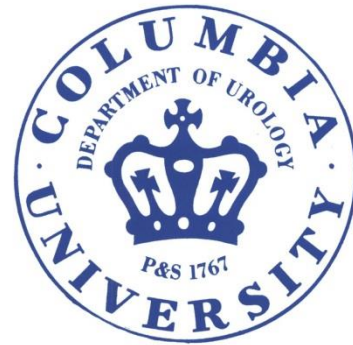


A Phase I trial for the use of Intravesical Cabazitaxel, Gemcitabine, and Cisplatin (CGC) in the treatment of BCG-Refractory Non- muscle invasive Urothelial Carcinoma of the Bladder

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Version 22: December 21, 2017



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Renal and urinary disorders					
Adverse Event	Grade				
	1	2	3	4	5
Acute kidney injury	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
Definition: A disorder characterized by the acute loss of renal function and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction).					
Bladder perforation	-	Extrapertoneal perforation, indwelling catheter indicated	Intrapertoneal perforation; elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the bladder wall.					
Bladder spasm	Intervention not indicated	Antispasmodics indicated	Hospitalization indicated	-	-
Definition: A disorder characterized by a sudden and involuntary contraction of the bladder wall.					
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death
Definition: A disorder characterized by gradual and usually permanent loss of kidney function resulting in renal failure.					
Cystitis noninfective	Microscopic hematuria; minimal increase in frequency, urgency, dysuria, or nocturia; new onset of incontinence	Moderate hematuria; moderate increase in frequency, urgency, dysuria, nocturia or incontinence; urinary catheter placement or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the bladder which is not caused by an infection of the urinary tract.					
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate blood in the urine.					
Hemoglobinuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of free hemoglobin in the urine.					
Proteinuria	1+ proteinuria; urinary protein <1.0 g/24 hrs	Adults: 2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Pediatric: urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Adults: urinary protein >=3.5 g/24 hrs; Pediatric: urine P/C >1.9	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of excessive protein in the urine. It is predominantly albumin, but also globulin.					
Renal calculi	Asymptomatic or mild symptoms; occasional use of nonprescription analgesics indicated	Symptomatic; oral antiemetics indicated; around the clock nonprescription analgesics or any oral narcotic analgesics indicated	Hospitalization indicated; IV intervention (e.g., analgesics, antiemetics); elective endoscopic or radiologic intervention indicated	Life-threatening consequences; urgent radiologic, endoscopic or operative intervention indicated	Death
Definition: A disorder characterized by the formation of crystals in the pelvis of the kidney.					
Renal colic	Mild pain not interfering with activity; nonprescription medication indicated	Moderate pain; limiting instrumental ADL; prescription medication indicated	Hospitalization indicated; limiting self care ADL	-	-
Definition: A disorder characterized by paroxysmal and severe flank marked discomfort radiating to the inguinal area. Often, the cause is the passage of kidney stones.					

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1.0 PROTOCOL SUMMARY (IRB-AAAM8506)

This is a phase I study to assess the safety and toxicity of intravesical Cabazitaxel, Gemcitabine, and Cisplatin (CGC) in the treatment of High Risk Non-muscle invasive Bladder Cancer that has recurred after standard first line treatment.

2.0 INTRODUCTION

The standard therapy for high-risk non-muscle invasive (stage Ta, T1, and Tis) urothelial carcinoma (UCC) of the bladder is intravesical immunotherapy (*i.e.*, delivery of agents directly into the bladder lumen), often with *Bacille Calmette-Guérin* (BCG). However up to 50% of patients treated this way will have disease recurrence. Response rates to second-line intravesical chemotherapy agents have been discouraging and average less than 20 percent. Patients who fail to respond to standard intravesical therapies are left with radical cystectomy as their only evidence-based curative option. This surgery carries significant morbidity and physiologic stress, and many patients are not appropriate surgical candidates for this procedure; others refuse surgery out of fear and concern for their future quality of life without a normal-functioning bladder. It is therefore incumbent upon the medical community to develop new therapeutic targets for non-muscle invasive bladder cancer (NMIBC) refractory to standard intravesical agents. We propose to conduct a combined phase I trial to assess the safety and toxicity of a novel multidrug intravesical regimen consisting of Cabazitaxel, Gemcitabine, and Cisplatin in the treatment of BCG resistant non-muscle invasive urothelial carcinoma of the bladder.

2.1 Background and significance

In 2013 it is estimated that 72,570 new cases of bladder cancer will be diagnosed in the United States and 14,880 will die from it, making it the fourth leading cause of cancer in men and the ninth leading cause of cancer in women in the United States.¹ NMIBC accounts for 70 to 80 percent of these cases and the natural history can vary widely, with recurrence being common. In individual cases with high-risk clinical and pathological features (high grade Ta, T1 and Tis) the use of intravesical therapy to prevent adverse outcomes has become the standard of care. However up to 50 percent of patients treated with intravesical therapy for high-risk NMIBC or

carcinoma in situ will recur.² Response rates to second-line intravesical therapy are 20 percent or less in this population.

When the currently available intravesical agents fail to control the disease, the option most likely to improve patient survival is radical cystectomy (the surgical removal of the bladder) with urinary diversion. Cystectomy is performed in patients with high-risk non-muscle invasive bladder tumors in order to prevent death from progressive metastatic bladder cancer. Many patients, however, do not undergo cystectomy either because several comorbid conditions prevent them from being good surgical candidates or because they refuse to undergo this major surgical procedure.³ For these patients, there is a paucity of active chemotherapeutic alternatives, and thus there is an urgent need to investigate other intravesical options.

Bladder cancer is a heterogeneous disease with 70 to 80 percent of patients initially presenting with non-muscle invasive disease (i.e. stages Ta, T1, or carcinoma in situ (CIS)). The majority of these patients (50-70%) will recur after initial treatment and 10 to 20 percent will eventually progress to muscle invasive disease. Efforts to improve recurrence free survival and the potential for progression include the use of intravesical immunomodulators such as BCG (Bacillus Calmette Guerin) and interferon alpha, and chemotherapeutic agents such as mitomycin C, doxorubicin, thiotepa, docetaxel, and gemcitabine. Unfortunately, patients with high-risk non-muscle invasive disease (i.e. high grade Ta, T1, or CIS) who are refractory to BCG treatment are at a high risk of progression and disease specific mortality. Preemptive early radical cystectomy prior to the development of muscle invasive disease has been offered in these patients to obviate this risk, however this subjects patients to life altering radical surgery, who may never have gone on to progress to invasive disease. As such there is a clear need for further therapeutic options which would improve chances for bladder preservation without sacrificing cancer control and survival.

Thus far, attempts to discover alternatives to BCG have primarily relied on studies involving single agent intravesical chemotherapy instillations. Intravesical gemcitabine and cisplatin take their intellectual justifications from their use as the 1st line systemic agents in advanced bladder

cancer.⁴ Similarly, taxane therapy has been used in combination with gemcitabine and cisplatin systemically for metastatic disease.⁵

As these three drugs are currently employed in combination for systemic disease, and each has been individually tested intravesically in prior human trials, there is a strong rationale for a multimodal regimen of intravesical Gemcitabine, Cisplatin, and an active taxane agent. Few if any single drug systemic therapy protocols have demonstrated durable disease free survival and for this reason the use of a multidrug regimen in this intravesical trial design is logical. This multidrug approach was first utilized by Chen *et al* using a regimen of Mitomycin, doxorubicin and Cisplatin administered sequentially in three weekly doses which was shown to have less toxicities and to be non-inferior to standard BCG treatment.⁶

Gemcitabine, a deoxycytidine analogue, inhibits DNA synthesis and is a commonly used drug in systemic bladder cancer. Intravesical gemcitabine has been studied in multiple Phase I and II trials. It appears to have very little systemic absorption, with plasma levels immeasurable or quite low, and metabolite difluorodeoxyuridine levels that reach at most 5 μ M in the blood, suggesting that low levels of the drug reach systemic circulation.⁷ Thus, although myelosuppression is a serious side effect when gemcitabine is used intravenously, it has a very favorable toxicity profile when administered intravesically, including infrequent urinary tract infection and maculopapillary rash. In a Phase II study of 30 patients, 15 (50%) had complete responses after 19 months of follow-up.⁸ Due to the reported efficacy and low toxicity profile, gemcitabine has been positively compared to and even combined with other intravesical agents such as Mitomycin.^{9,10} Furthermore, the feasibility of intravesical delivery of gemcitabine has recently been confirmed by the completion of the largest multicenter trial of intravesical gemcitabine in the United States in 2011 by the Southwest Oncology Group administering 2000mg/100mL weekly for 6 weeks, then monthly to 12 months (S0353). Gemcitabine is fairly well-studied, even intravesically and sequentially with mitomycin C, and is well tolerated and effective, with 6 of 10 patients cancer free at 14 months.¹⁰ Because of its low toxicity profile and efficacy as intravesical therapy, we initiate every patient with Gemcitabine 2000mg/100mL

and at least Cabazitaxel, leading up to Cabazitaxel and Cisplatin in later cohorts. (See Study Plan below.)

Cisplatin based chemotherapeutic regimens comprise the backbone of any first line systemic treatment for advanced urothelial carcinoma due to its effectiveness. In-vitro studies also demonstrate that it has potent anti-tumor activity when administered intravesically for non-muscle invasive bladder cancer.¹⁰ In a study that reviewed one institution's experience with a combined regimen of intravesical cisplatin, mitomycin, and doxorubicin, the cisplatin regimen was found to have fewer major adverse events (5.6%) compared with BCG, the standard of care (15%).⁶ In the cisplatin-treated group, all of the adverse events were lower urinary tract symptoms (LUTS). There were no systemic symptoms that would suggest absorption of the drug into the circulation. There is a paucity of data on intravesical platinum therapy with small cohort sizes, and the in vitro study referred to above completed more recently. Because of the paucity of data of in vivo trials, we order this drug as the third and last chemotherapy added to our regimen for latter cohorts of patients, as it may have a higher toxicity profile than gemcitabine and cabazitaxel.

In 2006, Columbia University Medical Center completed the first ever Phase I trial investigating intravesical taxanes for the treatment of TCC refractory to prior intravesical agents, specifically studying docetaxel.¹¹ Eighteen patients were enrolled and completed the study. The cohort was comprised of sixteen men and two women of median age 75 years; all patients were BCG-refractory with a mean of 3 prior intravesical treatments, nine patients undergoing only BCG therapy and nine undergoing BCG-interferon therapy. Over the course of 108 intravesical treatments, 108 high-performance liquid chromatography (HPLC) serum measurements demonstrated undetectable levels of docetaxel. Eight patients (44%) experienced grade 1 or 2 local toxicities. Ten patients (56%) experienced no toxicity, and no toxicities were encountered at the highest dose of docetaxel (75 mg/100ml). No systemic toxicities were observed. Although the study was not formally designed to evaluate efficacy, short term complete response (CR) rate at 12 weeks was noted at 56%, but the durability was only 22% at three years. This study completed with promising results and with all patients undergoing dose-escalation to the

maximum dose without consequence. Unfortunately, the initial convincing response to docetaxel was not durable in a portion of patients, suggesting that some patients may have become resistant to the drug's effects. In further establishing the potential efficacy of intravesical taxane therapy, a Phase I trial of intravesical nanoparticle bound paclitaxel (Abraxane) has recently been completed at Columbia University. After 108 instillations (18 patients x 6 weeks), there were no systemic toxicities; furthermore, 5 of 18 patients had complete responses at their 12 week cystoscopy. It has been observed that taxane cabazitaxel behave in a similar manner in that there will be little to no systemic toxicities.

An important limitation of docetaxel is that it has high substrate affinity for multidrug-resistance proteins, in particular the ATP-dependent drug efflux pump P-glycoprotein (P-gp; also known as ABCB1).^{12,13} Expression of P-gp by cancer cells can be responsible for both constitutive and acquired resistance to taxanes. P-gp expression is high in NMIBC, and its expression has been found to be correlated with shorter progression-free survival, suggesting that P-gp may play a role in the development of chemotherapy resistance in bladder cancer.¹⁴

In an attempt to overcome the development of chemotherapy resistance via the hypothesized P-gp-mediated pathway, Cabazitaxel has been promoted as a probable viable alternative therapy. Cabazitaxel (XRP6258) is a new taxoid that is characterized by convenient administration and a favorable pharmacokinetic and safety profile.¹⁵ It promotes tubulin assembly in vitro and stabilizes microtubules against cold-induced depolymerization as efficiently as docetaxel. In fact, in vitro cabazitaxel demonstrates equipotent cytotoxic activity of docetaxel. Cabazitaxel (also known as XRP6258, RPR116258A) is a semisynthetic compound derived from the 10-deacetyl Baccatin III, which is extracted from European yew needles. This new taxoid was selected for development based on a better antiproliferative activity on resistant cell lines than docetaxel. Using cell lines with acquired resistance to doxorubicin, vincristine, vinblastine, paclitaxel and docetaxel, the resistance factors ranged from 1.8 to 10 and 4.8 to 59, for cabazitaxel and for docetaxel, respectively. Cabazitaxel exhibited a broad spectrum of in vivo antitumor activity, not only in docetaxel sensitive tumor models, but also in tumors models in which docetaxel was poorly active or completely inactive. Phase I clinical trials established that the cabazitaxel side effect profile is similar to that reported for taxanes, with neutropenia and neuropathy being the

most commonly reported toxicities. A trend for schedule-dependency was observed with maximum tolerated dosages 4.8-fold higher with an intermittent schedule than with a split dose schedule. The best anti-tumor efficacy was obtained with the schedules allowing the administration of the highest amount of drug. In addition, this compound was found to penetrate the blood brain barrier and marked antitumor activity was obtained in nude mice bearing intracranial glioblastomas.

Currently cabazitaxel has not been used in any trials intravesically to specifically target bladder cancer. Thus, it is difficult to define a MTD for the drug intravesically, but based off studies completed to test its safety and tolerability intravenously and other taxane derivatives used intravesically to treat NMIBC, we can gauge our own protocol.^{11, 16, 17} The MTD combination will be estimated using a two-stage continual reassessment method (see Statistics below).

During clinical development, a total of 565 patients were enrolled and/or randomized to receive cabazitaxel in three Phase 1 studies (TED6188, TED6189, and TED6190), one study investigating the disposition of radiolabeled cabazitaxel (BEX6702), one Phase 2 study with single agent cabazitaxel in patients with breast cancer (ARD6191), and one Phase 3 pivotal study in patients with metastatic prostate cancer (EFC6193). In addition, there were 33 patients enrolled into a Phase 1 study (TCD6945) in combination with capecitabine in mBC. More information on the clinical data is available in the clinical Investigator's brochure.

Cabazitaxel Phase 1 Trials: The three Phase 1 studies in solid tumors (TED6188, TED6189, TED6190) have been completed. There were 2 partial responses in patients with prostate cancer in Phase 1 studies evaluating the every 3-week schedule; 2 partial responses out of 8 patients with metastatic, castration-resistant prostate cancer (mCRPC) in TED6190 at 25 mg/m²- suggesting potential biological and clinical activity in patients with prostate cancer.

The safety profile was comparable in TED6188 and TED6190, with the intermittent schedule (1-hour infusion every 3 weeks). The dose limiting toxicity (DLT) of cabazitaxel was neutropenia and its infectious complications at the highest dose tested, 30 mg/m² in TED6188 and 25 mg/m² in TED6190.

As a result, the dose levels of 20 mg/m² and 25 mg/m² every 3 weeks were defined as the recommended doses for further clinical development with the intermittent schedule.

In TED6189 with the weekly schedule, the maximum tolerated dose (MTD) was reached at 12 mg/m², at which the DLT was diarrhea. As a result, the dose level of 10 mg/m² was defined as the recommended dose for further clinical development with this weekly schedule.

In the TCD6945 study conducted in advanced breast cancer patients, the recommended dose was defined as cabazitaxel 20 mg/m² on D1 and capecitabine 1000 mg/m² twice daily from D1 to D14 every 3 weeks. DLT were all grade 4 neutropenia lasting more than 7 days.

Cabazitaxel Phase 2 Trials: One Phase 2 study in patients with taxane- and/or anthracycline-resistant metastatic breast cancer has been completed (ARD6191). In this study patients were treated with a starting dose of 20 mg/m² cabazitaxel every 3 weeks with the option to dose-escalate cabazitaxel based on favorable tolerability at Cycle 1. This was allowed further to a protocol amendment. In 21 of 71 patients, the cabazitaxel dose was escalated from 20 to 25 mg/m² after the first cycle. The most frequently occurring toxicities overall were: Grade 3 and 4 neutropenia (73.2%), fatigue (50.7%), nausea (43.7%), diarrhea (39.4%), myalgia (25.4%), anorexia (25.4%), weight loss (25.4%), and vomiting (23.9%). The overall response rate was 14.6% with 2 complete responses (CR) and 5 partial responses (PR).

Cabazitaxel Phase 3 Trials: One Phase 3 study was conducted in mCRPC patients previously treated with a docetaxel-containing regimen. This study compared cabazitaxel (CBZ) plus prednisone to mitoxantrone (MTX) plus prednisone (EFC6193). A total of 755 patients were recruited (378 patients in CBZ arm and 377 patients in MTX arm). A statistically significant increase in overall survival (OS) was observed in patients treated with CBZ plus prednisone compared to patients treated with MTX plus prednisone, with a hazard ratio (HR) of 0.70 (95%CI: 0.59 – 0.83), a log-rank p-value of 0.0001. The median OS was 15.1 months (95%CI: 14.1 – 16.3) in CBZ arm versus 12.7 months (95%CI: 11.6 – 13.7) in MTX arm. The secondary endpoints were supportive of the positive data regarding the primary OS endpoint. Progression-free survival (defined as the earliest date of radiological tumor progression, PSA progression, pain progression, or symptom deterioration or death due to any cause) was statistically

significantly longer in the CBZ group compared with the MTX group ($p < 0.0001$, HR = 0.74 [95% CI, 0.64 - 0.86]), and median progression-free survival was 2.8 months versus 1.4 months. Response rates for PSA and tumor assessments, as well as the time to PSA and tumor progression when defined as radiological progression or death, were statistically significant in favor of CBZ. If pain response and time to pain progression were not statistically different between CBZ and MTX, considering that MTX was approved based on its activity on pain management in mCRPC, the results show that CBZ achieves at least the same level of activity of MTX on these pain-related endpoints.

Treatment-emergent adverse events (TEAEs) were experienced by 95.7% of patients in the CBZ group and 88.4% of patients in the MTX group; 57.4% of patients in the CBZ group and 39.4% of patients in the MTX group had at least one Grade 3-4 TEAE. In the CBZ group 39.1% of patients had at least one Significant Adverse Event (SAE) compared with 20.8% of patients in the MTX group. Study treatment discontinuation due to a TEAE was reported in 18.3% of patients in the CBZ group and 8.4% of patients in the MTX group.

The most frequent toxicity in the CBZ group was neutropenia and its clinical consequences of febrile neutropenia and infections. Based on laboratory assessments, 81.7% of patients in the CBZ group and 58.0% of patients in the MTX group had Grade 3-4 neutropenia. Patients treated with CBZ also had higher rates of Grade 3-4 infections with or without concomitant severe neutropenia (10.2% CBZ, 5.1% MTX) and febrile neutropenia (7.5% CBZ, 1.3% MTX).

Gastrointestinal disorders of all types (Grade 3-4) were more common in the CBZ group (12.4% CBZ, 1.6% MTX). Notably, Grade 3-4 diarrhea was more common on CBZ (6.2%) compared with MTX (0.3%). Incidence of Grade 3-4 stomatitis (0% in both groups) and mucositis (0.3% in both groups) was similar in both treatment groups.

Adverse events in the renal and urinary disorders (Grade 3-4) also were more common in the CBZ group (8.6% CBZ, 2.4% MTX). These events consisted of renal failure and impairment (3.2% CBZ, 0.3% MTX) as well as renal obstructive disorders (0.8% CBZ, 0.5% MTX). In the CBZ group, 15 patients were reported to have acute renal AEs Grade 3-4, the etiology of which was multifactorial consisting of pre-renal, renal, or obstructive causes. According to laboratory

values, the incidence of all grade /grade 3-4 creatinine increase was 15.6%/1.3% in CBZ arm and 11.6%/0.5% in MTX. In addition, more hematuria was reported in the CBZ arm versus the MTX arm (62 patients/16.7% versus 14 patients/3.8%). In the CBZ arm, no clear possible explanation such as local infection/obstruction/progression, anticoagulation/aspirin therapy, or thrombocytopenia was found for 21 patients. In prior studies conducted in metastatic breast cancer, a total of 6 patients (2 in the ARD6191 and 4 in the TCD6945) experienced cystitis without local infection including 5 hemorrhagic cystitis (3 cystitis were documented with biopsy).

Deaths due to causes other than disease progression within 30 days of last study drug dose were reported in 18 (5%) in the CBZ group and 3 (<1%) in the MTX group. Of the 18 deaths in the CBZ group, 8 were the result of neutropenia and/or infection, 4 were due to cardiac events (2 cardiac arrest, 1 cardiac failure and 1 ventricular fibrillation), 1 was due to dehydration and hydro-electrolyte imbalance, 3 were pre- or post-renal events leading to renal failure, and 2 were due to other causes, including a death of unknown etiology and a death from a cerebral hemorrhage following a fall in a patient taking concomitant clopidogrel. Based on the results of this study, a dossier to register cabazitaxel in hormone-refractory metastatic prostate cancer patients previously treated with a Taxotere-containing regimen has been submitted in several countries worldwide. It was been approved in the US in June 2010 and is under review in other countries.

Because cabazitaxel is similar to docetaxel structurally and functionally *in vitro* and offers the same if not better antitumor activity than docetaxel with a decreased propensity for P-gp-mediated drug resistance, we believe it will be equally effective and well-tolerated *in vivo*. We hypothesize that intravesical cabazitaxel will achieve the same initial response as docetaxel, with improved durability and long term efficacy, which when combined with intravesical gemcitabine and cisplatin, will allow for improved drug response while avoiding resistance and recurrence.

The studies mentioned above reiterate how each agent has promising levels of efficacy but, like most drugs, it is difficult to pre-determine who will respond and to which degree to each drug individually or in combination. Thus, we believe that by giving 2 to 3 different drugs in a

regimen, as is often completed intravenously, we will increase the likelihood of treatment response. Given the evidence available about intravesical instillations, particularly combinations of intravesical agents, it is safe to assume that it is safest to start with gemcitabine and a low dose of cabazitaxel than with cisplatin, which has less data and research available.

3.0 OBJECTIVES

To assess the safety, toxicity, and efficacy of intravesical Cabazitaxel, Gemcitabine, and Cisplatin (CGC) in the treatment of non-muscle invasive urothelial carcinoma of the bladder that has recurred despite BCG use.

Phase I:

Primary Objective:

- To assess the safety and toxicity profiles of intravesically administered CGC.

Secondary Objective:

- To assemble a blood, urine, and tissue bank (with pre and post treatment samples) to assess molecular correlates for response to intravesical CGC. Potential targets of analysis would include p53, p63, Stathmin, Tau, S6 Kinase, P-gp and Ki67.
 - Pharmacokinetic Analyses and Correlative Studies: This clinical study offers an excellent opportunity to assemble a blood, urine, and tissue bank for further interrogation regarding the molecular correlative markers that may predict sensitivity and resistance to intravesical CGC therapy in NMIBC. There is not expected to be any formal impact on decision-making within this study based on molecular markers and patients will, of course, have the opportunity to refuse to participate in tissue banking and still participate in the clinical study.
- To evaluate the efficacy of intravesically administered Cabazitaxel, Gemcitabine and Cisplatin, defined as the number of complete responders after completion of six weeks of the instillation

4.0 STUDY PLAN

4.1 Study Design

This study is a single arm open label Phase I trial investigating the safety and tolerability of multimodal intravesical chemotherapy in the treatment of NMIBC. UCC BCG refractory patients will be enrolled in the Phase I study. These patients will receive instillations of Cabazitaxel, Gemcitabine, and Cisplatin in saline diluents initially at an approximate pH of 5 to 7.5. Patients will be instructed to avoid excessive fluid intake starting the day before treatment. Prior to instillation, the bladder will be emptied via the sterile urethral catheter.

Study drug instillations should ideally be on different days and separated by at least one day but no more than 3 days during the initial 6 weeks of treatment and during the first year of maintenance. If due to holiday or extenuating circumstance instillations may be performed on consecutive days. The order of instillations should be Cabazitaxel first, Gemcitabine second and if applicable Cisplatin third. For example; during the initial 6 weeks or first year of maintenance, Cabazitaxel can be administered on Mondays weekly, Gemcitabine on Wednesdays weekly and Cisplatin on Fridays every other week. Per Investigator discretion, if a subject is experiencing an adverse event or toxicity limiting his ability to have an instillation, the dose may be delayed until resolution of event. If a subject is mid instillation week (i.e. received Cabazitaxel and Gemcitabine, but not Cisplatin for the week) and has a toxicity the next sequential drug should be instilled.

In the second year of maintenance instillations can be done the same way as the first year or can be done sequentially on the same day per investigator discretion. Cabazitaxel should continue to be first, followed by gemcitabine second.

Patients should be instructed to aim for approximate dwell time of study drugs as follows: Gemcitabine - one hour, Cisplatin - one hour and Cabazitaxel - two hours. It is expected that these times will not always be possible for individual patients. Total dwell time will be recorded by study personnel. Study providers may utilize treatments for local symptoms to improve dwell time as per standard of care.

This phase I trial will have a combined dose and cycle-escalation scheme with enrollment of up to 24 patients, using a cohort size of one, resulting in 24 cohorts total for the study. All patients will receive six weeks of treatment at a fixed volume with varying concentrations throughout.

The dose of Gemcitabine will be 2000mg/100ml for all patients and we will evaluate five dose combinations of Gemcitabine with Cabazitaxel plus/minus Cisplatin.

The first two cohorts (aka patients one and two) will receive instillations weekly at dose level 1 (2000mg/100ml of Gemcitabine “Gem” and at 2.5mg/100ml of Cabazitaxel “Low Cab”) for six weeks.

Before a dose limiting toxicity (DLT) is observed, dose escalation will follow the dose sequence as described in the following: cohorts 3 and 4 will receive instillations weekly at dose level 2 (2000mg/100ml Gemcitabine “Gem” and 5mg/100ml Cabazitaxel “High Cab”) for six weeks.

Based on recently published data utilizing intravesical cisplatin in a combination regimen, the first patients (aka first cohorts) in our study to receive intravesical cisplatin as part of the study regimen are cohorts 5 and 6, and will receive it bi-weekly at a dose of 66mg/100ml, assuming no DLT is reached in previous cohorts (cohorts 1-4).⁶ Cohorts 5 and 6 will receive instillations at dose level 3 (2000mg/100ml Gemcitabine “Gem,” 5mg/100ml Cabazitaxel “High Cab,” and 66mg/100ml Cisplatin “Low Cis”). Cabazitaxel and Gemcitabine will be instilled weekly while Cisplatin will be given bi-weekly for 6 weeks.

Cohorts 7 and 8 will receive instillations at dose level 4 (2000mg/100ml Gemcitabine “Gem,” 5mg/100ml Cabazitaxel “High Cab,” and 80mg/100ml Cisplatin “Mod Cis”). Cabazitaxel and Gemcitabine will be instilled weekly while Cisplatin will be given bi-weekly for 6 weeks.

Lastly, if no DLTs are observed, cohorts 9 to 18 will receive instillations at dose level 5 (2000mg/100ml Gemcitabine “Gem,” 5mg/100ml Cabazitaxel “High Cab,” and 100mg/100ml

Cisplatin “High Cis”). Cabazitaxel and Gemcitabine will be instilled weekly while Cisplatin will be given bi-weekly for 6 weeks. If no DLTs are seen after cohort 9 and 10 have successfully completed the initial 6 weeks of treatment, then we may enroll up to 2 patients simultaneously. If no DLTs are seen after cohort 9, 10, 11 and 12 have successfully completed the initial 6 weeks of treatment, then we may be enrolled up to 3 patients simultaneously. If no DLTs are observed after 10 patients have been assigned to dose level 5, the trial will be stopped with a total of 18 patients enrolled in the trial.

The combined cycle and dose escalation schemas are shown in tables 1 and 2. If no patient in a given cohort develops a DLT, the subsequent patients will be treated with an escalated regimen as delineated in the design schema and explained above. If a DLT is observed at any of the dose levels, dose escalations will be determined using a two-stage continual reassessment method (CRM). The total sample size will be expanded to 24 with the CRM. The CRM uses an empirical dose-toxicity model and a normal prior distribution on the parameter with mean 0 and variance of 0.55 will be used.¹⁸ (See Statistics section)

At any visit after the midpoint of treatment (week 4 and beyond), the patient may undergo a safety cystoscopy at the discretion of the principal investigator. Six to nine weeks after the last treatment, the participant will undergo a response assessment which entails: cystoscopy and biopsy, urine cytology, and Chest X-ray, in addition to either Abdominal/pelvic CT, or urogram CT, or MRI Scan. A complete response is defined as a cancer-negative biopsy at the post-treatment cystoscopy, with no evidence of disease on the post-treatment CT or MRI scan. If patients are deemed complete responders, they will become eligible for up to 24 months of maintenance Cabazitaxel and Gemcitabine (CG) treatment. Cisplatin treatment will not continue in maintenance. The first 12 months of maintenance will be instilled at 1 cycle per month and the second 12 months at 1 cycle every other month. In the second year, at the investigator’s discretion the patient may opt to receive intravesical therapy sequentially (same-day).

Concentrations	Cabazitaxel	Gemcitabine	Cisplatin
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Low	2.5mg/100ml	Fixed: 2000mg/100ml	66mg/100ml
Moderate	NA		80mg/100ml
High	5mg/100ml		100mg/100ml

Table 1: Dose escalation regimen for the CGC Combination Therapy

Cohort #	Week 1			Week 2			Week 3			Week 4			Week 5			Week 6		
	M	W	F	M	W	F	M	W	F	M	W	F	M	W	F	M	W	F
1, 2	Low Cab	Gem		Low Cab	Gem		Low Cab	Gem		Low Cab	Gem		Low Cab	Gem		Low Cab	Gem	
3, 4	High Cab	Gem		High Cab	Gem		High Cab	Gem		High Cab	Gem		High Cab	Gem		High Cab	Gem	
5,6	High Cab	Gem	Low Cis	High Cab	Gem		High Cab	Gem	Low Cis	High Cab	Gem		High Cab	Gem	Low Cis	High Cab	Gem	
7,8	High Cab	Gem	Mod Cis	High Cab	Gem		High Cab	Gem	Mod Cis	High Cab	Gem		High Cab	Gem	Mod Cis	High Cab	Gem	
9 to 18	High Cab	Gem	High Cis	High Cab	Gem		High Cab	Gem	High Cis	High Cab	Gem		High Cab	Gem	High Cis	High Cab	Gem	

Table 2 – Dose Escalation Schema

Once a DLT is observed, dose escalations will be determined using the CRM. *This table is an example treatment schedule and it is not considered a violation if treatment is not given on designated weekday as above.

This phase 1 study would significantly contribute to literature examining molecular determinants of response to CGC and molecular markers of high progression risk in transitional cell carcinoma. The molecular markers analyzed in this study will include but not be limited to p53, p63, Stathmin, Tau, ribosomal s6 kinase, Ki67, and P-gp.

4.1.1 Prior and concomitant therapies

As per our inclusion criteria, any intravesical chemotherapy should have been instilled more than 6 weeks prior to start of this treatment protocol. While on this protocol, no other intravesical or systemic chemotherapies should be administered concurrently with this treatment. If the patient needs to initiate systemic or intravesical chemotherapy for another indication, he/she will be withdrawn from this protocol.

The patient population for this trial is by design, heavily pre-treated. As a result of this, they may be on or require anti-spasmodics or Alpha 1 Blockers. These are allowed through the trial period to improve dwell times.

4.2 Toxicity and Dose Modifications

The HICCC Data Safety and Monitoring Committee will be included in this process as the committee deems appropriate.

The dose limiting toxicity (DLT) monitoring period is defined as starting at the first study drug instillation (week 1 visit 1) and ending at the last treatment administration date during the initial 6 weeks of treatment (week 6 visit 2). Any toxicities observed during maintenance will not affect cohort enrollment or dose assignment.

4.2.1 Systemic toxicity

Dose limiting systemic toxicity will be defined as any non-hematologic Grade 3 or 4 systemic toxicity that is determined per Investigator discretion to be related to study drug using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. In the event of a Grade 3 or 4 non-hematologic systemic DLT, no dose modification will be permitted for the patient and the patient will be removed from the study due to risk of morbidity from treatment which is potentially greater than the uncertain gain from the experimental regimen. The patient will be removed from the trial and treated appropriately off study per SOC. These toxicities should be monitored and recorded until resolution.

The patient must have a hemoglobin level >8.0 g/dL, a white blood cell count $> 3.0 \times 10^9$, an absolute neutrophil count $> 1500/\text{mm}^3$, and a platelet count $>80,000/\text{mm}^3$ in order to undergo treatment. If these levels are not met treatment will be held and the patient will be monitored at least weekly until resolution at which time treatment may resume. Any patient that misses more than two total treatment cycles during the initial six weeks of treatment will be removed from the study.

4.2.2 Local toxicity

Dose limiting local toxicity will be defined as any Grade 3 or 4 hematuria, dysuria, urinary retention, urinary frequency/urgency, or bladder spasms that is determined by Investigator to be related to study drug using the CTCAE version 4.0. If a patient exhibits or if questioning patient reveals Grade 3 or 4 local toxicity, the patient will be removed from the trial and treated appropriately off study per SOC. The patient will be removed from the study for this DLT because the morbidity of the toxicity is a great risk, potentially greater than the uncertain gain from the experimental regimen.

In the event of grade 2 local toxicity during the initial 6 weeks of treatment, determined by the Investigator to be related to study drug, with the exception of bladder spasm, the next scheduled treatment will be postponed for one week pending the resolution of symptoms to a maximum of grade 1 toxicity. Grade 2 local toxicities should be treated at the discretion of the principle investigator. Any patient that must delay treatment for more than two weeks during the initial six weeks of treatment will be removed from the study, with the exception of holding treatment urinary tract infections.

If a patient develops a urinary tract infection during any time point of study treatment the next scheduled instillation of study drug may be postponed at investigator's discretion and patient should be treated with appropriate medical management. Urinary tract infections are allowed to be treated on study for as much time is necessary and patients will not be removed from study should urinary tract infection treatment result in more than a total of a two week delay of study treatment delay.

Grade 2 bladder spasms that require treatment with antispasmodics is expected of this patient population. Patients may be treated with ongoing antispasmodics throughout study participation and as pre-medication for instillation days. Occurrence of grade 2 bladder spasm will not necessitate holding study drug instillations and may be treated at the discretion of the investigator. If during study drug instillation a patient has a bladder spasm that results in loss of study drug this will not be considered a violation or a dosing error. The total amount of study drug that was able to instilled prior to spasm and total dwell time will be recorded.

No dose modifications will be permitted for toxicity.

Examples of questions patients should be asked include:

- For Grade 3 or 4 hematuria, the member of the treatment staff will ask about persistent gross hematuria and/or blood clots.
- For Grade 3 or 4 toxicity bladder spasm, patients will be asked if their symptoms are severe enough to require a narcotic.
- For Grade 3 or 4 toxicity urinary frequency and urgency, patients will be asked if they are urinating hourly or more with frequency or experiencing urgency than prior to beginning treatment.

4.3 Procedures

4.3.1 Pre-study

Patients will be seen and evaluated by a study team to determine study eligibility. Informed consent must be obtained prior to any study specific assessments. All assessments including informed consent must occur within 28 days prior to initiation of first study drug instillation, with the exception of cystoscopy and metastatic disease surveillance imaging with may be performed up to 12 weeks prior to first study drug instillation per standard of care.

During screening potential candidates will have to following assessment's performed:

- Review and documentation of medical history
- Physical examination
- inclusion and exclusion criteria assessment
- Review and documentation of all concomitant medications that patient has taken within 30 days prior to anticipated first study drug instillation
- Weight, vital signs, and Eastern Cooperative Oncology Group (ECOG, Appendix I) performance status will be checked by a member of the medical staff.
- Patients are required to undergo an initial cystoscopic examination and resection of all grossly visible tumors, as per standard management, performed by a study investigators.

- Laboratory assessments: complete blood count (CBC), Basic Metabolic Panel (BMP), Hepatic Function Panel, Coagulation Profile (PT, PTT, and INR) and urinalysis (macroscopic with reflex including analysis of pH).
- In female patients of reproductive potential, a serum Beta-HCG value will be checked to rule out evidence of pregnancy.
- Metastatic disease imaging: Chest X-ray, in addition to either Abdominal/pelvic CT, or urogram CT, or MRI Scan.
- Electrocardiogram (EKG)

4.3.2 Initial 6 Weeks

4.3.2.1 – Initial 6 Weeks of Instillations and Treatment Days

Laboratory analysis will be used to screen for systemic toxicity, lab results will be used to clear a patient for treatment at the next scheduled instillation. Patients will undergo a blood draw to collect CBC with differential and Hepatic Function Panel once a week, sample can be collected at any time during visit. On even-numbered weeks (weeks 2, 4, 6 of instillation), patients will also have BMP and Coagulation Profile checked. Urinalysis will be performed at each visit and sample will be collected prior to instillation. These laboratory studies will be reviewed by research clinicians as results are available prior to next scheduled instillation. If there is any laboratory evidence of Grade 3 or 4 systemic toxicity, the patient will be deemed to have systemic toxicity and immediately be removed from the trial.

At any visit after the midpoint of treatment (week 4 and beyond), the patient may undergo a safety cystoscopy at the discretion of the principal investigator. This cystoscopy will allow the physician to investigate any potential adverse reactions to the bladder wall such as ulceration. The principal investigator retains the right to label the participant as having an adverse event based on these cystoscopic findings and their clinical judgment.

Treatment Day Assessments Will Include:

- Updated medical history and adverse event assessment

- Patients will be asked specific questions to monitor for local bladder toxicity as defined by the CTCAE (see section 4.2.2)
- Updated concomitant medications
- Vitals will be performed, including weight, blood pressure, and pulse

Study Drug Instillation:

- Study drug instillation will be administered by a sterile urethral catheter via gravity flow.
- All material used in the storage, instillation and the handling of Cabazitaxel will be non PVC materials.
- Patients should be instructed to aim for approximate dwell time of study drugs as follows: Gemcitabine - one hour, Cisplatin - one hour and Cabazitaxel - two hours. It is expected that these times will not always be possible for individual patients. Total dwell time will be recorded by study personnel.
- Patients can void in a standard fashion. No special precautions are required regarding disposal of the study drug after voiding in a normal toilet.

4.3.2.2 Initial Treatment Completion & Initial Follow-Up

Between six and nine weeks following last week of initial treatment instillation, all study participants will have the following assessments performed:

- updated medical history and physical examination
- Weight and vital signs
- blood draw to obtain a CBC, hepatic function panel, BMP and Coagulation Studies.
- urine sample for urinalysis
- EKG
- Chest X-ray, in addition to either Abdominal/pelvic CT, or urogram CT, or MRI Scan (if possible, in concordance to whichever abdominal/pelvic imaging modality the patient received pre-study) .This is only required if progression is suspected by the investigator on the cystoscopy.

4.3.2.3 Initial response assessment

Between six and nine weeks following last week of initial treatment instillation, all study participants will undergo a response evaluation. This will consist of urinary cytology, examination under anesthesia and cystoscopy with bladder biopsy or tumor resection. This will serve as the primary endpoint for response for the clinical trial. A **complete response** will be defined as a negative biopsy and no signs of progression on chest x-ray and CT or MRI scan. **No response** will be defined as positive cystoscopic biopsy or evidence of progression on cross sectional imaging. A **partial response** will be defined as having recurrence with superficial (Ta) low grade disease or persistent positive urine cytology, but negative chest x-ray and CT or MRI scan. A CT or MRI is only required if progression is suspected on cystoscopy; it is not required to confirmed complete or no response.

4.3.3 Maintenance Treatment

If a patient has a complete or partial response (see section 4.3.2.3), the patient will be eligible to receive additional monthly maintenance instillations at the same dose received during the initial 6 weeks of treatment. The patient will receive maintenance therapy for a maximum of 2 years, or until recurrence with T1 or high grade disease, or disease progression. The first year of maintenance will be monthly, and the second year bi-monthly. A treatment cycle will be defined as 4 weeks during the first year and 8 weeks during the second year. Treatments may occur +/- 4 weeks from target date with at least 2 weeks between cycles. Initiation of maintenance will be per investigator discretion based on recover the cystoscopy exam.

4.3.3.1 Monthly Maintenance months 1-12

Laboratory analysis will be used to screen for systemic toxicity, lab results will be used to clear a patient for treatment at next scheduled instillation. Patients will undergo a blood draw to collect CBC with differential, hepatic function panel, basic metabolic panel, and coagulation profile once a month at any time during visit. Urinalysis will be performed at each visit and sample will be collected prior to instillation. These laboratory studies will be reviewed by research clinicians as results are available prior to next scheduled instillation. If there is any laboratory evidence of Grade 3 or 4 systemic toxicity per Investigator discretion, the patient will be deemed to have systemic toxicity and immediately be removed from the trial.

During maintenance study drug doses may be held per investigator discretion for any patient safety concerns. Doses will be allowed to be made up within a 2 week window from originally scheduled instillation date per investigator discretion.

Per standard of care, cystoscopic examinations and urine cytology will be performed after every 3 treatment cycle instillations but before the next scheduled treatment cycle instillation (3rd, 6th, 9th, 12th). EKG and imaging assessments (Chest X-ray, in addition to either Abdominal/pelvic CT, or urogram CT, or MRI Scan) will be performed after every 6 treatment cycle instillations but before the next scheduled treatment cycle instillation (6th, 12th). Results should be reviewed prior to the next scheduled treatment cycle per standard of care.

Treatment day assessments must include:

- Updated medical history and adverse event assessment
 - Patients will be asked specific questions to monitor for local bladder toxicity as defined by the CTCAE (see section 4.2.2)
- Updated concomitant medications
- Vitals will be performed, including weight, blood pressure, and pulse
- In month 12 only a physical exam will be done

Study Drug Instillation:

- Study drug instillation will be administered via a sterile urethral catheter by gravity flow
- All material used in the storage, instillation and the handling of Cabazitaxel will be non PVC materials.
- Patients should be instructed to aim for approximate dwell time of study drugs as follows: Gemcitabine - one hour and Cabazitaxel - two hours. It is expected that these times will not always be possible for individual patients. Total dwell time will be recorded by study personnel.
- Patients can void in a standard fashion. No special precautions are required regarding disposal of the study drug after voiding in a normal toilet.

4.3.3.2 Bi-Monthly Maintenance months 13-24

Treatment instillations will be performed on months 14, 16, 18, 20 and 24.

Laboratory analysis will be used to screen for systemic toxicity, lab results will be used to clear a patient for treatment at next scheduled instillation. Patients will undergo a blood draw to collect CBC with differential, hepatic function panel, basic metabolic panel, and coagulation profile once a month at any time during visit. Urinalysis will be performed at each visit and sample will be collected prior to instillation. These laboratory studies will be reviewed by research clinicians as results are available prior to next scheduled instillation. If there is any laboratory evidence of Grade 3 or 4 systemic toxicity, per Investigator discretion, the patient will be deemed to have systemic toxicity and immediately be removed from the trial.

During maintenance study drug doses may be held per investigator discretion for any patient safety concerns. Doses will be allowed to be made up within a 2 week window from originally scheduled instillation date per investigator discretion.

Per standard of care, cystoscopic examinations and urine cytology will be performed every 3 months (15th, 18th, 21st, 24th). EKG and imaging assessments (Chest X-ray, in addition to either Abdominal/pelvic CT, or urogram CT, or MRI Scan) will be performed at month 24 only, unless medically indicated to perform sooner. Month 18 and month 24 cystoscopy should occur prior to month 18 and month 24 instillation.

Treatment day assessments must include:

- Updated medical history and adverse event assessment
 - Patients will be asked specific questions to monitor for local bladder toxicity as defined by the CTCAE (see section 4.2.2)
- Updated concomitant medications
- Vitals will be performed, including weight, blood pressure, and pulse

Study Drug Instillation:

- Study drug instillation will be administered via a sterile urethral catheter by gravity flow
- All material used in the storage, instillation and the handling of Cabazitaxel will be non PVC materials.
- Patients should be instructed to aim for approximate dwell time of study drugs as follows: Cisplatin - one hour and Cabazitaxel - two hours. It is expected that these times will not always be possible for individual patients. Total dwell time will be recorded by study personnel.
- Patients can void in a standard fashion. No special precautions are required regarding disposal of the study drug after voiding in a normal toilet.

4.3.3.3 End of Treatment Visit

An end of treatment visit must be conducted within 28 days of study discontinuation. The following assessments will need to be done:

- Updated medical history and adverse event assessment
 - Patients will be asked specific questions to monitor for local bladder toxicity as defined by the CTCAE (see section 4.2.2)
 - Any ongoing clinically significant adverse events will need to be followed to resolution and treated appropriately off study per standard of care
- Updated concomitant medications
- Vitals signs and weight
- ECOG
- Physical exam
- EKG (does not need to be completed if most recent EKG was done within 28 days of last study drug instillation)
- Laboratory assessments: CBC with differential , hepatic function panel, basic metabolic panel, coagulation profile, and urinalysis (does not need to be completed if most recent laboratory assessments were done within 28 days of last study drug instillation)

4.3.4 Criteria for Discontinuation of Treatment

A patient may voluntarily discontinue study treatment or be dropped from it at the discretion of the investigator at any time.

Patients will discontinue study treatment if any of the following occur:

- Initial 6 week treatment response is found to be non-response per section 4.3.2.3
- Initial 6 week treatment response is found to be a complete response per section 4.3.2.3 and patient declines additional maintenance treatment
- Clinical disease progression
- Upon completion of maintenance treatment
- Participant non-compliance
- Inability to tolerate the study procedures other than bladder spasm which may be medically managed by investigator
- **Greater than** two total missed weeks of treatment during the initial 6 weeks of treatment or during maintenance
- Investigator's judgment in the best interest of the participant
- Evidence of Grade 3 or 4 non-hematologic systemic or Grade 3 or 4 local toxicity (See Section 4.2).

Participants who withdraw informed consent will not only discontinue from treatment with study drug, but from the study as well. Long-term follow up requirements are described in section 6.5.

4.4 Study site

This trial will be conducted as a phase I trial at Columbia University Comprehensive Cancer Center, Herbert Irving Pavilion, and 161 Fort Washington Ave, New York, NY 10032. The investigators may consider expanding this study to a multi-center trial depending on patient accrual.

4.5 Study Schedule

(Continued on next page)

	Pre-Treatment	Initial 6 weeks of treatment		Initial follow up	Monthly First Year of Maintenance	Bi-Monthly Second Year of Maintenance	Treatment Discontinuation
		weeks 1,3,5	weeks 2,4,6				
	-28 days			6-9 weeks after last study drug dose	Months 1-12 (4 week cycles +/- 2 weeks)	Months 14, 16, 18, 20, 22, 24 (8 weeks cycles +/- 2 weeks)	28 days post-treatment +/- 7 days
Informed Consent	x						
Medical History	x	x	x	x	x	x	x
Weight	x	x	x		x	x	x
Vital Signs	x	x	x	x	x	x	x
Physical Exam	x			x	x ^a		x
ECOG	x						x
Chest X-ray, in addition to either Abdominal/pelvic CT, or urogram CT, or MRI Scan. ^b	x			X ^c			
EKG	x			x	X ^c	X ^c	X ^d
Concomitant Medications	x	x	x	X ^e	x	x	x
Adverse Events	x	x	x	X ^e	x	x	x
Cabazitaxel Instillation		x	x		x	x	
Gemcitabine Insillation		x	x		x	x	
Cisplatin Instillation		x					
Cystoscopic Evaluation	x	X ^f	X ^f	x	X ^{f,g}	X ^{f,g}	
Biopsy				x			

	Pre-Treatment	Initial 6 weeks of treatment		Initial follow up	Monthly First Year of Maintenance	Bi-Monthly Second Year of Maintenance	Treatment Discontinuation
		weeks 1,3,5	weeks 2,4,6				
	-28 days	weeks 1,3,5	weeks 2,4,6	6-9 weeks after last study drug dose	Months 1-12 (4 week cycles +/- 2 weeks)	Months 14, 16, 18, 20, 22, 24 (8 weeks cycles +/- 2 weeks)	28 days post-treatment +/- 7 days
Laboratory Assessments^h							
CBC with Differential	x	x	x	x	x	x	x ^d
Hepatic Function Panel	x	x	x	x	x	x	x ^d
Basic Metabolic Panel	x		x	x	x	x	x ^d
Coagulation Profile	x		x	x	x	x	x ^d
Urinalysis (microscopic with reflex)	x	x	x	x	x	x	x ^d
Urine Culture			x ⁱ				
Serum HCG ^j	x						

^a During first year of maintenance physical exam will only be done at month 12

^b If possible the same modality used at screening should be used throughout study

^c CT Urogram will only be required if progression is suspected on cystoscopy during this time point.

^d Does not need to be repeated if most recent EKG was done within 28 days of last study drug instillation

^e AEs and concomitant medications may be assessed via telephone at initial follow up time-point

^f At any visit after the midpoint of treatment (week 4 and beyond), the patient may undergo a safety cystoscopy at the discretion of the principal investigator.

^g During Maintenance Months 1-24 Cystoscopic evaluation will be performed every 3 months per SOC

^h Blood work will be done only once per week at first instillation visit. Urinalysis will be done at every instillation visit.

ⁱ Urine Culture only obtained at Week 6 Visit 2, prior to induction cystoscopy.

^j Serum HCG is only necessary for female patients of child-bearing potential, following pre-treatment it may be done at investigators discretion

4.6 Correlative Studies

4.6.1 Tumor Biopsies

The subjects will undergo a cystoscopy and biopsy at their follow up visit 6 to 9 weeks after the last treatment of the initial weekly instillations. Should the patient choose to participate in this part of the study, his or her tumor tissue samples may be stored for evaluation of molecular correlative studies to predict response to therapy per investigator discretion. If collected, these tissue samples will be securely stored in the Tumor Bank at Columbia University until used for future analysis of molecular markers. Other researchers will not have access to tissue samples unless given permission by Dr. McKiernan, the Primary Investigator. The tissue samples will be collected into 15 ml cryovials, flash frozen on dry ice, and stored at -80°C until analysis.

4.6.2 Pharmacokinetic Sampling Method and Rationale

Blood samples may be taken after cabazitaxel administration per investigator discretion. If collected, they will be in EDTA-treated tubes, and stored at -80°C until analysis.

This phase 1 study would significantly contribute to literature examining molecular determinants of response to CGC and molecular markers of high progression risk in transitional cell carcinoma. Multiple genes and chromosomal locations have been linked to progression and lack of response in transitional cell carcinoma including p53, RB, p21, p16 and p27 and loss of chromosome 9,11, and 17.^{19,20} Aside from predicting a more aggressive and deadly natural history, certain genetic aberrations provide mechanisms for poor response to therapy. The molecular markers analyzed in this study will include but not be limited to p53, p63, Stathmin, Tau, ribosomal s6 kinase, Ki67, and P-gp.

4.7 Annual Report

An annual report will be submitted to the FDA as required by CFR 312.33.

5.0 PATIENT INCLUSION AND EXCLUSION CRITERIA

Patients must meet the inclusion and exclusion criteria to be enrolled in the study.

5.1 Inclusion

Patients must have a histologically confirmed diagnosis of non- muscle invasive urothelial carcinoma of the bladder at the study institution prior to the beginning of the study. This includes patients with:

- High grade Ta papillary lesion(s)
- High or low grade T1 papillary lesion(s)
- CIS, with or without Ta or T1 papillary tumor(s) of any grade

The patient must have BCG refractory or recurrent non-muscle invasive bladder cancer

- Refractory disease is defined as evidence of persistent high risk bladder cancer (high grade Ta, T1 and/or CIS) at the first cystoscopic exam after the initial 6 week induction course of BCG or at the 6 month cystoscopic exam.
- Recurrent disease is defined as reappearance of disease after achieving a tumor- free status by 6 months following a full induction course of BCG with or without maintenance BCG. Participants must have recurred within 18 months following the last dose of BCG.
 - Low-grade superficial (Ta) disease will not be considered recurrent.
 - Patients must exhibit disease recurrence after receiving some form of standard intravesical therapy that must include a minimum of one induction course of BCG and may also include prior exposure to mitomycin, interferon, single agent gemcitabine or taxane therapy or maintenance.
- Patients must be eligible for radical cystectomy and refuse this standard of care treatment or not be a surgical candidate for radical cystectomy based on other comorbidities.
- All grossly visible disease in the bladder must be fully resected and pathologic stage will be confirmed at the study institution.
- Patients enrolled in other clinical trials must have received their last treatment at least 6 weeks prior to enrollment.
- Age \geq 18 and must be able to read, understand and sign informed consent

- Patients must have an ECOG performance Status: ECOG of 0 or 1 (See Appendix I) including patients who are not surgical candidates due to comorbid conditions.
- Peripheral neuropathy: must be \leq grade 1
- Women of childbearing potential must have a negative pregnancy test.
- All patients of childbearing potential must be willing to consent to using effective contraception, i.e., IUD, Birth control pills, Depo-Provera, and condoms while on treatment and for 3 months after their participation in the study ends.
- No experimental intravesical therapy within 6 weeks of study entry

5.2 Exclusion

- History of severe hypersensitivity reaction (\geq grade 3) to docetaxel
- History of severe hypersensitivity reaction (\geq grade 3) to polysorbate 80 containing drugs
- Concurrent or planned treatment with strong inhibitors or strong inducers of cytochrome P450 3A4/5 (a one week wash-out period is necessary for patients who are already on I these treatments) (see Appendix IV)
- Concurrent malignancy diagnosed within 6 months of entry to the study.
- Concurrent treatment with any systemic chemotherapeutic agent.
- Inadequate organ and bone marrow function as evidenced by:
 - a) Hemoglobin \leq 8.0 g/dL
 - b) Absolute neutrophil count \leq 1.5 x 10⁹/L,
 - c) Platelet count \leq 80 x 10⁹/L,
 - d) AST/SGOT and/or ALT/SGPT \geq 2.5 x ULN;
 - e) Total bilirubin $>$ 1.0 x ULN,
 - f) Serum creatinine $>$ 2.0 x ULN. If creatinine 1.5 – 2.0 x ULN, creatinine clearance will be calculated according to CKD-EPI formula and patients with creatinine clearance $<$ 30 mL/min should be excluded (see Appendix V for formula).

- Women who are pregnant or lactating.
- Documented history of vesicoureteral reflux.
- Current indwelling urinary stent.
- Participation in any other research protocol involving administration of an investigational agent within 6 weeks prior to study entry.

No IRB approved signed consent form. 6.0 STATISTICS

6.1 Study Design and Sample Size

The phase I segment of the trial will have a dose-escalation scheme that will enroll at most 24 patients. The aforementioned schemas will be used to escalate treatment doses and the number of drugs. The objective of this study is to assess the safety, toxicity, and efficacy of intravesical CGC, and to find an acceptable combination of Gemcitabine, Cabazitaxel and Cisplatin doses for intravesical administration. The dose of Gemcitabine will be fixed at 2000mg/100ml for all patients. We evaluate five dose combinations of Cabazitaxel and Cisplatin. The ordering of these doses is seen in table 3:

Dose Level	Gemcitabine	Cabazitaxel Dose	Cisplatin Dose
1	2000mg/100ml	2.5mg/100ml	
2	2000mg/100ml	5mg/100ml	
3	2000mg/100ml	5mg/100ml	66mg/100ml
4	2000mg/100ml	5mg/100ml	80mg/100ml
5	2000mg/100ml	5mg/100ml	100mg/100ml

Table 3 – Dose levels of Gemcitabine, Cabazitaxel, and Cisplatin

6.2 Patient Population

6.2.1 Analysis Population.

The treated population, which includes all enrolled patients who receive at least 1 dose of study drug, will be the primary population used for all safety/tolerability and efficacy analyses. For the

estimation of the MTD, patients who are not given one of the specified dose levels in the trial will be replaced and a new patient will be enrolled for the analysis population.

6.2.2 Patient Characteristics

Patient characteristics including demographics, disease duration and severity at baseline, and relevant medical history will be summarized for the purpose of characterizing the patient population. Descriptive statistics including mean, standard deviation, frequency distributions, etc., as appropriate, will be presented.

6.2.3 Patient Disposition

Patient disposition, including the number of patients enrolled, treated, and reasons for discontinuation from the study will be summarized.

6.2.4 Prior and Concomitant Medications

All concomitant medications and prior medications taken within 30 days of first study drug administration will be recorded.

The incidence of prior and concomitant medication usage will be summarized by therapeutic drug class and generic drug names.

6.3 Safety

Safety and tolerability will be monitored through reporting of AEs and SAEs, laboratory abnormalities, incidence of patients experiencing dose modifications, and/or premature discontinuation of study drug. The Investigators Brochure for Cabazitaxel and Prescribing Information for cisplatin and gemcitabine will be used to determine if the AE and SAE are expected with the therapies.

The maximum tolerated dose (MTD) combination will be estimated using a two-stage continual reassessment method (CRM). In the first stage, a rule based design will be used. Once a DLT is observed, we will switch to the second stage using the CRM (For more information, see below).

Dose and drug escalation will continue as outlined previously if the first two participants of the first two cohorts undergo their six week instillation without experiencing a dose-limiting toxicity (DLT defined in Section 4.2 Definition of Toxicity). Any patient who experiences a DLT will be removed from the trial and treated appropriately. If no DLT occurs, the next two cohorts (participants 3 and 4) will have their dose levels increased as outlined in Table 2. However, if one of the first two cohorts develops a DLT, the study will be terminated. If the 3rd and 4th cohorts do not develop DLT, the dose of Cisplatin will be added as outlined in Table 2. If a participant develops a DLT in cohorts 3 and 4, we will switch to the second stage using the CRM. If no DLT is experienced, the dose escalation will proceed as defined in Tables 3 and 4. If no DLTs are observed the study will stop after 10 patients are enrolled at the highest dose for a total of 18 patients and we will conclude that the MTD was not identified.

A systemic dose-limiting systemic toxicity (DLT) will be defined as any Grade 3 or 4 systemic toxicity as defined by the National Cancer Institute Common Toxicity Criteria version 4.0. Local dose-limiting toxicity will be defined as any grade 3 or 4 hematuria, dysuria, urinary frequency/urgency or bladder spasm according to the National Cancer Institute Common Toxicity Criteria version 4.0. Any patient who experiences these DLT will be removed from the trial and treated appropriately. In the event of grade 2 local toxicity, the next scheduled treatment will be postponed for one week pending the improvement of symptoms to a maximum of grade 1 toxicity. Any patient that misses more than two total treatment cycles will be removed from the study.

The MTD combination is defined as the dose combination associated with a target probability of toxicity of 0.25.

The MTD combination will be estimated using a two-stage continual reassessment method (CRM). In the first stage, a rule based design will be used as specified below and in Table 4. Once a DLT is observed, we will switch to the second stage using the CRM. There are several advantages of the CRM compared to conventional designs. First, the CRM has been shown to have better performance than the 3+3 design and treat fewer patients at suboptimal doses.

Second, it allows for the specification of a fixed sample size for the trial. Third, it assigns a dose after the outcome of every patient is observed. The advantage of using a two-stage CRM over a one-stage-CRM is that it starts at the lowest dose, like conventional designs. This is desired because of safety concerns in starting with the combination of all three drugs for intravesical use. Thus, the design is expected to be more conservative than the one-stage CRM and outperform the 3+3 design in selecting the correct dose as the MTD. The specified sample size for the two-stage CRM is 24 patients using a cohort size of one. The first patient will be assigned dose level 1 (2000mg/100ml of Gemcitabine and 2.5mg/100ml of CAB). Before a DLT is observed, dose escalation will follow the dose sequence below in Table 4:

Patient Number	Gemcitabine	Cabazitaxel Dose	Cisplatin Dose
1, 2	2000mg/100ml	2.5mg/100ml	
3, 4	2000mg/100ml	5mg/100ml	
5, 6	2000mg/100ml	5mg/100ml	66mg/100ml
7, 8	2000mg/100ml	5mg/100ml	80mg/100ml
9 to 18	2000mg/100ml	5mg/100ml	100mg/100ml

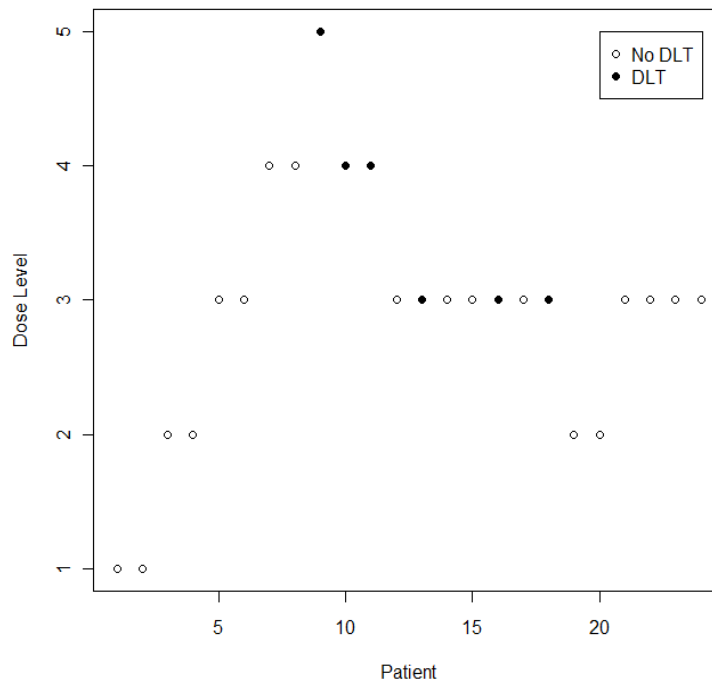
Table 4 – Dose Escalation Sequence for Patients 1-18, assuming no DLT

Once a DLT is observed, dose escalations will be determined using the CRM. The CRM with an empirical dose-toxicity model and a normal prior distribution on the parameter with mean 0 and variance of 0.55 will be used.¹⁹ The expected MTD is dose level 3. The dose-toxicity model is calibrated such that the method will eventually select a dose that yields between 20% and 30% DLT.^{20,21} (Lee and Cheung 2009, Cheung and Chappell 2002). The design will not allow for dose skipping and dose escalation immediately after a DLT is observed.²² A stopping rule will be implemented whereby if the first two patients experience toxicity the trial will be stopped for toxicity.

Figure 1 displays a simulation of a sample design using the method where the MTD is dose level 3. Each dot represents a patient and the dose level to which they were assigned. A circle indicates the patient did not experience a DLT. A solid dot indicates the patient experienced a DLT.

To evaluate the performance of the method, 2000 simulations under various scenarios of toxicity profiles were done. The operating characteristics of our design under these scenarios are displayed in Table 5 below. With 24 patients, the design selects the correct MTD with probabilities over 50% in all five scenarios, outperforming the conventional 3+3 design which selects the correct dose between 29% and 46% across scenarios. The scenarios were selected to have neighborhood doses with DLT rates within 10-15% of the MTD rate. If the neighboring doses have DLT rates significantly different from the target of 25%, the probability of correct selection will be improved.

Figure 1 Simulation of sample design using the method where the MTD is dose level 3



Method	MTD below Level 1	Dose Level				
		1	2	3	4	5
3+3 Design Two-Stage CRM		0.25	0.35	0.50	0.65	0.80
	0.44	0.36	0.18	0.02	0.00	0.00
	0.07	0.60	0.30	0.03	0.00	0.00
3+3 Design Two-Stage CRM		0.15	0.25	0.40	0.55	0.70
	0.21	0.34	0.33	0.11	0.01	0.00
	0.03	0.22	0.53	0.21	0.01	0.00
3+3 Design Two-Stage CRM		0.10	0.15	0.25	0.40	0.55
	0.10	0.19	0.30	0.30	0.10	0.02
	0.01	0.03	0.25	0.51	0.19	0.01
3+3 Design Two-Stage CRM		0.03	0.07	0.15	0.25	0.40
	0.01	0.06	0.17	0.36	0.29	0.10
	0.00	0.00	0.03	0.27	0.52	0.19
3+3 Design Two-Stage CRM		0.01	0.03	0.07	0.15	0.25
	0.00	0.01	0.05	0.17	0.32	0.46
	0.00	0.00	0.00	0.05	0.31	0.65

**Table 5
Operating
Characteristics
of CRM vs 3+3
Design**

6.4 Efficacy

Efficacy will be determined by the number of complete responders after six weeks of treatment. Each cohort of patients will be analyzed separately. A **complete response** will be defined as a negative biopsy and no signs of progression on Chest X-ray, in addition to either Abdominal/pelvic CT, or urogram CT, or MRI Scan. **No response** will be defined as positive cystoscopic biopsy or evidence of progression on cross sectional imaging. A persistent positive cytology despite negative biopsy and negative CT or MRI scan will be considered a **partial response**.

At the follow-up visit six to nine weeks after the last dose, patients will undergo a cystoscopy and biopsy. If a patient has a complete response, the patient will be eligible for a maximum of 24 months of maintenance therapy. In the first 12 months, they will receive monthly maintenance instillations at the dose that particular patient received in the treatment phase. In the second year, they will receive maintenance instillations every other month. Cystoscopic examinations will occur every 3 months throughout the maintenance period and CT/MRI will be obtained at the 6th, 12th, and 24th months as per standard of care.

6.5 Long term follow-up

Analyses will be conducted on long term follow up for patients at the five year time point after completion of the trial. No other interim follow up will be provided prior to this time point. At year 5, the longevity of the initial response, length of cystectomy free survival and other parameters will be analyzed.

6.6 Biomarker and Pharmaokinteic Analyses

This clinical study offers an excellent opportunity to assemble blood, urine, and tissue samples for further interrogation regarding the molecular correlative markers that may predict sensitivity and resistance to intravesical CGC therapy in NMIBC. This is not expected to be any formal impact on decision making within this study based on molecular markers and patients will, of course, have the opportunity to refuse tissue samples and still participate in the clinical study.

The molecular markers analyzed will include but not be limited to p53, p63, Stathmin, Tau, ribosomal s6 kinase, Ki67, and P-gp.

7.0 ADVERSE EVENTS

All serious, related, (unexpected) adverse events will be reported to the FDA as required by 21 CFR 312.32, to Columbia University’s Institutional review board, as well as to the HICCC Data Safety and Monitoring Committee. All serious, related or unrelated adverse events will be reported to Sanofi-Aventis Pharmaceuticals.

7.1 Definitions

7.1.1 Adverse Events

An **adverse event** (AE) is defined by the Columbia University Medical Center IRB Policy as “any experience or abnormal finding that has taken place during the course of a research project and was harmful to the participant participating in the research, or increased the risks of harm from the research, or had an unfavorable impact on the risk/benefit ratio.” This includes the development of an untoward medical occurrence, undesirable medical condition, and recurrence or deterioration of a pre-existing medical condition subsequent to exposure of a pharmaceutical product or treatment. An adverse event is additionally defined as occurring at any dose, independent of perceived causal relationship to the product. Adverse events may or may not be formal medical diagnoses, and can also include signs, symptoms or abnormal laboratory findings. Common examples include nausea, chest pain, tachycardia, enlarged liver, or electrocardiogram abnormalities.

The definition of an adverse event is independent to a perceived causal relationship to the drug. Causality is a separate assessment that is performed for AEs. Causality assessment to a study drug or regimen will be a medical judgment based made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions.

Any Common Toxicity Criteria Adverse Event grade 3 or 4, or any clinically significant grade 1 or 2 hematology or biochemistry laboratory values not solely considered a result of disease progression will be considered an AE.

"Lack of efficacy" or treatment non-response for an unproven therapy will not generally be considered an adverse event. If there is deterioration in the underlying condition for which the study regimen is designed to treat, there may be uncertainty as to whether this is an AE. In such a case, the investigating physician must judge the treatment as a possible contributor to the deterioration. Unless local governing regulations require otherwise, such deterioration will be considered to be an issue of treatment efficacy and not an AE. This situation constitutes an exception to the general rule that AEs are initially identified regardless of perceived causality attribution. Adverse events that are unequivocally due to progression of disease should be recorded as "progressive disease" rather than as AEs. However, the development of an additional (even if similar) disease will be regarded as an AE. For example, if a patient taking an experimental drug to treat underlying breast cancer develops a second primary cancer of non-metastatic origin, this would be considered a unique AE.

7.1.2 Types of Adverse Events

In the clinical study setting, adverse events are most often subcategorized as either SERIOUS or NON-SERIOUS. This distinction is critical, as SERIOUS AEs require additional documentation that is both time-sensitive and detailed.

7.1.3 Serious Adverse Events (SAE)

A **serious adverse event** (SAE) is defined as any adverse event that results in death, is immediately life-threatening, requires inpatient hospitalization (at least a 24-hour), prolongation of existing hospitalization, results in persistent or significant disability/ incapacity, or is a congenital anomaly/birth defect. Additionally, an SAE also includes any "important medical event" that may not have the immediate outcome of being life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent such outcomes.

Medical and scientific judgment will be exercised in deciding whether an AE is an "important medical event," and would therefore meet SAE criteria. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or

convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

7.1.4 "Serious" Versus "Severe" Adverse Events

There will be an acknowledged distinction between serious and severe AE's. Assessment of seriousness will be made solely by the serious criteria listed above. Severity of AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events v4.0. Therefore, serious events will not be automatically considered severe. For example, a stroke that results in only a limited degree of disability may be considered a mild (not severe) stroke, but it would still meet serious criteria and thus, be captured as an SAE. Similarly, severe events may not always be serious. An example would be an episode of severe, transient nausea, which persists for several hours. This would be classified as a "severe" episode of nausea, but if it did not require treatment, intervention, or somehow meet other serious criteria, it would not be considered an SAE.

7.1.5 Non-serious Adverse Events

Any adverse event that is not an SAE is, by default, a non-serious AE.

7.2 Documentation of Adverse Events Observed during the Study Period

All AEs (serious and non-serious) will be documented. Any experience or condition that is identified from the signing of the informed consent through the end of maintenance therapy must be captured as an AE. Information collected will include a description of the event, date of onset and resolution, assessment of SAE criteria, any action taken (e.g., changes to study treatment), final outcome, and the investigator's assessment of causality (i.e., the relationship to the study treatment).

7.3 AE Term Selection

To facilitate proper analysis of any observed adverse events within the study, consistent and medically accurate standards of AE term selection will be applied. Whenever possible, an AE term from the MedDRA coding system will be the formal diagnosis or disease term experienced by the patient. If the final diagnosis remains differential or is pending, then the presenting signs,

symptoms and/or abnormal laboratory results will be captured as AEs until a diagnostic term can be applied.

7.4 Causality

For each adverse event, an investigator will assess the possibility that a study drug or regimen may have caused or contributed to an adverse event as described in the previous section entitled "Definition and Types of Adverse Events."

7.5 Deaths

Any deaths occurring within the trial period or within 30 days after discontinuing protocol treatment will be captured without exception, regardless of perceived causal relationship to study drug. A single AE term will be selected, the event will be considered an SAE, and "death" will serve as the positive criteria applied to the seriousness assessment. If the cause of death is unknown, then "death" will be captured as the sole AE term. Whenever possible the underlying cause, not the specific mechanism, of death will be selected as the SAE term, unless the investigator feels the specific mechanism of death is clinically relevant or offers significance that might otherwise be lost if not captured.

7.6 Follow up Procedures for Adverse Events Observed During the Study Period

All study- related AE and SAE unresolved or unimproved since initial presentation will be followed until resolution or improvement of the AE. With respect to AEs that are abnormal laboratory or investigational results, an unresolved or persistent CTCAE grade 3 or 4 laboratory abnormality at study completion or withdrawal will be followed until the laboratory abnormality has either returned to a comparable baseline value, or is judged to have a severity of grade 2 or better.

If, in the investigator's medical judgment, any AE noted in the study is not likely to resolve or improve, the investigator will document that opinion in the patient's medical record. Should the patient become lost to follow-up or further information is otherwise unattainable, the investigator will note this in the patient's medical record.

For 30 days subsequent to study completion or withdrawal, new onset adverse events will be captured. Follow up of these events will follow the same procedure as described above for AEs observed during the study period.

7.7 Reporting of serious adverse events

The Investigators Brochure for Cabazitaxel and Prescribing Information for cisplatin and gemcitabine will be used to determine if the AE and SAE are related to the therapies. All serious, related adverse events will be reported, documented on MedWatch Form FDA3500A (www.fda.gov/medwatch/getforms.htm) and forwarded directly to the FDA. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All SAE's, regardless of causality or expectedness, must be reported to Sanofi-Aventis Pharmaceuticals US Pharmacovigilance within 24 hours of the investigators awareness of the event (Appendix II). Directions for completing and sending form FDA 3500A are found at www.fda.gov/medwatch/getforms.htm.

Form FDA 3500A may be sent by mail to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology 1 Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Reports by FAX should be sent to Sanofi Global Pharmacovigilance (+ 33 1.60.49.77.77 or 1 908 203-7783), within 24 hours of receipt by investigator/sponsor. **FAX transmission should include the following on the provided IST SAE REPORT, fax cover form (Appendix II):**

ISS study#:

Study Title: A phase I study to assess the safety and toxicity of intravesical Cabazitaxel, Gemcitabine, and Cisplatin (CGC) in the treatment of High Risk Non-muscle invasive Bladder Cancer that has recurred after standard first line treatment.

Name of Principle Investigator: Dr. James M. McKiernan, MD

Confirmed: This report will be submitted to FDA and Sanofi-Aventis Pharmaceuticals.

Reports by E-MAIL should be sent to: CL-CPV-Receipt@sanofi.com, within 24 hours of receipt by investigator/sponsor. **E-Mail transmission should include the following:**

ISS study#:

Study Title: A phase I study to assess the safety and toxicity of intravesical Cabazitaxel, Gemcitabine, and Cisplatin (CGC) in the treatment of High Risk Non-muscle invasive Bladder Cancer that has recurred after standard first line treatment.

Name of Principle Investigator: Dr. James M. McKiernan, MD

Confirmed: This report will be submitted to FDA.

For Comparator Drugs / Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer.

In addition to any suspected adverse reaction (SAR), all SAEs shall be sent to Sanofi-Aventis on an ongoing basis.

Results of any relevant complementary exams performed to obtain the final diagnosis of any SAE (e.g. hospital discharge summary, autopsy report, consultations, etc.) will be made available to Sanofi-Aventis upon request.

A **Suspected Adverse Reaction (SAR)** is any AE for which there is a reasonable possibility that it was caused by the drug.

Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE. Examples of reasonable possibility are:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure.
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug.

- An aggregate analysis of specific events observed in a clinical trial that indicates that those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

The Senior Investigator (S-I) must report the following SARs:

- To the FDA, as soon as possible, but no later than 7 calendar days after the S-I's initial receipt of the information, **any unexpected fatal or life-threatening SAR.**
- To the FDA and all participating investigators, as soon as possible but no later than 15 calendar days after the S-I determines that information qualifies for reporting, in an IND safety report, **any other SAR (non-fatal, non-life threatening) that is both serious and unexpected.**
- To the FDA and all participating investigators, as soon as possible but no later than 15 calendar days after the S-I determines that the information qualifies for reporting, **any findings from epidemiological studies, pooled analysis of multiple studies or clinical studies, whether or not conducted under an Investigation New Drug (IND) or by the S-I, that suggest a significant risk in humans exposed to the drug.**
- To the FDA and all participating investigators, as soon as possible, but no later than 15 calendar days after the S-I determines that the information qualifies for reporting, **any findings from animal or *in vitro* testing, whether or not conducted by the S-I, that suggest a significant risk in humans exposed to the drug.**
- To the FDA and all participating investigators, as soon as possible, but no later than 15 calendar days after the S-I determines that the information qualifies for reporting, **any clinically important increase in the rate of a Serious SAR over that listed in the protocol or Investigator Brochure.**
- Expected SAEs and AEs should be included in the IND Annual Reports.

Follow-up information to a safety report should be submitted as soon as the relevant information is available. However, if the results of a sponsor's investigation show that an adverse drug experience not initially determined to be reportable are so reportable, the sponsor must report such experience as soon as possible, but no later than 15 calendar days after the determination is made.

To the IRB:

1. Unanticipated Problems (UPs) must be reported promptly, but not later than 7 calendar days following the occurrence of the UP or the Principal's Investigator's acquiring knowledge of the UP.
2. Expected AEs must be reported at the time of continuing review of a protocol.

7.8 Monitoring Plan

The monitoring plan will examine data integrity and safety monitoring. The specifics of each of these aspects are outlined below.

Study Title: A Phase I trial for the use of Intravesical Cabazitaxel, Gemcitabine, and Cisplatin (CGC) in the treatment of BCG-Refractory Non-muscle invasive Urothelial Carcinoma of the Bladder.

Participants

Principal Investigator (P.I): Dr. J.M McKiernan

Co-Investigators: Dr. G.J DeCastro, Dr. C.B Anderson

7.8.1 Data Collection & Integrity Monitoring

All experimental data will be collected by the research staff and entered into Clinical Research Forms (CRF) per each individual patient. Data will be reviewed for accuracy against the patient's electronic medical record by the Urology clinical research team until completion of the study. Findings of these reviews will be submitted to the PI who will then submit all reports to the IRB as required. Any discrepancies that need to be reconciled will be discussed with the research staff and the PI with subsequent actions taken.

7.8.2 Safety Monitoring

All experimental data will be continually monitored for safety by the Principal Investigator, Dr. James McKiernan, and independently by the Herbert Irving Comprehensive Cancer Center (HICCC) Data and Safety Monitoring Committee (DSMC). Dr. McKiernan will review the incidence of adverse events and will report in accordance to local IRB and federal regulations. Based on the NCI Common Toxicity Criteria Version 4.0, he will determine the severity of each adverse event and its relationship to the investigational product and/or study. Based on the safety data, the protocol may be modified or revised, in addition to any documents

that will be submitted to the participant. These modifications will be submitted to the IRB and FDA for review and approval.

The DSMC is a separate and distinct entity from the clinical trial staff, and our staff will follow all responsibilities and requirements to work with the DSMC to fulfill its purpose. As per the Columbia University Human Research Protection Program, the DSMC will oversee the progress of our clinical trial and ensure that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, GCP, and the applicable regulatory requirements.

Dr. McKiernan and the clinical trial staff will submit reports of unanticipated problems involving risks to participants or others to the Columbia University Medical Center (CUMC) Institutional Review Board (IRB), and AEs to the HICCC Clinical Research Management Office to be reviewed by the HICCC Data and Safety Monitoring Committee (DSMC), and the study sponsor. The DSMC will ensure the focus on participant safety issues and close review of toxicities.

8.0 STUDY MEDICATIONS: Preparation and administration

Cisplatin and Gemcitabine are both commonly used pharmaceutical formulations, and their preparation will be according to routine institutional pharmacy protocols.

Cabazitaxel is supplied for parenteral administration as a sterile, non-pyrogenic non-aqueous solution contained in a 15 mL clear glass vial closed with a rubber closure. To clarify, Cabazitaxel has never been used intravesically before, however the storage and preparation for this drug is the same as the storage and preparation as when it is used for parenteral administration, and this is described below.

The closure is crimped to the Cabazitaxel vial with an aluminium cap covered with a light green plastic flip-off cap. The solution is clear and yellowish to brownish-yellow. Each vial contains 60 mg of cabazitaxel, expressed on anhydrous and solvent-free basis, per 1.5 mL of solution. The fill volume has been established to include an overfill [i.e., 1.5 mL (nominal volume) + 0.33 mL]. This overfill was determined to ensure that a 10 mg/mL (corresponding to 60 mg/mL) concentration is obtained in the premix and that 60 mg dose can be extracted. This must be done

with the entire contents [i.e., 4.5 mL (nominal volume) + 1.17 mL] of the solvent for dilution for cabazitaxel.

Solvent vial:

The solvent used for the preparation of the premix is a sterile, non-pyrogenic solution containing a 13 % w/w ratio of ethanol 95 % in water for injection. This solution is contained in a 15 mL clear type I glass vial closed with a rubber closure. The closure is crimped to the vial with either an aluminum cap covered with a light grey plastic flip-off cap or a gold-colored aluminum cap covered with a colorless plastic flip off cap. The solution is a clear colorless liquid. Each vial is overfilled to ensure that a 10 mg/mL concentration is obtained in the Premix and that 60 mg dose can be extracted. [i.e., 4.5 mL (nominal volume) + 1.17 mL].

Excipients:

Polysorbate 80 from vegetable origin, for the drug product vial. Water for injection and ethanol for the solvent vial.

Storage conditions:

Vials should be stored according to their labeling and kept in their kit until use.

Preparation

Cabazitaxel drug products have been used previously for intravenous route, and they will be used uniquely for intravesical route in this protocol. It is supplied as a kit containing one single-use vial of cabazitaxel concentrate for solution for instillation and one single vial of solvent for dilution. The administration of the product requires two dilutions prior to administration. This pharmaceutical dosage form is a concentrate for solution for instillation and must be diluted before administration. First the dosage form is diluted with the solvent supplied (preparation of the “cabazitaxel premix solution”). Then this premix solution must be diluted in an infusion vehicle (an IV bag) (preparation of the “cabazitaxel infusion solution”). Each cabazitaxel vial and each corresponding solvent vial are overfilled to ensure that a 60 mg dose can be withdrawn after the preparation of the premix.

- **Preparation of cabazitaxel premix solution under aseptic conditions:**

Use one solvent vial per each vial of cabazitaxel concentrate.

Withdraw, under aseptic conditions, the **entire** contents of the solvent vial and inject it into the corresponding vial of cabazitaxel concentrate. **Gently** mix the reconstituted solution by repeated inversions for at least 45 seconds until obtaining clear and homogenous solution. **Do not shake**. Let the premix solution stand for a few minutes at room temperature to allow foam to dissipate. The solution is homogeneous and contains no visible particulate matter. It is normal for foam to persist after this time period.

In order to compensate for liquid loss during preparation and to ensure that the JEVTANA initial diluted solution (premix) can be prepared at the concentration of 10 mg/mL and that a nominal volume of at least 6 mL can be withdrawn from the premix vial, the JEVTANA 60 mg/1.5 mL concentrate vials are filled with a 22% overfill (total fill volume 1.83 mL) and the diluent vials with a 26% overfill (total fill volume 5.67 mL).

The concentration of 10 mg/mL in the premix [60mg/1.5 mL (concentrate) + 4.5 mL (diluent)] can be calculated as follows taking into account the overfilling: $73.2\text{mg} / 1.83\text{ ml}$ (22 % overfill concentrate) + 5.49 mL (overfill diluent *) = 10 mg/mL.

Thus, the preparation obtained ensures a minimal extractable volume of the premix solution of 6 mL corresponding to a concentration of 10 mg/mL of cabazitaxel corresponding to 60mg/6 mL.

- **Preparation of cabazitaxel infusion solution under aseptic conditions:**

WARNING: Since foam is normally present, the required dose must be accurately adjusted using a graduated syringe.

Withdraw, under aseptic conditions, the volume of the premix solution containing 10 mg/mL of cabazitaxel that corresponds to the required dose (mg) and inject the required premix volume into a 125 to 500 mL infusion container (either 5 % glucose solution or 0.9 % sodium chloride solution). Mix the content of the infusion container (the IV bag)

manually by gently inverting the bag. The concentration of the infusion should be between 0.10 mg/mL and 0.26 mg/mL (based on Maximum Tolerated Dose of 30 mg/m² and a Body Surface Area of 2.1 m²). Attach the IV bag to the sterile catheter for instillation.

- **Infusion conditions:**

The instillation duration is generally less than one hour. The instillation solution should be used within 8 hours at ambient temperature (including the one hour infusion time) or within a total of 48 hours if refrigerated (including the one hour infusion time).

The instillation solution should be administered at room temperature under normal lighting conditions.

- **Do not use PVC infusion containers for cabazitaxel preparation and administration.**
- **Do not use polyurethane infusion sets for cabazitaxel preparation and administration**

Glass bottles could also be used.

- **Shelf life:**

Cabazitaxel premix solution

Premix solution should be used immediately after preparation and within 1 hour at ambient temperature.

Cabazitaxel infusion solution

The infusion solution is stable for 8 hours at ambient conditions (including the 1 hour infusion time) or a total of 48 hours if refrigerated, from preparation to end of infusion.

- **Recommendation for the safe handling:**

Cabazitaxel is an antineoplastic agent and, like other potentially toxic compounds, caution should be exercised in handling and preparing cabazitaxel solutions. The use of gloves is recommended.

If cabazitaxel concentrate, premix solution or infusion solution should come into contact with skin, wash immediately and thoroughly with soap and water. If cabazitaxel

concentrate, premix solution, or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.

Appendix I: ECOG PERFORMANCE STATUS

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Appendix II: Sanofi-Aventis IST SAE Report Form

Sanofi Global Pharmacovigilance

sanofi-aventisUS

Fax: IST SAE REPORT
 To: Sanofi Global Pharmacovigilance

Fax: + 33 1.60.49.77.77 or 1 908 203-7783 or CL-CPV-Receipt@sanofi.com	
Date:	Pages:
From:	Phone:

IST#:	
Study Title:	
PI Name:	
Causality:	<p>Is there a reasonable possibility the IP or the investigational combination caused the event? Yes _____ No _____</p> <p>All serious, related adverse events will be reported and documented on MedWatch Form FDA 3500A (www.fda.gov/medwatch/getforms.htm) and forwarded directly to sanofi-aventis Pharmaceuticals. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences.</p> <p>For Comparator Drugs / Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer.</p>
Check one:	
	<u>Unrelated:</u> The adverse event is clearly <u>NOT</u> related.
	<u>Unlikely to be related:</u> The adverse event is doubtfully related.
	<u>Possibly related:</u> The adverse event may be related.
	<u>Probably related:</u> The adverse event is likely related.
	<u>Definitely related:</u> The adverse event is clearly related.

Appendix III National Cancer Institute Common Toxicity Criteria Version 4.0

Renal and urinary disorders					
Adverse Event	Grade				
	1	2	3	4	5
Acute kidney injury	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
Definition: A disorder characterized by the acute loss of renal function and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction).					
Bladder perforation	-	Extraperitoneal perforation, indwelling catheter indicated	Intrapertoneal perforation; elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the bladder wall.					
Bladder spasm	Intervention not indicated	Antispasmodics indicated	Hospitalization indicated	-	-
Definition: A disorder characterized by a sudden and involuntary contraction of the bladder wall.					
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death
Definition: A disorder characterized by gradual and usually permanent loss of kidney function resulting in renal failure.					
Cystitis noninfective	Microscopic hematuria; minimal increase in frequency, urgency, dysuria, or nocturia; new onset of incontinence	Moderate hematuria; moderate increase in frequency, urgency, dysuria, nocturia or incontinence; urinary catheter placement or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the bladder which is not caused by an infection of the urinary tract.					
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate blood in the urine.					
Hemoglobinuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of free hemoglobin in the urine.					
Proteinuria	1+ proteinuria; urinary protein <1.0 g/24 hrs	Adults: 2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Pediatric: urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Adults: urinary protein >=3.5 g/24 hrs; Pediatric: urine P/C > 1.9	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of excessive protein in the urine. It is predominantly albumin, but also globulin.					
Renal calculi	Asymptomatic or mild symptoms; occasional use of nonprescription analgesics indicated	Symptomatic; oral antiemetics indicated; around the clock nonprescription analgesics or any oral narcotic analgesics indicated	Hospitalization indicated; IV intervention (e.g., analgesics, antiemetics); elective endoscopic or radiologic intervention indicated	Life-threatening consequences; urgent radiologic, endoscopic or operative intervention indicated	Death
Definition: A disorder characterized by the formation of crystals in the pelvis of the kidney.					
Renal colic	Mild pain not interfering with activity; nonprescription medication indicated	Moderate pain; limiting instrumental ADL; prescription medication indicated	Hospitalization indicated; limiting self care ADL	-	-
Definition: A disorder characterized by paroxysmal and severe flank marked discomfort radiating to the inguinal area. Often, the cause is the passage of kidney stones.					

Renal and urinary disorders					
Adverse Event	Grade				
	1	2	3	4	5
Renal hemorrhage	Mild symptoms; Intervention not indicated	Analgesics and hematocrit monitoring indicated	Transfusion, radiation, or hospitalization indicated; elective radiologic, endoscopic or operative Intervention indicated	Life-threatening consequences; urgent radiologic or operative Intervention indicated	Death
Definition: A disorder characterized by bleeding from the kidney.					
Urinary fistula	-	Noninvasive Intervention indicated; urinary or suprapubic catheter placement indicated	Limiting self care ADL; elective radiologic, endoscopic or operative Intervention indicated; permanent urinary diversion indicated	Life-threatening consequences; urgent radiologic or operative Intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between any part of the urinary system and another organ or anatomic site.					
Urinary frequency	Present	Limiting Instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by urination at short intervals.					
Urinary incontinence	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated; limiting Instrumental ADL	Intervention indicated (e.g., clamp, collagen injections); operative Intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by inability to control the flow of urine from the bladder.					
Urinary retention	Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual	Placement of urinary, suprapubic or intermittent catheter placement indicated; medication indicated	Elective operative or radiologic Intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative Intervention indicated	Death
Definition: A disorder characterized by accumulation of urine within the bladder because of the inability to urinate.					
Urinary tract obstruction	Asymptomatic; clinical or diagnostic observations only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated	Symptomatic and altered organ function (e.g., hydronephrosis, or renal dysfunction); elective radiologic, endoscopic or operative Intervention indicated	Life-threatening consequences; urgent Intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of contents of the urinary tract.					
Urinary tract pain	Mild pain	Moderate pain; limiting Instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the urinary tract.					
Urinary urgency	Present	Limiting Instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by a sudden compelling urge to urinate.					
Urine discoloration	Present	-	-	-	-
Definition: A disorder characterized by a change in the color of the urine.					
Renal and urinary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; Intervention not indicated	Moderate, local or noninvasive Intervention indicated; limiting Instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent Intervention indicated	Death

Appendix IV: List of Potent CYP3A Inhibitors

List of CYP3A Inhibitors

Precipitant	Therapeutic Class	Object (oral)	AUC _{ratio}	PMID or NDA #	Published
Potent CYP3A Inhibitors (yielding substrate AUC_r > 5)					
ritonavir	Protease Inhibitors	triazolam	40.70	16513448	2006 Mar
indinavir	Protease Inhibitors	varafenafil	16.25	NDA # 021400	2003 Aug
ketoconazole	Antifungals	<u>midazolam</u> ¹	15.90	8181191	1994 May
troleandomycin	Antibiotics	<u>midazolam</u>	14.80	15536460	2004 Dec
itraconazole	Antifungals	<u>midazolam</u>	10.80	8181191	1994 May
voriconazole	Antifungals	<u>midazolam</u>	9.40	16580904	2006 Apr
saquinavir / RIT	Protease Inhibitors	maraviroc	9.23	18333863	2008 Apr
mibefradil	Calcium Channel Blockers	<u>midazolam</u>	8.86	14517191	2003 Oct
clarithromycin	Antibiotics	<u>midazolam</u>	8.39	16432272	2006 Feb
lopinavir / RIT	Protease Inhibitors	aplaviroc	7.71	16934050	2006 Sep
nelfinavir	Protease Inhibitors	simvastatin	6.07	11709322	2001 Dec
telithromycin	Antibiotics	<u>midazolam</u>	6.0	NDA# 021144	2004
grapefruit juice DS ²	Food Products	<u>midazolam</u>	5.95	12953340	2003 Aug
conivaptan	Diuretics	<u>midazolam</u>	5.76	NDA # 021697	2005
nefazodone	Antidepressants	<u>midazolam</u>	5.44	14551182	2003 Nov
saquinavir	Protease Inhibitors	<u>midazolam</u>	5.18	10430107	1999 Jul

Appendix V: CKI-EPI (Chronic Kidney Disease Epidemiology Collaboration) GFR Formula

$$eGFR = 141 \times \min(Scr/k, 1)^a \times \max(Scr/k, 1)^{-1.209} \times 0.993^{Age} \times 1.018 [if\ female] \times 1.159 [if\ black]$$

sCr is serum creatinine, k is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males, min indicates the minimum of sCr/k or one, and max indicates the maximum of sCr/k or one.

Appendix VI: Common Toxicities, Prophylaxis and Treatment of Systemic Toxicities for Intravenous Cabazitaxel

Hematological toxicity

The dose cabazitaxel depending on the treatment arm will be modified in case of haematological toxicity. Dose modifications are summarized in Table 1

Table 1 - Dose modifications for hematological toxicity

Toxicity	Grade 2	Grade 3	Grade 4
Neutropenia	<p>If not recovered on D21, delay** next infusion until recovery to grade ≤ 1 (neutrophil $\geq 1.5 \times 10^9/L$).</p> <p>- 1st episode: No dose reduction required.</p> <p>- 2nd episode; reduce by 1 dose level</p>	<p>No dose reduction if isolated and duration ≤ 7 days.</p> <p>If duration more than 7 days or not recovered on D21</p> <p>Delay** next infusion until ANC $\geq 1.5 \times 10^9/L$ and:</p> <p>- 1st episode: Administer prophylactic G-CSF treatment in subsequent cycles.</p> <p>- 2nd episode or 1st episode despite prophylactic G-CSF: Reduce dose by 1 dose level.</p> <p>- 3rd episode or 2nd episode despite prophylactic G-CSF: Withdraw from study treatment</p>	
Febrile neutopenia or neutopenic infection	Not applicable	<p>Delay** next infusion until recovery and ANC $\geq 1.5 \times 10^9/L$ and:</p> <p>- 1st episode: reduce the dose and administer prophylactic G-CSF treatment in subsequent cycles.</p> <p>- 2nd episode: Withdraw from study treatment</p>	
Thrombocytopenia	<p>Delay** next infusion until recovery to grade ≤ 1 (platelets $\geq 75 \times 10^9/L$).</p> <p>No dose reduction required.</p>	<p>Delay** infusion until platelets $\geq 75 \times 10^9/L$.</p> <p>If grade 3 without delay, no dose reduction required.</p> <p>If grade 4 with or without delay, or grade 3 with delay</p> <p>- 1st episode: Reduce dose by 1 dose level.</p> <p>- 2nd episode: Withdraw from study treatment in case of recurrence</p>	

** maximum of 2 weeks delay, otherwise the patient will discontinue cabazitaxel

Blood counts will be performed in case of fever or infection. Blood count should be monitored weekly for the first 3 cycles to determine if G-CSF or dosage modification is needed. Study treatment should not be given to patients with neutrophil counts <1,500 cells/mm³.

Deaths due to sepsis following severe neutropenia have been reported in patients treated with cabazitaxel. Neutropenic complications should be managed promptly with antibiotic support and use of G-CSF should be considered according to ASCO guidelines. Infections concomitant with grade 3-4 neutropenia should be reported with the term “neutropenic infection” in the eCRF.

No dose modification will be made for anemia; patients will be supported appropriately by the treating physician (the investigator can refer to ASCO guidelines).

Allergy (Anaphylactic and Hypersensitivity reactions)

Hypersensitivity reactions that occur despite premedication are very likely to occur within a few minutes of start of the first or of the second infusion of Cabazitaxel. Therefore, during the 1st and the 2nd infusions, careful evaluation of general sense of well being and of blood pressure and heart rate will be performed for at least the first 10 minutes, so that immediate intervention would occur in response to symptoms of an untoward reaction.

Facilities and equipment for resuscitation along with the medications (i.e., antihistamine, corticosteroids, aminophylline, and epinephrine) must be immediately available. If a reaction occurs, the specific treatment that can be medically indicated for a given symptom (e.g., epinephrine in case of anaphylactic shock, aminophylline in case of bronchospasm, etc) will be instituted. In addition, it is recommended to take the measures listed below:

<p>Mild: localized cutaneous reaction, such as: pruritus, flushing, rash.</p>	<ul style="list-style-type: none"> ○ Consider decreasing the rate of infusion until recovery of symptoms, stay at bedside ○ Complete cabazitaxel infusion at the initial planned rate.
<p>Moderate: Generalized pruritus, more severe flushing or rash, mild dyspnea, hypotension with systolic B.P. >80 mmHg</p>	<ul style="list-style-type: none"> ○ Stop cabazitaxel infusion ○ Give IV diphenhydramine 50 mg and/or IV dexamethasone 10 mg ○ Once all signs and/or symptoms of hypersensitivity reaction disappear, cabazitaxel may be reinfused within 24 hours from the interruption, if medically appropriate, and whenever possible. ○ Re-administer premedication regimen as described in Section 8.6 when cabazitaxel is reinfused more than 3 hours after the interruption ○ Administer cabazitaxel over 2 hours for all subsequent infusions
<p>Severe: bronchospasm, generalized urticaria, hypotension with systolic B.P. ≤80 mmHg, angioedema.</p>	<ul style="list-style-type: none"> ○ Stop cabazitaxel infusion ○ Give IV diphenhydramine 50 mg and/or IV dexamethasone 10 mg ○ Add epinephrine** or bronchodilators and/or IV plasma expanders if indicated

	<ul style="list-style-type: none"> ○ Once all signs and/or symptoms of hypersensitivity reaction disappear, cabazitaxel may be reinfused within 24 hours from the interruption, if medically appropriate, and whenever possible ○ <input type="checkbox"/> Re-administer premedication regimen as described in Section 8.6 when cabazitaxel is reinfused more than 3 hours after the interruption ○ <input type="checkbox"/> Administer cabazitaxel over 2 hours for all subsequent infusions ○ <input type="checkbox"/> If a severe reaction recurs, patient will go off protocol therapy
Anaphylaxis (Grade 4 reaction)	Withdraw treatment

Nausea/Vomiting

A prophylactic anti-emetic treatment should be given to the patients in all cycles. The use of metoclopramide is recommended. More aggressive anti-emetic prophylaxis (i.e., ondansetron, etc.) should be given to the patient who has experienced grade ≥ 3 nausea/vomiting in a preceding cycle. If despite the appropriate medication, grade ≥ 3 nausea/vomiting still occur, reduce the dose of cabazitaxel. If despite dose reduction and prophylaxis, nausea/vomiting still occur at grade ≥ 3 , the patient should be withdrawn from treatment with cabazitaxel.

Stomatitis

If grade 3 stomatitis occurs, cabazitaxel should be withheld until resolution to grade ≤ 1 . Treatment may then be resumed, but the dose of cabazitaxel should be reduced for all subsequent doses. In case of grade 4 stomatitis, the patient will be withdrawn from treatment with cabazitaxel.

Diarrhea

No prophylactic treatment for diarrhea is recommended in Cycle 1. However, following the first episode of diarrhea, the patient should be treated with rehydration or antidiarrheal medications as needed. In case of Grade ≥ 3 diarrhea or persisting diarrhea despite appropriate medication, fluid and electrolytes replacement, delay treatment until improvement or resolution, then reduce the dose. If despite dose reduction, diarrhea still occurs at grade ≥ 3 , the patient will be withdrawn from treatment with cabazitaxel.

Renal function

1) To plan microscopic urinal

ysis (not a dispstick):

- at baseline (reference value)

- and during study treatment if creatinine increase by at least 1.5 x ULN with the following parameters:

Na, K, Ca, Cl for ionogramme (unit = mmol/L)

Urea (unit = mmol/L)
Protein (unit = mg/dL)
Creatinine (unit = mg/dL)
Leucocytes (unit = /mm³)
Red blood cells (unit = /mm³)
Proteinuria/creatininuria ratio (UPCR)

- 2) To ask to consider nephrologist advice in case of creatinine increase by at least 2 x ULN or eGFR (according to CKD-EPI formula) decrease by 50%.
- 3) To recommend iv hydration for CT scan with contrast in case of eGFR < 60 ml/min and to provide some examples of hydration protocol in Appendices (see Appendix C)
- 4) In case of renal function impairment, to make any effort to identify the cause and to report the cause as adverse event. The existing renal failure should be considered in the grading of the event. If no cause is identified (no diagnostic), report in eGFR decrease as adverse event.

Creatinine and eGFR should be assessed until recovery or stabilisation.

Hematuria

An imbalance in the incidence of hematuria was observed in the Phase III study in second line mCRPC (EFC6193). More hematuria was reported in cabazitaxel arm versus mitoxantrone arm (62 patients/16.7% versus 14 patients/3.8%). In cabazitaxel arm, no clear possible explanation such as local infection/obstruction/progression, or anticoagulation/aspirin therapy, or thrombocytopenia was found for 21 patients. In addition, in prior studies conducted in metastatic breast cancer, a total of 6 patients (2 in the ARD6191 and 4 in the TCD6945) experienced cystitis without local infection including 5 hemorrhagic cystitis (3 cystitis were documented with biopsy).

Therefore, in case of hematuria with no clear possible explanation every efforts should be undertaken to document the cause (eg, urine cultures, urinary tract ultrasound, and if no cause identified cystoscopy with or without biopsy).

Peripheral neuropathy

Dose modification should be performed as follows:

- Grade ≤1: No change
- Grade 2: Retreat with reduced dose
- Grade 3: Patient will be withdrawn from treatment with cabazitaxel

Liver toxicity

In case of increase of SGOT(AST) and/or SGPT(ALT) to >2.5 x ULN or bilirubin to >ULN, delay cabazitaxel treatment for up to 2 weeks until SGOT(AST) and/or SGPT(ALT) returned to ≤2.5 x ULN and bilirubin to ≤ULN. Then retreat patient at reduced dose for rest of the treatment.

Other Toxic Effects

For \geq grade 3 toxicities except fatigue, local reaction, fluid retention, anemia and other toxicities that merely are uncomfortable but do not cause serious morbidity to patients, chemotherapy should be held for a maximum of 2 weeks from the planned date of reinfusion until resolution to \leq grade 1, then reinstated, if medically appropriate. A dose reduction of subsequent doses will be left to the investigator's judgment. These patients will be withdrawn from study treatment if >2 dose reductions are needed. Any measures such as frozen gloves or socks or scalp cooling cap to prevent nail toxicity or alopecia are left to the investigator's judgment.

Appendix VII: RESOURCES

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