EUROPEAN JOURNAL OF CANCER 47 (2011) 1037–1045

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

# A multicentre dose-escalating study of cabazitaxel (XRP6258) in combination with capecitabine in patients with metastatic breast cancer progressing after anthracycline and taxane treatment: A phase I/II study

*C. Villanueva* [a], *A. Awada* [b], *M. Campone* [c], *J.P. Machiels* [d], *T. Besse* [b], *E. Magherini* [e], *F. Dubin* [e], *D. Semiond* [e], *X. Pivot* [a,*]

[a] *University Hôpital Jean Minjoz, Besançon, France*
[b] *Institut Jules Bordet, Brussels, Belgium*
[c] *Centre René Gauducheau, Saint Herblain, Nantes, France*
[d] *Centre du cancer, Cliniques universitaires Saint Luc, Brussels, Belgium*
[e] *Sanofi-aventis Oncology, France*

ARTICLE INFO

*Article history:*
Received 23 May 2010
Received in revised form 12 December 2010
Accepted 19 January 2011
Available online 19 February 2011

*Keywords:*
Chemotherapy
Metastatic breast cancer
Resistance
Taxane
Taxoid
XRP6258

ABSTRACT

*Background:* Most patients with metastatic breast cancer (MBC) progress after chemotherapy. Cabazitaxel (XRP6258) is a new taxoid that is active in chemotherapy-resistant tumour cell lines. The objectives of this phase I/II study were to assess the maximum tolerated dose (MTD), safety profile, pharmacokinetics, and activity of cabazitaxel plus capecitabine in patients with MBC who had been previously treated with taxanes and anthracyclines.

*Patients and methods:* In part I, we used a 3 + 3 dose–escalation scheme to assess the MTD of intravenous cabazitaxel (day 1) with oral capecitabine twice daily (days 1–14) every 3 weeks. In part II, we evaluated the objective response rate (ORR) at the MTD.

*Results:* Thirty-three patients were enrolled and treated (15 in part I; 18 in part II). Cabazitaxel 20 mg/m$^2$ plus capecitabine 1000 mg/m$^2$ was the MTD. Pharmacokinetic analysis showed no apparent drug–drug interaction. In all patients, the main grade 3–4 toxicities were asthenia ($n$ = 5), hand–foot syndrome ($n$ = 5), neutropenia ($n$ = 21), neutropenic infection ($n$ = 1), and neutropenic colitis ($n$ = 1). One patient had febrile neutropenia. Antitumour activity was observed at all dose-levels with two complete responses, five partial responses (PRs), and 20 disease stabilisations (seven unconfirmed PR). At the MTD, 21 patients were evaluable for efficacy. The ORR was 23.8% (95% CI: 8.2–47.2%). The median response duration was 3.1 months (95% CI: 2.1–8.4 months), with four of five lasting for more than 3 months. Median time to progression was 4.9 months.

*Conclusions:* Cabazitaxel combined with capecitabine is active, has a safety profile consistent with a taxane plus capecitabine combination and warrants further investigation in patients with MBC.



* *Corresponding author*: Address: Centre Hospitalier Universitaire de Besançon, Service d'Oncologie Médicale, 25030 Besancon cedex, France. Tel.: +33 (0) 3 81 66 88 58; fax: +33 (0) 2 81 66 88 58.
E-mail address: Xavier.pivot@univ-fcomte.fr (X. Pivot).
0959-8049/$ - see front matter 
doi:10.1016/j.ejca.2011.01.001

## 1. Introduction

There are currently several acceptable combination chemotherapy regimens for the treatment of metastatic breast cancer (MBC), with most first-line treatments including an anthracycline or a taxane.[1–4] In this setting, the combination of capecitabine and docetaxel has been shown to prolong time to progression (TTP) and survival in patients who failed a prior anthracycline exposure. In a study of 511 patients randomised to capecitabine plus docetaxel or docetaxel alone, median survival in the capecitabine plus docetaxel group was 14.5 months compared with 11.5 months for docetaxel alone ($p = 0.0126$).[5] TTP was 6.1 months versus 4.2 months ($p = 0.0001$), and the objective response rate (ORR) was 42% versus 30% ($p = 0.006$), respectively.[5] This trial led to the approval of this combination regimen as a first-line treatment for MBC and supported the synergistic activity of these two drugs.

There is an urgent need to find new active agents in the metastatic setting as most patients with MBC develop chemotherapy-resistant tumours. Anthracycline-resistant tumours are a major clinical issue, and it is in this setting that taxanes provided a further clinical benefit. Resistance to taxane-containing regimens appears to be one of the next challenges. Several mechanisms of taxane resistance have been proposed.[6,7]

Cabazitaxel (XRP6258) is a new taxoid that was selected for clinical development based on its pharmacological profile, its efficacy in a broad spectrum of tumour models that are sensitive as well as resistant or refractory to docetaxel, and its activity against intra-cranial tumours.[8–11] Single-agent cabazitaxel has an acceptable safety profile and appears to be active in docetaxel- or paclitaxel-resistant breast cancer, even when the most stringent criterion of resistance (progression on therapy) was used.[12] Pivot and colleagues reported an ORR of 14% (95% CI: 7–24%) in patients with taxane-resistant MBC receiving 20 mg/m$^2$ of cabazitaxel, with intra-patient dose escalation to 25 mg/m$^2$ at cycle 2 (for patients without toxicity grade 2 or higher at cycle 1), as 1 h infusion on day 1, every 3 weeks.[13]

Nevertheless, after failure of a first-line taxane-containing regimen, several agents are considered possible therapy options. Among them, capecitabine monotherapy is currently approved in this setting on the basis of a large phase II study that demonstrated significant antitumour activity in MBC refractory to paclitaxel.[14] In a trial of 162 patients, a dose of 2510 mg/m$^2$/day for 2 weeks followed by a 1-week rest every 3 weeks resulted in an ORR of 20% (95% CI: 14–28%).[14]

The rationale supporting an evaluation of the combination of cabazitaxel and capecitabine is based on the preclinical profile of cabazitaxel, its clinical activity in taxane- and anthracycline-pretreated MBC, the synergistic activity between capecitabine and docetaxel,[15–17] as well as the relative lack of overlapping toxicities between the two drugs. The present study was designed to determine the recommended phase II dose by assessing the maximum tolerated dose (MTD) of cabazitaxel plus capecitabine and the efficacy of this MTD in patients with MBC whose disease progressed after anthracycline- and taxane-containing treatments.

## 2. Patients and methods

This open-label multicentre phase I/II study was conducted in four study centres in Europe between 5th December, 2006 and 31st March, 2009 (study cut-off date). The study design involved two stages: a dose-escalation stage (part I), whose primary objectives were to assess the maximum administered dose and the MTD during the first cycle, and a second stage (part II), which was designed to assess the activity and the safety profile of cabazitaxel in combination with capecitabine at the MTD. The primary end-point for the second stage of the study was the ORR, according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.0.[18] Secondary efficacy end-points were the safety profile, duration of response, TTP, and pharmacokinetics (PK). The protocol complied with recommendations of the 18th World Health Congress (Helsinki, 1964) and was approved by the ethics committee of each participating institution. All patients provided written informed consent.

### 2.1. Main eligibility criteria

Eligibility criteria included: age $\geqslant$ 18 years, histologically proven breast cancer that was metastatic or locally recurrent and inoperable with curative intent, Eastern Cooperative Oncology Group performance status (PS) 0–2, and adequate haematologic, renal, and hepatic function. To enter into part II of the study, patients were required to have at least one measurable lesion according to RECIST.[18] Prior exposure to taxane and anthracycline therapy was required for all patients, administered either in the neoadjuvant, adjuvant, or metastatic settings, either concurrently or sequentially, or in combination with other drugs.

### 2.2. Definitions and treatment scheme

The dose limiting toxicities (DLTs) were defined during the first treatment cycle based on the drug-related toxicity according to the National Cancer Institute common terminology criteria for adverse events (NCI-CTCAE) version 3.0. A dose escalation to the subsequent dose level was made if no DLT was seen in a cohort of three patients. If a DLT was seen in one of these patients, the cohort was expanded to six patients, with the maximum administered dose reached if two or more patients experienced a DLT. If none of the additional three patients had a DLT, then the dose could be escalated to the next level. The maximum administered dose was reached at the dose when two or more patients developed DLTs at the first cycle. The MTD was defined as the highest dose at which no more than one of three or six patients experienced a DLT during the first 3 weeks of treatment with cabazitaxel and capecitabine. Patients enrolled in the second part of the study received the combination at the determined MTD, with the aim of assessing the safety profile and response rate.

Patients received capecitabine orally twice daily from day 1 to day 14 within 30 min of a meal. Two hours after the morning capecitabine dose, patients received cabazitaxel, administered intravenously over 1 h on day 1 at the dose specified for each level in part I of the trial (Table 1), and at the MTD in part

**Table 1 – Planned dose-escalation schedule.**

| Dose levels | Cabazitaxel, mg/m$^2$ | Capecitabine mg/m$^2$ twice daily |
|---|---|---|
| –I[a] | 15 | 825 |
| I | 20 | 825 |
| II | 20 | 1000 |
| –III[a] | 25 | 825 |
| III | 25 | 1000 |
| IV | 25 | 1250 |

a Optional dose level.

II of the trial. Cycles were repeated at 3-week intervals. Intrapatient dose escalation was not permitted. Patients received intravenous antihistamine (anti-H1) premedication 30 min before study drug administration. No steroid premedication was used. No prophylactic anti-emetic drugs were allowed at the first cycle because nausea and vomiting in the absence of antiemetic therapy were considered DLTs. In the case of nausea or vomiting, patients could receive preventive anti-emetic treatment in subsequent cycles in compliance with the conventional anti-emetic protocol of the centre. In the event of a treatment-related serious adverse event occurring during any cycle, a 20–25% dose reduction of each drug at subsequent cycles and a treatment delay (up to 2 weeks) was required, depending on the type of toxicity. Treatment was continued until disease progression, the occurrence of unacceptable adverse events, or the withdrawal of patient consent.

### 2.3. Data analysis

We planned to enrol a total of approximately 50 patients in this study. For part I (dose-ranging), approximately 35 patients were to be included in the dose-escalation component in order to establish the maximum administered dose and the MTD of the combination. The actual sample size depended on the dose-limiting toxicities observed and resultant cohort sizes and number of dose levels enrolled. For part II (efficacy), the statistical plan specified that approximately 15 patients with measurable disease who were evaluable for response must be added to the three or six patients who received the MTD during part I.

Adverse events/signs and symptoms of disease, as observed by the investigator or reported by the patient, were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0. The primary and comprehensive analysis of safety was based on the treatment-emergent adverse event principle, which defines an adverse event regardless of the relationship to treatment that started or worsened during the treatment period compared to baseline. The safety population included all treated patients.

Efficacy was assessed in the treated patients who were eligible for the study and evaluable for response. Duration of response was measured for patients who had complete response (CR) or partial response (PR) as the best overall response, and calculated as the time from first documentation of CR or PR until the first documented progression or death due to any cause. Time to tumour progression (TTP) was defined as the time between the date of first treatment administration and the date of documented progression, or the date of last tumour assessment (if there was no documented progression), or the date of last tumour assessment before the start of further anti-tumour therapy before documented progression. TTP was estimated using the Kaplan–Meier method.[19]

### 2.4. Pharmacokinetic subgroup analysis

PK parameters were calculated by non-compartmental analysis using WinNonLin version 4.0.1 (Pharsight Corporation, Mountain View, CA, USA). The following parameters were determined for cabazitaxel, capecitabine, and their metabolites: peak concentration ($C_{max}$), time to $C_{max}$ ($T_{max}$), area under the curve from time 0 to the last measurable concentration at time $t$ ($AUC_{0-t}$), and, where possible, area under the curve (AUC) and half-life of the terminal phase ($T_{½}$). In addition, the plasma clearance (CL) and the volume of distribution at steady state ($V_{ss}$) were determined for cabazitaxel only, where possible.

### 2.5. Evaluations prior to and during therapy

Prior to registration, a complete medical history was taken and a physical examination was carried out that included complete blood counts (CBCs), blood chemistry analyses and tumour assessments by chest, abdominal and pelvis computed tomography scans or magnetic resonance imaging and bone scan. During treatment, CBCs were performed weekly or more often if grade 4 neutropenia occurred (until recovery to grade 3), or in the case of fever. Patients were regularly assessed for potential adverse events and disease-related signs and symptoms.

Tumour measurements were made every 6 weeks. Responses had to be confirmed by two evaluations taken at least 4 weeks apart. Follow-up, including physical examination, tumour assessments and survival data were collected every 6 weeks until the study cut-off date.

For PK evaluations, blood samples were collected from all patients at cycle 1. For cabazitaxel and its active metabolite RPR123142 (10-O demethyl derivative), samples were collected at day 1, before the infusion, 5 min before the end of infusion, and then 5, 15, 30 min, 1, 2, 3, 5, 7, 10 h, day 2 (2–24 h), day 3 (approximately 48 h), day 4 (approximately 72 h), day 6 (approximately 120 h), and finally day 8 (approximately 168 h) after the end of infusion. For capecitabine and its active metabolite 5-fluorouracil (5-FU), samples were collected at day 1, before the first oral administration, 15, 30 min, 1, 2, 3, 4, 5, 6, 8, and 10 h after the morning dose (before the evening dose).

Cabazitaxel and RPR123142 were assayed by a validated liquid chromatography/mass spectrometry (LC/MS) method with a limit of quantification of 1 ng/mL for cabazitaxel and 0.5 ng/mL for RPR123142. The accuracy of the assay (defined as the percentage difference between the nominal and the mean measured concentrations of quality controls) ranged from –1.67% to –3.75% for cabazitaxel, and from –1.33% to –6.50% for RPR123142 in plasma over the analysis period. The

**Table 2 – Patient characteristics.**

| | |
|---|---|
| Patients enrolled and treated | 33 (100) |
| Median age, years (range) | 55 (34–74) |
| *ECOG PS at study entry* | |
| 0 | 20 (61) |
| 1 | 13 (39) |
| *Histologic type at diagnosis* | |
| Infiltrating ductal carcinoma | 25 (76) |
| Infiltrating lobular carcinoma | 4 (12) |
| Infiltrating mixed carcinoma | 4 (12) |
| Negative HER2 status (FISH) | 33 (100) |
| *Hormonal receptor status* | |
| ER+ and/or PR+ | 29 (88) |
| ER– and PR– | 4 (12) |
| Organs involved, median (range) | 3 (1–6) |
| *Affected sites* | |
| Bone | 27 (82) |
| Liver | 20 (61) |
| Lung | 10 (30) |
| Pleura | 7 (21) |
| Distant lymph nodes | 13 (39) |
| Regional lymph nodes | 4 (12) |
| Other[a] | 6 (18) |
| Time from initial breast cancer diagnosis to first cabazitaxel infusion, median years (range) | 5.0 (1.2–21.5) |
| Prior treatment with taxanes or anthracyclines | 33 (100) |
| *Prior treatment settings* | |
| Neoadjuvant | 14 (42) |
| Adjuvant | 15 (45) |
| Advanced | 28 (85) |
| *Lines of chemotherapy for advanced disease* | |
| 0 | 5 (15) |
| 1 | 28 (85) |
| *Prior treatments for advanced disease* | |
| Taxanes | 19 (58) |
| Taxanes and anthracyclines | 9 (27) |
| Time from last taxane to first cabazitaxel infusion, median months (range) | 10.9 (0.9–93.9) |
| *Best response to last taxane therapy* | |
| Partial response | 11 (33) |
| Progressive disease | 4 (12) |
| Stable disease | 14 (42) |
| Not applicable/not assessed | 4 (12) |

CT, chemotherapy; ECOG, Eastern European Cooperative group; PS, FISH, fluorescence *in situ* hybridisation; ER, oestrogen receptor; PR, progesterone receptor.

Data shown are number of patients (%), unless otherwise stated.

[a] Includes adrenal, muscle soft tissue, peritoneum, pericardial effusion.

precision of the assay, established by the coefficient of variation (CV) of the quality controls, was lower than 9.5% for both compounds. Capecitabine and 5-FU were measured in plasma by a validated LC/MS method with a limit of quantification of 10 ng/mL for capecitabine and 2 ng/mL for 5-FU.

## 3. Results

### 3.1. Patients

Of 33 enrolled and treated MBC patients, all were eligible to participate in the trial. Fifteen patients were accrued in part I (dose escalation) and were evaluable for assessment of dose-limiting toxicities. Eighteen patients were accrued in the part II cohort. All patients were evaluable for safety and efficacy.

At study entry, the median age was 55 years (range 34–74) and 100% of patients had PS 0–1. All patients had previously received chemotherapy containing anthracyclines and taxanes and all had metastatic disease with multiple organ involvement, with a median number of three organs (mainly bone, liver, and lymph nodes) involved (range 1–6). The majority of patients (78.8%) discontinued previous anticancer therapy, mainly due to progressive disease and 85% were receiving second-line chemotherapy. Hormone receptor status was positive in 88% of tumours and HER2 status was negative for all patients. Patient and disease characteristics are summarised in Table 2.

### 3.2. Exposure to study medication and safety

In part I of the study, 15 patients were enrolled across three dose levels (DLs). At all DLs, cabazitaxel was administered intravenously on day 1 and capecitabine was dosed orally twice daily on days 1–14, every 3 weeks. The first cohort of three patients was treated at DL1 (cabazitaxel 20 mg/m$^2$ + capecitabine 825 mg/m$^2$) and one DLT (grade 4 neutropenia lasting more than 7 d) was observed in one patient. This group was expanded to six patients and no new DLTs were observed. The next cohort of three patients was treated with DL2 (cabazitaxel 20 mg/m$^2$ + capecitabine 1000 mg/m$^2$) with no DLTs observed. The subsequent cohort of three patients was treated at DL3 (cabazitaxel 25 mg/m$^2$ + capecitabine 1000 mg/m$^2$) and one DLT (grade 4 neutropenia lasting more than 7 d) was observed in one patient. This group was expanded to six patients and, as a second DLT of the same type occurred in an additional patient, this was the maximum administered dose (Table 3). Dose level 2 was deemed to be the MTD to be evaluated in part II of the study.

The MTD was defined as cabazitaxel 20 mg/m$^2$ on day 1 plus capecitabine 1000 mg/m$^2$ twice daily on days 1–14, given every 3 weeks. An expansion cohort of 18 additional patients

**Table 3 – Dose limiting toxicities.**

| Cabazitaxel + capecitabine (mg/m$^2$) | *N* | Patients with DLT at cycle 1/DLT type |
|---|---|---|
| DL1: 20 + 825 | 6 | 1/grade 4 neutropenia lasting more than 7 d |
| DL2: 20 + 1000 | 3 | 0 |
| DL3: 25 + 1000 | 6 | 2/grade 4 neutropenia lasting more than 7 d |

DL, dose level; DLT, dose-limiting toxicity.

with measurable disease was enrolled and treated at this dose. Taking into account the three first patients treated during the first step, a total of 21 patients were treated at the MTD.

A total of 112 cycles (median, 5 [2–13]) were administered to 21 patients at the MTD. A dose delay was required for 10 of 21 patients, representing 18 cycles. Dose reductions of cabazitaxel or capecitabine were required in four of 21 patients (four cycles) and three of 21 patients (five cycles), respectively. The median relative dose intensity (actual dose intensity/planned dose intensity) was 0.97

**Table 4 – Treatment administration.**

| Dose level | | DL1 | DL2 | DL3 | All |
|---|---|---|---|---|---|
| Number of patients | | 6 | 21[a] | 6 | 33 |
| Cycles of the combination | Total | 30 | 112 | 36 | 178 |
| Cabazitaxel | Total | 30 | 109 | 36 | 175 |
| | median | 4.5 | 5 | 5.5 | 5 |
| | (range) | (2–12) | (2–13) | (4–9) | (2–13) |
| Capecitabine | Total | 30 | 112 | 36 | 178 |
| | median | 4.5 | 6 | 5.5 | 5 |
| | (range) | (2–12) | (2–13) | (4–9) | (2–13) |
| Patients with treatment delay | | 1 | 10 | 5 | 16 |
| Patients with at least one dose reduction | Cabazitaxel | 1 | 4 | 5 | 10 |
| | Capecitabine | 0 | 3 | 4 | 7 |
| RDI median (min–max) | Cabazitaxel | 0.96 (0.86–1.01) | 0.97 (0.69–1.00) | 0.82 (0.74–0.91) | 0.96 (0.69–1.01) |
| | Capecitabine | 0.92 (0.64–1.00) | 0.89 (0.55–1.02) | 0.83 (0.71–1.03) | 0.87 (0.55–1.03) |

Data shown are N, unless otherwise stated.
DLT, dose limiting toxicity; RDI, relative dose intensity.
[a] Including three patients in the dose-escalation part and 18 patients in the expansion cohort.

**Table 5 – Most frequent non-haematologic and haematologic adverse events[a] occurring in >20% of patients, for all patients across all dose levels.**

| Preferred term, N (%) | Cabazitaxel 20 mg/m$^2$ + capecitabine 825 mg/m$^2$ N = 6 | | Cabazitaxel 20 mg/m$^2$ + capecitabine 1000 mg/m$^2$ N = 21[b] | | Cabazitaxel 25 mg/m$^2$ + capecitabine 1000 mg/m$^2$ N = 6 | |
|---|---|---|---|---|---|---|
| | Grade 3/4 | All grade | Grade 3/4 | All grade | Grade 3/4 | All grade |
| *Non-haematologic* | | | | | | |
| All | 3 (50) | 6 (100) | 15 (71) | 21 (100) | 5 (83) | 6 (100) |
| Asthenia/fatigue | 1 (17) | 4 (67) | 2 (10) | 11 (52) | 2 (33) | 4 (67) |
| Diarrhoea | 0 | 4 (67) | 1 (5) | 12 (57) | 0 | 3 (50) |
| Nausea | 0 | 3 (50) | 0 | 13 (62) | 0 | 3 (50) |
| Anorexia | 0 | 4 (67) | 1 (5) | 11 (52) | 0 | 2 (33) |
| Palmar–plantar syndrome | 0 | 1 (17) | 2 (10) | 12 (57) | 3 (50) | 4 (67) |
| Vomiting | 0 | 2 (33) | 0 | 7 (33) | 0 | 3 (50) |
| Constipation | 0 | 2 (33) | 0 | 6 (29) | 0 | 3 (50) |
| Abdominal pain | 0 | 0 | 0 | 7 (33) | 1 (17) | 3 (50) |
| Myalgia | 0 | 5 (83) | 0 | 3 (14) | 0 | 2 (33) |
| Weight decreased | 0 | 3 (50) | 0 | 6 (29) | 0 | 1 (17) |
| Headache | 0 | 3 (50) | 1 (5) | 3 (14) | 0 | 3 (50) |
| Arthralgia | 0 | 2 (33) | 0 | 4 (19) | 0 | 2 (33) |
| Pyrexia | 0 | 3 (50) | 0 | 5 (24) | 0 | 0 |
| Stomatitis | 0 | 2 (33) | 0 | 4 (19) | 0 | 2 (33) |
| Alopecia | 0 | 2 (33) | 0 | 5 (24) | 0 | 0 |
| Dyspnea | 0 | 1 (16) | 2 (10) | 5 (24) | 0 | 1 (17) |
| *Haematologic* | | | | | | |
| Anaemia | 1 (17) | 5 (83) | 1 (5) | 17 (81) | 1 (17) | 5 (83) |
| Neutropenia | 4 (67) | 4 (67) | 12 (57) | 17 (81) | 5 (83) | 6 (100) |
| Thrombocytopenia | 0 | 3 (50) | 0 | 8 (38) | 0 | 3 (50) |
| Neutropenic infection | 0 | 1 (17) | 0 | 0 | 0 | 0 |
| Neutropenic colitis | 1 (17) | 1 (17) | 0 | 0 | 0 | 0 |
| Febrile neutropenia | 0 | 0 | 1 (5) | 1 (5) | 0 | 0 |

[a] Worst grade per patient reported. Adverse events are presented regardless of relationship to treatment.
[b] Including three patients in the dose-escalation cohort and 18 patients in the expansion cohort of the trial.

(0.69–1.00) for cabazitaxel and 0.89 (0.55–1.02) for capecitabine (Table 4).

At the MTD, 71.4% of patients experienced grade 3–4 treatment-emergent adverse events. The most frequent grade 3–4 non-haematologic adverse events were asthenia/fatigue, hand–foot syndrome, and dyspnea (9.5% each). All-grade and grade 3–4 treatment-emergent adverse events by patient are listed in Table 5. The most common grade 3–4 haematologic toxicity was neutropenia, occurring in 57.1% of patients. One patient had febrile neutropenia, one had a grade 3–4 neutropenic infection, and one had grade 3–4 neutropenic colitis. Grade 3–4 anaemia occurred in one patient and no grade 3–4 thrombocytopenia was reported. No toxic deaths were reported.

In the treated population (all patients), the most frequent reasons for treatment discontinuation were disease progression (14 patients), adverse event regardless of relationship to treatment (9 patients; $n = 4$ cystitis/haematuria; $n = 2$ renal colic; $n = 1$ prolonged neutropenia; $n = 2$ asthenia/general health deterioration) and other reasons (10 patients; $n = 9$ investigator decision/no further benefit and $n = 1$ patient's decision). At the cut-off date for the analysis, four patients had died. All deaths were considered to be related to disease progression.

### 3.3. *Antitumour activity*

Among of the 21 evaluable patients treated with the MTD, the investigator-determined ORR was 23.8% (95% CI: 8.2–47.2%), with one CR and four PRs (Table 6). In addition, 11 patients had a disease stabilisation (including two unconfirmed PRs) and five had progressive disease (PD). The median duration of response was 3.1 months (95% CI: 2.1–8.4 months) with four of five responses lasting more than 3 months. The median TTP was 4.9 months (95% CI: 2.7–not reached) (Table 6). At DL1 and DL2, we observed one CR, one PR, and nine SDs. Two of four patients who had PD as best response to prior taxanes experienced disease stabilisation with cabazitaxel plus capecitabine, whereas four patients who had stabilisation as best response to prior taxanes had a response (two CRs and two PRs).

### 3.4. *Pharmacokinetics*

A non-compartmental PK analysis was carried out in 26 patients for cabazitaxel and 32 patients for capecitabine. The mean (±SD) PK parameters of cabazitaxel and RPR123142 are summarised in Table 7. As shown in Fig. 1, cabazitaxel exhibited a triphasic elimination profile, characterised by a prolonged terminal phase, (mean [coefficient of variation %]

**Table 6 – Efficacy of the combination of cabazitaxel and capecitabine.**

| Best overall response[a] | Cabazitaxel 20 mg/m$^2$ + capecitabine 825 mg/m$^2$ $N = 6$ | Cabazitaxel 20 mg/m$^2$ + capecitabine 1000 mg/m$^2$ $N = 21$[b] | Cabazitaxel 25 mg/m$^2$ + capecitabine 1000 mg/m$^2$ $N = 6$ |
|---|---|---|---|
| Complete response, *n* (%) | 0 | 1 (5)[d] | 1 (17) |
| Partial response, *n* (%) | 0 | 4 (19) | 1 (17) |
| Stable disease[c], *n* (%) | 5 (83) | 11 (52) | 4 (67) |
| Progressive disease, *n* (%) | 1 (17) | 5 (24) | 0 |
| Objective response rate, % (95% CI) | – | 24 (8–47) | – |
| Median response duration, months (range) | – | 3.06 (2.1–8.4) | 4.42 (3.1–5.8) |
| Median time to progression, months (95% CI) | | (2.7–NA) | NA |

CI, confidence interval; NA, not available.

[a] Response/disease stabilisation confirmed by analyses at least 1 month apart.

[b] Including three patients in the dose-escalation cohort and 18 patients in the expansion cohort of the trial.

[c] Including seven patients with an unconfirmed partial response (four patients with cabazitaxel 20 mg/m$^2$ + capecitabine 825 mg/m$^2$; two patients with cabazitaxel 20 mg/m$^2$ + capecitabine 1000 mg/m$^2$ and one patient with cabazitaxel 25 mg/m$^2$ + capecitabine 1000 mg/m$^2$).

[d] Patient with only non-target lesions at baseline who experienced confirmed complete response.

**Table 7 – Mean (CV %) PK parameters of cabazitaxel.**

| DL CBZ/C (mg/m$^2$) | *N* | $C_{max}$ (ng/mL) | $T_{last}$[a] (h) | $AUC_{0-t}$ (ng h/mL) | AUC(ng h/mL) | $t_{1/2\lambda}$ (h) | CL (L/h/m$^2$) | $V_{ss}$ (L/m$^2$) |
|---|---|---|---|---|---|---|---|---|
| DL1 (20/825) | 1 | 100 (76)[b] | 121 (70–169)[b] | 367 (37)[b] | 666 | 98.6 | 30 | 3040 |
| DL2 (20/1000) | 6 | 199 (161)[c] | 96 (49–169)[c] | 442 (46) [c] | 627 (39) | 48 (64) | 38.4 (54) | 1848 (91) |
| DL3 (25/1000) | 4 | 214(48)[d] | 169 (102–169)[d] | 786 (99)[d] | 1254 (75) | 121 (29) | 27.2 (52) | 2889 (60) |
| Overall | 11 | – | | – | – | 79.0 (59) | 33.6 (52) | 2335 (69) |

CBZ, cabazitaxel; C, capecitabine; CV, coefficient of variation; DL, dose level; PK, pharmacokinetics.

[a] Median and range for $T_{last}$.

[b] $n = 6$.

[c] $n = 13$.

[d] $n = 7$.

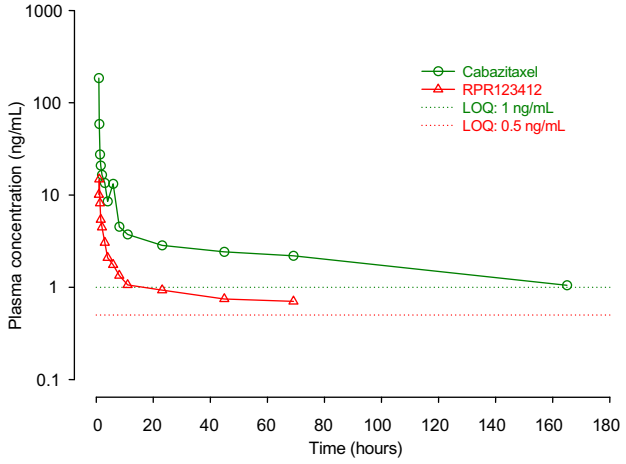


**Fig. 1 – Typical plasma concentration–time profile of cabazitaxel (DL2) and its metabolite RPR123412.**

$t_{1/2\lambda}$ of 79 h). Cabazitaxel has a high CL of 33.6 L/h/m$^2$ (52%) representing 66% of the hepatic blood flow (87 L/h) with a large volume of distribution at steady state, averaging 2335 L/m$^2$. Large interpatient variability in all PK parameters was observed (52–69%). Exposure of RPR123142 was low and represented on average only 2.2% of the cabazitaxel exposure (data not shown). The mean (±SD) PK parameters of capecitabine and 5-FU are summarised in Table 8. Capecitabine was rapidly absorbed and metabolised into 5-FU with a $t_{max}$ between 15 min and 3 h and a median value of 0.50–1 h for both compounds. Thereafter, the plasma concentrations of both compounds rapidly decreased over time with a mean $T_{½}$ of approximately 30 min–1.4 h for capecitabine and 40 min to 1.1 h for 5-FU. The mean AUC was 8870 ng/h/mL for capecitabine and 495 ng/h/mL for 5-FU after administration of 1000 mg/m$^2$/day capecitabine coadministered with 20 mg/m$^2$ cabazitaxel (DL2) (Fig. 2).

## 4. Discussion

Treatment with chemotherapy in patients with MBC is limited by the development of resistance to commonly used chemotherapeutic agents, resulting in treatment failure in almost all MBC patients. The determination of ORR permits an assessment of active drugs in this setting.[20] However, current chemotherapy regimens are rarely able to provide encouraging ORRs after failure with anthracyclines and taxanes, including monotherapy with capecitabine (28% ORR), ixabepilone (11.5%), cabazitaxel (14%), and the combination of ixabepilone with capecitabine (35%).[13,21–24] A precedent for synergy between taxanes and capecitabine was suggested by preclinical studies[15–17] and confirmed in a phase III study[5] that led to the recommended dose for capecitabine of 1250 mg/m$^2$ twice daily for 14 d followed by a 1-week rest, either as monotherapy or in combination with docetaxel.

In the present study, the MTD of 20 mg/m$^2$ for cabazitaxel (day 1) in combination with capecitabine 1000 mg/m$^2$ twice a day (day 1–14) every 3 weeks was well tolerated, with no exacerbation of the already-known toxicities of each drug. Interestingly, at this dose in this group of patients progressing on

**Table 8 – Mean (CV %) PK parameters of capecitabine and 5-FU.**

| DLCBZ/C (mg/m$^2$) | N | Capecitabine | | | | | | | 5-FU | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $T_{max}$ (h) | $C_{max}$ (ng/mL) | $T_{last}$ (h) | $AUC_{0-t}$ (ng h/mL) | AUC (ng h/mL) | $t_{1/2\lambda}$ (h) | $T_{max}$ (h) | $C_{max}$ (ng/mL) | $T_{last}$ (h) | $AUC_{0-t}$ (ng h/mL) | AUC (ng h/mL) | $t_{1/2\lambda}$ (h) |
| DL1 (20/825) | 6 | 0.99 (0.25–2.02) | 5260(97) | 4.75 (3.12–10.00) | 4570 (45) | 4250 (40) | 0.895 (80) | 0.99 (0.43–3.00) | 179 (88) | 5.64 (3.95–10.00) | 245 (38) | 261[a] (40) | 1.09[a] (54) |
| DL2 (20/1000) | 19 | 0.50 (0.17–1.97) | 11600(71) | 4.00 (2.00–8.00) | 9190 (65) | 8870 (68) | 0.485 (50) | 0.88 (0.25–1.98) | 424 (87) | 5.00 (4.00–8.00) | 487 (78) | 429[b](93) | 0.753[b] (46) |
| DL3 (25/1000) | 7 | 0.97 (0.25–3.17) | 6070 (68) | 3.12 (2.00–6.15) | 5110 (25) | 6060 (22) | 1.42 (133) | 0.99 (0.25–3.17) | 284 (60) | 4.22 (2.92–8.10) | 340 (32) | 334[c] (34) | 0.669[c](25) |

Median and range for $T_{last}$ and $T_{max}$.
One patient scheduled to be treated at 20 mg/m$^2$ CBZ /1000 mg/m$^2$ C (DL2) received 25 mg/m$^2$ CBZ and was included in DL3 for PK analysis.
CV, coefficient of variation; DL, dose level; PK, pharmacokinetics; 5-FU, 5-fluorouracil.
[a] $n = 5$.
[b] $n = 17$.
[c] $n = 6$.

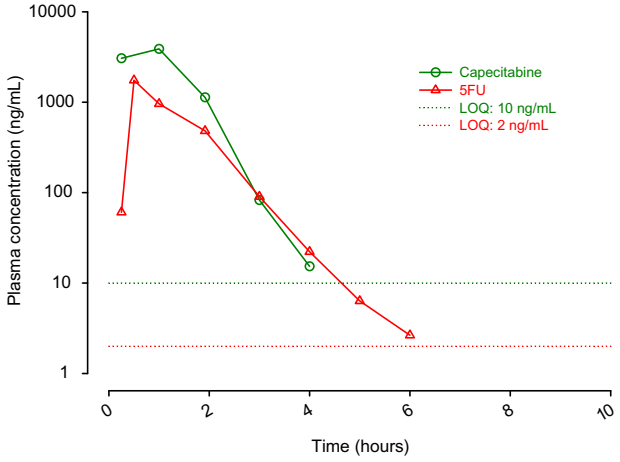


**Fig. 2 – Typical plasma concentration–time profile of capecitabine and 5-FU (DL2).**

mainly anthracyclines and taxanes, treatment with the combination of cabazitaxel and capecitabine provided an ORR of 23.8%. This regimen showed activity in patients previously treated with a taxane and anthracyclines across all dose levels with either disease stabilisation or responses in patients who had either progression or stabilisation as best response under prior taxanes, respectively.

It has been demonstrated *in vitro* that cabazitaxel is mainly metabolised by CYP3A and the conversion to one of its primary metabolites, RPR123142, occurs via this pathway. Capecitabine is preferentially converted into 5-FU in tumours through a cascade of three enzymes, carboxylesterase, cytidine deaminase, and thymidine phosphorylase (dThdPase).[25] In addition, other *in vitro* experiments have shown that capecitabine does not inhibit CYP3A. Based on these findings, a PK drug–drug interaction is theoretically unlikely.

In the present study, the PK results for cabazitaxel are in agreement with results of a previously published phase I study with single-agent cabazitaxel[26], showing a high plasma clearance, a long $T_{½}$, and a very large volume of distribution at steady state. Similar to humans, a large volume of distribution at steady state was also observed after intravenous infusions of cabazitaxel in mice and rats, suggesting a large diffusion in rodent species. These findings were confirmed by distribution studies performed in tumour-free and tumour-bearing mice and in rats showing a rapid distribution of the drug into most organs, including the brain and tumour. This large diffusion of the drug in the human body explains the long exposure despite a relatively high plasma clearance. Furthermore, the easy penetration of cabazitaxel into tissues could play a major role in drug efficacy. The long elimination half-life of cabazitaxel appears to support the intermittent dose administration schedule.

Mean AUCs of capecitabine appeared to be in the range of those previously reported in the literature (AUC range: 5580–7915 ng h/mL)[27] at DL1 and DL3, but appeared to be higher at DL2, mainly due to four out of 19 patients (AUC 10900–25700 ng h/mL). Mean AUC of 5-FU was in the low range of values previously reported in the literature (AUC range: 422–610 ng h/mL).[25,27–29] Therefore, as expected, the PK analysis in our study revealed no observed drug–drug interaction between cabazitaxel and capecitabine; the PK of cabazitaxel did not seem to be altered by the co-administration of capecitabine for 14 d and the PK of capecitabine and its metabolite appeared not to be modified by the co-administration of cabazitaxel.

In conclusion, the combination of cabazitaxel and capecitabine demonstrated a favourable safety profile and an encouraging activity that warrants further investigation. The recommended dose to be used for further testing in phase II studies in MBC is cabazitaxel 20 mg/m$^2$ day 1 with capecitabine 1000 mg/m$^2$ twice a day, days 1–14, every 3 weeks.

## Conflict of interest statement

E. Magherini, F. Dubin and D. Semiond are employees of sanofi-aventis. C. Villanueva and X. Pivot have received consultancy fees from sanofi-aventis.

## Acknowledgements

We would like to thank the patients who enrolled on this trial and the medical staff who contributed to their care. The study was supported by sanofi-aventis R&D, France. Editorial assistance was provided by Cancer Communications and Consultancy Ltd and MediTech Media Ltd., and was funded by sanofi-aventis.

## REFERENCES

1. Cardoso F, Bedard PL, Winer EP, et al. International guidelines for management of metastatic breast cancer: combination vs sequential single-agent chemotherapy. *J Natl Cancer Inst* 2009;**101**:1174–81.
2. NCCN Clinical Practice Guidelines in Oncology—Breast Cancer V.2.2010. <http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf>. Accessed August 31, 2010.
3. Beslija S, Bonneterre J, Burstein HJ, et al. Third consensus on medical treatment of metastatic breast cancer. *Ann Oncol* 2009;**20**:1771–85.
4. Dufresne A, Pivot X, Tournigand C, et al. Impact of chemotherapy beyond the first line in patients with metastatic breast cancer. *Breast Cancer Res Treat* 2008;**107**:275–9.
5. O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol* 2002;**20**:2812–23.
6. Cabral F. Factors determining cellular mechanisms of resistance to antimitotic drugs. *Drug Resist Updat* 2001;**4**:3–8.
7. Dumontet C, Sikic BI. Mechanisms of action of and resistance to antitubulin agents: Microtubule dynamics, drug transport, and cell death. *J Clin Oncol* 1999;**17**:1061–70.
8. Bissery MC, Bouchard H, Riou JF, et al. Preclinical evaluation of TXD258, a new taxoid. 91st Annual Meeting of the American Association for Cancer Research, San Fancisco, April 1–5, 1364, 41, 2000.
9. Bissery MC. Preclinical evaluation of new taxoids. *Curr Pharm Des* 2001;**7**:1251–7.

10. Vrignaud P, Lejeune P, Chaplin D, et al. In vivo efficacy of TXD258, a new taxoid, against human tumor xenografts. 91st Annual Meeting of the American Association for Cancer Research, San Fancisco, April 1–5, #1365, 41, 2000.
11. Dykes DJ, Sarsat JP, Bissery MC. Efficacy evaluation of TXD258, a taxoid compound, against orthotopic and subcutaneous glioblastomas. 91st Annual Meeting of the American Association for Cancer Research, San Fancisco, April 1–5, #1916, 41, 2000.
12. Pivot X, Asmar L, Buzdar AU, et al. A unified definition of clinical anthracycline resistance breast cancer. *Br J Cancer* 2000;**82**:529–34.
13. Pivot X, Koralewski P, Hidalgo JL, et al. A multicenter phase II study of XRP6258 administered as a 1 – h i v infusion every 3 weeks in taxane-resistant metastatic breast cancer patients. *Ann Oncol* 2008;**19**:1547–52.
14. Blum JL, Jones SE, Buzdar AU, et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol* 1999;**17**:485–93.
15. Sawada N, Ishikawa T, Fukase Y, et al. Induction of thymidine phosphorylase activity and enhancement of capecitabine efficacy by taxol/taxotere in human cancer xenografts. *Clin page Cancer Res* 1998;**4**:1013–9.
16. Fujimoto-Ouchi K, Tanaka Y, Tominaga T. Schedule dependency of antitumor activity in combination therapy with capecitabine/5′-deoxy-5-fluorouridine and docetaxel in breast cancer models. *Clin Cancer Res* 2001;**7**:1079–86.
17. Nadella P, Shapiro C, Otterson GA, et al. Pharmacobiologically based scheduling of capecitabine and docetaxel results in antitumor activity in resistant human malignancies. *J Clin Oncol* 2002;**20**:2616–23.
18. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;**92**:205–16.
19. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;**53**:457–81.
20. Pivot X, Thierry-Vuillemin A, Villanueva C, et al. Response rates: a valuable signal of promising activity? *Cancer J* 2009;**15**:361–5.
21. Fumoleau P, Largillier R, Clippe C, et al. Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. *Eur J Cancer* 2004;**40**:536–42.
22. Perez EA, Lerzo G, Pivot X, et al. Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. *J Clin Oncol* 2007;**25**:3407–14.
23. Pivot X, Villanueva C, Chaigneau L, et al. Ixabepilone, a novel epothilone analog in the treatment of breast cancer. *Expert Opin Investig Drugs* 2008;**17**:593–9.
24. Thomas ES, Gomez HL, Li RK, et al. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. *J Clin Oncol* 2007;**25**:5210–7.
25. Reigner B, Blesch K, Weidekamm E. Clinical pharmacokinetics of capecitabine. *Clin. Pharmacokinet* 2001;**40**:85–104.
26. Mita AC, Denis LJ, Rowinsky EK, et al. Phase I and pharmacokinetic study of RPR 116258A, a novel taxane derivative, administered as a 1-hour infusion every three weeks in patients with advanced solid tumors. *Clin Cancer Res* 2009;**15**:723–30.
27. Soepenberg O, Dumez H, Verweij J, et al. Phase I and pharmacokinetic study of oral irinotecan given once daily for 5 days every 3 weeks in combination with capecitabine in patients with solid tumors. *J Clin Oncol* 2007;**25**:3753–8.
28. Pronk LC, Vasey P, Sparreboom A, et al. A phase I and pharmacokinetic study of the combination of capecitabine and docetaxel in patients with advanced solid tumours. *Br J Cancer* 2000;**83**:22–9.
29. Chaigneau L, Royer B, Montange D, et al. Influence of capecitabine absorption on its metabolites pharmacokinetics: a bioequivalence study. *Ann Oncol* 2008;**19**:1980–1.