A Combined Phase I and Phase II trial of Abraxane (ABI-007) for BCG-Refractory Superficial Transitional Cell Carcinoma

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A. Study Purpose and Rationale

In 2006, it is estimated that 61,420 new cases of bladder cancer will be diagnosed in the United States and 13,060 people will die from the disease. This makes bladder cancer the fourth leading cause of cancer in men and the ninth leading cause of cancer in women in the United States (American Cancer Society, 2006). Superficial bladder cancer 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 (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 superficial bladder cancer or carcinoma in situ will recur (Kim & Steinberg, 2001). Response rates to second-line intravesical therapy are 20 percent or less in this population.[1]

When 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 superficial bladder tumors in order to prevent death from 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 the major procedure (Crawford 2002). For these patients, there are currently no active chemotherapeutic alternatives, and thus there is an urgent need to investigate other intravesical options.

Paclitaxel and docetaxel are semi-synthetic members of the taxane family of chemotherapeutic agents. Both paclitaxel and docetaxel function as antimicrotubule agents; they bind to tubulin and promote the assembly and stabilization of microtubules by inhibiting depolymerization. This effectively prevents cell division, specifically centrosome organization and mechanisms of motility, attachment and intracellular transport essential components of S-phase and of mitosis. (Bissey 1995, Hennequin 1995)

Similarly, both paclitaxel and docetaxel when administered systemically, have demonstrated anti-tumor activity in a number of cancer lines and currently carry FDA approval for treatment of breast cancer, non-small cell lung cancer and ovarian cancers. The taxanes have been regarded as potentially "ideal" intravesical treatment for TCC of the bladder. An ideal therapy for intravesical treatment should be: (1) a highly efficacious anti-cancer therapy as either an agent that prevents the progression of cancer or kills cancer cells outright, (2) demonstrate minimal to no systemic absorption (and therefore systemic side effects) and (3) exhibit little if any local side effects from treatment. In preclinical studies as intravesical agents, they have proven both safe and effective with excellent cytotoxicity in cell culture. They have been shown to be highly effective agents in inhibiting growth in human bladder tumor cell lines (HBTCL) at concentrations as low as 0.1 micromolar, suppressing clonal growth in 100 percent of cell lines tested at this concentration (Rangel et al., 1994). Systemic absorption of chemotherapeutic drugs through the bladder wall is negligible for compounds which have a molecular weight greater than 300 daltons (Crawford 2002). The molecular weights of docetaxel and paclitaxel are 862 and 853 daltons respectively and have demonstrated minimal systemic absorption in animal models (Rangel et al, 1994 and Song et al., 1997). In a study involving beagle dogs, Song et al. instilled 500 micrograms of paclitaxel in 20mL water into the bladder of each dog and found that the plasma concentration of paclitaxel after intravesical instillation was <0.05 percent of the maximally tolerated plasma concentration of paclitaxel in humans (1 microgram/mL), concluding that intravesical paclitaxel produces a substantial chemotherapeutic targeting advantage with a

6000-fold higher average bladder tissue concentration of the drug compared to the steady-state plasma concentration (Song et al, 1997). Furthermore, in order to be maximally effective as intravesical agents, it is essential that both paclitaxel and docetaxel be stable inside the bladder while urine production is occurring simultaneously. It has been shown that both paclitaxel and docetaxel are stable within the normal narrow pH range (pH 5-7) of human urine. Rangel et al were able to recover 85 percent of both paclitaxel and docetaxel 4 hours after incubation in urine samples with pH values of 5, 6 and 7 (Rangel et. al, 1994).

Columbia University Medical Center recently completed the first phase I trial investigating intravesical taxanes for the treatment of TCC refractory to prior intravesical agents. 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 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. No systemic toxicities were observed.
Although the study was not formally designed to evaluate efficacy and was therefore not powered to make any clear conclusions regarding efficacy, cancer control response rates were promising. Ten patients (56%) demonstrated a complete response to the combination of bladder resection and intravesical docetaxel; two patients (11%) achieved a partial response defined as a negative final biopsy but persistent positive cytology; six patients (33%) had no clinical response to the treatment protocol. Four of the six patients with no response proceeded to cystectomy without progression to muscle-invasive disease.

The study completed with all patients undergoing dose-escalation to the maximum dose without consequence and promising results described above. Unfortunately, a maximum tolerated dose (MTD) at which toxicity was apparent was not able to be reached for the following reasons. As an intravesical treatment requires retention of the medication for a minimum of two hours, the volume of instilled docetaxel was limited to 100mL and, as the chemical solubility of docetaxel prevented higher concentrations of drug from instilled into the bladder, a maximum dose of 75mg/100mL was achieved without consequence.

Abraxane (ABI-007), a biologically interactive albumin-bound paclitaxel, offers the novel approach to chemotherapy by increasing the intra-tumoral concentration of drug by receptor-mediated transport involving transcytosis across the endothelial cell wall. Importantly, the chemical nature of ABI-007 allows concentrations of 500mg/mL to be achieved in aqueous solutions. Preclinical studies comparing systemic Abraxane to systemic paclitaxel demonstrated lower toxicities and an approximately 50% higher MTD. It is therefore hypothesized that Abraxane may improve the MTD experienced in the phase I trial of intravesical docetaxel for superficial bladder cancer and may provide a therapeutic benefit to patients when compared to the lower concentration form of the drug. The purpose of this study is to examine the safety and tolerability of Abraxane as an intravesical treatment for superficial bladder cancer resuming the dose-escalation where the previous phase I trial was stopped until the maximum solubility of ABI-007 in 100mL of saline is reached.

In a phase III study of Abraxane versus paclitaxel for metastatic breast cancer (Gradishar 2005), the incidence of hypersensitivity reactions for ABI-007 has been low and not statistically different from the rate in the paclitaxel group (1% versus 2% respectively) while rates of neutropenia have been demonstrably lower in the Abraxane group. However, treatment-related sensory neuropathy was more common in the higher concentration Abraxane group (10% versus 2%; $p<0.001$) with the same number of patients having durable neuropathy after treatment in both treatment groups. Care will be required to ensure that systemic absorption of Abraxane does not occur following intravesical treatments as well as close monitoring of the toxicity profile associated with this drug.

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B. Study Design and Statistical Analysis

Power Calculations and Statistics: The phase I segment of the trial is not powered, and is simply designed in the 3-patient cohort dose-escalation model that is standard for chemotherapy phase I trials, and will enroll a maximum of 18 patients. The following scheme will be used to escalate dosages. Abraxane in a constant concentration of 5mg/ml will initially be given at a dose level of 150mg and will be raised in increments of 50-75mg to a maximum of 500 mg in a maximum of 100ml. Dosages can be escalated if three to six patients have undergone the first instillation of the medication without experiencing a dose-limiting toxicity (DLT), as follows. Initially three patients will be treated. If none develops DLT, the dose can be escalated. If only one of the first three patients develops DLT, then an additional three patients will be treated at that dose. If the fourth, fifth, and sixth patients do not develop DLT, the dose can be escalated. Otherwise the prior dose will be defined as the MTD. At any dose level, if two or more cases develop DLT, the prior dose will be defined as the maximum tolerated dose (MTD) once six patients have been treated at this level with less than two patients experiencing a DLT. The following table gives the operating characteristics of this scheme.

True rate of DLT (%)	Probability of Escalation (%)
10	91
20	71
30	49
40	31
50	17
60	8

The dose-limiting systemic toxicity will be defined as a plasma paclitaxel level of 10ng/mL or greater or any grade 2, 3 or 4 toxicity as defined by the National Cancer Institute Common Toxicity Criteria version 3.0. Dose-limiting local 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 3.0. Any patient who experiences a DLT will be removed from the trial and treated appropriately.

The primary objective of the phase II segment of this study is to evaluate the utility of Abraxane in the treatment of refractory superficial transitory cell bladder cancer as measured by response rate. This part of the study will use a Simon two-stage design[2]. We will enroll 10 patients in the first stage. If 2 or more respond, we will enroll an additional 19 patients to be evaluated in the second stage, and if 1 or fewer respond in the first stage, we will terminate the study for lack of efficacy. Furthermore, if more than 5 patients respond overall, we will consider the agent promising. The probability of correctly concluding the therapy is worthy of further study is 80% if the true underlying response rate is 30%. The probability of incorrectly concluding the therapy is promising is 5% if the true response rate is 10%. The expected sample size for this study design is 15 patients with a maximum of 29 patients.

Definitions: Systemic dose-limiting toxicity (DLT) will be defined as plasma paclitaxel values greater than 10 ng/ml or any grade systemic toxicity using the National Cancer Institute Common Toxicity Criteria version 3.0 (Appendix III). If any systemic DLT is encountered, the patient will be removed from the trial and treated appropriately. In the event of a systemic DLT, no dose modification will be permitted. Local dose limiting toxicity will be defined as Grade 3 or 4 bladder toxicity using the National Cancer Institute Common Toxicity Criteria version 3.0 (Appendix III). In the event of Grade 2 bladder toxicity, Abraxane instillation will be postponed one week, provided that resolution of symptoms to a maximum of Grade 1 occurs.

A successful treatment will be defined as negative cytology and negative biopsy at 6-month follow-up after the last treatment. Either positive cytology or positive biopsy, even in the absence of the other will be considered a treatment failure. An adverse event is defined as the development of an untoward medical occurrence, undesirable medical condition, 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 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. 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. 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. 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 v3.0. 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. Any adverse event that is not an SAE is, by default, a non-serious AE. 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 30-day follow-up period 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). 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 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.

Outcome: The primary outcome measured in this study is the incidence of toxicities and adverse effects in the phase I segment of the trial as defined above. The primary outcome of the phase II segment of the trial will be presence or absence of transitional cell cancer with the failure of treatment and the presence of cancer defined above as EITHER positive urine cytology for cancerous cells, positive bladder biopsy for cancer, or radiographic evidence of progression.

C. Study Procedure

Prestudy: Patients will be seen and evaluated by the principle investigator. Potential candidates will have a history and physical examination performed by the principle investigator in order to make sure they meet the proper inclusion and exclusion criteria. Weight, vital signs, and ECOG performance status will are checked by a member of the medical staff. Patients will provide a urine sample, which will be sent for urine analysis to check the pH value. Patients are required to undergo an initial cystoscopic examination performed by one of the study investigators. If not already performed, all grossly visible tumor will be resected prior to enrollment. Patient will give a blood sample, which will be sent for a Complete Blood Count (CBC), Basic Metabolic Panel (BMP), Hepatic Function Panel, and Coagulation Profile (PT, PTT, and INR). In female patients, a serum Beta-HCG value will be checked to rule out evidence of pregnancy. However, the HCG levels will be checked only once if the patient is subsequently enrolled in the phase II trial less than 6 months after completing phase I. Patients are also required to have a Chest X-ray and Abdominal CT Scan within 3 months, and an Electrocardiogram (EKG) within thirty-days or solely before the previous phase I trial if enrolled

in the phase II trial less than 3 months afterwards. If these tests have not been performed within the specified time-lines, they will be performed prior to study enrollment.

Week of instillation and treatment day: Before the day of treatment, a member of the treatment staff will evaluate the patient's CBC (done within two weeks prior to the treatment date. The patient must have a hemoglobin level > 8.0 g/dL, a white blood cell count > 3.0 x 10^9, an absolute neutrophil count > 1500/mm_3, and a platelet count > 100,000/mm^3 in order to undergo treatment. During the treatment day, each patient will be seen and have an updated history taken by the principle investigator. At each visit, every patient will be asked specific questions to monitor for local bladder toxicity as defined by the National Cancer Institute Common Toxicity Criteria version 3.0. For example, when monitoring for Grade 3 or 4 hematuria, the member of the treatment staff will ask about persistent gross hematuria and/or blood clots. In order to monitor for Grade 3 or 4 toxicity bladder spasm, patients will be asked if their symptoms are severe enough to require a narcotic. In order to monitor 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. If questioning reveals any Grade 3 or 4 toxicity as defined by the National Cancer Institute Common Toxicity Criteria version 3.0, the patient will be considered to have local toxicity and will be removed from the trial and treated appropriately. Questioning to monitor for Grade 2 local toxicity will also be performed and the patient will be treated at the discretion of the principle investigator.

At every visit, all study subjects will also have a physical examination performed, including weight, blood pressure, and pulse. Patients will provide a urine sample, which will be checked by dipstick for pH and then sent to the laboratory for urine analysis. If urine pH is outside the range of paclitaxel solubility (pH 6-7.5, the dose will be held. If urine pH is found to be below this range, the oral alkalinizing agent potassium citrate will be prescribed and the treatment will be administered one week later pending a normalized urine pH. If the urine pH is greater than 7.5, oral intake of citrus juices and increased fluid intake will be encouraged and the dose will be administered one week after later pending a normalized urine pH.

Patients will be administered Abraxane treatment via sterile urethral catheter. Patients will retain the study drug within their bladder for two hours and then void in a standard fashion. No special precautions are required regarding disposal of the study drug after voiding in a normal toilet. Four hours after the treatment, the patient's blood will be drawn and sent to the Columbia University Comprehensive Cancer Center Clinical Research laboratory for assessment of serum HPLC docetaxel level, after which they will conclude the treatment visit. Additionally, a CBC will be drawn at every visit. On even-numbered instillations, patients will have BMP, Hepatic Functional Panel, and Coagulation Profile checked. If there is any evidence of Grade 3 or 4 systemic toxicity according to these lab values or plasma Abraxane values greater than 10 ng/mL, the patient will be immediately removed from the trial and be deemed to have systemic toxicity.

Day of study termination: At the end of the six-week treatment periods, study subjects will have an updated history taken by the medical staff. Blood will be drawn and a CBC, CMP and Coagulation Profile will be ordered before the visit. The medical staff will perform a physical examination and check the patient's weight, vital signs and ECOG performance status. Similar to previous treatment days, the patient will receive the appropriate dose of intravesical Abraxane, have a urine sample checked by dipstick for pH value and have a serum HPLC drawn for Abraxane. The patient will also have an EKG at this visit.

Six week/4 month/6 month follow-up: All study subjects will undergo an updated history and perform a physical examination. Weight, vital signs and ECOG performance status will be obtained by the medical staff. Subjects will have blood drawn and a CBC, BMP and Coagulation Studies will be obtained. Subjects will provide a urine sample for pH value, an EKG, Chest X-ray and abdominal and pelvic CT scan performed.

Six-week, 4-month, and 6-month response assessments: All study subjects will undergo response evaluation after a minimum of six weeks, 4 months, and 6 months following the last

treatment. This will consist of urinary cytology, examination under anesthesia and cystoscopy with bladder biopsy or tumor resection. This will serve as the endpoint for response for the clinical trials. A response will be defined as a negative biopsy, negative cytology, and stable cross-sectional imaging. No response will be defined as positive cystoscopic biopsy, urine cytology or evidence of progression on cross sectional imaging.

Study schedule:

Parameter	Pre- study	Weekly Treatment Day	Every Other Week (even-numbered visits)	Study Termination	6 week/4-month/6-month Follow-Up**
History	X	X		X	X
Physical examination	X	X		X	X
Weight	X	X		X	X
Vital signs	X	X		X	X
Intravesical Abraxane administration		X		X	
Cystoscopy and biopsy	X				X
Performance status (ECOG)	X			X	X
CBC, differential, platelet count	X	X		X	X
Creatinine, Serum bilirubin, glucose, alkaline phosphatase, SGOT &/or SGPT	X		X	X	X
Electrolytes (Na, K, C1, CO_2)	X		X	X	X
Coagulation Profile	X		X	X	X
Urine pH	X	X		X	X
Serum HCG	X				
Chest x-ray	X				X
Liver scan or abdominal CT	X				X
EKG	X			X	X
Plasma Abraxane Levels *		X*		X*	

All other blood work will be available prior to weekly instillation

*Plasma Abraxane levels will be drawn approximately 2 hours after drug is voided from bladder in the first 19 patients. Plasma Abraxane levels will not be drawn in the remaining patients if no systemic toxicity is observed in the first 19 patients. If one or more of the first 19 patients demonstrates systemic toxicity or Abraxane levels greater than 10ng/dL, then all patients will have weekly plasma Abraxane levels drawn. 6-week, 4-month, and 6-month follow-ups will include cystoscopy and biopsy for all patients not undergoing cystectomy.

**Pre-treatment EKG and HCG will be only drawn prior to initiation of phase I if patients enrolled in phase II within 3 months of cessation of trial I.

D. Study Drugs

Abraxane is a cytotoxic anticancer drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling Abraxane. The use of gloves is recommended. If Abraxane (lyophilized cake or reconstituted suspension) contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure to paclitaxel, events may include tingling, burning and redness. If Abraxane contacts mucous membranes, the membranes should be flushed thoroughly with water.

E. Medical Devices

None.

F. Study Questionnaires

None.

G. Study Subjects

Inclusion Criteria:

- Patients must have a diagnosis of transitional cell carcinoma (TCC) of the urinary bladder confirmed at the study institution. The patient must have demonstrated superficial recurrent bladder cancer refractory to standard intravesical therapy. This will include stage Ta, T1, Tis and exclude all patients with muscle invasion (T2). All patients with stage Ta will require documentation of high-grade histology. All grossly visible disease must be fully resected and pathologic stage will be confirmed at the institution where the patient is enrolled. Patients must exhibit disease recurrence after receiving some form of standard intravesical therapy, including BCG, mitomycin, interferon or any combination thereof.
- Age $\geq$ 18 and must be able to read, understand and sign informed consent
- Performance Status: ECOG 0,1, 2
- Peripheral neuropathy: must be $\leq$ grade 1
- **Hematologic-Inclusion within 2 weeks of start of treatment**
    - Absolute neutrophil count $\geq$ 1,500/mm^3
    - Hemoglobin $\geq$ 8.0 g/dl
    - Platelet count $\geq$ 100,000/mm^3
- **Hepatic-Inclusion within 2 weeks of entry**
    - Total Bilirubin must be within normal limits.
    - Transaminases (SGOT and/or SGPT) may be up to 2.5 x institutional upper limit of normal (ULN) if alkaline phosphatase is $\leq$ ULN, or alkaline phosphatase may be up to 4 x ULN if transaminases are $\leq$ ULN.
- Women of childbearing potential must have a negative pregnancy test.
- Women of childbearing potential must be willing to consent to using effective contraception, i.e., IUD, Birth control pills, Depo-Provera while on treatment and for 3 months after their participation in the study ends.
- No intravesical therapy within 6 weeks of study entry
- No prior radiation to the pelvis

Exclusion Criteria:

- Patients with a history of severe hypersensitivity reaction to docetaxel, paclitaxel, or other drugs formulated with polysorbate 80 must be excluded.
- Prior systemic docetaxel or paclitaxel therapy.
- Any other malignancy diagnosed within 2 years of study entry (except basal or squamous cell skin cancers or non-invasive cancer of the cervix) is excluded.
- Concurrent treatment with any chemotherapeutic agent.
- Women who are pregnant or lactating.
- History of vesicoureteral reflux or an indwelling urinary stent.
- Participation in any other research protocol involving administration of an investigational agent within 3 months prior to study entry aside from the phase I segment of this study.
- Subjects who cannot be prescribed immunosuppressive medications due to confounding medical condition.

H. Recruitment

Patients meeting our inclusion criteria will be recruited primarily from within the Department of Urology, the Division of Oncology by the principle investigator.

I. Confidentiality

We will maintain HIPAA and GCP guidelines for confidentiality with all identifying patient information kept in a locked cabinet in the private office of the clinical research coordinator.

J. Conflict of Interest

Although the study is investigator-initiated, sponsored and run, the study medication and funding is being provided by Abraxis Bioscience Inc. which produces Abraxane.

K. Location

This is a prospective trial being conducted at Columbia University Medical Center; no other institution is participating.

L. Potential Risks

There have not been any studies using Abraxane as an *intravesical* agent in humans as of yet. In the randomized phase III metastatic breast cancer study with *intravenous* Abraxane administration, the most important adverse events included neutropenia (all cases 80%; severe 9%), anemia (all 33%; severe 1%), infections (24%), sensory neuropathy (any symptoms 71%; severe 10%), nausea (any 30%; severe 3%), vomiting (any 18%; severe 4%), diarrhea (any 26%; severe <1%), myalgia/arthralgia (any 44%; severe 8%), and mucositis (any 7%; severe <1%). Other adverse reactions included asthenia (any 47%; severe 8%), ocular/visual disturbances (any 13%; severe 1%), fluid retention (any 10%; severe 0%), alopecia (90%), hepatic dysfunction (elevations in bilirubin 7%, alkaline phosphatase 36%, AST [SGOT] 39%), and renal dysfunction (any 11%; severe 1%). Thrombocytopenia (any 2%; severe <1%), hypersensitivity reactions (any 4%; severe 0%), cardiovascular reactions (severe 3%), and injection site reactions (1%) were uncommon[3].

M. Potential Benefits

Current treatment regimens for BCG-refractory transitional cell carcinoma have an approximately 10% remission rate. Our recent Taxotere (another member of the Taxane chemotherapy medication family mechanistically similar to Abraxane) phase I trial, which was not powered for efficacy, showed a 56% success rate (10/18 patients). Thus our consideration of 30% likely successful rate allows us to present reasonable expectations considering both the current of care as well as our previous taxotere trial[3].

N. Alternative Therapies

Patients always have the right to decline treatment. Patients may also opt for cystectomy, intravesical BCG, Mitomycin C, Interferon, Thiotepa, or Gemcitobine.

O. Compensation to Subjects

None.

P. Costs to Subjects

None.

Q. Minors as Research Subjects

None.

R. Radiation and Radioactive Substances

None.

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Appendix 1

The ECOG PS score used in this study

ECOG/WHO score

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

(PS score 5 was omitted from the trial questionnaire).