

Critical appraisal of cabazitaxel in the management of advanced prostate cancer

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Abstract: Docetaxel remains a cornerstone of therapy for the patient with metastatic castration-resistant prostate cancer (CRPC). However, the landscape of CRPC therapy is changing rapidly – recently, data from the phase III TROPIC study revealed a survival advantage with the novel taxane cabazitaxel/prednisone (compared with mitoxantrone/prednisone) in a cohort of 755 men with docetaxel-refractory metastatic CRPC. Interestingly, cabazitaxel bears substantial structural similarity to docetaxel but appears to be mechanistically distinct. In preclinical studies, the agent has antitumor activity in a variety of docetaxel-refractory in vitro and in vivo models. Subsequent to phase I testing in advanced solid tumors (where neutropenia was identified as a dose-limiting toxicity), the agent was assessed in a phase II trial in advanced, taxane-refractory breast cancer and in the aforementioned phase III TROPIC study. This review describes in detail the preclinical and clinical development of cabazitaxel.

Keywords: cabazitaxel, castration resistant prostate cancer, Jevtana, breast cancer, taxane

Introduction

In 2010, it is estimated that prostate cancer will account for 28% of newly diagnosed cancers among males in the United States.¹ A large majority of these cases (approximately 92%) will be diagnosed at a local or regional stage, with 5-year survival rates approaching 100%. However, for individuals who are diagnosed with (or subsequently develop) metastatic prostate cancer the prognosis remains limited.² Until recently, the treatment algorithm for metastatic disease remained relatively simple. Observations by Huggins et al in 1941 suggested that castration could induce regression of prostatic tumors.^{3,4} Thereafter, permutations of synthetic luteinizing hormone releasing hormone (LHRH) agonists and antiandrogen therapy supplanted surgical intervention.^{5–8} Upon failure of these therapies, further options were limited until recently. Two large, randomized phase III trials demonstrated an overall survival (OS) advantage with docetaxel compared to mitoxantrone-based regimens.^{9,10} Beyond docetaxel, strategies such as crossing over to mitoxantrone-based regimens appear to be of limited efficacy.^{11,12}

Clinical data have amassed over the past several years that now position several agents in either the pre- or postdocetaxel space (and potentially both) in the prostate cancer treatment paradigm.¹³ The phase III IMPACT trial assessed sipuleucel-T, an autologous cellular vaccine, in a largely chemotherapy-naïve cohort of patients with castration-resistant prostate cancer (CRPC).¹⁴ Relative to placebo, sipuleucel-T significantly prolonged OS (25.8 vs 21.7 months, $P = 0.04$), leading to Food and Drug Administration (FDA) approval of this agent. As an alternative, several novel endocrine therapies have shown substantial efficacy in the setting of CRPC. Promising phase II

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data for abiraterone, MDV3100, and TAK700 have led to the design of large, randomized trials.^{15–21} Notably, a placebo-controlled, phase III study enrolling patients with docetaxel-refractory CRPC demonstrated a survival advantage with abiraterone therapy.²² Just as these novel therapies challenge the paradigm of ‘castration resistance’ in the setting of CRPC (Figure 1), clinical data for the novel taxane cabazitaxel suggest that a chemotherapeutic strategy may be effective even after failure of docetaxel. Herein, the development and clinical implementation of cabazitaxel are reviewed in detail.

Mechanism of action/preclinical data

Whereas vinca alkaloids inhibit incorporation of tubulin into microtubules, the taxanes appear to inhibit microtubule disassembly.^{23–25} Although the microtubular binding mechanism of cabazitaxel does not appear to be distinct from docetaxel or paclitaxel, the agent is structurally distinct. As noted in Figure 2, hydroxyl groups present in docetaxel are replaced with methoxy groups in cabazitaxel.

Bissery et al reported preclinical data suggesting the *in vitro* activity of cabazitaxel.²⁶ Four cell lines were assessed, including P388 (lymphoblastic leukemia), HL60 (promyelocytic leukemia), KB (cervical adenocarcinoma), and Calcl8 (breast carcinoma). With a 4-day exposure to the drug, cytotoxicity was noted with relatively low cabazitaxel concentrations (IC_{50} = 3–29 ng/mL). In accompanying *in vivo* models, the agent was noted to have significant antitumor activity. In murine tumor xenografts (colon C38 and pancreas P03), cabazitaxel elicited complete tumor

regressions. Two schedules of the drug were assessed: 1) a day 1 and 5 schedule with a dose of 58 mg/kg and 2) thrice daily dosing on a day 1 to 5 schedule at 12 mg/kg. The maximally tolerated dose (MTD) was 4.8-fold higher using the former schedule. Notably, in cell lines resistant to a variety of other cytotoxic agents (ie, anthracyclines, vinca alkaloids, and the older taxanes), cabazitaxel was noted to still induce tumor regression.

The activity of cabazitaxel was subsequently documented in human tumor xenografts using a variety of intravenous schedules.²⁷ In 3 human colorectal cell lines (HCT-116, HCT-8, and HT-29), high antitumor activity was observed. For instance, on a thrice daily schedule given every 3 days, cabazitaxel induced a 3.34 log cell kill (LCK) at the total highest nontoxic dose (THNTD), 36 mg/kg. In lung models, dosing at the THNTD yielded 2.7 LCK in the NCI-H460 cell line, and 2.2 LCK in the A549 cell line. As observed in murine tumor xenograft studies, multiple cases of complete regression were observed using human tumor xenografts. Notably, long-term tumor-free survival (exceeding 133 days) and complete tumor regression were observed in pancreatic xenografts (MIA PaCa-2), head and neck xenografts (SR475), and prostate xenografts (DU145, a cell line that represents a hormone-resistant entity established from a prostate cancer brain metastasis).²⁸

Pharmacokinetics/pharmacodynamics

Pharmacokinetic parameters associated with cabazitaxel were first documented in animal studies.²⁹ Using ¹⁴C-labeled cabazitaxel, doses of 15, 30, and 90 mg/m² were delivered to

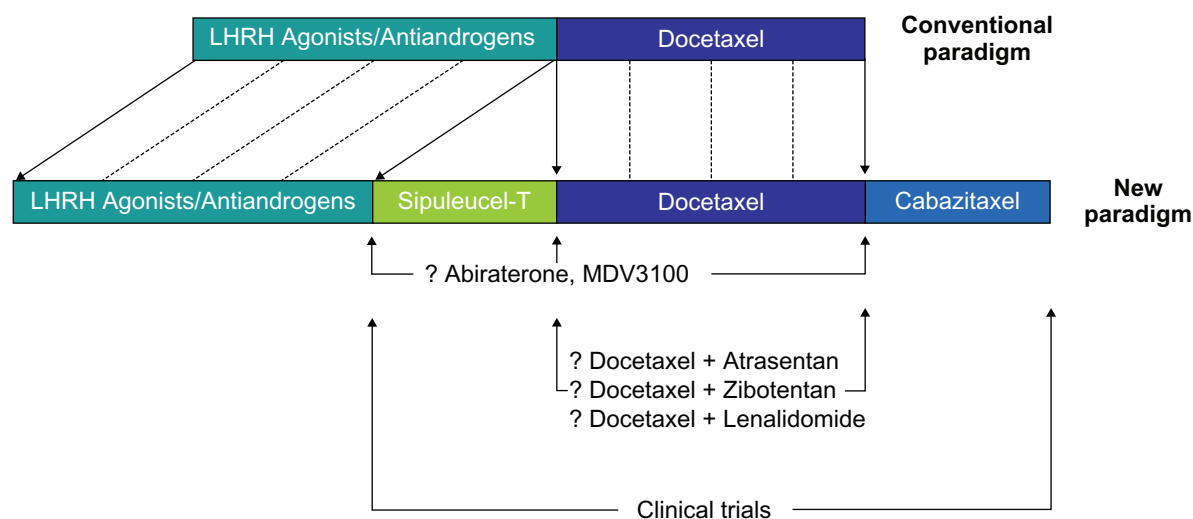


Figure 1 Existing and evolving paradigms in the treatment of metastatic prostate cancer.

Abbreviation: LHRH, luteinizing hormone releasing hormone.

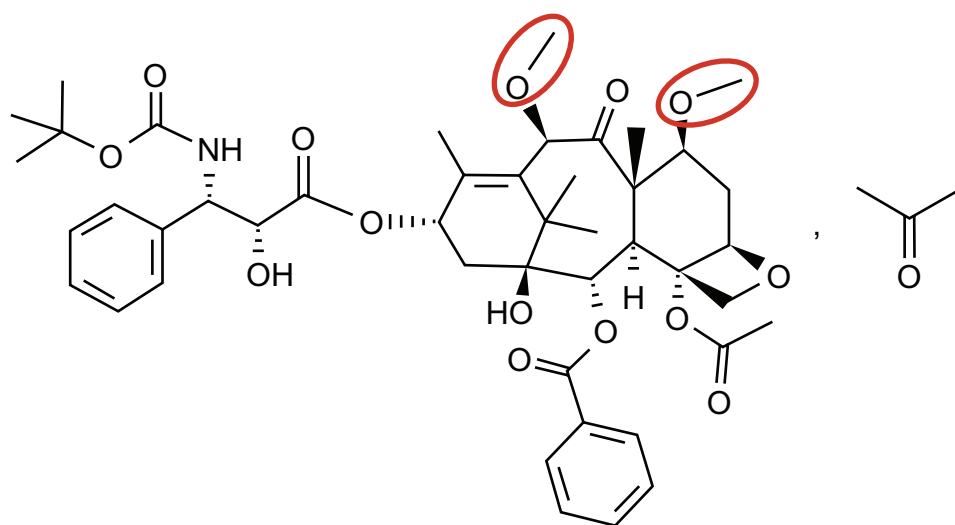


Figure 2 The chemical structure of cabazitaxel ($C_{45}H_{57}NO_{14}$, C_3H_6O , MW = 894.01). Highlighted in red are methoxy side chains that substitute hydroxyl groups found in docetaxel.

mice as either 1-minute or 1-hour infusions. Radioactivity was measured in the blood, plasma, and brain. There was a correlation between dose and plasma exposure within the aforementioned dosing range, whereas brain exposure increased more than proportionally over the same range. The peak of brain concentrations occurred between 2 minutes and 1 hour post-infusion. Parallel assessments performed in dogs using a dose of 15 mg/m² over 80 minutes suggested lesser brain exposure as compared to mice. Of note, brain concentrations of ¹⁴C-labeled cabazitaxel were detectable up to 168 hours after infusion in mice, and for up to 24 hours in dogs. This ability to concentrate in the brain is not typical for other taxanes.

The role of P-glycoprotein (P-gp) in the accumulation of cabazitaxel in the brain was assessed more extensively in a report by Cisternino et al.³⁰ Again using ¹⁴C-labeled cabazitaxel, doses ranging between 15 and 90 mg/m² were delivered to mice, and doses of either 15 or 60 mg/m² were delivered to rats. It was noted that brain uptake of cabazitaxel was enhanced when concentrations exceeded 11 μM. These saturable kinetics suggested the role of a critical transporter (ie, P-gp) in transporting cabazitaxel across the blood–brain barrier (BBB) upon a certain threshold (saturation was found to be at 13 μM). To further test this hypothesis, animals were concomitantly dosed with the P-gp inhibitor verapamil. Verapamil co-administration led to a 2.9-fold and 4.7-fold increase in brain uptake in mice and rats, respectively. Harnessing these pharmacokinetic properties, the activity of cabazitaxel has been documented in brain tumor models.³¹ Using SF-295 and U251 human glioblastoma cell lines, both orthotopic and subcutaneous murine xenografts

were generated. Cabazitaxel treatment led to complete regression in the majority of subcutaneously implanted tumors. Furthermore, in orthotopic models, cabazitaxel led to complete tumor regression in 4 out of 10 U251 tumors.

A phase I clinical trial of 3-weekly cabazitaxel enrolled patients with advanced solid malignancies refractory to conventional treatments.³² With respect to prior therapy, patients were limited to less than 2 prior chemotherapy regimens for metastatic disease and radiation affecting less than 25% of the available hematopoietic reserve. A starting dose of 10 mg/m² was selected, representing one-tenth the severe toxic dose in mice (STD₁₀). Given that the STD₁₀ in mice corresponded to a plasma level of 10.8 μg/mL, pharmacokinetic monitoring was performed during the first course of therapy and dose-escalation was to be terminated for plasma levels beyond this value.

In total, 25 patients were treated with 102 courses of 3-weekly cabazitaxel at 4 dose levels, ranging from 10 mg/m² to 25 mg/m².³² A total of 22 patients had received prior chemotherapy (88%), and 8 patients had received prior taxane-based therapy (32%). Although a diverse array of tumor types was enrolled, the largest subgroup comprised patients with prostate cancer (8 patients, 32%). A median of 4 cycles (range 1–9) was administered. Pharmacokinetic analyses suggested that cabazitaxel absorption best fit a tri-phasic model. A rapid initial phase was followed by a longer intermediate phase ($t_{1/2}$ = 2.5 minutes and 1.3 hours, respectively). Finally, a prolonged terminal phase ($t_{1/2}$ = 77.3 hours) was observed.

The dose-limiting toxicity (DLT) of cabazitaxel was neutropenia, with 1 case of febrile neutropenia and 2 cases

of grade 4 neutropenia occurring at a dose of 25 mg/m². Accordingly, the recommended phase II dose emerging from this study was 20 mg/m².³² Notably, support with granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor was not utilized in these studies, although it was ultimately administered in patients incurring grade 4 neutropenia. Nonhematologic toxicities were generally mild in nature; the most commonly encountered adverse events were diarrhea (52%), nausea (40%), and vomiting (15%). Only 1 grade 3 nonhematologic event was recorded – diarrhea in a patient dosed at 15 mg/m² (resolving shortly after therapy with loperamide). In this initial clinical experience, 2 confirmed partial responses were observed, both in patients with prostate cancer. One patient had previously received mitoxantrone, while the other had progressed on docetaxel. An unconfirmed partial response was observed in a patient with bladder cancer, and minor responses were seen in 2 patients with osteosarcoma and prostate cancer, respectively. Stable disease (SD) was recorded as a best response in 12 patients (48%).

Phase II data in breast cancer

A phase II study in breast cancer was originally designed as a randomized 3-arm study to explore 2 distinct dosing regimens of cabazitaxel and to further assess the activity of the novel taxane larotaxel. (the activity of larotaxel has been documented in phase I and II studies in breast and lung cancer).^{33–36} Due to poor accrual, it was ultimately modified to be a single-arm study evaluating cabazitaxel alone in patients with taxane-resistant metastatic breast cancer. In the setting of patients who had received adjuvant or neoadjuvant taxane therapy, resistance was defined as metastatic progression within 12 months of systemic therapy. For patients with metastatic disease, the definition was more complex; resistance was characterized as: 1) progressive disease (PD) representing the best response to treatment, 2) PD occurring within 4 months after first- or second-line therapy (after an initial clinical benefit), or 3) SD representing the best response if a taxane had been administered for 3 or more months. Patients were treated initially with a dose of 20 mg/m², which was escalated to 25 mg/m² in those patients who did not incur a significant adverse event during the first cycle of therapy. Patients who were HER2-positive were allowed to enroll if they had progressed on a trastuzumab-based regimen; otherwise, the study was limited to HER2-negative patients.

The study was powered to assess objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, with secondary endpoints including

duration of response, time to progression, and OS.³⁶ The study was stratified by the number of lines of previous taxane-based therapy. Stratum 1 consisted of 47 patients who had progressed after either first-line systemic therapy for advanced disease or adjuvant/neoadjuvant taxanes; stratum 2 consisted of 20 patients who had progressed on second-line therapy for advanced disease. The median age of enrolled patients was 53 years, with an expected distribution of hormone receptor-positive and HER2-positive tumors (52% and 27%, respectively). The majority of patients had received prior chemotherapy for advanced disease, with only 1 patient having received adjuvant therapy. Seven patients (10%) had received multiple forms of taxane therapy.

Among treated patients, the ORR was 14% (95% confidence interval [CI], 7%–24%), with no differences between the two pre-defined strata (14% for stratum 1 and 12% for stratum 2).³⁶ The median duration of response was 7.6 months (range 2.6–18.7 months). A significant proportion of patients also exhibited SD as a best response (38%). Two patients were noted to have a complete response to cabazitaxel therapy. Mirroring the phase I experience, the most common grade 3/4 toxicity incurred was neutropenia, present in 73% of the patients. Two patients developed febrile neutropenia, while 3 patients developed neutropenic infections. Two deaths were recorded within 30 days of on-study therapy; both were secondary to nonhematologic toxicities. In the first patient, death occurred due to respiratory failure that was possibly related to study therapy, and in the second patient, the cause of death was unknown. The results for cabazitaxel in breast cancer have drawn multiple comparisons to the novel epothilone ixabepilone, which also impacts microtubule function and has been assessed in phase III trials in this disease.³⁷

Phase III data

The information garnered from phase I and II studies, encompassing multiple malignancies, were used to inform the design of the phase III TROPIC trial comparing cabazitaxel/prednisone with mitoxantrone/prednisone in patients with docetaxel-refractory prostate cancer.³⁸ The study itself represented somewhat of a paradigm shift, given the absence of prior phase II studies assessing cabazitaxel specifically in the setting of prostate cancer. However, no viable therapeutic options were available to the docetaxel-refractory patient at the time the study was initiated, generating a substantial area of need. Furthermore, abundant preclinical data in docetaxel-refractory cell lines and an initial clinical demonstration of safety and efficacy in solid tumors supported this larger undertaking.

In TROPIC, progression on docetaxel was defined by RECIST in patients with measurable disease, or by 2 consecutive prostate-specific antigen (PSA) rises (at least 1 week apart) in patients with nonmeasurable disease.³⁸ Orchiectomy or prior pharmacologic androgen deprivation was mandated, and patients who were receiving LHRH agonists were instructed to continue taking them during protocol therapy.

Ultimately, 755 men were randomized (378 to cabazitaxel and 377 to mitoxantrone) in a total of 26 countries. The median age of the study population was 68 years, and the majority of patients were Caucasian (84%).³⁸ Although enrollment was originally conducted irrespective of the amount of prior docetaxel therapy, the study was ultimately modified to exclude patients who had received a cumulative dose of less than 225 mg/m². This amendment was made in light of guidelines suggesting that castrate-resistant prostate cancer therapy be maintained for a period of at least 3 cycles prior to instituting any change. The mean docetaxel dose in the experimental arm was 576.6 mg/m², compared with 529.2 mg/m² in the control arm. A substantial proportion of patients progressed on docetaxel therapy either during treatment (29%) or within 3 months of its completion (45%); the mean time from the last docetaxel dose to disease progression was 0.8 months in the experimental arm and 0.9 months in the control arm. Although most patients had bony metastases (84%), a considerable proportion did have visceral metastases (25%).

Whereas the phase II experience in breast cancer initiated 3-weekly dosing of cabazitaxel at 20 mg/m², in TROPIC, patients were initiated at 25 mg/m². Patients randomized to receive mitoxantrone were started on a conventional dose of 12 mg/m² every 3 weeks. Both arms received prednisone 10 mg oral daily. In order to limit the risk of mitoxantrone-induced cardiac dysfunction, therapy on both arms was limited to a total of 10 cycles. While growth factor support was not allowed at the initiation of therapy, it was permitted to treat extended neutropenia (>7 days), neutropenic infection, or neutropenic fever.

The primary endpoint of the study was OS, with a secondary endpoint of progression-free survival (PFS). PFS was defined by the occurrence of one of several clinical events, including PSA progression, radiographic progression, progression of pain (measured by the McGill-Melzack present pain intensity scale, PPI) or death. The study met its primary endpoint, with an improvement in OS of 2.4 months favoring cabazitaxel therapy (15.1 vs 12.7 months; hazard ratio [HR] 0.70, 95% CI 0.59–0.83, $P < 0.001$). The benefit

of cabazitaxel for survival appeared to extend across the majority of subgroups assessed, including subgroups divided by performance status (ECOG 0-1 or ECOG 2), measurable disease (absent or present), number of previous chemotherapeutic agents (1 or ≥ 2), age (<65 or ≥ 65), and pain (at baseline, absent or present). Furthermore, subset analyses favored cabazitaxel across groups divided by cumulative docetaxel dose. Cumulative PFS (using the composite endpoint) was also improved with cabazitaxel therapy (2.8 vs 1.4 months, HR 0.74, 95% CI 0.64–0.86, $P < 0.0001$), although time to pain progression (as defined by the PPI inventory) did not significantly improve. PSA response rate was 39.2% vs 17.8% ($P = 0.002$) and median time to PSA progression was 6.1 vs 3.1 months ($P = 0.001$), both favoring cabazitaxel.

Mirroring the phase I and II experiences, the most common toxicity associated with cabazitaxel therapy was neutropenia. Grade ≥ 3 neutropenia occurred in 82% of cabazitaxel patients, with 8% of patients developing febrile neutropenia. Common nonhematologic toxicities in patients receiving cabazitaxel included diarrhea, fatigue, and asthenias (all grades: 47%, 37%, and 20%, respectively). A total of 18 patients (5%) died within 30 days of the last cabazitaxel infusion, compared with 9 patients (2%) receiving mitoxantrone therapy within the same time frame. In the cabazitaxel arm, 7 patients (2%) died of complications related to neutropenia, while 5 patients (1%) died of cardiac causes.

Safety considerations

Several factors may influence the toxicities associated with cabazitaxel therapy. In the TROPIC trial, diarrhea appeared to be more prevalent in older patients (55.7% vs 44.5% in patients aged ≥ 75 or < 75 , respectively; $P < 0.1$) and in patients who had previously received radiotherapy (50.0% vs 41.4% in patients with and without prior exposure, respectively).³⁹ The most prevalent toxicity, neutropenia, occurred at a frequency 6.6% higher in patients aged ≥ 65 compared with those < 65 . Furthermore, the incidence of neutropenia varied significantly by region, with rates of neutropenia in North America exceeding those in the Europe. Analyses are currently underway to determine the extent of growth factor use both in the study population at large and within these subgroups (notably, cycle 1 prophylaxis with growth factors was not allowed in the TROPIC protocol). Until these data are available, the currently available FDA label suggests the use of primary prophylaxis with G-CSF in those patients who are considered high risk, as delineated in Table 1.

Table 1 Special precautions for use of cabazitaxel

Toxicity	Description
Neutropenia	Neutropenic deaths have been reported with cabazitaxel therapy. Administration of G-CSF may be considered to reduce the risks of neutropenic complications. Primary prophylaxis should be considered in high-risk groups defined by the following features: <ul style="list-style-type: none"> • Age >65 years • Extensive prior radiation • Poor nutrition • Previous febrile neutropenia • Poor performance status • Other serious medical co-morbidities
Diarrhea	Mortality related to diarrhea has been reported with cabazitaxel. Hydration, antiemetics and antidiarrheals should be used to treat symptoms; however, for grade >3 diarrhea, dose reduction should be considered.
Hepatic impairment	Cabazitaxel should not be used in the setting of hepatic impairment; these patients were excluded from current trials of cabazitaxel therapy.
Hypersensitivity	Given that severe hypersensitivity reactions have been observed with cabazitaxel, premedication with H ₂ -antagonists and corticosteroids is recommended.

Abbreviation: G-CSF, granulocyte colony-stimulating factor.

As yet, there are no head-to-head trials comparing docetaxel and cabazitaxel, making it challenging to juxtapose both the efficacy and toxicity of these agents. Nonetheless, the rates of neuropathy with cabazitaxel were relatively low, only 1% of patients reporting a grade 3/4 event (14% for all grades).³⁸ It should be noted that patients with grade 2 or higher peripheral neuropathy in association with docetaxel were excluded from TROPIC, confounding any comparisons with this agent. Another important distinction between cabazitaxel and docetaxel is the premedication regimen proposed for each. In SWOG 9916 and TAX 327, patients receiving 3-weekly docetaxel received 60 mg and 24 mg of oral dexamethasone divided over 3 doses, respectively.^{9,10} In contrast, patients receiving cabazitaxel in the TROPIC study received 8 mg of intravenous dexamethasone in conjunction with an antihistamine and H₂-antagonist.³⁸ In the setting of certain co-morbidities (ie, diabetes), the latter regimen may be preferable.

Conclusions

Therapy with cabazitaxel in docetaxel-refractory CRPC has already been adopted as a category 1 recommendation in National Comprehensive Cancer Network Criteria.⁴⁰

However, the challenge that lies ahead is multifold. Given the efficacy of cabazitaxel in the heavily pretreated population in the TROPIC study, could cabazitaxel potentially be moved forward in the current therapeutic algorithm for prostate cancer (Figure 1)? Furthermore, underway are numerous clinical studies assessing synergy of docetaxel with a range of agents. Some of the reports thus far have been sobering. For instance, the phase III Cancer and Leukemia Group B (CALGB) 90401 trial showed no OS benefit with the addition of bevacizumab to docetaxel.⁴¹ Nonetheless, several other phase III efforts are underway, including studies pairing docetaxel with the endothelin antagonists zibotentan and atrasentan, and the antiangiogenic/immunomodulatory agent lenalidomide.^{42–44} With its efficacy now demonstrated, the investigator may be inclined to assess cabazitaxel in the same combinations currently being investigated with docetaxel. The research community is cautioned to perform appropriate preclinical and clinical safety testing prior to embarking on larger efforts assessing such combinations. Several ongoing clinical trials of cabazitaxel both alone and in combination with other cytotoxic agents are denoted in Table 2. Furthermore, cabazitaxel/prednisone (dosed at both 20 and 25 mg/m²) will be compared to docetaxel/prednisone (at a standard dose of 75 mg/m²) as first-line chemotherapy

Table 2 Listed studies evaluating the clinical efficacy and safety of cabazitaxel^{47–50}

Identifier	Planned enrollment	Primary objective
NCT01140607	75	To determine the MTD and safety of cabazitaxel when administered every 3 weeks in patients with advanced solid tumors with varying degrees of hepatic impairment.
NCT00925743	30	To determine the DLT of cabazitaxel in combination with cisplatin when administered every 3 weeks in patients with advanced solid tumors.
NCT01001221	30	To determine the MTD and DLT of cabazitaxel in combination with gemcitabine when administered every 3 weeks in patients with advanced solid tumors. To determine the antitumor activity of cabazitaxel with gemcitabine in an expanded cohort (treated at the determined MTD) as assessed by objective response.
NCT01087021	45	To determine the potential effect on QTcF interval (QTc Fridericia) of cabazitaxel in patients with advanced solid tumors.

Abbreviations: DLT, dose-limiting toxicity; MTD, maximally tolerated dose.

in metastatic CRPC. The primary endpoint in this study is OS. Problematic in the trial design is the fact patients progressing on docetaxel (but not cabazitaxel) will have a known effective salvage therapy.

The role of docetaxel in distinct settings of prostate cancer may similarly guide clinical implementation of cabazitaxel. For instance, CALGB 90203 is a randomized, phase III effort comparing 6 cycles of neoadjuvant docetaxel therapy preceding prostatectomy with prostatectomy alone in the setting of high-risk, localized disease.⁴⁵ If the trial yields promising results, the application of cabazitaxel as neoadjuvant therapy could be explored. Further, it remains to be seen whether cabazitaxel has specific activity in the context of aggressive prostatic cancer histologies, such as tumors bearing neuroendocrine features. Available clinical data suggest limited efficacy of docetaxel and other standard cytotoxic agents in this setting.⁴⁶ Questions remain about the dosing regimen chosen in the TROPIC study; ie, could toxicity have been mitigated by starting with a dose of 20 mg/m²? As previously noted, this represented the initial dose utilized in a phase II study of cabazitaxel in breast cancer. In that study, allowance of dose escalation to 25 mg/m² was contingent upon completion of the first cycle of therapy with no toxicity. The aforementioned phase III first line trial in metastatic CRPC will help to address this issue.

Finally, it is not known yet whether the activity of cabazitaxel in docetaxel-refractory CRPC will translate to other tumor types. The previously noted phase II study assessing the agent in taxane-refractory advanced breast cancer may stimulate further trials in this disease.³⁶ Furthermore, urothelial carcinoma, lung cancer, ovarian cancer, and countless other malignancies where taxanes have a described clinical benefit may represent new domains where cabazitaxel therapy could be examined.

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