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Title: A randomized Phase II/III study of cabazitaxel versus vinflunine in metastatic or locally advanced transitional cell carcinoma of the urothelium (SECAVIN)

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Running title: cabazitaxel versus vinflunine in urothelial cancer.

Abstract:

BACKGROUND: Despite the advent of immunotherapy in urothelial cancer, there is still a need to find effective cytotoxic agents beyond first and second line. Vinflunine is the only treatment approved in this setting by the European Medicines Agency (EMA) and taxanes are also widely used in second line. Cabazitaxel is a taxane with activity in docetaxel-refractory cancers. A randomized study was conducted to compare its efficacy vs vinflunine.

PATIENTS AND METHODS: This is a multicenter, randomized, open-label, phase II/III study, following a Simon's optimal method with stopping rules based on an interim futility analysis and a formal efficacy analysis at the end of the phase II. ECOG Performance Status, anaemia and liver metastases were stratification factors. Primary objectives were overall response rate for the phase II and overall survival for the phase III.

RESULTS: Seventy patients were included in the phase II across 19 institutions in Europe. Baseline characteristics were well balanced between the two arms. Three patients (13%) obtained a partial response on cabazitaxel (95% CI, 2.7–32.4) and six patients (30%) in the vinflunine arm (95% CI, 11.9–54.3). Median progression free survival for cabazitaxel was 1.9 months versus 2.9 months for vinflunine (p=0.039). The study did not proceed to phase III since the futility analysis showed a lack of efficacy of cabazitaxel. A trend for overall survival benefit was found favouring vinflunine (median 7.6 versus 5.5 months). Grade 3-4 related adverse events were seen in 41% patients with no difference between the two arms.

CONCLUSION: This phase II/III second line bladder study comparing cabazitaxel with vinflunine was closed when the phase II showed a lack of efficacy of the cabazitaxel arm. Vinflunine results were consistent with those known previously.

Trial number: NCT01830231

Key words: urothelial cancer, cabazitaxel, vinflunine

Key message:

There is a clear lack of randomized trials in the second line setting of bladder cancer. In this randomized phase II/III study investigating cabazitaxel versus vinflunine in patients with metastatic bladder cancer failing platinum based chemotherapy it was found in the phase II part of the study that cabazitaxel had only modest activity and therefore the study did not continue into phase III.

Introduction

Urothelial tumors are chemosensitive. The percentage of patients who respond to active cytostatics administered in monotherapy is modest (1), but several combinations have demonstrated survival benefit, including the M-VAC regimen (methotrexate, vinblastine, adriamycin and cisplatin) and cisplatin-gemcitabine doublet (1-3), with response rates ranging 40-70% (2-6).

Almost all patients who respond initially will ultimately progress, and survival in second line is approximately 6-7 months (7). Vinflunine was approved by EMA in this second line setting based on a 2 month overall survival (OS) benefit versus best supportive care (BSC) (8). Both docetaxel and paclitaxel are also widely used in second line based on phase II data (7,9). Recent data indicate that immunotherapeutic agents confer a survival benefit, but these are effective in only 20% of the patients (10).

Cabazitaxel is a taxane active in tumors sensitive to docetaxel, and also in tumor models insensitive to several chemotherapy agents, including docetaxel (11). Cabazitaxel is an active drug in prostate cancer, commonly used after docetaxel failure (11).

A randomized study was designed to compare vinflunine versus cabazitaxel in patients with advanced or metastatic urothelial cancer failing first-line chemotherapy.

Patients and Methods

This is a phase II/III clinical trial of cabazitaxel versus vinflunine as second-line treatment in patients with advanced or metastatic urothelial cancer, excluding the subset of patients with an anticipated OS less than 4 months, based on the prognostic model previously described in second line (12).

Due to limited experience with cabazitaxel in urothelial tumors, the study started as a randomized phase II study. Primary objective of this phase II study was to assess the efficacy of cabazitaxel compared to vinflunine in terms of improved overall response rate (ORR) in subjects with metastatic or locally advanced transitional cell carcinoma of the urothelium (TCCU). The aim of this phase II is to evaluate if the ORR was sufficiently high to further study the treatment in a phase III setting. In the phase II, 35 patients were included in each arm; five responses were required (ORR<15%) in the cabazitaxel group to conclude that the regimen warranted further testing. At the end of the phase II study an interim analysis was planned before proceeding to the phase III.

Eligibility criteria

Inclusion criteria were as follows: patients older than 18 years old with ECOG ≤1 and proven histology of confirmed transitional cell carcinoma of the urothelium. Eligible patients included: patients having T4bN0M0, T any with N2-3 M0 or TxNxM1 with measurable disease, as defined by the RECIST criteria v1.1; one prior platinum-based chemotherapy treatment for locally advanced or stage IV TCCU was mandatory (prior

platinum-based adjuvant or neoadjuvant therapy was allowed if more than 6 months had elapsed since the end of adjuvant or neoadjuvant therapy till tumor relapse); and adequate hematological, coagulation, hepatic, renal were required. Cardiac function was assessed in all patients. A signed informed consent was obtained from each participant prior to any study specific procedure.

The study was carried out with the approval of the Institutional Ethics committee of all the participating institutions. This study was registered in clinicaltrials.gov as NCT01830231.

Random assignment of treatment was stratified by the presence of 0 versus 1 of the following unfavourable prognostic risk factors proposed by Bellmunt et al (14): ECOG performance status (PS) 1, anaemia with Hb <10 g/dl and presence of liver metastases.

Treatment schedule

Patients received the study drugs with the following doses: cabazitaxel 25 mg/m^2 as a 1-hour intravenous infusion or vinflunine, starting at a dose of 320 mg/m^2 in patients aged ≤75 years with PS 0 and no prior pelvic radiation; of 280 mg/m2 in patients aged >75-≤80 years, and/or with PS 1 and/or prior pelvic radiation; and of 250 mg/m2 in patients aged >80 years. Cycles with both drugs were scheduled every 21 days.

For cabazitaxel, dose could be reduced from 25 mg/m^2 to 20 mg/m^2. Only one intrapatient dose reduction was permitted. Dose reductions were considered in case of grade 3-4 neutropenia lasting more than 7 days, febrile neutropenia, grade 3-4 thrombocytopenia, or grade 3 non-hematologic toxicity.

Vinflunine dose reduction or delay was handled according to the summary of product characteristics. Up to two dose reductions were allowed.

Tumor evaluations were scheduled every 6 weeks (±2 weeks) until progression.
Patients with disease progression during the treatment phase were withdrawn from the study and received subsequent treatment according to the investigator's judgment and were followed for OS.

Patients were assessed for toxicity, according to the National Cancer Institute Common Toxicity Criteria Adverse event (NCI-CTCAE) version 4.0 and were codified according to MedDRA dictionary.

Evaluations during the study

Pre-treatment evaluation included a complete medical history, physical examination, hematology and biochemistry test, coagulation profile, LEVF assessment, ECG, tumor evaluation by imaging techniques, and pregnancy test for women with childbearing potential. Complete blood cell counts and differential, biochemistry and coagulation profile were repeated every 3 weeks, as well as medical history and physical examination.

Statistical considerations

The primary objective for the phase II part was to determine ORR, which included the sum of the complete and partial responses (CR+PR) according to RECIST criteria v1.1.

Sample size for the phase II part of the study was calculated using Simon's optimal method (13), in which cabazitaxel would be considered to be effective in each prognostic sub-group if an ORR of 15% were reached. 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 interim analysis were scheduled: first one after 12 patients were included in each arm, requiring at least one response in the cabazitaxel arm to continue the study as planned, and one formal analysis after phase II was completed to evaluate whether to move to phase III. In the first preliminary analysis, according to the stopping rules, if one or fewer responses were observed in the cabazitaxel arm, the study should have been stopped. At this point, only one partial response was achieved in the cabazitaxel arm. However, these data were reviewed by an Independent Assessment Committee and, since a trend of improvement in PFS was seen in the cabazitaxel arm, it was recommended to complete the phase II.

Consequently, at the end of the phase II study, an interim efficacy analysis was performed in order to decide whether proceeding to the phase III. At this interim analysis, a minimum response rate of 15% was required in the overall patient population lumping together patients with 0 or 1 adverse risk factors (20% in patients with 0 risk factors).

Results

From June 2013 to April 2015, 70 patients were included in the phase II study across 19 institutions in Europe, comprising sites from the Spanish Oncology Genito-Urinary Group (SOGUG) and the Dutch Uro-Oncology Studygroup (DUOS). Patients were randomly assigned 1:1 to vinflunine (35 patients) or cabazitaxel (35 patients). All of them were considered for the intention to treat (ITT) and safety analysis. Baseline characteristics were well balanced between the two arms. The mean age was 63 years with a range of 35-80 years, 56 (80%) were men. Most patients had received previously a platinum doublet. In the cabazitaxel arm six patients (17.1%) had received carboplatin-gemcitabine and 28 patients (80%) received cisplatin-gemcitabine whereas, in the vinflunine arm, 14 patients (40%) received carboplatin-gemcitabine and 20 patients (57.1%) received cisplatin-gemcitabine. Additional patient characteristics are presented in Supplementary table 1.

Treatment compliance

Median duration of treatment was 1.41 months (Q1 1.38, Q3 3.98) for cabazitaxel and 2.76 months (Q1 1.38, Q3 7.13) for vinflunine.

Median number of cycles administered per patient was 2 for cabazitaxel (range 1-10) and 4 for vinflunine (range 1-33). Twelve patients (34.3%) had dose delays in the cabazitaxel arm, and 16 (45.7%) in the vinflunine arm. Fifteen (42.9%) had a dose reduction in at least one treatment cycle in the vinflunine arm, mainly due to non-hematologic toxicity (eight patients); seven patients (20%) had a dose reduction in the cabazitaxel arm, mainly because of hematologic toxicity (three patients). Progressive disease was the cause of treatment discontinuation for most patients (49 patients in total, 70%). 21 patients withdrew prematurely from the study due to the following reasons: withdrawal of consent (1 patient in cabazitaxel arm, 6 patients in vinflunine arm); death (3 patients in cabazitaxel arm: two due to suspected disease progression; and one due to grade 5 adverse event); adverse events (4 patients in cabazitaxel arm, 3 patients in vinflunine arm); investigator's decision (2 patients in vinflunine arm), deterioration of ECOG (2 patients in vinflunine arm); and maximum benefit reached (one patient, after eight cycles, in cabazitaxel arm).

Adverse events in the cabazitaxel arm causing treatment withdrawal were pneumonia, sepsis, peripheral neuropathy and allergic reaction, whereas in the vinflunine arm those included asthenia in two patients and grade 4 neutropenia in one patient.

Efficacy

Efficacy results are first presented in both the evaluable and the ITT population.

Three patients (13%) obtained a partial response on cabazitaxel (95% CI, 2.7–32.4) and six patients (30%) in the vinflunine arm (95% CI, 11.9–54.3). No complete responses were seen. No statistically significant differences were detected between two treatment arms for ORR (p=0.26).

Median PFS for cabazitaxel was 1.9 months versus 2.9 months for vinflunine (p=0.039) for the evaluable population (44 patients).
(Figure 1).

Statistically significant differences were not seen for OS, but a non-significant trend for OS was found in favor of vinflunine (median 7.6 versus 5.5 months, p=0.34). See Figure 2.

Focusing on the ITT population (70 patients), median PFS was 1.8 months for cabazitaxel versus 2.9 months for vinflunine (p=0.0192). Median OS for cabazitaxel was 5.49 versus 8.35 months for vinflunine (p=0.1193).

The study did not proceed to phase III since the interim analysis showed a lack of efficacy of cabazitaxel based on ORR.

Toxicity

All 70 patients were included in the safety analysis. Fifty-six (80%) patients had at least one grade 3-4 adverse event (AE), but only 29 (41%) had grade 3-4 related adverse events, with no difference between arms. A detailed description of toxicity is shown in supplementary table 2.

Discussion

Cabazitaxel failed to demonstrate sufficient activity in the phase II part of the study to be further tested in a phase III study in patients with advanced TCCU that recurred or progressed following platinum-based chemotherapy.

It is now known that response rates to treatment vary depending on factors related to the patient and the disease. Recently, prognostic factors have been defined in pretreated patients. Multivariate analyses and internal validation identified the following prognostic factors: ECOG performance status >0, hemoglobin level <10 g/dL, and the presence of liver metastases (12). Because of well recognized patient heterogeneity in the second line setting, this trial took into account patient selection based on these prognostic factors.

In the last decade, several compounds have been investigated in this setting. Pemetrexed was analyzed in two phase II studies as with good results in the first of them (response rate 28% and OS 9.8 months) (14), and negative results in a second study (15). Recent MSKCC retrospective analysis has confirmed the limited of efficacy of this agent (16). Vinflunine has arisen as a reasonable option. A phase III study compared vinflunine plus best supportive care (BSC) versus BSC (8) matching its primary endpoint, despite response rate was low (ORR 8.6 %).

Taxanes are widely used in second line despite the limited responses seen in small phase II trials (9, 17). Paclitaxel was extensively used in Europe before vinflunine's approval. Paclitaxel was investigated in three small phase II trials. In a cohort of 31 patients, response rate (RR) was 10% and median OS was 7.2 months. However, in the other two trials, RR was much lower (5%–7%). Similarly, docetaxel was investigated in a phase II with a RR 13% and median OS of 9 months (9,17).

Other chemotherapeutic drugs (irinotecan, oxaliplatin, topotecan, nab-paclitaxel, lapatinib, gefitinib, ixabepilone, bortezomib, ifosfamide, piritrexim, gemcitabine and doublets as paclitaxel-gemcitabine) have been tested, with modest response rates of 10-20%, median PFS ranging from 2-3 months and median OS ranging from 6-9 months (7).

There has been limited number of randomized trials in second line. The vandetanib trial (18) was unable to show a benefit of adding an anti EGF/VEGFr to docetaxel. The German trial (AUO) comparing short-term versus prolonged treatment with gemcitabine and paclitaxel was also negative (19). Other trials adding targeted agents like cetuximab have failed to show a benefit (20). A phase III trial is currently randomizing patient to ramucirumab + docetaxel vs docetaxel (NCT02426125) and a second trial of docetaxel

+ B-701 (a monoclonal antibody against FGFR3) vs docetaxel is recruiting patients in a phase II randomized (NCT02401542).

Overall, no chemotherapeutic agent has been able to demonstrate superiority in terms of survival against another active comparison.

Currently there are two drugs approved for second line treatment of bladder cancer: in USA, atezolizumab has been approved recently based on the positive results of a phase II study (10); in Europe, vinflunine was granted approval by EMA based on the phase III study comparing vinflunine plus BSC versus BSC (8).

Immunotherapy has been incorporated to the field of research in bladder cancer, with agents that block the interaction between programmed death-1 receptor and its ligand (PD-1/PD-L1), being atezolizumab the first to get FDA approval (10). Also nivolumab achieved a substantial and durable clinical response and a manageable safety profile in a recent phase II study. Objective response was achieved in 19 of 78 patients (24.4%, 95% CI 15.3-35.4) (21). More recently, durvalumab has granted breackthrough therapy designation by FDA for treatment of patients with PD-L1 positive urothelial cancer, with RR of 46% in patients with PD-L1–positive TCCU; it is also being tested as monotherapy and in combination with tremelimumab (CTLA-4 mAb) in the phase III DANUBE trial as 1st-line treatment (22).

In November 2016 the results of the KEYNOTE-045 (NCT02256436), a randomized phase III trial of pembrolizumab (200 mg q3w) versus chemotherapy in patients with previously treated metastatic urothelial cancer, were presented. The trial showed an OS of 10.3 months with pembrolizumab versus 7.4 months with chemotherapy with a hazard ratio 0.73 (95% CI: 0.59-0.91) showing for the first time ever a survival improvement over an active compound (chemotherapy) in the second-line setting. In addition, the incidence of adverse events was lower in the pembrolizumab arm (23).

This result and others that might confirm the survival benefit of immunotherapy in second line will change the way that we treat bladder cancer in the near future. The results of the other phase III trial in second line comparing atezolizumab vs chemotherapy (NCT02302807) are eagerly awaited.

Despite the recently shown benefit of immunotherapy in TCCU, there is still a need to find effective cytotoxic agents beyond first and second line. Second-line treatment and now third after failing immunotherapy will continue to be an unmet medical need as only 20% of patients are presently deriving benefit from immunotherapy.

Our study is the first phase II/III trial to compare a potentially active treatment like cabazitaxel with an already approved drug, vinflunine, which is considered standard of care treatment. We confirmed the safety profile of both cabazitaxel and vinflunine with findings being consistent with those previously reported in prostate and bladder cancer (8,24).

In our study, median OS was 5.5 months for cabazitaxel and 7.6 months for vinflunine; confirming the results observed in the phase III (6.9 months). Similar survival results have been observed with the use of vinflunine in daily clinical practice, as assessed by

Retz et al, in 77 TCCU patients, where vinflunine was administered predominantly in second and subsequent lines, (25) with a median OS being 7.7 months

A weakness of our study is the high number of patients that were excluded from the evaluable population (33%). This could bias the results, since early toxicity or progressions could have been excluded from the analysis.

New check point inhibitors other that PD-1/PD-L1 are now in clinical trials. Further studies beyond single agent immunotherapy and chemotherapy in second line bladder cancer are needed. The future will involve combination approaches. Based on the non-overlapping toxicity and completely different mechanism of action, studies combining pembrolizumab or atezolizumab with vinflunine and other agents are now planned or ongoing.

As a conclusion, this phase II/III second line bladder study comparing cabazitaxel with vinflunine was closed early due to lack of efficacy of the cabazitaxel arm in the phase II part. Vinflunine survival results were consistent with those observed in the phase III. Cabazitaxel had minimal activity in TCCU, not confirming the findings observed with cabazitaxel in prostate cancer.

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Disclosure

J. Bellmunt. Received lecture's fee from Pierre Fabre, Sanofi-Aventis, Genentech and Merck. Honoraria was received for adboard participation with Pierre Fabre, Sanofi-Aventis, Genentech and Merck.

E. Grande. Received lecture's fee from Pierre Fabre and Genentech. Honoraria was received for adboard participation with Pierre Fabre, Genentech and Celgene.

A. Medina. Received fee from Sanofi.

R. de Wit. Received lecture and advisory board fees from Sanofi.

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All authors had full control over all primary data and agree to allow the journal to review it if requested.

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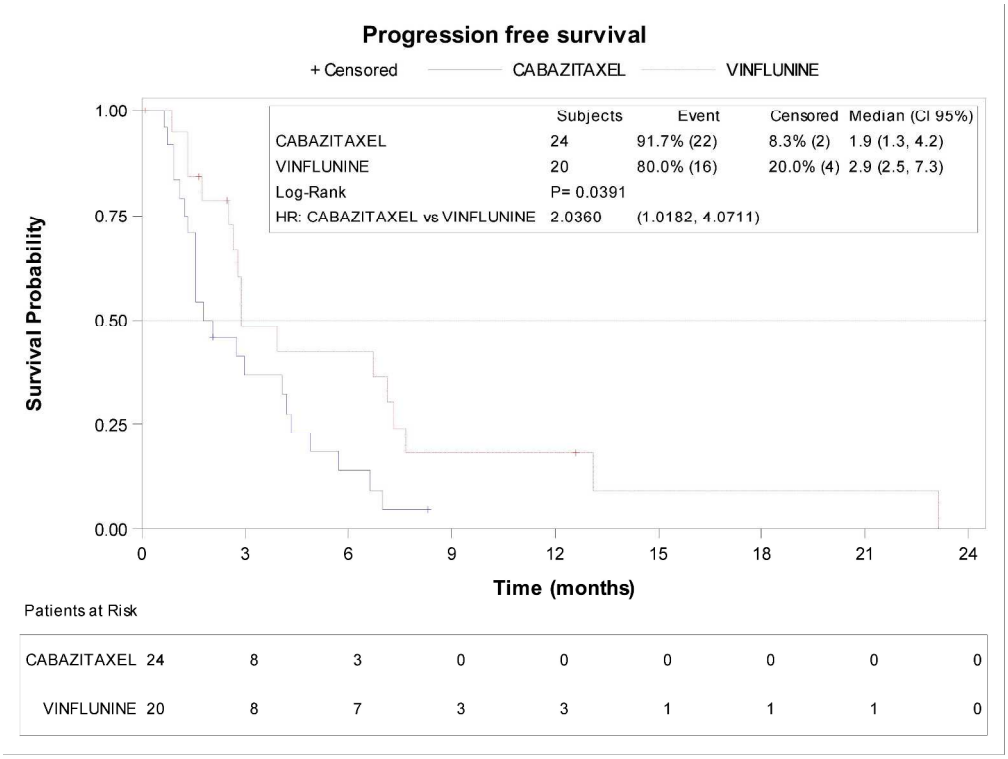
Supplementary table 1: Baseline characteristics (ITT population)
Supplementary Table 2: Worst grade per patient (Related to treatment) (Most frequent>5%)
Figure 1. PFS in per protocol population
Figure 2. OS in per protocol population

		CABAZITAXEL (*n*=35)	VINFLUNINE (*n*=35)	Total (*n*=70)	*p* Value Test
Number of unfavourable prognostic criteria found					
0	*n* (%)	13 (37.14)	13 (37.14)	26 (37.14)	Chi-Square: 1.0000
1	*n* (%)	22 (62.86)	22 (62.86)	44 (62.86)	
ECOG=1					
Yes	*n* (%)	11 (31.43)	13 (37.14)	24 (34.29)	Chi-Square: 0.6145
No	*n* (%)	24 (68.57)	22 (62.86)	46 (65.71)	
Hemoglobine < 10 g/dl					
Yes	*n* (%)	4 (11.43)	2 (5.71)	6 (8.57)	Fisher: 0.6733
No	*n* (%)	31 (88.57)	33 (94.29)	64 (91.43)	
Liver metastasis					
Yes	*n* (%)	7 (20.00)	7 (20.00)	14 (20.00)	Chi-Square: 1.0000
No	*n* (%)	28 (80.00)	28 (80.00)	56 (80.00)	
Age					
	n	35	35	70	
	Mean (SD)	62.09 (8.4)	64.29 (9.6)	63.19 (9.1)	
	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 (97.1)	35 (100.00)	69 (98.6)	Fisher: 1.0000
Black	*n* (%)	1 (2.9)	0 (0.00)	1 (1.4)	
Previous antineoplasic treatments					
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 (74.3)	33 (94.3)	59 (84.3)	Chi-Square: 0.0215
No	*n* (%)	9 (25.7)	2 (5.7)	11 (15.7)	
Prior chemotherapy schemes					
Carboplatin-gemcitabine	*n* (%)	6 (17.1)	14 (40)	20 (28.6)	

		CABAZITAXEL (*n*=35)	VINFLUNINE (*n*=35)	Total (*n*=70)	*p* Value Test
Cisplatin-gemcitabine		28 (80)	20 (57.1)	48 (68.6)	
Other	*n* (%)	9 (25.7)	6 (17.1)	15 (21.4)	

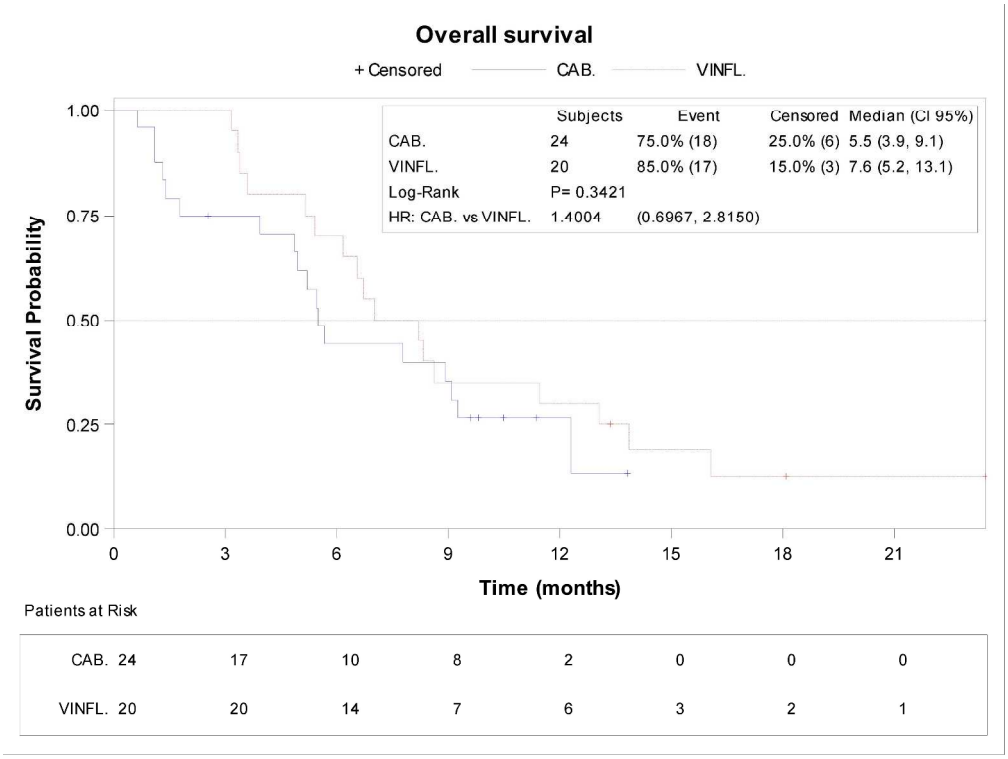
Preferred MedDRA Term	Treatment/Grade																		Total(*n*=70)	
	CABAZITAXEL(*n*=35)										VINFLUNINE(*n*=35)									
	G1		G2		G3		G4		G5		G1		G2		G3		G4			
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Constipation	2	5.71	.	.	.	.	.	.	.	.	9	25.71	6	17.14	3	8.57	.	.	20	28.57
Nausea	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
Sepsis	.	.	.	.	.	.	.	.	1	3*										
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

*One patient had pneumonia and sepsis causing death; due to the importance of this event, this has been included in the table



PFS in per protocol population

1055x792mm (96 x 96 DPI)



OS in per protocol population

1055x792mm (96 x 96 DPI)