The total score for this scale was calculated as the sum of all the positive responses (yes=1)

| Baseline visit | Mean | SD | Median | Minimum | Maximum | Q1 | Q3 | N |
|---|---|---|---|---|---|---|---|---|
| **Total score geriatric depression scale** | 1.1 | 1.3 | 1.0 | 0.0 | 5.0 | 0.0 | 2.0 | 26 |

### 12.5 Nutritional level: BMI

| Baseline visit | Mean | SD | Median | Minimum | Maximum | Q1 | Q3 | N |
|---|---|---|---|---|---|---|---|---|
| **BMI** | 25.9 | 3.6 | 26.5 | 18.0 | 34.3 | 23.5 | 28.5 | 19 |

### 12.6 Nutritional level: Unintentional weight loss (%)

| Baseline visit | Mean | SD | Median | Minimum | Maximum | Q1 | Q3 | N |
|---|---|---|---|---|---|---|---|---|
| **Percentage of unintentional weight loss** | 2.0 | 4.3 | 0.0 | 0.0 | 17.0 | 0.0 | 0.5 | 26 |

### 12.7 Nutritional level: Time

| Baseline visit | Mean | SD | Median | Minimum | Maximum | Q1 | Q3 | N |
|---|---|---|---|---|---|---|---|---|
| **Time (months)** | 1.0 | 2.1 | 0.0 | 0.0 | 6.0 | 0.0 | 0.8 | 26 |

### 12.8 Nutritional level: Albumin

| Baseline visit | Mean | SD | Median | Minimum | Maximum | Q1 | Q3 | N |
|---|---|---|---|---|---|---|---|---|
| **Albumin** | 3.5 | 1.2 | 3.9 | 0.0 | 4.8 | 3.1 | 4.3 | 21 |

### 12.9 Geriatric syndromes

2 patients (7.7%) indicated that they had a syndrome.

| | | N | % |
|---|---|---|---|
| **Geriatric syndromes** | **Depression** | 1 | 3.8 |
| | **Falls** | 1 | 3.8 |
| | **Dementia** | 0 | 0.0 |
| | **Delirium** | 0 | 0.0 |
| | **Abandonment, abuse** | 0 | 0.0 |
| | **Spontaneous fracture** | 0 | 0.0 |

Percentages calculated from the total number of patients analysed (N=26)

### 12.10 Balducci Frailty Criteria

| | | N | % |
|---|---|---|---|
| **Balducci Frailty Criteria** | **Dependent in 1 or more ADLs** | 1 | 3.8 |
| | **>3 co morbidities** | 1 | 3.8 |
| | **≥85 years** | 0 | 0.0 |
| | **> 1 geriatric syndrome** | 0 | 0.0 |

Percentages calculated from the total number of patients analysed (N=26)

# 13 ANALYSIS OF THE OBJECTIVES

## 13.1 Principal objective

- **To evaluate the toxicity of treatment with bevacizumab, carboplatin and paclitaxel in elderly patients (≥ 70 years) with non-small-cell lung cancer that meet the inclusion criteria for bevacizumab and have been selected based on a geriatric evaluation.**

To answer this objective the number of patients is described that present with toxicity, neutropaenia 3/4.

One patient presented with toxicity of febrile neutropaenia grade 3 (3.8% of total patients).

**Therefore the rate of toxicity of neutropaenia grade 3/4 was 3.8% (95%CI: 0.2 - 21.6).**

## 13.2 Secondary objectives

The secondary objectives were:

- **Determine the predictive factors of toxicity in an elderly population (>70 years).**

To respond to this objective, a logistic regression analysis was proposed to evaluate the predictors of toxicity in the elderly population. The **presence of grade 3/4 neutrophil toxicity** was the dependent variable and the **geriatric evaluation data** as independent variables.

Bivariate analyses were performed using logistic regression, taking as a dependent variable **the presence of grade 3/4 neutropaenia** (S / N) and the independent variables were each of the geriatric approximation factors detailed below:

- ECOG screening visit (reference category ECOG 0).
- Total KATZ index score in screening visit (continuous variable).
- Total Simplified Lawton scale score in screening visit (continuous variable).
- Total Charlson Comorbidity Index score in screening visit (continuous variable).
- Comorbidity index score in screening visit (continuous variable).
- Number of medications in screening visit (continuous variable).
- Total FOLSTEIN score in screening visit (continuous variable).
- Total geriatric depression scale score in screening visit (continuous variable).
- BMI in screening visit (continuous variable).

- Unintentional weight loss in screening visit (continuous variable).
- Time screening visit (continuous variable).
- Albumin in screening visit (continuous variable).
- Geriatric syndromes in screening visit: Dementia (S/N).
- Geriatric syndromes in screening visit: Delirium (S/N).
- Geriatric syndromes in screening visit: Depression (S/N).
- Geriatric syndromes in screening visit: Falls (S/N).
- Geriatric syndromes in screening visit: Abandonment, abuse (S/N).
- Geriatric syndromes in screening visit: Spontaneous fracture (S/N).
- Balducci Frailty Criteria in screening visit: ≥85 years (S/N).
- Balducci Frailty Criteria in screening visit: Dependent in 1 or more ADLs (S/N).
- Balducci Frailty Criteria in screening visit: > 3 Co morbidities (S/N).
- Balducci Frailty Criteria in screening visit: > 1 geriatric syndrome (S/N).

Finally, it was proposed to perform a multivariate logistic regression analysis, taking as a dependent variable the **presence of grade 3/4 neutropaenic toxicity** (S/N) and as independent variables each of the variables that were significant (<0.20) in the previous analysis.

**These analyses could not be performed due to the results, as only one of the patients presented with grade 3/4 neutropaenic toxicity.**

- **Determine the rate of objective response.**

This objective has been analysed via the descriptive analysis of the variables as detailed in sections 7.1 and 7.2 of this document.

- **Determine the rate of disease control.**

This objective has been analysed via the descriptive analysis of the variables as detailed in sections 7.1 and 7.2 of this document.

- **Determine progression-free survival.**

This objective has been analysed via the survival analysis as detailed in section 10.2 of this document.

- **Determine global survival.**

This objective has been analysed via the survival analysis as detailed in section 10.3 of this document.

- **Determine the safety profile of the combination.**

This objective has been analysed via the descriptive analysis of the variables as detailed in section 11 of this document.