Pivotal

ASSOCIACIÓ PER A LA RECERCA ONCOLÒGICA(APRO)

FINAL STUDY REPORT

(VERSION 1.0-16-JUNE-2016)

STUDY CODE: SECAVIN-12

SPAIN: VERSION PROTOCOL V.4.0 - DATE: 30 NOV 2015

NETHERLANDS: VERSION PROTOCOL: V.2.0 - DATE: 12 JUL 2013

Study title: A randomised Phase II/III study of cabazitaxel versus vinflunine in metastatic or locally advanced transitional cell carcinoma of the urothelium.

Investigational product: Cabazitaxel

Indication studied: Metastatic or locally advanced transitional cell carcinoma of the urothelium.

Name of Sponsor: Associació Per a la Recerca Oncològica (APRO)

Protocol number: SECAVIN-12

EudraCT No.: 2012-002826-55

Phase of study: II/III

Principal investigator(s): Dr. Joaquim Bellmunt

Date: 16-June-2016	Version: 1.0
Pages No.: 56	

1 TABLE OF CONTENTS

1.1 INDEX OF TABLES

1.2 INDEX OF FIGURES

1.3 INDEX OF LISTINGS

2 ABBREVIATIONS

AE	Adverse event
AEMPS	Agencia Española del Medicamento y Productos Sanitarios / Spanish Agency of Medicines and Medical Devices
ANC	Absolute neutrophil count
APRO	Associació Per a la Recerca Oncològica
AR	Adverse reaction
ASCO	American Association of Clinical Oncology
BSC	Best Supportive Care
CKD-EPI	Chronic Kidney Disease Epidemiology group
CMV	cisplatin, methotrexate, vinblastine
CR	Complete response
CRO	Contract Research Organization
CT	Computed tomography
DBP	Diastolic blood pressure
DLT	Dose limiting toxicity
DVFL	4Odeacetyl-vinflunine
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group performance status scale
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
ESMO	European Society for Medical Oncology
GC	Gemcitabine plus cisplatin
FSR	Final Statistical Report
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transpeptidase
Hb	Haemoglobin
IAC	Independent Assessment Committee
IB	Investigator's brochure
ICH	International Conference on Harmonisation
IEC	Investigational Ethics Committee
ITT	Intent-to-treat population
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
mCRPC	Metastatic, castration-resistant prostate cancer
MDR	Multidrug resistance
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
MTX	Mitoxantrone
MVAC	methotrexate, vinblastine, adriamycin and cisplatin
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association.
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PP	Per-protocol population
PR	Partial response
PS	Performance status
PSA	Prostate-specific antigen
q3w	Every three weeks

RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SBP	Systolic blood pressure
SGOT/AST	Aspartate aminotransferase
SGPT/ALT	Alanine aminotransferase
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TCC	Transitional cell carcinoma
TCCU	Transitional cell carcinoma of the urothelium
TEAE	Treatment emergent adverse event
ULN	Upper limit of normality
VEGF	Vascular endothelial growth factor

3 INTRODUCTION

3.1 PREFACE

Bladder cancer is common around the world and its incidence is increasing. As a rule, it is three times more common in men than in women. Worldwide an estimated 386,000 (3.0%) new cases of bladder cancer occur each year in both sexes, and it is responsible for 2.0% of cancer-related deaths a year (150,000 deaths) (2). In Europe, the number of new cases in 2008 was 139,500 in both sexes, and bladder cancer caused 51,300 deaths (3), being the fourth most frequent tumour in men (110,000 cases, 6.4% of total).

The great majority of neoplasms of the bladder and upper urinary tract correspond histologically to transitional cell carcinomas of the urothelium (TCCU) or urothelial cancer. Although only 20% of newly diagnosed cases of urothelial cancer are in an advanced phase, many patients with superficial or locally invasive tumours will end up with recurrence or the development of metastasis, which is why the management of advanced urothelial cancer is a frequent problem in clinical practice. The so-called advanced stages include locally advanced disease (T4b, N1, N2 or N3) that cannot be resolved by means of surgical bladder resection, as well as stage IV according to the TNM classification (4). Systemic chemotherapy is the mainstay of therapy of these patients (5).

Note: The references and appendices referred to in this document correspond to the ones mentioned in the protocol of the study.

3.2 PURPOSE OF THE PLANNED ANALYSES AND THIS DOCUMENT

The aim of the phase II study was to evaluate if the response rates (complete response [CR] + partial response [PR]) were sufficiently high and the severe acute toxicity rates acceptably low to further study the treatment regimens in a phase III setting. At the end of the phase II study, an interim analysis was planned before proceeding to the phase III part of the study.

Firstly, seventy patients were included in the study, thirty-five in the cabazitaxel arm and thirty-five in the vinflunine arm, as it was planned for the phase II setting.

At the end of phase II, after evaluation of the first 70 patients (35 + 35 for cabazitaxel and vinflunine), an IAC meeting took place on 26th November 2015 to evaluate the efficacy results of the phase II study and determine whether to continue with phase III of the study.

The present document provides the final study report(FSR) of the study in which all the results of the phase II part of the study are analyzed.

The following table provides the treatment arms of the study.

Table 1. Treatment arms

		Total (N=70)
Treatments		
CABAZITAXEL	n (%)	35 (50.00)
VINFLUNINE	n (%)	35 (50.00)

A table with the centers that participated in the study is provided in the appendix 1 of the FSR.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 STUDY OBJECTIVES FOR FSR

4.1.1 Phase II part:

Primary objective

To assess the efficacy of cabazitaxel compared to vinflunine in terms of improved objective response rate (ORR) of patients with metastatic or locally advanced previously treated TCCU.

Secondary objectives

To assess the efficacy of cabazitaxel compared to vinflunine in terms of improved progression-free survival (PFS) and overall survival (OS).

To assess the safety profile and tolerability of cabazitaxel.

4.2 ENDPOINTS

4.2.1 Phase II part:

Primary endpoint:

- ORR, which included the sum of the complete and partial responses (CR+PR), (according to Response Evaluation Criteria in Solid Tumours [RECIST criteria v1.1]).

Secondary endpoints:

- PFS defined as the time from randomization to either documented disease progression or death from due to any cause (whichever occurs earlier).
- OS defined as the time from randomization to death due to any cause.
- Adverse events (AEs) were coded and evaluated using the National Cancer Institute, Common Toxicity criteria for Adverse Events (NCI-CTCAE) v4.0 toxicity criteria (if NCI-CTCAE were not applicable, the Medical Dictionary for Regulatory Activities (MedDRA 18.1) were used).

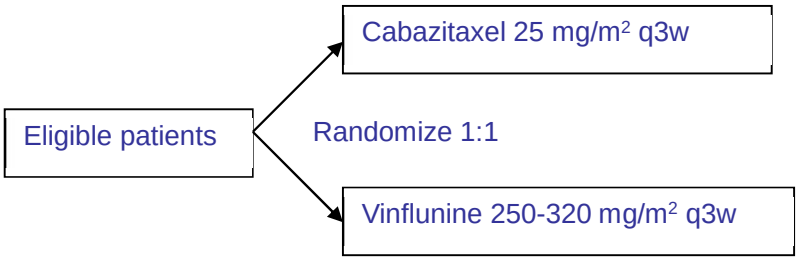
Note: The Aes coding referred to the severity of the AE when it was reported in the eCRF. In the clinical database the AE's term was coded according to the Medical Dictionary of Regulatory Activities (MedDRA 18.1) system.

5 STUDY METHODS

5.1 GENERAL STUDY DESIGN AND PLAN

Due to limited experience with cabazitaxel in TCCU, the study was designed to start as randomized phase II study. The aim of the phase II study was to evaluate if the response rates (CR + PR) were sufficiently high to further study the treatment regimens in a phase III setting. At the end of the phase II study, an interim analysis was planned to be performed to proceed to the phase III portion of the study.

Once it was confirmed that the patients fulfilled the eligibility criteria and had signed the informed consent, they were randomized to receive treatment based on cabazitaxel or vinflunine according to the following study schema:



Random assignment of treatment was stratified by the presence of 0 versus 1 of the following unfavourable prognostic risk factors proposed recently by Bellmunt et al. (1):

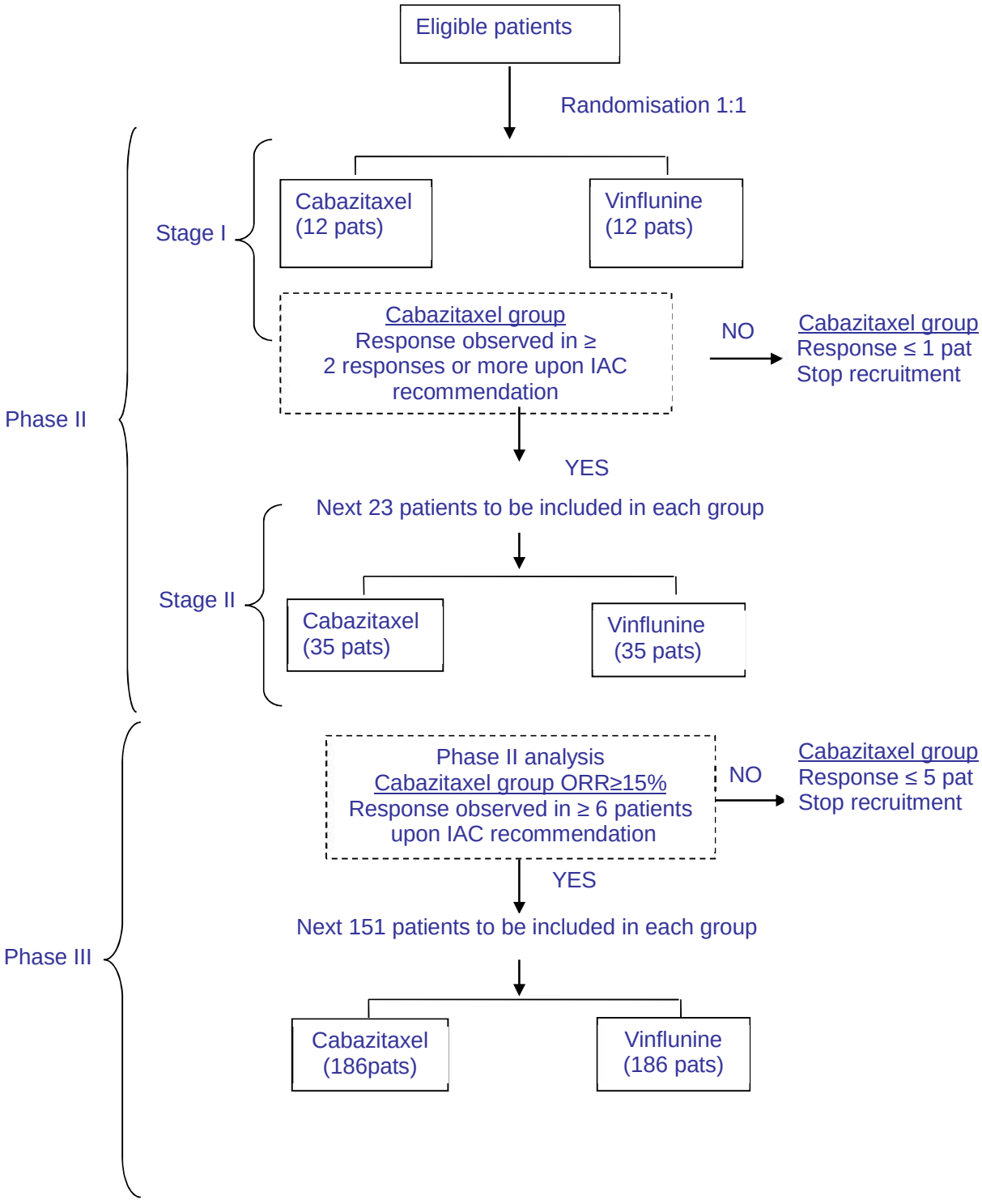
- ECOG PS 1.
- Anaemia with Hb <10 g/dL.
- Presence of liver metastases.

All patients enrolled in the study received a cycle of treatment with the study medication (cabazitaxel or vinflunine) every 21 days until disease progression or intolerable/unacceptable toxicity. Tumour evaluations were scheduled every 6 weeks (±2 weeks) until progression (in case of cycle delay this tumour evaluations every 6 weeks should be maintained to avoid any bias in the assessment of date of progression with appropriate imaging studies for response evaluation). A radiologic-morphologic evaluation was made with thoraco–abdomino-pelvic computed tomography (CT) or MRI (magnetic resonance imaging).

Patients with disease progression during the treatment phase were withdrawn from the study and received their treatment according to the investigator's judgment and monitored to evaluate OS.

If a patient withdrawn consent and refused to receive more treatment, the patient had to be followed up for survival. If a patient withdrawn consent and refused to continue in the study, the follow-up evaluations had to be discontinued.

Graph 1. Study design



5.2 INCLUSION-EXCLUSION CRITERIA AND GENERAL STUDY POPULATION

5.2.1 Inclusion criteria

Only patients who fulfilled all the criteria listed below were enrolled in the study:

- 1.The patient has given written informed consent stating that he or she understands the purpose of the study and the procedures involved and agrees to participate in the study.
- 2.The patient has histologically confirmed TCCU (urinary bladder, urethra, ureter or renal pelvis). Patients with mixed histology may be enrolled if transitional cell carcinoma is the predominant component (i.e., > 50% of the histopathology sample), with the exception of neuroendocrine or small cell carcinoma.
- 3.The patient has advanced disease defined as a locally advanced tumour considered being unresectable (T4b), node involvement in the inguinal area or above the aortic bifurcation (that are considered to be distant nodes and so metastasis) or metastasis in distant organs.
- 4.The patient should have received one prior platinum-based chemotherapy treatment for locally advanced or stage IV TCCU. Prior platinum-based adjuvant or neoadjuvant therapy is allowed if more than 6 months have elapsed since the end of adjuvant or neoadjuvant therapy till tumour relapse.
- 5.The patient has at least one measurable tumour lesion (measurable disease, as defined by the RECIST criteria v1.1), for the phase II part of the study. If all sites of measurable disease have been irradiated, one site must have demonstrated growth after irradiation. For phase III part, patients with only non measurable disease are allowed for enrolment.
- 6.Age ≥18 years.
- 7.ECOG PS 0 or 1.
- 8.The patient may have no more than ONE of the following unfavorable risk factors:
    - Haemoglobin <10 g/dL
    - Presence of liver metastasis
    - ECOG PS 1
- 9.Life expectancy of at least 12 weeks.
- 10. Adequate hematologic, hepatic, and renal function, defined by:
    - Platelet count ≥100 x10^9/L
    - Absolute neutrophil count (ANC) >1.5x10^9/L
    - Serum creatinine ≤1.5 times the upper limit of normality (ULN). If creatinine 1.0-1.5 xULN, creatinine clearance will be calculated according to Chronic Kidney Disease Epidemiology group (CKD-EPI) formula and patients with creatinine clearance <50 mL/min should be excluded

NOTE: The CKD-EPI formula for creatinine clearance is as follows:
GFR = 141 X min(Scr/κ,1)α X max(Scr/κ,1)-1.209 X 0.993Age X 1.018 [if female] X 1.159 [if black]. Where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. See Appendix VII for details.

  - Alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT) and alkaline phosphatase (AP) ≤2.5 ×ULN (<5 ×ULN in the presence of liver metastasis), and serum total bilirubin ≤1.0 ×ULN.

- 11. Females of childbearing potential must have a negative serum pregnancy test within 7 days of study entry. Patients of childbearing potential who participate in this study must use effective contraceptive methods (e.g., abstinence, intrauterine device, oral or injectable contraceptives, a double barrier method or surgical sterility) to prevent pregnancy starting as soon as the informed consent form is signed and continuing for at least 13 weeks after the last dose of the study medication is administered.

5.2.2 Exclusion criteria

Patients were excluded from the study if they present any of the criteria listed below:

- 1.Patients that have 2 or more of the following unfavorable risk factors:
  - Haemoglobin <10 g/L
  - Liver metastasis
  - ECOG PS 1
- 2.Women who are currently pregnant or breast-feeding.
- 3.Any unresolved non-hematologic AE grade >1 (NCI-CTCAE, Version 4.0) from previous anti-cancer therapy (other than alopecia).
- 4.Patients who had undergone major surgery, radiation therapy or treatment with chemotherapy or any investigational agent within 28 days prior to Study day 1.
- 5.Evidence of severe or uncontrolled systemic disease or any concurrent condition (including uncontrolled diabetes mellitus) which in the Investigator's opinion makes it undesirable for the patient to participate in the study or which would jeopardize compliance with the protocol.
- 6.History of another neoplasm. Patients with prior history of either non-metastatic non-melanoma skin cancers; carcinoma in situ of the cervix; or cancer cured by surgery, small field radiation or chemotherapy ≥3 years prior to randomization; or treated patients with early stage and low risk prostate cancer (≤pT2 N0 M0, Gleason ≤6 and PSA ≤0.5 ng/mL) at study entry will be eligible.
- 7.History of hypersensitivity reactions to taxanes (docetaxel) (cabazitaxel specific criteria), vinca alkaloids (vinflunine specific criteria) or to any of the formulation excipients, including polysorbate 80 (cabazitaxel specific criteria).

- 8.Patients with clear evidence or symptoms of central nervous system metastasis (cabazitaxel specific criteria).
- 9.Clinically significant cardiac condition demonstrated by myocardial infarction or thromboembolic events in the 6 months prior to the study treatment initiation, serious or unstable angina pectoris, New York Heart Association (NYHA) class III or IV congestive heart failure (see Appendix VI) (vinflunine specific criteria).
- 10.Concurrent or planned treatment with strong inhibitors or strong inducers of cytochrome P450 3A4/5 (one week wash-out period is necessary for patients who are already on these treatments) (see Appendix XII of the study protocol).

5.3 RANDOMISATION

Random assignment of treatment was stratified by the presence of 0 versus 1 of the following unfavorable prognostic risk factors proposed recently by Bellmunt et al. (1):

- Poor performance status (PS) according to Eastern Cooperative Oncology Group (ECOG) scale: ECOG PS 1.
- Anaemia with Hb <10 g/dL.
- Presence of liver metastases.

6 SAMPLE SIZE

Phase II

The primary objective was to determine the ORR which included the sum of the complete and partial responses (CR+PR) according to RECIST criteria v1.1. The aim of this phase II was to evaluate if the response rates (ORR) were sufficiently high and the severe acute toxicity rates acceptably low to further study the treatment regimens in a phase III setting.

To calculate the sample size of the phase II part of the study, it was hypothesized that the ORR for vinflunine and cabazitaxel would be 10% and 30%, respectively. A response rate of 10% was considered as insufficient to further investigate the regimen of cabazitaxel in second line urothelial tumours (RR of vinflunine in second line = 8.6%).

Using Simon's (28) optimal method, cabazitaxel was considered to be effective in each prognostic sub-group if an ORR of 15% is reached, which included the sum of the complete and partial responses (CR+PR). Assuming $\pi 0=10\%$ and $\pi 1=30\%$, and establishing errors $\alpha=0.1$ (unilateral) and $\beta=0.1$ for ORR, 35 evaluable patients in each group were needed to demonstrate or to reject the hypothesis.

Two stages were established in each of the groups:

- In the first step 12 evaluable patients were needed to be randomized in the study on each treatment arm. If one or fewer responses were observed in the cabazitaxel arm, the study was stopped due to an inadequate response rate unless it was recommended by the independent assessment committee (IAC) to go on based on PFS data. Efficacy data for the patients included at this first step were reviewed by an independent assessment committee (IAC) (see Section 10 of the protocol).
- If 2 or more responses were observed recruitment continued until the group had 35 evaluable patients, so 23 additional patients were randomized in each arm.
- If five or fewer responses were detected among these 35 patients (ORR<15%) in the cabazitaxel group, it was concluded that the regimen was not sufficiently active to warrant further testing. If six or more responses were observed in each arm, then the study continued as a randomized phase III study. Efficacy data for the patients included at the end of the phase II second step was reviewed by the IAC (see Section 10 of the protocol).

Consequently, at the end of the phase II study, it was planned an interim analysis to proceed to phase III. This did not imply a delay in the recruitment process. At this interim analysis, a minimum response rate of 15% was considered of interest in the overall patient population lumping together patients with 0 or 1 adverse risk factors (20% in patients with 0 risk factors). Patients included in the phase II part were planned to be included in the final analysis of Phase III.

Phase III

The median duration of survival on the vinflunine arm was estimated to be 6 months. In order to detect an increase of 37% in median survival on the cabazitaxel arm to 8.2 months based on a two sided log rank test at error rates alpha = 0.05 and beta = 0.20, assuming an exponential dropout rate of 0.01, a total of 321 events were needed. Therefore, it was estimated that it was necessary to include up to 372 patients (186 patients per arm) over 18 months followed by 18 months of follow-up.

7 STATISTICAL METHODS

7.1 STUDY VARIABLES

The next calendar of evaluations, describes the frequency and timing of all the relevant variable observations or assessments:

	Baseline		**Treatment**	**End-of-treatment visit / early withdrawal**	**Follow-up / Survival until progression or death**
	≤ 4 weeks	≤ 7 days	≤72h before drug administration:	30 ± 5 days after last dose of study medication	Every 3 months ± 2 weeks
Informed consent[1] and eligibility criteria	X				
Histological confirmation of TCCU	X				
Medical history and relevant previous and concomitant treatments[2]	X				
Oncologic history: date of diagnosis, staging, previous treatments	X				
Anthropometric data[3]		X	X	X	
ECOG PS[4]		X	X	X	X
Vital signs[5]		X	X	X	X
Physical examination[6]		X	X	X	X
ECG[7]		X	X	X	
Haematology / Blood biochemistry[8]		X	X	X	X
Pregnancy test[9]		X			
Concomitant medication		X	X	X	X
Evaluation of the disease: thoraco –abdomino -pelvic CT or MRI[10]	X		X	X	X
Bone scan[11]	X		X	X	X
Other clinically indicated tests: brain CT or MRI[12]	X		X	X	X
LVEF (radionuclide scan or ultrasound) [13]	X				
Randomisation		X			
Study treatment [14]			X		
AE review			X	X	X
Patient survival					X

	Baseline		Treatment	End-of-treatment visit / early withdrawal	Follow-up / Survival until progression or death
	≤ 4 weeks	≤ 7 days	≤72h before drug administration:	30 ± 5 days after last dose of study medication	Every 3 months ± 2 weeks
Subsequent oncologic treatments					X

1 Informed consent must be obtained before performing any procedure specific to the study.

2 Relevant past or active conditions shall be recorded. Relevant concomitant treatments or treatments interrupted in the seven days prior to the planned start date of the study shall be recorded.

3 Includes age, sex, height, body surface and weight. The patient shall be weighed before each cycle for purposes of any dose adjustment required, as well as on the final visit or early withdrawal visit

4 ECOG PS shall be determined at all visits (except for the first treatment cycle if PS was determined in the last 7 days prior to the start of treatment).

5 SBP, DBP and HR (measured in sitting position after 5 minutes of rest) and temperature.

6 Basic physical examination at baseline, including a neurological examination. In the case of neurological symptoms, cranial CT or magnetic resonance imaging (MR) shall be performed.

Before each cycle and during follow-up, indicate the signs and symptoms present.

7 At baseline, every 6 weeks (±2 weeks), end-of-treatment visit and when clinically indicated.

8 Haematology: Complete blood cell count with leukocyte formula, platelet count and coagulation parameters. Biochemistry: SGOT/AST, SGPT/ALT, GGT, LDH, alkaline phosphatase, sodium, potassium, albumin, total proteins, glucose, total bilirubin and creatinine. Creatinine clearance will be calculated using the CKD-EPI formula. Blood biochemistry and haematology shall be evaluated at all visits, except for the first cycle of treatment if blood biochemistry parameters have been measured in the last 7 days prior to the start of treatment. However, during the first cycle weekly monitoring of the granulocyte count will be necessary.

9 In women of childbearing potential

10 At baseline, end-of-treatment visit and every 6 weeks (2 cycles) (±2 weeks) until progression. In case of cycle delay the tumour evaluation every 6 weeks should be maintained to avoid any bias in the assessment of date of progression with the appropriate imaging technique for response evaluation**.**

The same imaging test should be used throughout the study to minimize variability. In order to assign a status of PR or CR, the changes in tumour measurements must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

11 At baseline visit if bone metastasis is suspected and only if clinically indicated during treatment, end-of-treatment visit and follow-up. In the case of positive radionuclide scan at initiation (baseline visit), the bone scan will be repeated every 6 weeks (±2 weeks) if clinically indicated.

12 Only if clinically indicated at baseline, during treatment, end-of- treatment visit and follow-up.

13 Only if clinically indicated at baseline

14 The dose and date of administration of the chemotherapy treatment shall be recorded. Administration shall begin on day 1 of each cycle following the corresponding schedule.

7.2 SUMMARY OF STUDY DATA

Continuous variables were summarized using the mean, standard deviation (Std), median, Q1, Q3, minimum and maximum with the total number of patients contributing values. Shapiro-Wilk test was used to contrast if the continuous measure followed a Normal distribution.

Categorical variables were summarized in contingency tables by presenting the number and percentage of patients in each category. CI 95% for the main variables were included in the efficacy analysis.

Kaplan-Meier model were used to analyze PFS and OS. In all these analysis, in addition to the Kaplan-Meier curve, median, Q1, Q3 and their corresponding CI 95%, number of events and censored cases distribution were shown.

Treatment groups were tested at the 2-sided 5% significance level for all analysis expected in the protocol.

7.3 MISSING DATA

Missing data were not imputed and were considered as missing values for the analysis. In case there was any incomplete date that was necessary for the analysis, in which the day was missing, it was imputed to day 1. For dates for which month and day were missing these values were imputed to June 30th.

7.4 REPORTING CONVENTIONS

P-values ≥0.001 were reported to 3 decimal places; p-values less than 0.001 were presented as "<0.001".
The statistical parameters were reported to 2 decimal places.

7.5 TECHNICAL DETAILS

SAS programs, SAS Logs and SAS outputs generated during the creation of the Statistical Report were archived in the PIVOTAL's File System.

7.6 SOFTWARE DOCUMENTATION

All analyses and reporting were performed using SAS® for Windows Version 9.4.

8 STATISTICAL RESULTS

8.1 PROTOCOL DEVIATIONS

Given that protocol deviations were not defined in the protocol, before the database locked of the study took place these deviations were defined and agreed with the sponsor.
Nevertheless, a listing with the major deviations for the patients that were excluded from the PP population is provided in the appendices of the FSR.

8.2 ANALYSIS POPULATIONS

The following study populations were defined for the analysis:

8.2.1 Intent to treat population (ITT)

ITT population which included all the patients randomized in the study.

8.2.2 Per protocol population (PP)

PP population which included the set of patients of the ITT population who did not present major protocol deviations.

8.2.3 Safety population (SAF)

Safety population included all the patients that had received at least a first administration of the study drugs.

All primary analyses and analyses of the efficacy data were conducted using the intent-to-treat (ITT) population.
A secondary analyses of the efficacy data were conducted using the per protocol (PP) population.
All primary analyses of the safety data were conducted using the safety population.

In the table below the analysis populations are described. All the patients were included in the ITT population and SAF population. Forty-four(62.9%) of the patients were included in the PP population, 68.6% in the cabazitaxel arm and 57.1% in the vinflunine arm.

Table 2. Analysis populations

		CABAZITAXEL (N=35)	VINFLUNINE (N=35)	Total (N=70)	P Value Test
ITT population					
Yes	n (%)	35 (100.00)	35 (100.00)	70 (100.00)	NA
PP population					
Yes	n (%)	24 (68.57)	20 (57.14)	44 (62.86)	Chi-Square: 0.3224
No	n (%)	11 (31.43)	15 (42.86)	26 (37.14)	
SAF population					
Yes	n (%)	35 (100.00)	35 (100.00)	70 (100.00)	NA

8.3 DEMOGRAPHIC AND BASELINE VARIABLES

Demographics, anthropometric data, variables related to vital signs and electrocardiogram, as well as any other variables that described the medical history of the patient, i.e. histological confirmation of the TCCU and metastatic disease history, are summarized in this section.

The baseline laboratory parameters, in particular, the parameters that were determined in the inclusion and exclusion criteria are also described in a table.

Table 3. Demography

		CABAZITAXEL (N=35)	VINFLUNINE (N=35)	Total (N=70)	P Value Test
Age					
	N	35	35	70	
	Mean (SD)	62.09 (8.43)	64.29 (9.62)	63.19 (9.05)	
	Median [Q1,Q3]	64.00 [56.00, 68.00]	66.00 [59.00, 70.00]	65.00 [59.00, 69.00]	Wilcoxon: 0.2855
	Min, Max	42.00, 77.00	35.00, 80.00	35.00, 80.00	
	Shapiro Wilk	0.2478	0.0810	0.0436	
Gender					
Male	n (%)	28 (80.00)	28 (80.00)	56 (80.00)	Chi-Square: 1.0000
Female	n (%)	7 (20.00)	7 (20.00)	14 (20.00)	
Race					
Caucasian	n (%)	34 (97.14)	35 (100.00)	69 (98.57)	Fisher: 1.0000
Black	n (%)	1 (2.86)	0 (0.00)	1 (1.43)	

Table 4. Anthropometrics

		CABAZITAXEL (N=35)	VINFLUNINE (N=35)	Total (N=70)	P Value Test
Weight(kg)					
	N	35	35	70	
	Mean (SD)	77.88 (18.25)	79.46 (12.60)	78.67 (15.59)	T-Test: 0.6752
	Median [Q1,Q3]	83.00 [60.00, 91.50]	80.00 [72.00, 88.00]	80.00 [67.00, 90.00]	
	Min, Max	47.00, 114.00	48.90, 99.80	47.00, 114.00	
	Mean CI 95%	(71.62, 84.15)	(75.13, 83.79)	(74.96, 82.39)	
	Shapiro Wilk	0.2444	0.3827	0.2593	
Height(cm)					
	N	35	35	70	
	Mean (SD)	171.60 (10.15)	173.74 (9.01)	172.67 (9.59)	T-Test: 0.3534
	Median [Q1,Q3]	171.00 [165.00, 179.00]	173.00 [169.00, 181.00]	172.00 [166.00, 180.00]	
	Min, Max	151.00, 197.00	159.00, 195.00	151.00, 197.00	
	Mean CI 95%	(168.11, 175.09)	(170.65, 176.84)	(170.39, 174.96)	
	Shapiro Wilk	0.8085	0.3991	0.8863	
Body surface(m(2))					
	N	35	35	70	
	Mean (SD)	1.91 (0.25)	1.94 (0.18)	1.92 (0.22)	T-Test: 0.5287
	Median [Q1,Q3]	1.94 [1.70, 2.09]	1.98 [1.81, 2.07]	1.95 [1.74, 2.09]	
	Min, Max	1.42, 2.40	1.59, 2.30	1.42, 2.40	
	Mean CI 95%	(1.82, 1.99)	(1.88, 2.00)	(1.87, 1.97)	
	Shapiro Wilk	0.7606	0.3848	0.4437	

Table 5. Vital signs

		CABAZITAXEL (N=35)	VINFLUNINE (N=35)	Total (N=70)	P Value Test
SPB(mmHg)					
	N	29	31	60	
	Missing	6	4	10	
	Mean (SD)	134.48 (19.05)	133.55 (15.43)	134.00 (17.13)	T-Test: 0.8349
	Median [Q1,Q3]	136.00 [126.00, 140.00]	133.00 [121.00, 145.00]	135.00 [122.00, 144.50]	
	Min, Max	90.00, 180.00	109.00, 177.00	90.00, 180.00	
	Mean CI 95%	(127.24, 141.73)	(127.89, 139.21)	(129.57, 138.43)	
	Shapiro Wilk	0.2423	0.3653	0.3101	
DBP(mmHg)					
	N	29	31	60	
	Missing	6	4	10	
	Mean (SD)	78.79 (8.84)	79.13 (7.28)	78.97 (8.00)	T-Test: 0.8725
	Median [Q1,Q3]	80.00 [72.00, 85.00]	79.00 [75.00, 83.00]	80.00 [73.00, 83.50]	
	Min, Max	60.00, 96.00	59.00, 100.00	59.00, 100.00	
	Mean CI 95%	(75.43, 82.15)	(76.46, 81.80)	(76.90, 81.03)	
	Shapiro Wilk	0.7418	0.1871	0.5487	
HR(bpm)					
	N	28	31	59	
	Missing	7	4	11	
	Mean (SD)	85.00 (17.82)	84.10 (15.00)	84.53 (16.26)	
	Median [Q1,Q3]	83.00 [73.50, 91.50]	82.00 [75.00, 90.00]	82.00 [75.00, 91.00]	Wilcoxon: 0.8440
	Min, Max	56.00, 144.00	62.00, 135.00	56.00, 144.00	
	Shapiro Wilk	0.0344	0.0010	0.0002	
Temperature(ºC)					
	N	24	27	51	
	Missing	11	8	19	
	Mean (SD)	36.50 (0.47)	36.48 (0.50)	36.49 (0.48)	
	Median [Q1,Q3]	36.50 [36.10, 36.80]	36.50 [36.00, 36.80]	36.50 [36.10, 36.80]	Wilcoxon: 0.9323
	Min, Max	35.90, 38.00	35.60, 37.50	35.60, 38.00	
	Shapiro Wilk	0.0126	0.4325	0.0401	

8.4 PRIOR AND CONCURRENT MEDICATIONS

Previous antineoplastic treatments are described in terms of radiotherapy, surgery and chemotherapy. As it can be observed in the following table, all the patients had received previous chemotherapy.

However, only thirteen (18.6%) of the patients had received radiotherapy before being included in the study.

There were more patients in the vinflunine arm (94.3%) than in the cabazitaxel arm (74.3%) who had previously undergone surgery and this difference is statistically significant (p=0.0215).

Table 6. Previous antineoplasic treatments

		CABAZITAXEL (N=35)	VINFLUNINE (N=35)	Total (N=70)	P Value Test
Radiotherapy					
Yes	n (%)	7 (20.00)	6 (17.14)	13 (18.57)	Chi-Square: 0.7586
No	n (%)	28 (80.00)	29 (82.86)	57 (81.43)	
Chemotherapy					
Yes	n (%)	35 (100.00)	35 (100.00)	70 (100.00)	NA
Surgery					
Yes	n (%)	26 (74.29)	33 (94.29)	59 (84.29)	Chi-Square: 0.0215
No	n (%)	9 (25.71)	2 (5.71)	11 (15.71)	

The prior radiotherapy and the prior surgery treatments are listed in the appendices document of the FSR.

In the table below the main prior chemotherapy schemes are detailed.

Table 7. Main prior chemotherapy schemes

	Treatment				Total(N=70)	
	CABAZITAXEL (N=35)		VINFLUNINE (N=35)			
	n	%	n	%	n	%
Prior chemotherapy schemes						
CARBOPLATIN+GEMCITABINE	6	17.14	14	40.00	20	28.57
CISPLATIN+GEMCITABINE	28	80.00	20	57.14	48	68.57
OTHER(1)	9	25.71	6	17.14	15	21.43

Note: One patient could had received more than one scheme. This means that the total in each row is the total of patients that received at least one of the scheme, however the total by columns is the total of schemes.

(1) Other schemes included the following: CARBOPLATIN, CISPLATIN, CISPLATIN + GEMCITABINE + ERIBULIN, CISPLATIN+GEMCITABINE+PACLITAXEL, INVESTIGATIONAL DRUG, MITOMYCIN, VINBLASTINE+DOXORUBICIN+METHOTREXATE and XELOX.

8.5 EFFICACY ANALYSES

The ITT population was analyzed for all the efficacy analyses. A secondary analysis was also performed based upon the Per Protocol (PP) Population.

8.5.1 ITT population

8.5.1.1 Primary endpoint(ORR)

The Objective Response rate(ORR) was defined as the percentage of patients who attained CR or PR according to RECIST criteria v1.1.

For the definition of the ORR, the following assumptions were taken into account (*):

- To define the best overall response, tumor assessments performed during the treatment period were considered. In the case of patients who have received other antitumor therapies (chemotherapy, radiotherapy or surgery), the subsequent tumor assessments were not considered for this definition.
- In order to assign a status of PR or CR, the changes in tumour measurements had to be confirmed by repeated assessments performed no less than 4 weeks after the criteria for response were first met.

In this circumstance, the best overall response could be interpreted as in next table:

Table 8. Best overall response when confirmation of CR and PR required

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point (confirmation)	BEST overall response
CR	CR	CR
CR	No CR or missing data	SD
PR	CR or PR	PR
PR	SD, PD or missing data	SD

*NOTE: These assumptions were not specified in the protocol but they determined the criteria to perform the analysis of the primary endpoint.

The absolute and relative frequencies and its corresponding CI 95% are provided in the next tables. Both the best overall response without confirmation and the best overall response with confirmation according to the previous table were analyzed.

Non-evaluable patients were defined as patients without tumour evaluation during the study treatment period for any reason.

A listing with these patients describing the reasons for non-evaluability are also presented.

In the following tables the responses were analyzed in terms of confirmed or not confirmed partial responses (PRc or PRnc), since there were not any 'Complete responses' in the study.

Table 9. Best overall response(ITT)

		CABAZITAXEL (N=35)	VINFLUNINE (N=35)	Total (N=70)	P Value Test
Best overall response					
PRc	n (%)	4 (11.43)	8 (22.86)	12 (17.14)	Fisher: 0.3097
PRnc	n (%)	0 (0.00)	2 (5.71)	2 (2.86)	
SD	n (%)	11 (31.43)	12 (34.29)	23 (32.86)	
PD	n (%)	15 (42.86)	11 (31.43)	26 (37.14)	
NE	n (%)	5 (14.29)	2 (5.71)	7 (10.00)	

*2 out of 14 PR were not confirmed.

(Patients no.:1402 and 1404).

As it can be seen in the next tables, no statistically significant differences were detected between the treatment arms for the main efficacy endpoint (ORR) (p=0.0730). Four patients reached a partial response in the cabazitazel arm, 11.43% (95% CI, 3.20 - 26.74) and ten patients in the vinflunine arm, 28.6% (95% CI, 14.64 - 46.30).

Table 10.(ORR)(ITT)

		CABAZITAXEL (N=35)	VINFLUNINE (N=35)	Total (N=70)	P Value Test
Objective response rate					
CR or PR	n (%)	4 (11.43)	10 (28.57)	14 (20.00)	Chi-Square: 0.0730
No CR or PR	n (%)	31 (88.57)	25 (71.43)	56 (80.00)	

Table 11. ORR (CI 95%)(ITT)

	CABAZITAXEL			VINFLUNINE			Total		
Objective response rate	n	%	IC 95%	n	%	IC 95%	n	%	IC 95%
CR or PR	4	11.43	[3.20; 26.74]	10	28.57	[14.64; 46.30]	14	20.00	[11.39; 31.27]
No CR or PR	31	88.57	[73.26; 96.80]	25	71.43	[53.70; 85.36]	56	80.00	[68.73; 88.61]

In the following tables the best overall response and the ORR are analyzed taking into account the RECIST criteria v1.1 in terms of the confirmation of the partial responses, as have been defined in the previous page. The unconfirmed partial responses for the patients that progressed after having reached a partial response (2) were considered as SD in the next tables.

Table 12. Best overall response (confirmation according to RECIST criteria v1.1.)(ITT)

		CABAZITAXEL (N=35)	VINFLUNINE (N=35)	Total (N=70)	P Value Test
Best overall response					
PRc	n (%)	4 (11.43)	8 (22.86)	12 (17.14)	Fisher: 0.3854
SD	n (%)	11 (31.43)	14 (40.00)	25 (35.71)	
PD	n (%)	15 (42.86)	11 (31.43)	26 (37.14)	
NE	n (%)	5 (14.29)	2 (5.71)	7 (10.00)	

Table 13. ORR(confirmation according to RECIST criteria v1.1.)(ITT)

		CABAZITAXEL (N=35)	VINFLUNINE (N=35)	Total (N=70)	P Value Test
Objective response rate					
CR or PR	n (%)	4 (11.43)	8 (22.86)	12 (17.14)	Chi-Square: 0.2046
No CR or PR	n (%)	31 (88.57)	27 (77.14)	58 (82.86)	

Table 14. ORR(CI 95%)(confirmation according to RECIST criteria v1.1.)(ITT)

	CABAZITAXEL			VINFLUNINE			Total		
Objective response rate	n	%	IC 95%	n	%	IC 95%	n	%	IC 95%
CR or PR	4	11.43	[3.20; 26.74]	8	22.86	[10.42; 40.14]	12	17.14	[9.18; 28.03]
No CR or PR	31	88.57	[73.26; 96.80]	27	77.14	[59.86; 89.58]	58	82.86	[71.97; 90.82]

Five patients in the cabazitaxel arm and two in the vinflunine arm were not evaluable for response. In the next listing the reasons are given.

Listing 1. NE patients: End of study treatment reasons

Treatment group	Patient ID	Reasons for early withdrawal	Adverse events specify	Other reasons, specify
CABAZITAXEL	1103	Death		
CABAZITAXEL	1508	Other reasons,specify		ECOG 3
CABAZITAXEL	2711	Adverse event	PNEUMONIA	
CABAZITAXEL	2712	Disease progression		
CABAZITAXEL	3104	Death		
VINFLUNINE	2306	Withdrawal of inform consent and/or rejection of the treatment and/or uncooperativeness		
VINFLUNINE	2903	Withdrawal of inform consent and/or rejection of the treatment and/or uncooperativeness		

8.5.1.2 Secondary endpoints. PFS

Progression free survival(PFS), is defined as the time from randomization date to objective tumour progression or death due to any cause (whichever occurs first). For PFS analysis, patients who had not progressed and were still alive at the time of data analysis, were censored at the date of last adequate tumour assessment. Patients with undocumented clinical progression or change of cancer treatment were censored at the last adequate tumour assessment.

Patients with no tumor evaluation performed after the baseline evaluation, were censored at the study day 1.

In order to obtain a proper evaluation of PFS, patients who received other antitumor therapies (chemotherapy, radiation) during the follow-up evaluations were given particular attention. These patients were censored at the date of the last tumor evaluation before the new treatment was initiated, even though the patients had progressed after the new treatment start date.

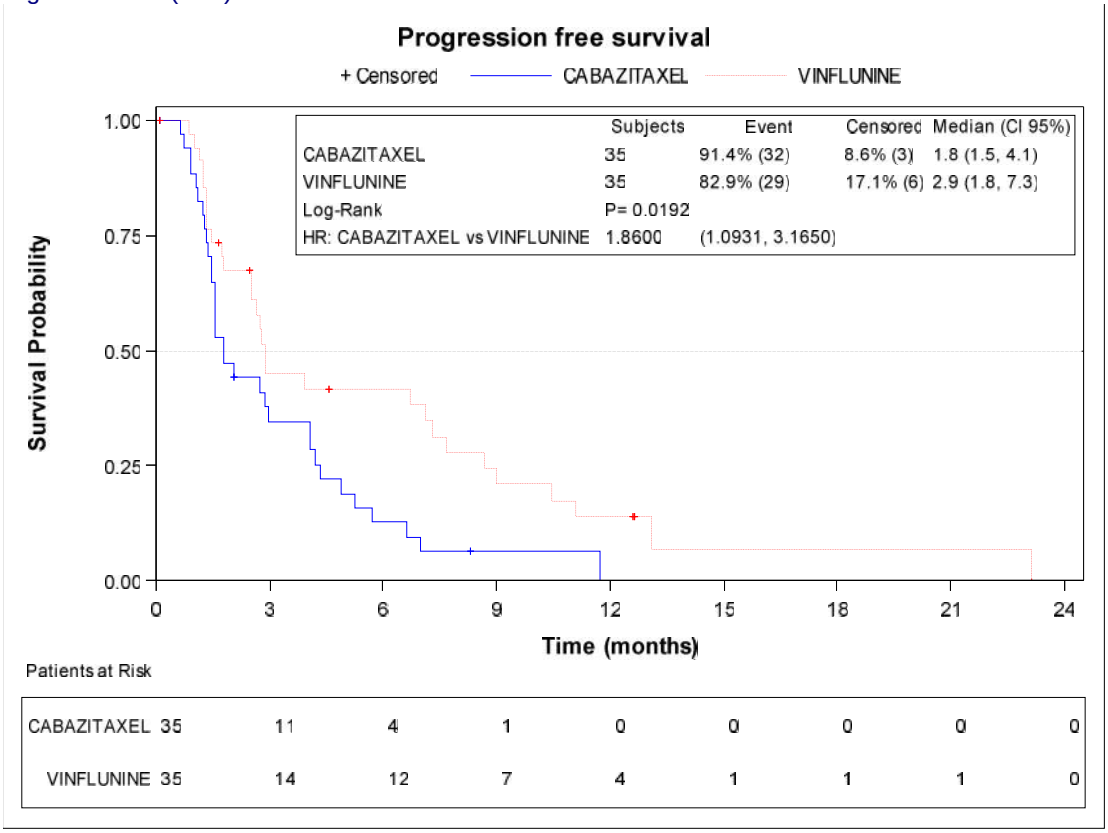
In the next table the main Kaplan-Meier and Cox model estimations are described. As it can be observed, statistical significant differences were detected according to Log-rank text(p=0.0192). This difference was also found through the Cox model(p=0.0221), HR 1.86(95% CI 1.09-3.17).

Table 15. PFS resume(ITT)

	CABAZITAXEL	VINFLUNINE
Summary of events		
No of patients	35	35
No of patients with event	32 (91.43%)	29 (82.86%)
Earliest contributing event:		
Progressed	26	26
Death	6	3
No of censored patients	3 (8.57%)	6 (17.14%)
Progression free survival		
Median (95% CI)	1.78 (1.48, 4.08)	2.89 (1.78, 7.30)
25th-75th percentile	1.35 - 4.34	1.45 - 8.68
Percent PFS (%)		
0 Months	100.00	100.00
6 Months	12.61	41.73
12 Months	0.00	13.91
18 Months	0.00	6.95
24 Months	0.00	0.00
Stratified analysis		
P-value (Log-rank)		0.0192
Cox Model	Hazard ratio (95% CI)	Cox Model P-value
CABAZITAXEL vs VINFLUNINE	1.8600 (1.0931, 3.1650)	0.0221

The following figure shows the Kaplan Meier curve of PFS (ITT).

Figure 1. PFS(ITT)



8.5.1.3 Secondary endpoints. OS

Overall survival(OS), is defined as the time from randomization date to death date, due to any cause. For the OS analysis, patients who were lost to follow-up were censored at the date of last contact.

Table 16. OS resume(ITT)

	CABAZITAXEL	VINFLUNINE
Summary of events		
No of patients	35	35
No of patients with event	29 (82.86%)	28 (80.00%)
No of censored patients	6 (17.14%)	7 (20.00%)
Overall survival		
Median (95% CI)	5.49 (3.95, 9.07)	8.35 (6.18, 11.08)
25th-75th percentile	3.65 - 11.74	5.03 - 13.87
Percent Survival (%)		
0 Months	100.00	100.00
6 Months	44.44	68.57
12 Months	20.74	31.43
18 Months	10.37	17.63
Stratified analysis		
P-value (Log-rank)		0.1193
Cox Model	Hazard ratio (95% CI)	Cox Model P-value
CABAZITAXEL vs VINFLUNINE	1.5173 (0.8946, 2.5735)	0.1219

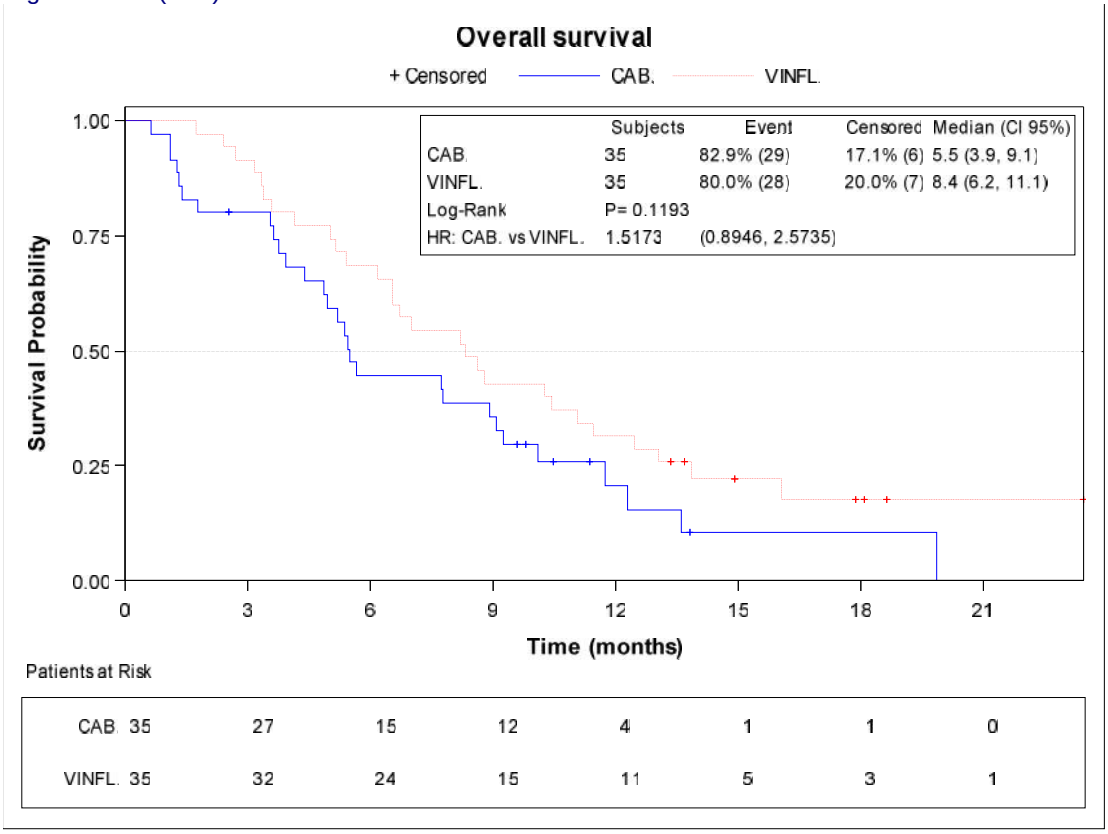
The causes for death were reported as ‘Malignant disease’ for fifty-one of the patients.

There were five patients with “Unknown” as cause of death. These patients, except for patient no. 2306, had progressed some months before death event. The patient no. 2306 ended treatment due to withdrawal of inform consent and/or rejection of the treatment and/or uncooperativeness but later the patient died.

The patient no. 3108 was lost to follow-up, but it was known that the patient died.

The death reasons are also described in ‘End of study’ section.

Figure 2. OS(ITT)



8.5.2 PP population

In this section, efficacy analyses were performed for the PP population.

8.5.2.1 Primary endpoint(ORR)

Table 17. Best overall response(PP)

		CABAZITAXEL (N=24)	VINFLUNINE (N=20)	Total (N=44)	P Value Test
Best overall response					
PRc	n (%)	3 (12.50)	5 (25.00)	8 (18.18)	Fisher: 0.2599
PRnc	n (%)	0 (0.00)	1 (5.00)	1 (2.27)	
SD	n (%)	8 (33.33)	8 (40.00)	16 (36.36)	
PD	n (%)	10 (41.67)	4 (20.00)	14 (31.82)	
NE	n (%)	3 (12.50)	2 (10.00)	5 (11.36)	

*1 out of 9 PR were not confirmed.(Patient no.1404)

In the following tables it can be observed that no statistically significant differences were detected between the treatment arms for the main efficacy endpoint (ORR) (p=0.2607). Three patients reached a partial response in the cabazitazel arm, 12.5% (95% CI, 2.66 – 32.36) and six patients in the vinflunine arm, 30% (95% CI, 11.89 – 54.28).

Table 18. Objective response rate(ORR)(PP)

		CABAZITAXEL (N=24)	VINFLUNINE (N=20)	Total (N=44)	P Value Test
Objective response rate					
CR or PR	n (%)	3 (12.50)	6 (30.00)	9 (20.45)	Fisher: 0.2607
No CR or PR	n (%)	21 (87.50)	14 (70.00)	35 (79.55)	

Table 19. ORR (CI 95%)(PP)

	CABAZITAXEL			VINFLUNINE			Total		
Objective response rate	n	%	IC 95%	n	%	IC 95%	n	%	IC 95%
CR or PR	3	12.50	[2.66; 32.36]	6	30.00	[11.89; 54.28]	9	20.45	[9.80; 35.30]
No CR or PR	21	87.50	[67.64; 97.34]	14	70.00	[45.72; 88.11]	35	79.55	[64.70; 90.20]

In the following tables, the best overall response and the ORR are analyzed taking into account the RECIST criteria v1.1 in terms of the confirmation of the partial responses as it was defined in this document.

Table 20. Best overall response (confirmation according to RECIST criteria v1.1.) (PP)

		CABAZITAXEL (N=24)	VINFLUNINE (N=20)	Total (N=44)	P Value Test
Best overall response					
PRc	n (%)	3 (12.50)	5 (25.00)	8 (18.18)	Fisher: 0.2659
SD	n (%)	8 (33.33)	9 (45.00)	17 (38.64)	
PD	n (%)	10 (41.67)	4 (20.00)	14 (31.82)	
NE	n (%)	3 (12.50)	2 (10.00)	5 (11.36)	

Table 21. ORR(confirmation according to RECIST criteria v1.1.)(PP)

		CABAZITAXEL (N=24)	VINFLUNINE (N=20)	Total (N=44)	P Value Test
Objective response rate					
CR or PR	n (%)	3 (12.50)	5 (25.00)	8 (18.18)	Fisher: 0.4361
No CR or PR	n (%)	21 (87.50)	15 (75.00)	36 (81.82)	

Table 22. ORR(CI 95%)(confirmation according to RECIST criteria v1.1.) (PP)

	CABAZITAXEL			VINFLUNINE			Total		
Objective response rate	n	%	IC 95%	n	%	IC 95%	n	%	IC 95%
CR or PR	3	12.50	[2.66; 32.36]	5	25.00	[8.66; 49.10]	8	18.18	[8.19; 32.71]
No CR or PR	21	87.50	[67.64; 97.34]	15	75.00	[50.90; 91.34]	36	81.82	[67.29; 91.81]

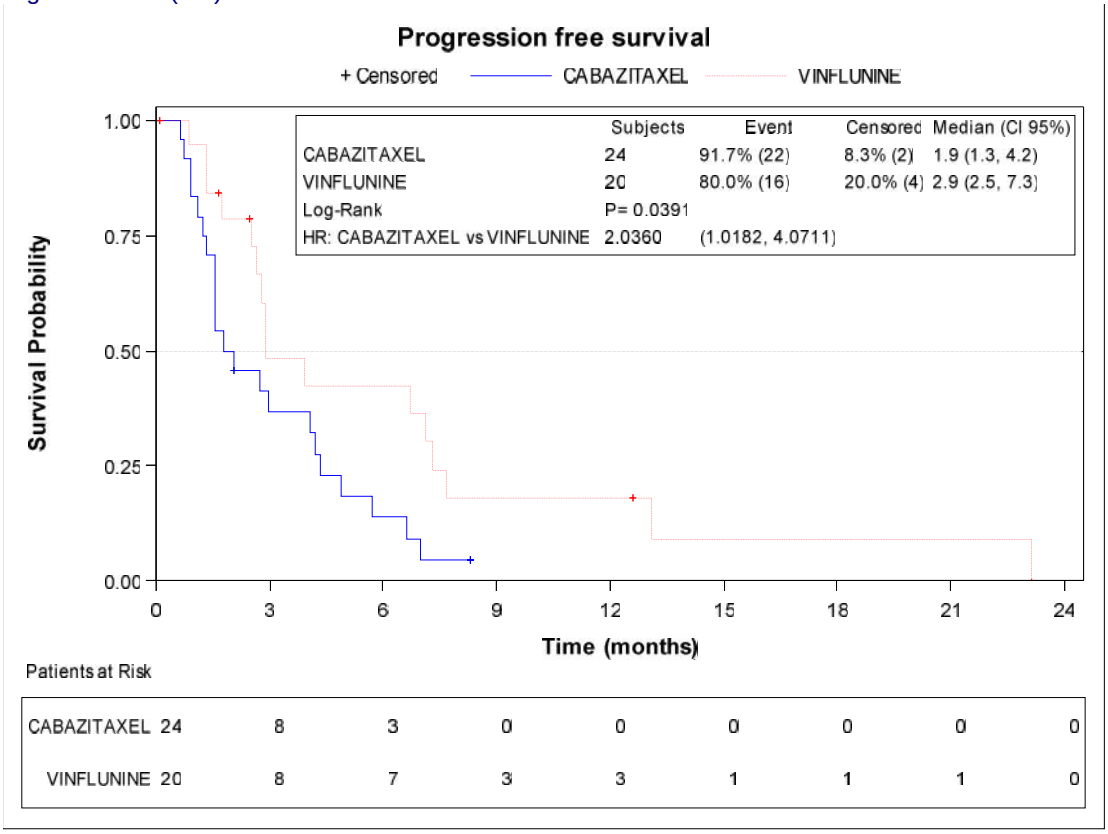
8.5.2.2 Secondary endpoints. PFS

Statistical significant differences were detected for this population also according to Log-rank (p=0.0391) and through the Cox model (p=0.0.443), HR 2.04(95% CI 1.02-4.07).

Table 23. PFS resume(PP)

	CABAZITAXEL	VINFLUNINE
Summary of events		
No of patients	24	20
No of patients with event	22 (91.67%)	16 (80.00%)
Earliest contributing event:		
1	18	15
2	4	1
No of censored patients	2 (8.33%)	4 (20.00%)
Progression free survival		
Median (95% CI)	1.91 (1.35, 4.21)	2.89 (2.50, 7.30)
25th-75th percentile	1.28 - 4.34	2.50 - 7.30
Percent PFS (%)		
0 Months	100.00	100.00
6 Months	13.75	42.32
12 Months	.	18.14
18 Months	.	9.07
24 Months	.	0.00
Stratified analysis		
P-value (Log-rank)		0.0391
Cox Model	Hazard ratio (95% CI)	Cox Model P-value
CABAZITAXEL vs VINFLUNINE	2.0360 (1.0182, 4.0711)	0.0443

Figure 3. PFS(PP)

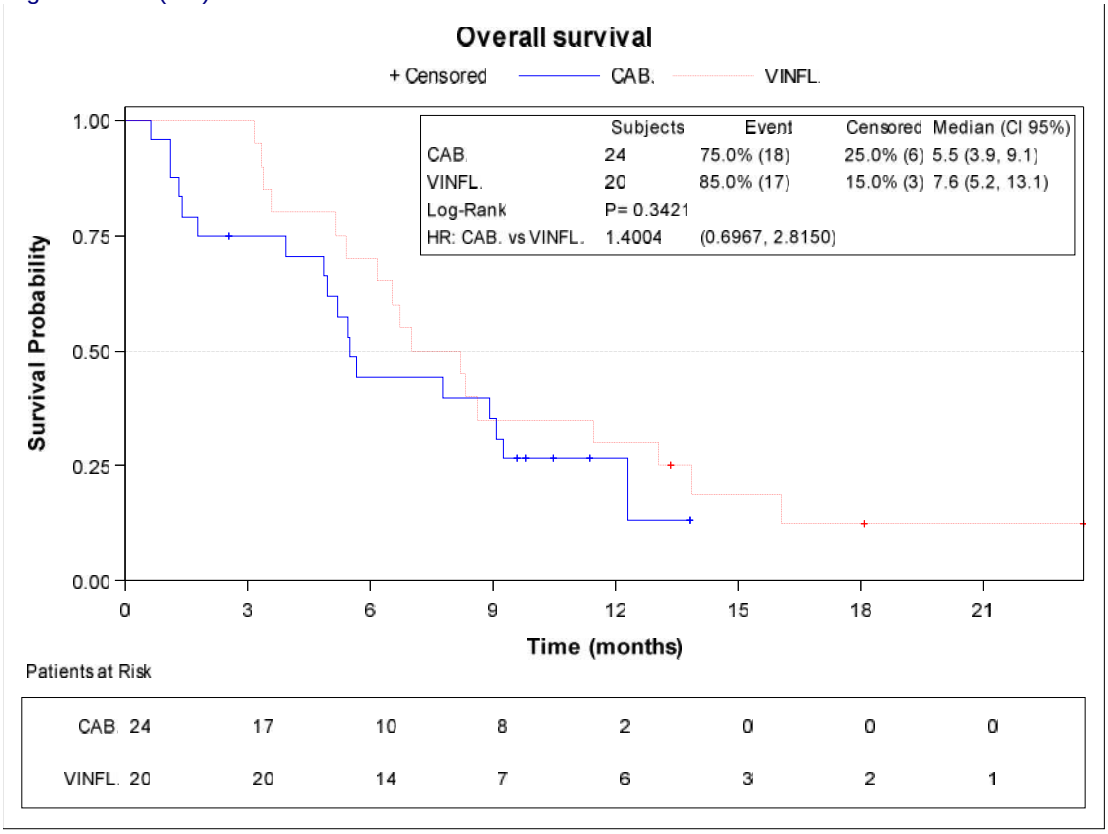


8.5.2.3 Secondary endpoints. OS

Table 24. OS resume(PP)

	CABAZITAXEL	VINFLUNINE
Summary of events		
No of patients	24	20
No of patients with event	18 (75.00%)	17 (85.00%)
No of censored patients	6 (25.00%)	3 (15.00%)
Overall survival		
Median (95% CI)	5.49 (3.95, 9.07)	7.59 (5.16, 13.05)
25th-75th percentile	2.86 - 12.30	5.29 - 13.46
Percent Survival (%)		
0 Months	100.00	100.00
6 Months	44.12	70.00
12 Months	26.47	30.00
18 Months	.	12.50
Stratified analysis		
P-value (Log-rank)		0.3421
Cox Model	Hazard ratio (95% CI)	Cox Model P-value
CABAZITAXEL vs VINFLUNINE	1.4004 (0.6967, 2.8150)	0.3445

Figure 4. OS(PP)



8.6 SAFETY ANALYSES

The safety evaluation was performed on the safety population.

8.6.1 Extent of Exposure

8.6.1.1 Follow-up time

The follow-up time is defined as the time from randomization date to the last contact date.

This endpoint was calculated taking into account the overall survival results but patients who died were censored at the death date.

Table 25. Follow-up time

	CABAZITAXEL	VINFLUNINE
Summary of events		
No of patients	35	35
No of patients with event	6 (17.14%)	7 (20.00%)
No of censored patients	29 (82.86%)	28 (80.00%)
Follow-up time resume		
Median (95% CI)	13.81 (9.80, NA)	17.88 (13.35, 23.47)
25th-75th percentile	10.49 - NA	14.92 - 18.64
Percent Survival (%)		
0 Months	100.00	100.00
6 Months	96.43	100.00
12 Months	55.10	100.00
18 Months	27.55	48.61
24 Months	.	0.00
Stratified analysis		
P-value (Log-rank)		0.1077
Cox Model	Hazard ratio (95% CI)	Cox Model P-value
VINFLUNINE vs CABAZITAXEL	0.3971 (0.1244, 1.2679)	0.1189

8.6.1.2 Duration of treatment

The duration of treatment for each patient was computed as the time from the date of the first drug administration to the end of treatment date+21 days (1 cycle), then this time was converted into months.

Table 26. Duration of treatment(months)

		CABAZITAXEL (N=35)	VINFLUNINE (N=35)	Total (N=70)	P Value Test
Duration of treatment(months)					
	N	35	35	70	
	Mean (SD)	2.43 (1.89)	4.42 (4.78)	3.43 (3.75)	
	Median [Q1,Q3]	1.41 [1.38, 3.98]	2.76 [1.38, 7.13]	1.59 [1.38, 4.37]	Wilcoxon: 0.1357
	Min, Max	0.69, 7.07	0.69, 22.92	0.69, 22.92	
	Shapiro Wilk	< 0.0001	< 0.0001	< 0.0001	

8.6.1.3 End of treatment

In this section the reasons for ending the treatment are described as were reported in the clinical database. According to the Fisher exact test(p=0.0401), there is an association between end of treatment reasons and treatment arm.

Table 27. End of treatment reasons

		CABAZITAXEL (N=35)	VINFLUNINE (N=35)	Total (N=70)	P Value Test
End of treatment reasons					
Withdrawal of inform consent and/or rejection of the treatment and/or uncooperativeness	n (%)	1 (2.86)	6 (17.14)	7 (10.00)	Fisher: 0.0401
Death	n (%)	3 (8.57)	0 (0.00)	3 (4.29)	
Disease progression	n (%)	24 (68.57)	23 (65.71)	47 (67.14)	
Adverse event	n (%)	4 (11.43)	3 (8.57)	7 (10.00)	
At the discretion of the Investigator or Sponsor	n (%)	0 (0.00)	1 (2.86)	1 (1.43)	
Other reasons,specify	n (%)	3 (8.57)	0 (0.00)	3 (4.29)	
Missing[(1)]	n (%)	0 (0.00)	2 (5.71)	2 (2.86)	

Note: [(1)] Patients no. 2301 and 3109 did not withdraw early from study treatment and that is why the end of treatment reason was missing.

The reasons that were specified are listed below.

Listing 2. Reasons specified by patient

Treatment group	Patient number	Reasons for early withdrawal	Adverse events specify	Other reasons, specify	Death cause	No. of received cycles	Duration of treatment (months)
CABAZITAXEL	1103	Death			Malignant disease	1	0.69
CABAZITAXEL	1504	Other reasons,specify		INVESTIGATOR CRITERIA DUE MAXIMUM BENEFIT REACHED		8	5.52
CABAZITAXEL	1505	Other reasons,specify		ECOG 4 (11FEB2014)		2	1.41
CABAZITAXEL	1508	Other reasons,specify		ECOG 3		1	0.69
CABAZITAXEL	2711	Adverse event	PNEUMONIA			1	0.69
CABAZITAXEL	2905	Adverse event	ABCESO			2	1.38
CABAZITAXEL	2906	Death			Malignant disease	1	0.69
CABAZITAXEL	3104	Death			Malignant disease	1	0.69
CABAZITAXEL	3110	Adverse event	PERIPHERAL NEUROPATHY WITH DIFFICULTY WALKING			10	7.00
CABAZITAXEL	3401	Adverse event	SEVERE ALLERGIC REACTION			2	1.55
VINFLUNINE	1701	Adverse event	LOW AWARENESS LEVEL DUE TO PROGRESSION DISEASE			33	22.92

Treatment group	Patient number	Reasons for early withdrawal	Adverse events specify	Other reasons, specify	Death cause	No. of received cycles	Duration of treatment (months)
VINFLUNINE	2701	Adverse event	MALAISE			1	0.69
VINFLUNINE	3002	Adverse event	SEVERAL NEUTROPHENIA GRADE 3-4			7	5.49

8.6.1.4 End of study

The reasons for withdrawal from the study are detailed in the table below as they were reported.

		CABAZITAXEL (N=35)	VINFLUNINE (N=35)	Total (N=70)	P Value Test
End of study reasons					
Completion of the study period	n (%)	0 (0.00)	4 (11.43)	4 (5.71)	Fisher: 0.1290
Withdrawal of inform consent and/or uncooperativeness	n (%)	1 (2.86)	0 (0.00)	1 (1.43)	
Lost to follow-up	n (%)	0 (0.00)	1 (2.86)	1 (1.43)	
Death	n (%)	29 (82.86)	27 (77.14)	56 (80.00)	
At the discretion of the Investigator or Sponsor	n (%)	5 (14.29)	3 (8.57)	8 (11.43)	

The patient no. 3108 was lost to follow-up, but it was known that the patient died.

The causes for death were reported as 'Malignant disease' for fifty-one of the patients.

The five patients with "Unknown" as cause of death, are listed below.

These patients, except for patient no. 2306, had progressed some months before death event. The patient no. 2306 ended treatment due to withdrawal of inform consent and/or rejection of the treatment and/or uncooperativeness. Later, the patient died.

Listing 3. Patients for whom death reason was unknown

Treatment group	Patient number	Reasons for early withdrawal	Other cause, specify	Adverse Events, specify	Death cause	No. of received cycles	Duration of treatment(months)
CABAZITAXEL	2305	Death			UK	2	1.38
CABAZITAXEL	2311	Death	UNKNOWN		Other	2	1.38
VINFLUNINE	2306	Death	UNKNOWN		Other	1	0.69
VINFLUNINE	2309	Death	UNKNOWN		Other	4	2.86
VINFLUNINE	2310	Death	UNK		Other	4	2.76

8.6.1.5 Relative dose intensity

In this section the relative dose intensity and its components are described for each of the drugs administered in the study:

- Dose intensity is defined as the drug dose delivered per time unit and is expressed as mg/m2 per week.
- Relative dose intensity (RDI) is the ratio of administered dose intensity to planned (referenced) dose intensity, and can be expressed as a percentage:
    - RDI (%) = (Delivered Dose Intensity/Standard Dose Intensity) *100

In the vinflunine arm, RDI was calculated based on the following assumptions that were described in the study protocol:

Vinflunine will be given intravenously once every 21 days, starting at a dose of:

- 320 mg/m^2 in patients aged ≤75 years with PS 0 and no prior pelvic radiation
- 280 mg/m^2 in patients aged >75 - ≤80 years, or with PS 1 or prior pelvic radiation,
- 250 mg/m^2 in patients aged >80 years.

During the review of these assumptions to calculate the RDI, it was noted that some patients did not received the study first dose according to them. For some of these patients, PS from baseline was considered instead of PS from visit 1. But for the patients listed below there was a deviation:

- Patient no. 1502 should have received 280 mg/m^2 instead of 320 mg/m^2 in the first visit because of a PS 1. This deviation was notified to the sponsor but it was not considered as relevant.
- Patient no. 2701 received 280 mg/m^2 instead of 320 mg/m^2. This patient had just received 1 cycle of treatment.

Table 28. Relative dose intensity

		CABAZITAXEL (N=35)	VINFLUNINE (N=35)	Total (N=70)	P Value Test
Dose intensity(mg/wk)					
	N	35	35	70	
	Mean (SD)	7.60 (0.94)	92.80 (8.49)	50.20 (43.33)	
	Median [Q1,Q3]	7.95 [7.36, 8.13]	91.12 [86.05, 101.27]	41.98 [7.95, 91.12]	
	Min, Max	3.96, 8.45	75.52, 106.67	3.96, 106.67	
	Shapiro Wilk	< 0.0001	0.2147	< 0.0001	
Cumulative dose intensity(mg)					
	N	35	35	70	
	Mean (SD)	81.72 (65.34)	1809.29 (2030.93)	945.51 (1670.78)	
	Median [Q1,Q3]	50.00 [42.11, 125.62]	1028.16 [559.75, 2809.88]	250.28 [50.00, 1028.16]	
	Min, Max	24.50, 250.84	249.73, 10019.30	24.50, 10019.30	
	Shapiro Wilk	< 0.0001	< 0.0001	< 0.0001	
Weeks of treatment					
	N	35	35	70	
	Mean (SD)	7.71 (8.21)	16.36 (20.78)	12.04 (16.28)	
	Median [Q1,Q3]	3.29 [3.14, 14.43]	9.14 [3.14, 28.14]	4.07 [3.14, 16.14]	Wilcoxon: 0.1357
	Min, Max	0.14, 27.86	0.14, 96.71	0.14, 96.71	
	Shapiro Wilk	< 0.0001	< 0.0001	< 0.0001	
Relative Dose Intensity(%)					
	N	35	35	70	
	Mean (SD)	91.19 (11.31)	93.81 (7.47)	92.50 (9.61)	
	Median [Q1,Q3]	95.45 [88.32, 97.57]	94.37 [88.52, 98.38]	95.16 [88.52, 97.58]	Wilcoxon: 0.8699
	Min, Max	47.50, 101.36	79.25, 111.55	47.50, 111.55	
	Shapiro Wilk	< 0.0001	0.2935	< 0.0001	

8.6.1.6 Number of administered cycles

The absolute and relative frequencies of the number of administered cycles per patient are given in the next table.

It can be noted that when converting the number of cycles into a categorical variable, an assotiation between the number of cycles and the treatment arm were detected(p=0.0178).

Table 29. Number of cycles

		CABAZITAXEL (N=35)	VINFLUNINE (N=35)	Total (N=70)	P Value Test
Number of cycles					
	N	35	35	70	
	Mean (SD)	3.40 (2.68)	6.17 (6.71)	4.79 (5.26)	
	Median [Q1,Q3]	2.00 [2.00, 5.00]	4.00 [2.00, 10.00]	2.00 [2.00, 6.00]	Wilcoxon: 0.0586
	Min, Max	1.00, 10.00	1.00, 33.00	1.00, 33.00	
	Shapiro Wilk	< 0.0001	< 0.0001	< 0.0001	
Number of cycles					
1-3 cycles	n (%)	23 (65.71)	17 (48.57)	40 (57.14)	Fisher: 0.0178
4-10 cycles	n (%)	12 (34.29)	11 (31.43)	23 (32.86)	
>10 cycles	n (%)	0 (0.00)	7 (20.00)	7 (10.00)	

8.6.1.7 Dose delays

Dose delays are described in this section, twenty-eight (40%) of the patients had at least one dose delay for different reasons that are detailed below.

Table 30. Patients with at least one dose delay

		CABAZITAXEL (N=35)	VINFLUNINE (N=35)	Total (N=70)	P Value Test
Patients with any dose delay					
Yes	n (%)	12 (34.29)	16 (45.71)	28 (40.00)	Chi-Square: 0.3291
No	n (%)	23 (65.71)	19 (54.29)	42 (60.00)	

Table 31. Number of delays per patient

		CABAZITAXEL (N=35)	VINFLUNINE (N=35)	Total (N=70)	P Value Test
Number of delays per patient					
No delays	n (%)	23 (65.71)	19 (54.29)	42 (60.00)	Fisher: 0.3035
1 delay	n (%)	8 (22.86)	6 (17.14)	14 (20.00)	
2 delays	n (%)	3 (8.57)	5 (14.29)	8 (11.43)	
>=3 delays	n (%)	1 (2.86)	5 (14.29)	6 (8.57)	

In the following table the reasons for delays are provided. There is an assotiation between the reasons and the treatment arm according to the Fisher exact test(p=0.0408).

A patient could have had more than one delays, therefore the percentages in this table were calculated per cycle, i.e. a total of 28 cycles were delayed.

Table 32. Reasons for delays

		CABAZITAXEL (N=12)	VINFLUNINE (N=16)	Total (N=28)	P Value Test
Reasons for dose delays by cycle					
Tox.Hemat	n (%)	2 (11.11)	13 (33.33)	15 (26.32)	Fisher: 0.0408
Tox.Non.Hemat	n (%)	1 (5.56)	2 (5.13)	3 (5.26)	
Both	n (%)	2 (11.11)	0 (0.00)	2 (3.51)	
Non treatment related	n (%)	6 (33.33)	5 (12.82)	11 (19.30)	
Other	n (%)	7 (38.89)	19 (48.72)	26 (45.61)	

The texts that were specified were classified and are detailed in the table below.

Table 33. Reasons for dose delays specified in 'Other'

		CABAZITAXEL (N=7)	VINFLUNINE (N=19)	Total (N=26)	P Value Test
Reasons specified in other reasons					
ADMINISTRATIVE OR LOGISTICAL REASONS	n (%)	3 (42.86)	13 (68.42)	16 (61.54)	Fisher: 0.1790
ASRTENIA	n (%)	1 (14.29)	0 (0.00)	1 (3.85)	
NO MEDICATION IN PHARMACY	n (%)	0 (0.00)	2 (10.53)	2 (7.69)	
DISEASE PROGRESSION	n (%)	1 (14.29)	0 (0.00)	1 (3.85)	
PATIENT´S DIARY	n (%)	0 (0.00)	1 (5.26)	1 (3.85)	
RESPIRATORY INFECTION	n (%)	0 (0.00)	1 (5.26)	1 (3.85)	
SAE	n (%)	1 (14.29)	1 (5.26)	2 (7.69)	
URINARY INFECCION	n (%)	1 (14.29)	0 (0.00)	1 (3.85)	
SUSPICIONS OF DISEASE PROGRESSION	n (%)	0 (0.00)	1 (5.26)	1 (3.85)	

8.6.1.8 Dose reductions

Fifteen patients (42.9%) had a dose reduction in the vinflunine arm and seven patients (20%) in the cabazitaxel arm (p=0.0394).

Since dose reductions were allowed only once according to protocol, these patients had only one dose reduction through the study period.

Table 34. Patients with a dose reduction

		CABAZITAXEL (N=35)	VINFLUNINE (N=35)	Total (N=70)	P Value Test
Patients with a dose reduction					
Yes	n (%)	7 (20.00)	15 (42.86)	22 (31.43)	Chi-Square: 0.0394
No	n (%)	28 (80.00)	20 (57.14)	48 (68.57)	

Table 35. Reasons for dose reduction

		CABAZITAXEL (N=7)	VINFLUNINE (N=15)	Total (N=22)	P Value Test
Reasons for dose reductions per patient					
Tox.Hemat	n (%)	3 (42.86)	4 (23.53)	7 (29.17)	Fisher: 0.0595
Tox.Non.Hemat	n (%)	2 (28.57)	8 (47.06)	10 (41.67)	
Both	n (%)	2 (28.57)	0 (0.00)	2 (8.33)	
Other	n (%)	0 (0.00)	5 (29.41)	5 (20.83)	

The following table lists the specified reasons for the patients for whom 'Other' reason was reported.

Listing 4. Reasons for dose reductions specified in 'Other'

Treatment group	Patient number	Visit	Reduction reason	2-3-4 specify
VINFLUNINE	1902	VISIT 3	Other	PERIPHERAL NEUROPATHY
VINFLUNINE	2101	VISIT 5	Other	WEIGHT LOSS
VINFLUNINE	2701	VISIT 1	Other	RENAL INSUFFICIENCY
VINFLUNINE	2706	VISIT 2	Other	WHO=2
VINFLUNINE	2710	VISIT 1	Other	WHO=1

8.6.2 Adverse Events

For the statistical tables, adverse events terms were coded according to the Medical Dictionary of Regulatory Activities (MedDRA 18.1) system. Their intensity was coded when it was reported in the eCRF by (NCI-CTCAE) v4.0 toxicity criteria.

An adverse event (AE) is any untoward medical event that occurs in a patient who has received the study investigational drug, and does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of the study investigational product, whether or not related to the product.

A treatment-emergent AE (TEAE) is defined as an AE that begins or that worsens in severity after at least one dose of the study investigational drug has been administered.
Any event for which the onset date was missing, was assumed to be treatment-emergent.
The analysis of adverse events was performed based on the TEAEs.
The frequency of patients experiencing any TEAE were summarized using counts and percentages. For any given MedDRA preferred term, a patient contributed only a single count to the incidence by its maximum severity (AE grade), even if the patient had multiple occurrences of the event over the study treatment period.
According to the definition of TEAEs, a listing with the adverse events that were not considered as TEAEs is provided in the appendix 1 of the FSR.

The following table summarizes the patients with TEAEs according to its main features.

Table 36. Summary of patients according to TEAEs

		CABAZITAXEL (N=35)	VINFLUNINE (N=35)	Total (N=70)	P-Value
Summary of patients according to TEAEs					
Patients with at least one TEAE	n (%)	35 (100.00)	35 (100.00)	70 (100.00)	NA
Patients with at least one grade 3/4 TEAE	n (%)	21 (60.00)	21 (60.00)	42 (60.00)	Chi-Square: 1.0000
Patients with at least one TEAE that led to permanently treatment discontinuation	n (%)	9 (25.71)	4 (11.43)	13 (18.57)	Chi-Square: 0.1243
Patients with at least one TEAE that led to death	n (%)	4 (11.43)	0 (0.00%)	4 (5.71)	Fisher: 0.1142
Patients with at least one serious TEAE	n (%)	20 (57.14)	18 (51.43)	38 (54.29)	Chi-Square: 0.6313
Patients with at least one TEAE that the investigator considered related with study medication	n (%)	29 (82.86)	32 (91.43)	61 (87.14)	Fisher: 0.4773
Patients with at least one grade 3/4 TEAE that the investigator considered related with study medication	n (%)	15 (42.86)	14 (40.00)	29 (41.43)	Chi-Square: 0.8083
Patients with at least one TEAE that the investigator considered related with study medication and lead to death	n (%)	1 (2.86)	0 (0.00%)	1 (1.43)	Fisher: 1.0000
Patients with at least one TEAE that the investigator considered related and led to permanently treatment discontinuation	n (%)	4 (11.43)	3 (8.57)	7 (10.00)	Fisher: 1.0000

A listing with all the AEs (TEAEs and not TEAEs) is provided in the appendix 1 of the FSR.

The following listing shows the four TEAEs in the cabacitaxel arm that led to death and for which severity reported was 5='Death'.

Listing 5. TEAEs that led to death

Patient number	AE Verbatim term	Preferred Term	AE or Disease Grade	AE serious ?	Outcome	Action Taken	Relation with study treatment	Onset date (char)	Stop date (char)
1103	CLINICAL DETERIORATION	General physical health deterioration	5	Yes	Death	Permanently discontinued/omitted	No	26/05/2015	02/06/2015
1405	DISEASE PROGRESSION	Disease progression	5	Yes	Death	Permanently discontinued/omitted	No	23/10/2014	13/11/2014
2906	RENAL FAILURE	Renal failure	5	Yes	Death	Permanently discontinued/omitted	Yes	05/12/2014	10/12/2014
3104	RESPIRATORY INSUFICIENCY	Respiratory failure	5	Yes	Death	None	No	03/03/2014	05/03/2014

Table 37. TEAEs.Worst grade per patient (Most frequent>5%)

Preferred MedDRA Term	Treatment/Grade																		Total(N=70)	
	CABAZITAXEL(N=35)										VINFLUNINE(N=35)									
	G1		G2		G3		G4		G5		G1		G2		GG3		4			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Constipation	4	11.43	2	5.71	.	.	.	.	.	.	12	34.29	8	22.86	4	11.43	.	.	30	42.86
Fatigue	6	17.14	5	14.29	.	.	.	.	.	.	6	17.14	2	5.71	6	17.14	.	.	25	35.71
Decreased appetite	6	17.14	4	11.43	1	2.86	.	.	.	.	2	5.71	8	22.86	2	5.71	.	.	23	32.86
Nausea	5	14.29	1	2.86	1	2.86	.	.	.	.	14	40.00	2	5.71	.	.	.	.	23	32.86
Asthenia	2	5.71	3	8.57	3	8.57	.	.	.	.	5	14.29	9	25.71	.	.	.	.	22	31.43
Diarrhoea	4	11.43	7	20.00	2	5.71	.	.	.	.	3	8.57	2	5.71	.	.	.	.	18	25.71
Pyrexia	5	14.29	2	5.71	1	2.86	.	.	.	.	10	28.57	.	.	.	.	.	.	18	25.71
Neutropenia	.	.	.	.	2	5.71	3	8.57	.	.	.	.	4	11.43	.	.	4	11.43	13	18.57
Urinary tract infection	.	.	4	11.43	5	14.29	.	.	.	.	1	2.86	1	2.86	1	2.86	.	.	12	17.14
Anaemia	2	5.71	3	8.57	4	11.43	.	.	.	.	.	.	3	8.57	.	.	.	.	12	17.14
Vomiting	3	8.57	.	.	1	2.86	.	.	.	.	6	17.14	1	2.86	.	.	.	.	11	15.71
Febrile neutropenia	1	2.86	.	.	3	8.57	3	8.57	.	.	.	.	.	.	1	2.86	2	5.71	10	14.29
Mucosal inflammation	2	5.71	.	.	.	.	.	.	.	.	6	17.14	1	2.86	.	.	.	.	9	12.86
Back pain	5	14.29	.	.	.	.	.	.	.	.	1	2.86	2	5.71	.	.	.	.	8	11.43
Alopecia	1	2.86	2	5.71	.	.	.	.	.	.	2	5.71	3	8.57	.	.	.	.	8	11.43
Abdominal pain	.	.	2	5.71	.	.	.	.	.	.	5	14.29	1	2.86	.	.	.	.	8	11.43
Musculoskeletal pain	2	5.71	1	2.86	1	2.86	.	.	.	.	2	5.71	1	2.86	.	.	.	.	7	10.00
Respiratory tract infection	.	.	1	2.86	.	.	.	.	.	.	1	2.86	3	8.57	1	2.86	.	.	6	8.57
Myalgia	.	.	.	.	.	.	.	.	.	.	6	17.14	.	.	.	.	.	.	6	8.57
Dyspnoea	1	2.86	.	.	1	2.86	.	.	.	.	1	2.86	1	2.86	2	5.71	.	.	6	8.57
Pain	.	.	1	2.86	2	5.71	.	.	.	.	.	.	2	5.71	.	.	.	.	5	7.14
Pain in extremity	2	5.71	1	2.86	.	.	.	.	.	.	1	2.86	1	2.86	.	.	.	.	5	7.14
Cough	2	5.71	1	2.86	.	.	.	.	.	.	1	2.86	.	.	1	2.86	.	.	5	7.14
Oedema peripheral	1	2.86	.	.	.	.	.	.	.	.	4	11.43	.	.	.	.	.	.	5	7.14
Malaise	.	.	2	5.71	.	.	.	.	.	.	1	2.86	2	5.71	.	.	.	.	5	7.14
Dysgeusia	2	5.71	.	.	.	.	.	.	.	.	1	2.86	1	2.86	.	.	.	.	4	5.71
Dry mouth	1	2.86	1	2.86	.	.	.	.	.	.	2	5.71	.	.	.	.	.	.	4	5.71
Paraesthesia	2	5.71	2	5.71	.	.	.	.	.	.	.	.	.	.	.	.	.	.	4	5.71
Abdominal pain upper	.	.	1	2.86	.	.	.	.	.	.	2	5.71	1	2.86	.	.	.	.	4	5.71
Dyspepsia	1	2.86	1	2.86	.	.	.	.	.	.	.	.	2	5.71	.	.	.	.	4	5.71
Arthralgia	1	2.86	1	2.86	.	.	.	.	.	.	1	2.86	1	2.86	.	.	.	.	4	5.71
Somnolence	1	2.86	.	.	.	.	.	.	.	.	2	5.71	1	2.86	.	.	.	.	4	5.71
Haematuria	1	2.86	.	.	1	2.86	.	.	.	.	2	5.71	.	.	.	.	.	.	4	5.71

Note: The table that provides with all the adverse events independently of their frequency, are listed in the appendix 1 of the FSR.

Table 38. TEAEs.Worst grade per patient (grades 3-4-5)(Most frequent>5%)

Preferred MedDRA Term	Treatment/Grade										Total(N=70)	
	CABAZITAXEL(N=35)						VINFLUNINE(N=35)					
	G3		G4		G5		G3		G4			
	n	%	n	%	n	%	n	%	n	%	n	%
Neutropenia	2	5.71	3	8.57	.	.	.	.	4	11.43	9	12.86
Febrile neutropenia	3	8.57	3	8.57	.	.	1	2.86	2	5.71	9	12.86
Fatigue	.	.	.	.	.	.	6	17.14	.	.	6	8.57
Urinary tract infection	5	14.29	.	.	.	.	1	2.86	.	.	6	8.57
Constipation	.	.	.	.	.	.	4	11.43	.	.	4	5.71
Anaemia	4	11.43	.	.	.	.	.	.	.	.	4	5.71

Note: The table that provides with all the adverse events independently of their frequency, are listed in the appendix 1 of the FSR.

Table 39. Worst grade per patient (Related to treatment) (Most frequent>5%)

Preferred MedDRA Term	Treatment/Grade																		Total(N=70)	
	CABAZITAXEL(N=35)										VINFLUNINE(N=35)									
	G1		G2		G3		G4		G5		G1		G2		G3		G4			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Constipation	2	5.71	.	.	.	.	.	.	.	.	9	25.71	6	17.14	3	8.57	.	.	20	28.57
Nausea	4	11.43	1	2.86	.	.	.	.	.	.	12	34.29	2	5.71	.	.	.	.	19	27.14
Asthenia	1	2.86	3	8.57	2	5.71	.	.	.	.	5	14.29	6	17.14	.	.	.	.	17	24.29
Fatigue	3	8.57	2	5.71	.	.	.	.	.	.	6	17.14	1	2.86	5	14.29	.	.	17	24.29
Decreased appetite	3	8.57	2	5.71	.	.	.	.	.	.	1	2.86	6	17.14	2	5.71	.	.	14	20.00
Neutropenia	.	.	.	.	2	5.71	2	5.71	.	.	.	.	4	11.43	.	.	4	11.43	12	17.14
Diarrhoea	3	8.57	3	8.57	1	2.86	.	.	.	.	4	11.43	.	.	.	.	.	.	11	15.71
Anaemia	2	5.71	2	5.71	2	5.71	.	.	.	.	.	.	3	8.57	.	.	.	.	9	12.86
Febrile neutropenia	1	2.86	.	.	2	5.71	3	8.57	.	.	.	.	.	.	1	2.86	2	5.71	9	12.86
Alopecia	1	2.86	2	5.71	.	.	.	.	.	.	2	5.71	2	5.71	.	.	.	.	7	10.00
Pyrexia	2	5.71	1	2.86	.	.	.	.	.	.	4	11.43	.	.	.	.	.	.	7	10.00
Mucosal inflammation	2	5.71	.	.	.	.	.	.	.	.	4	11.43	1	2.86	.	.	.	.	7	10.00
Vomiting	1	2.86	.	.	.	.	.	.	.	.	5	14.29	.	.	.	.	.	.	6	8.57
Dry mouth	1	2.86	1	2.86	.	.	.	.	.	.	2	5.71	.	.	.	.	.	.	4	5.71
Paraesthesia	2	5.71	2	5.71	.	.	.	.	.	.	.	.	.	.	.	.	.	.	4	5.71
Malaise	.	.	2	5.71	.	.	.	.	.	.	.	.	2	5.71	.	.	.	.	4	5.71

Note: The table that provides with all the adverse events independently of their frequency, are listed in the appendix 1 of the FSR.

9 APPENDIX

The following appendix is part of the final statistical report:

- SECAVIN-12. FSR. Appendix 1(Version 1.0-16-June-2016).docx