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Sponsor: Sanofi **Drug substance(s):** XRP6258	**Study Identifiers:** U1111-1123-9025, NCT01649635 **Study code:** CABAZ_L_06003

Title of the study: Multicenter, national, non-comparative, open-label, phase IV study of cabazitaxel combined with prednisone and prophylaxis of neutropenia complications in the second-line treatment of patients with metastatic castration-resistant prostate cancer and post-failure to docetaxel. Descriptive assessment of the circulation tumor cells in this context.

Study center(s): 6 active centers in Brazil

Study period:

Date first patient enrolled (Date of first signed informed consent): 16/Jul/2012

Date last patient completed the treatment period: 18/Jun/2015 (Last Patient Last Treatment: 28/May/2015)

Phase of development: Phase IV

Objectives:

Primary

- To assess hematological effectiveness of prophylactic treatment of hematological complications (neutropenia grade ≥ 3) resulting from cabazitaxel treatment for 21 days after treatment initiation.

Secondary

- Assess the prostate-specific antigen (PSA) response rate;
- Assess descriptively the CTC (Circulating Tumor Cells);
- Assess the rates of neutropenia (grade ≥ 3), febrile neutropenia (grade ≥ 3) and diarrhea (grade ≥ 3) over the treatment period
- To describe Health Quality of Life of the patients;
- Assess incidence of adverse events.

Methodology:

Patients who had signed the informed consent form were assessed for eligibility at screening visit (V0) 15 days before the first treatment visit (V1). At V1 eligibility was confirmed and study treatment started followed by a complete blood count after completion of chemotherapy. Weekly visits were performed (V1 to V4) during the first treatment cycle at which samples for hematology and blood chemistry were collected, results from previous visits were reviewed, and a full physical examination was performed. Visits were conducted every 21 days from the second treatment cycle (V4) with the same procedures as previously described, in addition to disease progression assessment by PSA. The total number of visits throughout the treatment was variable. The treatment period was considered as completed when disease progression was documented by PSA, clinical progression as evaluated by the treating physician, or following the advent of unacceptable toxicity, unless death, consent withdrawal, or loss to follow-up occurred before that period. After discontinuation of chemotherapy, patients were to be assessed every three months up to 12 months, in order to collect any subsequent anticancer treatments. The “End of Study” visit was defined as been the last visit of the follow-up period.

Number of patients:	Planned: 45
	Randomized: NA
	Screened: 60
	Evaluated: 46
	Treated: 45

Safety: 45
Diagnosis and criteria for inclusion: Diagnosis: metastatic castration-resistant prostate cancer (CRPC) and post-failure to docetaxel Main inclusion criteria: • Men aged ≥ 65 years or <65 years provided that 25% of bone marrow is irradiated; • Histologically proven CRPC, with marrow, liver and kidney function within acceptable levels; • Performance status 0 or 1, according to Eastern Cooperative Oncology Group scale; • Life expectancy greater than 12 weeks.
Study treatments **Investigational medicinal product(s):** **Jevtana® (Cabazitaxel)** Formulation: Each package of Jevtana® contains a single-dose vial of Cabazitaxel 60 mg/1.5 mL of polysorbate 80 and a vial of diluent. Route(s) of administration: Intravenous Dose regimen: 25 mg/m2 on day 1 (D1), every 21 days **Ciprofloxacin** Formulation: Tablet of 500 mg of ciprofloxacin and inert components Route(s) of administration: Oral Dose regimen: 500 mg for 8 days (D5 to D12), twice daily (total dose of 1.0g), every cycle of 21 days **G-CSF** Formulation: Syringe filled with 0.5 mL of solution for injection containing 300 µg of filgrastim and the excipients sodium hydroxide, glacial acetic acid, sorbitol, polysorbate 80 and water. Route of administration Subcutaneous. Dose regimen: 5 µg/kg/day (maximum dose of 600 µg) for 7 days (D2 to D8), every cycle of 21 days or until absolute neutrophil count (ANC) reach levels ≥ 2,000/mm3. Administration of 1 vial (300 mcg) for patients weighing up to 90 kg and 1.5 to 2 vials for patients over 90 kg
Noninvestigational medicinal product(s): Prednisone Formulation: Tablet of 5 mg of prednisone and the excipients lactose monohydrate, maize starch, povidone and magnesium stearate Route(s) of administration: Oral Dose regimen: 5 mg, twice daily (total dose of 10 mg), during all treatment with Cabazitaxel
Duration of treatment: The duration of treatment was variable. Treatment phase was considered as completed at the time disease progression was documented. **Duration of observation:** Screening period: 15 days; Treatment: variable (up to disease progression); Post-treatment: 12 months.

Criteria for evaluation:

The current report is a synopsis style report, and as such, only the main results are being presented in full. The following endpoints were evaluated:

- The primary endpoint consisted of proportion of patients with some episode of neutropenia classified as grade ≥ 3 (according to National Cancer Institute - Common Terminology Criteria for Adverse Events [NCI-CTCAE], version 4.03) during the first treatment cycle (21 days). It was assessed on a weekly basis in this treatment cycle.

The following were considered as secondary endpoints:

- Proportion of patients with neutropenia grade ≥3 (according to NCI-CTCAE, version 4.03) over the treatment period;
- Proportion of patients with febrile neutropenia over the treatment period;
- Proportion of patients with diarrhea grade ≥ 3 over the treatment period;
- Proportion of patients with PSA response (≥50% reduction) over the treatment period;
- Assessment of the number of circulating tumor cells was performed before the study and after the 2nd, 4th and 6th cycles of treatment with cabazitaxel;
- Proportion of patients with Cytokeratin 19 (CK-19) gene expressing circulating tumor cells before the study and after the 2nd, 4th and 6th cycles of treatment with cabazitaxel;
- Assessment of Health Quality of Life using the changes from baseline in scores derived from FACT P (total and domain scores) and its Trial Outcome Index (TOI). In addition, the analysis included responder of FACT-P which was defined as the proportion of patients with 7-point improvement in the total score at any evaluation over the treatment.

Safety

- Incidence of adverse events over treatment period.

Statistical methods:

Sample size

Considering a two-sided alpha error of 5% and a 90% statistical power, the study required the inclusion of 40 patients in order to reject a 65% rate of neutropenia grade ≥ 3 according to NCI-CTCAE version 4.03 (based on historical results), under the assumption of a true rate of 40% after the first treatment cycle when using prophylactic G-CSF. Assuming a 10% of invalid data or lost to follow-up patients, 45 patients should be included in the study.

Analysis populations

All efficacy analyses were conducted on the Intent-To-Treat (ITT) population, defined as all registered patients (ie, patients who signed the informed consent and were able to be enrolled in the study according to inclusion and exclusion criteria).

Safety analyses were conducted on the Safety population, defined as all registered patients who received at least one dose of any of the study drugs (ie, Cabazitaxel and/or Ciprofloxacin and/or G-CSF and/or Prednisone).

Data analysis

Continuous data were summarized using the number of non-missing data, mean, standard deviation (SD), median, minimum and maximum. Categorical and ordinal data were summarized with absolute and relative frequencies.

The primary endpoint was the proportion of neutropenia grade ≥ 3 during the first treatment cycle (21 days). A two-sided 95% confidence interval (CI) for the proportion was presented. The proportion was compared to the historical value (65%) using the t-test for one proportion (z approximation).

The secondary endpoints – proportion of neutropenia grade ≥ 3, febrile neutropenia, diarrhea grade ≥ 3, PSA response (≥50% reduction from baseline) and FACT-P response (7-point improvement in total score from baseline) during the treatment period – were presented along with 95% CI. Changes in FACT-P total and domain scores were evaluated using the paired t-test. CTC and Cytokeratin 19 gene expression were summarized using basic descriptive statistics. Time to neutropenia grade ≥ 3, time to progression and overall survival were determined using the Kaplan-Meier method.

Statistical significance was accepted when $p < 0.05$ (two-sided).

Summary:

This report presents the statistical results of the Study CABAZ_L_06003, regarding the treatment and follow-up period.

Patients' disposition

Between 16-Jul-2012 (FPFV) and 14-Jan-2014 (LPFV), 60 patients were screened for the study of whom 14 were screening failures and did not proceed to the study treatment phase. There were 7 subjects with at least one inclusion criterion not met, 12 met at least one exclusion criterion, 1 subject withdrew the consent and 4 did not proceed because the bone scan was not performed. A total of 46 subjects were included in the ITT population and 45 in the safety population. One patient met all Inclusion/exclusion criteria and was then included in to the study (ITT population), but not treated (thus not included in Safety population) since the investigator did not confirm the subject's eligibility with a scintigraphy (Tables 1.1 and 1.2).

Table 1.1 - Patients' disposition (all patients)

n (%)		All (N=60)
Patients screened	60	(100.0%)
Screen failures	14	(23.3%)
ITT population	46	(76.7%)
Safety population (treated patients)	45	(75.0%)

Table 1.2 - Reason for patients' non-eligibility (all patients)

n (%)		All (N=60)
Inclusion criteria not met	7	(11.7%)
Exclusion criteria met	12	(20.0%)
Withdrawal of consent	1	(1.7%)
Other - bone scan not performed	4	(6.7%)

Multiple answers were possible

All treated subjects (n=45) discontinued the study treatment, mainly due to disease progression (62.2%) (Table 1.3).

Table 1.3 - Reason to discontinue/end of study treatment (Safety population)

n (%)		Safety (N=45)
Disease progression	28	(62.2%)
Worsening of ECOG Performance Status	2	(4.4%)
Death	1	(2.2%)
Intolerable AE related to the administration of study treatment	1	(2.2%)
Other	13	(28.9%)
Maximum benefit / response to treatment	6	(13.3%)
AE	2	(4.4%)
Treatment delayed for more than 2 weeks due to hospitalization	2	(4.4%)
Optimal response to treatment / toxicity	1	(2.2%)
AE and ECOG worsening	1	(2.2%)
Medical decision	1	(2.2%)

Demographic and baseline characteristics

Majority of ITT population (n=46) was Caucasian (84.8%). The mean age of patients was 71.8 ± 5.5 years (mean ± SD), ranging from 57.0 to 81.0 years. The mean values of height and weight were 167.5 ± 6.3 cm and 77.5 ± 16.4 kg, respectively (Table 2.1).

Table 2.1 - Demographic characteristics (ITT population)

		ITT (N=46)
Ethinicity - n (%)		
Number (non missing data)	46	
Caucasian / White	39	(84.8%)
Black	4	(8.7%)
Asian	0	(0.0%)
Other	3	(6.5%)
Mixed	2	(4.3%)
Hispanic	1	(2.2%)
Age (years)		
Number (non missing data)		46
Mean ± SD		71.8 ± 5.5
Median		71.5
Minimum - Maximum		57 - 81
Height (cm)		
Number (non missing data)		46
Mean ± SD		167.5 ± 6.3
Median		167.5
Minimum - Maximum		156 - 180
Weight (kg)		
Number (non missing data)		46
Mean ± SD		77.5 ± 16.4
Median		75.9
Minimum - Maximum		51.7 - 114.8

One patient (2.2%) had allergy history due to amoxicillin; 32 patients (72.7%) reported some medical or surgical history related to prostate cancer, with bone pain (18.2%) being the most common abnormality and 41 patients (93.2%) reported some medical history not related to prostate cancer with arterial hypertension as the most frequent abnormality (Table 2.2).

Table 2.2 - Medical or surgical history (ITT population)

		ITT (N=46)
Any drug hypersensitivity/allergy - n (%)		
Number (non missing data)	45	
Yes	1	(2.2%)
Amoxicillin	1	(2.2%)
No	44	(97.8%)
Any history related to prostate cancer - n (%)		
Number (non missing data)	44	
Yes	32	(72.7%)
Reported by more than 1 patient		
Bone pain	8	(18.2%)
Bone metastasis	5	(11.4%)
Dysuria	3	(6.8%)
Urinary retention	3	(6.8%)
Anemia	2	(4.5%)
Hematuria	2	(4.5%)
Nocturia	2	(4.5%)
Urinary incontinence	2	(4.5%)
No	12	(27.3%)
Any history not related to prostate cancer - n (%)		
Number (non missing data)	44	
Yes	41	(93.2%)
Reported by more than 1 patient		
Systemic arterial hypertension	10	(22.7%)
Arterial hypertension	8	(18.2%)
Constipation	6	(13.6%)
Diabetes mellitus type II	5	(11.4%)
Chronic obstructive pulmonary disease	4	(9.1%)
Dyslipidaemia	4	(9.1%)
Acute myocardial infarction	3	(6.8%)
Cardiopathy	3	(6.8%)
Lumbar pain	3	(6.8%)
Nausea	3	(6.8%)
Depression	3	(6.8%)
Arrhythmia	2	(4.5%)
Dyspepsia	2	(4.5%)
Epigastralgia	2	(4.5%)
Insomnia	2	(4.5%)
Osteopenia	2	(4.5%)
Appendectomy	2	(4.5%)
Coronary bypass	2	(4.5%)
No	3	(6.8%)

From 17 patients from whom this data could be retrieved, thirteen patients (76.5%) had been submitted to prior surgery for prostatic carcinoma (excluding androgen ablation), on average, 84.2 ± 54.4 months before study initiation and the most common procedure was radical prostatectomy (64.7%). Twenty-one patients were submitted to surgery for androgen ablation, on average, 44.7 ± 40.7 months prior to study initiation and bilateral orchiectomy was reported by all these patients (Table 2.3).

Table 2.3 - Prior surgery (ITT population)

		ITT (N=46)
Any surgery for prostatic carcinoma excluding androgen ablation - n (%)		
Number (non missing data)	17	
Yes	13	(76.5%)
Radical prostatectomy	11	(64.7%)
Pelvic lymphadenectomy	3	(17.6%)
Transurethral resection of prostate	2	(11.8%)
Other	5	(29.4%)
No	4	(23.5%)
Time from surgery (mean ± SD, in months)		84.2 ± 54.4
Any surgery for androgen ablation - n (%)		
Number (non missing data)	23	
Yes	21	(91.3%)
Bilateral orchiectomy	21	(91.3%)
Other	5	(21.7%)
No	2	(8.7%)
Time from surgery (mean ± SD, in months)		44.7 ± 40.7

Mean time since histological diagnosis of prostatic cancer was 75.2 ± 44.8 months (range: 11.0 to 184.0). According to TNM staging, 55.6% of the patients had tumors on NX, 51.1% M1, 42.2% TX, 35.6% N0 and 35.6% M0. The majority of patients had grade 4 tumors (42.2%) and 4 or more metastases (43.5%), mostly in bone (Tables 2.4.1 and 2.4.2).

Table 2.4.1 - Prostatic cancer history (ITT population)

		ITT (N=46)
Time since histological diagnosis (months)		
Number (non missing data)		41
Mean ± SD		75.2 ± 44.8
Median		69.0
Minimum - Maximum		11 - 184
Actual TNM staging - n (%)		
Number (non missing data)	45	
TX	19	(42.2%)
T1, T1a, T1c	3	(6.7%)
T2, T2a, T2c	8	(17.8%)
T3, T3a, T3b	10	(22.2%)
T4	5	(11.1%)
NX	25	(55.6%)
N0	16	(35.6%)
N1	4	(8.9%)
MX	6	(13.3%)
M0	16	(35.6%)
M1	23	(51.1%)

Table 2.4.2 - Prostatic cancer history (ITT population)

		ITT (N=46)
Tumor histological grading - n (%)		
Number (non missing data)	45	
Grade 1	1	(2.2%)
Grade 2	8	(17.8%)
Grade 3	7	(15.6%)
Grade 4	19	(42.2%)
Grade X	3	(6.7%)
Unknown	7	(15.6%)
Number of metastasis [1] - n (%)		
Number (non missing data)	46	
1	16	(34.8%)
2	5	(10.9%)
3	5	(10.9%)
4 or more	20	(43.5%)

[1] Mostly in bone

Treatments

All patients reported previous treatments for prostate cancer: chemotherapy, 100%; biological therapy, 2.2%, hormonal therapy (91.1%) and non-drug therapy, 48.9% (Table 3.1).

Table 3.1 - Previous treatments for prostate cancer (TT population)

n (%)		ITT (N=46)
Any previous treatment		
Number (non missing data)	45	
Chemotherapy	45	(100.0%)
Biological therapy	1	(2.2%)
Hormonal therapy	41	(91.1%)
Non-drug therapy	22	(48.9%)

From 435 cycles during study treatment period, antihistamines and corticosteroids were used as pre-chemotherapies in 427, H2 antagonists in 411 and antiemetics in 417 (Table 3.2).

Table 3.2 - Pre-chemotherapy medications (ITT population)

Nº cycles / total cycles (non missing data)	ITT (N=46)
Pre-chemotherapy medication	
Antihistamines	427 / 435
Corticosteroids	427 / 435
H2 Antagonists	411 / 435
Antiemetics	417 / 435

The mean number of Cabazitaxel doses administered was 9.5 ± 5.7 (range: 1 to 26), generating a duration of exposure of 210.0 ± 5.7 days. The actual mean dose received by visit was 24.2 ± 1.4 mg (range: 20.6 to 25) (Table 3.3).

Table 3.3 - Cabazitaxel exposure (Safety population)

	Safety (N = 45)
Number of doses administered	
Number (non missing data)	45
Mean ± SD	9.5 ± 5.7
Median	9.0
Minimum - Maximum	1 - 26
Duration of exposure (days)	
Number (non missing data)	45
Mean ± SD	210.0 ± 124.3
Median	190.0
Minimum - Maximum	22 - 560
Actual mean dose received by visit (mg)	
Number (non missing data)	45
Mean ± SD	24.2 ± 1.4
Median	25.0
Minimum - Maximum	20.6 - 25.0

Study drugs were not administered or administered with delay in 49 out of 477 cycles of Cabazitaxel, 75 out of 433 cycles of Prednisone, 17 out of 433 cycles of G-CSF and 25 out of 433 cycles of Ciprofloxacin, Table 3.4.

Table 3.4 - Compliance of IMP (Safety population)

Nº cycles / total cycles (non missing data)	Safety (N=45)
IMP not administered or administered with delay	
Cabazitaxel	49 / 477
Prednisone	75 / 433
G-CSF	17 / 433
Ciprofloxacin	25 / 433

Results of primary analysis

Eighteen patients (40.0%) had neutropenia grade ≥ 3 within the 21 days following the initiation of treatment (95% CI, 25.7% to 54.3%): 8 cases of grade 3 and 10 cases of grade 4 (Table 4.1). The percentage of patients with neutropenia was statistically different from the historical value of 65% (p=0.001).

Table 4.1 - Occurrence of neutropenia grade ≥3 during the 21 days following the initiation of treatment (Safety population)

		Safety (N=45)
Neutropenia grade ≥ 3 - n (%)		
Number (non missing data)	45	
No	27	(60.0%)
Yes[1]	18	(40.0%)
95% CI (for %)		[25.7% - 54.3%]
Comparison with historical value (65%)		p = 0.001
Grade 3	8	(17.8%)
Grade 4	10	(22.2%)

[1] These patients had 1 occurrence during the period

Results of secondary analyses

During the treatment period, 19 patients (42.2%) had neutropenia grade ≥ 3 (95% CI, 27.8% to 56.6%): 12 patients with neutropenia grade 3 and 11 with grade 4. Fourteen patients (31.1%) had one event and 5 patients (11.1%) had from 2 to 7 events (Table 4.2).

Table 4.2 - Occurrence of neutropenia grade ≥3 during the treatment period (Safety population)

		Safety (N=45)
Neutropenia grade ≥ 3 - n (%)		
Number (non missing data)	45	
No	26	(57.8%)
Yes	19	(42.2%)
95% CI (for %)		[27.8% - 56.6%]
Grade 3	12	(26.7%)
Grade 4	11	(24.4%)
No. of events per patient		
1	14	(31.1%)
2	3	(6.7%)
5	1	(2.2%)
7	1	(2.2%)

One patient (2.2%) had one episode of febrile neutropenia during the treatment period (95% CI, 0.0% to 6.5%) (Table 4.3).

Table 4.3 - Occurrence of febrile neutropenia during the treatment period (Safety population)

		Safety (N=45)
Febrile neutropenia - n (%)		
Number (non missing data)	45	
No	44	(97.8%)
Yes[1]	1	(2.2%)
95% CI (for %)		[0.0% - 6.5%]

[1] This patient had 1 occurrence after visit 5 (cycle 3)

One patient (2.2%) had one episode of diarrhea grade ≥ 3 during the treatment period (95% CI, 0.0% to 6.5%) (Table 4.4).

Table 4.4 - Occurrence of diarrhea grade ≥3 during the treatment period (Safety population)

		Safety (N=45)
Diarrhea grade ≥ 3 - n (%)		
Number (non missing data)	45	
No	44	(97.8%)
Yes[1]	1	(2.2%)
95% CI (for %)		[0.0% - 6.5%]

[1] This patient had 1 occurrence after visit 5 (cycle 3)

Twenty-nine patients (64.4%) presented a ≥50% reduction on PSA at least in one visit during the treatment period in comparison with baseline (95% CI, 50.5% to 78.4%). Considering only the patients who reached the PSA response, the mean time to reach and the duration of PSA response were 80.9 ± 64.5 days and 150.5 ± 126.7 days, respectively (Table 4.5).

Table 4.5 - PSA response (≥50% reduction from baseline) during the treatment period (ITT population)

		Safety (N=45)
PSA response rate - n (%)		
Number (non missing data)	45	
No	16	(35.6%)
Yes	29	(64.4%)
95% CI (for %)		[50.5% - 78.4%]
Time to PSA response (days)		80.9 ± 64.5
Duration of PSA response (days)[1]		150.5 ± 126.7

[1] Two patients achieved response and discontinued and it was not possible to obtain the duration of PSA response.

Tables 4.6 and 4.7 show the counting of circulating tumor cells (CTC) test per 7.5 mL of blood and the CTC - Cytokeratin 19 (CK-19) gene expression at each time point of evaluation.

Table 4.6 - Counting of circulating tumor cells (CTC) test (ITT population)

Visit n (%)		ITT (N=46)
Baseline		
Number (non missing data)	46	
≥5 CTCs	6	(13.0%)
<5 CTCs	40	(87.0%)
After 2nd cycle		
Number (non missing data)	42	
≥5 CTCs	10	(23.8%)
<5 CTCs	32	(76.2%)
After 4th cycle		
Number (non missing data)	40	
≥5 CTCs	9	(22.5%)
<5 CTCs	31	(77.5%)
After 6th cycle		
Number (non missing data)	32	
≥5 CTCs	10	(31.3%)
<5 CTCs	22	(68.8%)

Table 4.7 - CTC - Cytokeratin 19 (CK-19) Gene expression (ITT population)

Visit n (%)		ITT (N=46)
Baseline		
Number (non missing data)	44	
No	2	(4.5%)
Yes	42	(95.5%)
95% CI (for %)		[89.3% - 100%]
After 2nd cycle		
Number (non missing data)	42	
No	5	(11.9%)
Yes	37	(88.1%)
95% CI (for %)		[78.3% - 97.9%]
After 4th cycle		
Number (non missing data)	40	
No	3	(7.5%)
Yes	37	(92.5%)
95% CI (for %)		[84.3% - 100%]
After 6th cycle		
Number (non missing data)	32	
No	3	(9.4%)
Yes	29	(90.6%)
95% CI (for %)		[80.5% - 100%]

Thirty-four patients (77.3%) achieved a 7-point improvement in the FACT-P total score in at least one visit. Changes from baseline in FACT-P total score at visits 5 and 7, physical score at visits 5 and 7, emotional score at visits 5, 7, 9 and 11, prostate-specific score at visits 5, 7 and 11 and TOI (Trial Outcome Index) score at visits 5 and 7were statistically significant at $p < 0.05$ (Table 4.8).

Table 4.8 - Counting of circulating tumor cells (CTC) test (ITT population)

Visit (non missing data)	No. of responders[1]	Change in FACT-P score from baseline (mean ± SD)						
		Total	Physical	Social/Family	Emotional	Functional	Prostate-specific	TOI
V5 (N=43)	26 (60.5%)	8.8 ± 16.8*	2.2 ± 5.2*	0.1 ± 5.6	1.8 ± 4.1*	1.5 ± 4.8	3.3 ± 7.1*	7.0 ± 12.8*
V7 (N=38)	19 (50.0%)	8.1 ± 18.5*	2.3 ± 5.6*	-0.1 ± 4.3	2.1 ± 3.4*	0.8 ± 4.3	2.9 ± 8.4*	6.0 ± 14.7*
V9 (N=33)	14 (42.4%)	3.7 ± 18.4	1.1 ± 6.7	-0.9 ± 4.4	1.4 ± 4.0*	0.0 ± 4.4	1.8 ± 7.4	3.1 ± 15.1
V11 (N=24)	11 (45.8%)	5.7 ± 19.0	0.9 ± 5.8	-0.0 ± 4.3	1.4 ± 3.2*	-0.1 ± 4.1	3.7 ± 7.3*	4.4 ± 14.8
V13 (N=15)	3 (20.0%)	-3.0 ± 12.0	0.1 ± 4.8	-1.3 ± 4.2	0.1 ± 2.5	-1.3 ± 3.1	-0.7 ± 6.5	-1.8 ± 10.5
V15 (N=12)	3 (25.0%)	3.2 ± 20.9	2.9 ± 6.7	-1.1 ± 4.0	0.3 ± 3.0	-0.8 ± 4.3	2.0 ± 7.8	4.0 ± 16.9
V17 (N=8)	1 (12.5%)	7.1 ± 17.0	2.0 ± 7.8	0.1 ± 3.7	0.4 ± 3.4	1.2 ± 5.3	3.5 ± 8.0	6.7 ± 15.9
V19 (N=6)	3 (50.0%)	6.3 ± 26.4	0.8 ± 5.9	1.1 ± 4.3	1.4 ± 4.7	-0.2 ± 4.3	3.3 ± 10.8	4.0 ± 19.3
V21 (N=5)	1 (20.0%)	-3.2 ± 10.9	-0.4 ± 4.8	-1.7 ± 2.9	0.6 ± 2.9	-3.0 ± 1.8	1.0 ± 7.0	-2.3 ± 10.4
V23 (N=3)	1 (33.3%)	-8.3 ± 18.1	0.5 ± 9.0	-2.1 ± 2.7	-0.7 ± 3.1	-2.3 ± 2.1	-3.3 ± 9.8	-5.4 ± 17.5
V25 (N=3)	1 (33.3%)	-6.1 ± 25.2	1.0 ± 13.1	-3.4 ± 4.5	-1.3 ± 4.0	-2.7 ± 4.7	0.3 ± 9.5	-1.3 ± 24.0
V27 (N=2)	1 (50.0%)	0.0 ± 29.7	2.0 ± 14.1	-2.0 ± 0.0	-2.5 ± 5.0	1.0 ± 5.7	1.5 ± 16.3	4.5 ± 24.8
Overall [2]	34 (77.3%)							

[1] 7-point improvement in FACT-P total score from baseline

[2] At least one visit

* Significant at p<0.05

As exploratory analyses, the median time to progression was 8.7 months (95% CI, 5.9 to 12.4 months) and median overall survival was 18.2 months (95% CI, 10.3 to 21.3 months). Median time to neutropenia grade ≥ 3 (measured during treatment phase only) was not determined because the corresponding number of events was less than 50% of the sample assessed (Table 4.9).

Table 4.9 - Exploratory analyses (ITT population)

Visit n (%)		**ITT (N=46)**
Time to neutropenia grade ≥3 (months)		
Number assessed		45
Number censored - n (%)	26	(57,8%)
Number of events - n (%)	19	(42,2%)
Median		ND
95% CI (for median)		ND
Time to progression (months)		
Number assessed		45
Number censored - n (%)	10	(22,2%)
Number of events - n (%)	35	(77,8%)
Median		8,7
95% CI (for median)		[5,9 - 12,4]
Overall survival (months)		
Number assessed		45
Number censored - n (%)	18	(40,0%)
Number of events - n (%)	27	(60,0%)
Median		18,2
95% CI (for median)		[10,3 - 21,3]

Kaplan-Meier method
ND = not determined

Safety results:

Adverse events

All patients in the safety population (45 patients) had at least one adverse event, totaling 814 treatment emergent adverse events (TEAEs), being 92 of these TEAEs with grade 3 or 4. Nineteen patients (42.2%) had 31 serious TEAEs, being 7 related to study treatment: 1 febrile neutropenia, 1 urinary tract infection and 5 haematuria cases. Three TEAEs leaded to death, being that 2 out of the 3 deaths occurred during the treatment emergent period (one due to disease progression and another due to respiratory tract infection) and 1 occurred after treatment emergent period (due to urinary tract infection), none related to study treatment. Six patients (13.3%) had 7 TEAEs leading to treatment discontinuation, being 3 related to study treatment: asthenia, general physical health deterioration and haematuria. Forty-three patients (95.6%) reported 508 TEAEs related to study treatment, of which neutropenia (55.6%), anaemia (53.3%), fatigue (44.4%) and nausea (42.2%) were the most frequent events. Considering Medical Dictionary for Regulatory Activities (MedDRA), general disorders and administration site conditions (88.9%), gastrointestinal disorders (82.2%) and blood and lymphatic system disorders (77.8%) were the most frequent system organ classes (SOC) of TEAEs reported (Tables 5.1 to 5.5).

Pretreatment adverse events were registered in 46.7% of the patients but none was serious or resulted in death. Most frequent pretreatment adverse events were blood and lymphatic system disorders (17.8%), Table 5.6.

Observation: initial date of some events could not be confirmed precisely, and then, as a conservative way, these events were registered as TEAE.

Table 5.1 - Overview of adverse event profile: Treatment emergent adverse events - TEAEs (Safety population)

	Safety (N=45)		
	No. of patients (%)		No. of events
Any TEAE	45	(100,0%)	814
Any grade 3-4 TEAE	38	(84,4%)	92
Any serious TEAE	19	(42,2%)	31
Any TEAE leading to death[1]	3	(6,7%)	3
Any TEAE leading to permanent treatment discontinuation	6	(13,3%)	7
Any TEAE related to study treatment	43	(95,6%)	508
Any serious TEAE and related to study treatment	4	(8,9%)	7
Any TEAE related to study treatment and leading to death	0	(0,0%)	0
Any TEAE related to study treatment and leading to permanent treatment discontinuation	3	(6,7%)	3

[1] One death occurred after treatment emergent period

Table 5.2 - Serious TEAEs, by Primary SOC and PT according to MedDRA (Safety population)

Primary SOC: System Organ Class PT: Preferred Term - n(%)		Safety (N=45)
Blood and lymphatic system disorders	2	(4,4%)
Anaemia	1	(2,2%)
Febrile neutropenia [1]	1	(2,2%)
Gastrointestinal disorders	1	(2,2%)
Duodenal ulcer	1	(2,2%)
General disorders and administration site conditions	1	(2,2%)
Disease progression [4]	1	(2,2%)
Infections and infestations	10	(22,2%)
Pneumonia	3	(6,7%)
Pyelonephritis	1	(2,2%)
Respiratory tract infection [4]	1	(2,2%)
Sepsis	1	(2,2%)
Urinary tract infection [1,3]	5	(11,1%)
Musculoskeletal and connective tissue disorders	1	(2,2%)
Pathological fracture	1	(2,2%)
Renal and urinary disorders	9	(20,0%)
Renal failure acute	2	(4,4%)
Renal impairment	1	(2,2%)
Haematuria [2]	7	(15,6%)
Respiratory, thoracic and mediastinal disorders	2	(4,4%)
Pleural effusion	1	(2,2%)
Pulmonary embolism	1	(2,2%)
Vascular disorders	1	(2,2%)
Aortic aneurysm	1	(2,2%)

[1] One case related to study treatment

[2] Four cases related to study treatment

[3] One case leading to death after treatment emergent period

[4] One case leading to death during treatment emergent period

Table 5.3 - TEAEs leading to treatment discontinuation, by Primary SOC and PT according to MedDRA (Safety population)

Primary SOC: System Organ Class **PT: Preferred Term - n(%)**		**Safety (N=45)**
General disorders and administration site conditions	2	(4,4%)
Asthenia[1]	1	(2,2%)
General physical health deterioration[1]	1	(2,2%)
Infections and infestations	1	(2,2%)
Pyelonephritis	1	(2,2%)
Urinary tract infection	1	(2,2%)
Renal and urinary disorders	2	(4,4%)
Haematuria[1]	2	(4,4%)
Respiratory, thoracic and mediastinal disorders	1	(2,2%)
Pulmonary embolism	1	(2,2%)

[1] One case related to study treatment

Table 5.4.1 - TEAEs related to study treatment, by Primary SOC and PT according to MedDRA (Safety population)

Primary SOC: System Organ Class PT: Preferred Term - n(%)		Safety (N=45)
Blood and lymphatic system disorders	32	(71.1%)
Anaemia	24	(53.3%)
Haematotoxicity	1	(2.2%)
Thrombocytopenia	8	(17.8%)
Febrile neutropenia	1	(2.2%)
Leukocytosis	1	(2.2%)
Leukopenia	2	(4.4%)
Lymphopenia	2	(4.4%)
Neutropenia	25	(55.6%)
Cardiac disorders	1	(2.2%)
Arrhythmia	1	(2.2%)
Eye disorders	1	(2.2%)
Vision blurred	1	(2.2%)
Gastrointestinal disorders	32	(71.1%)
Rectal haemorrhage	1	(2.2%)
Constipation	6	(13.3%)
Diarrhoea	17	(37.8%)
Abdominal distension	1	(2.2%)
Abdominal pain	2	(4.4%)
Abdominal pain upper	2	(4.4%)
Dyspepsia	2	(4.4%)
Nausea	19	(42.2%)
Vomiting	12	(26.7%)
Odynophagia	2	(4.4%)
General disorders and administration site conditions	34	(75.6%)
Application site pain	1	(2.2%)
Asthenia	9	(20.0%)
Chest pain	1	(2.2%)
Fatigue	20	(44.4%)
General physical health deterioration	1	(2.2%)
Malaise	1	(2.2%)
Mucosal inflammation	3	(6.7%)
Oedema peripheral	6	(13.3%)
Pain	3	(6.7%)
Infections and infestations	4	(8.9%)
Erysipelas	1	(2.2%)
Oral candidiasis	1	(2.2%)
Urinary tract infection	2	(4.4%)
Injury, poisoning and procedural complications	1	(2.2%)
Fall	1	(2.2%)
Investigations	16	(35.6%)
Blood alkaline phosphatase increased	4	(8.9%)
Monocyte count decreased	2	(4.4%)
Alanine aminotransferase increased	2	(4.4%)
Blood bilirubin increased	1	(2.2%)

Table 5.4.2 - TEAEs related to study treatment, by Primary SOC and PT according to MedDRA (Safety population)

Primary SOC: System Organ Class PT: Preferred Term - n(%)		Safety (N=45)
Weight decreased	6	(13,3%)
Blood creatinine increased	2	(4,4%)
Blood urea increased	2	(4,4%)
Metabolism and nutrition disorders	21	(46,7%)
Decreased appetite	18	(40,0%)
Hypercalcaemia	1	(2,2%)
Hypomagnesaemia	3	(6,7%)
Hypernatraemia	1	(2,2%)
Hyponatraemia	1	(2,2%)
Hyperglycaemia	1	(2,2%)
Musculoskeletal and connective tissue disorders	12	(26,7%)
Arthralgia	1	(2,2%)
Muscle spasms	1	(2,2%)
Myalgia	5	(11,1%)
Back pain	3	(6,7%)
Pain in extremity	3	(6,7%)
Nervous system disorders	23	(51,1%)
Headache	1	(2,2%)
Dizziness	1	(2,2%)
Dysgeusia	13	(28,9%)
Hypoaesthesia	2	(4,4%)
Paraesthesia	3	(6,7%)
Neuropathy peripheral	12	(26,7%)
Psychiatric disorders	1	(2,2%)
Anxiety	1	(2,2%)
Insomnia	1	(2,2%)
Renal and urinary disorders	12	(26,7%)
Renal failure acute	1	(2,2%)
Renal impairment	1	(2,2%)
Dysuria	1	(2,2%)
Haematuria	9	(20,0%)
Haemoglobinuria	2	(4,4%)
Proteinuria	1	(2,2%)
Respiratory, thoracic and mediastinal disorders	2	(4,4%)
Rales	1	(2,2%)
Epistaxis	1	(2,2%)
Skin and subcutaneous tissue disorders	3	(6,7%)
Alopecia	1	(2,2%)
Hyperhidrosis	1	(2,2%)
Night sweats	1	(2,2%)

Table 5.5 - Primary SOC for TEAEs according to MedDRA (Safety population)

		Safety (N=45)
Primary SOC: System Organ Class - n (%)		
Blood and lymphatic system disorders	35	(77,8%)
Cardiac disorders	4	(8,9%)
Ear and labyrinth disorders	2	(4,4%)
Eye disorders	3	(6,7%)
Gastrointestinal disorders	37	(82,2%)
General disorders and administration site conditions	40	(88,9%)
Infections and infestations	27	(60,0%)
Injury, poisoning and procedural complications	5	(11,1%)
Investigations	21	(46,7%)
Metabolism and nutrition disorders	25	(55,6%)
Musculoskeletal and connective tissue disorders	31	(68,9%)
Nervous system disorders	24	(53,3%)
Psychiatric disorders	5	(11,1%)
Renal and urinary disorders	27	(60,0%)
Respiratory, thoracic and mediastinal disorders	9	(20,0%)
Skin and subcutaneous tissue disorders	6	(13,3%)
Vascular disorders	7	(17,8%)

Table 5.6 - Overview of pretreatment adverse events (Safety population)

		Safety (N=45)
Pretreatment adverse event - n (%)		
Any AE[1]	21	(46.7%)
Primary SOC: System Organ Class		
Blood and lymphatic system disorders	8	(17.8%)
Cardiac disorders	1	(2.2%)
Gastrointestinal disorders	1	(2.2%)
General disorders and administration site conditions	2	(4.4%)
Infections and infestations	3	(6.7%)
Investigations	7	(15.6%)
Metabolism and nutrition disorders	2	(4.4%)
Musculoskeletal and connective tissue disorders	2	(4.4%)
Nervous system disorders	1	(2.2%)
Renal and urinary disorders	5	(11.1%)
Vascular disorders	1	(2.2%)

[1] No serious AE, no AE leading to death

Follow-up period

Thirty (65.2%) patients preformed at least one post-treatment follow-up visit, and 25 (54.3%) received at least one anti-neoplasic therapy at this period, being 16 (34.8%) chemotherapy, 5 (10.9%) radiotherapy, 3 (6.5%) biologic therapy and 11 (23.9%) other therapies (Table 6.1).

Total of 27 (60.0%) patients had died, being 2 (4.4%) during treatment emergent period and 25 (55.6%) during follow-up period. Cause of death was disease progression for 20 (44.4%) patients, 3 (6.7%) due to adverse events and 3 (6.7%) due to other causes (one patient had a cardiac arrest on the way to the hospital, one patient had respiratory insufficiency and multiple metastasis, and one patient renal insufficiency). For one (2.2%) patient, primary cause of death was unknown (Table 6.2).

Five (11.1%) patients presented six adverse events at follow-up period (one patient had 2 distinct adverse events of gastrointestinal disorders). One event was considered serious (not leading to death) and two were related to study treatment, Table 6.3.

Table 6.1 - Subsequent antineoplasic therapy at follow-up visits (ITT population)

		ITT (N=46)
Any antineoplastic therapy received at follow-up visits - n	25	(54,3%)
Chemotherapy	16	(34,8%)
Radiotherapy	5	(10,9%)
Biologic therapy	3	(6,5%)
Surgical procedure	0	(0,0%)
Any other antineoplastic therapy	11	(23,9%)

Table 6.2 - Deaths occurred during study (Safety population)

Deaths **primary cause of death**		**ITT (N=46)**
Total deaths occurred during study	27	(60,0%)
Deaths occurred during treatment period	2	(4.4%)
adverse event	2	(4.4%)
Deaths occurred during follow-up period	25	(55.6%)
disease progression	20	(44,4%)
adverse event	1	(2.2%)
other causes	3	(6,7%)
cardiac arrest (on the way to the hospital)	1	(2,2%)
respiratory insufficiency and multiple metastasis	1	(2,2%)
renal insufficiency	1	(2,2%)
unknown primary cause of death	1	(2,2%)

Table 6.3 - Overview of post treatment adverse events (Safety population)

		Safety (N=45)
Post treatment adverse event - n (%)		
Any AE	5	(11.1%)
Primary SOC: System Organ Class		
Gastrointestinal disorders	1	(2.2%)
Infections and infestations[1]	1	(2.2%)
Metabolism and nutrition disorders[2]	1	(2.2%)
Musculoskeletal and connective tissue disorders	1	(2.2%)
Renal and urinary disorders[2]	1	(2.2%)

[1] One serious AE; [2] One AE related to study treatment

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