A Phase II Multi-Strata Study of PM01183 as a Single Agent or in Combination With Conventional Chemotherapy in Metastatic and/or Unresectable Sarcomas

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Other Agent(s):

- PM01183, PharmaMar Inc
- Doxorubicin, commercial, generic
- Gemcitabine, commercial, Eli Lilly and Co.

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SCHEMA

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1. OBJECTIVES

Study Hypothesis:

PM01183, as a single agent or in combination with either doxorubicin or gemcitabine chemotherapy, will lead to objective response and/or durable disease control in patients with metastatic and /or unresectable sarcoma.

1.1 Study Design

We propose a three strata phase II study of PM01138 administered either alone or in combination with chemotherapy (doxorubicin or gemcitabine) with the primary endpoint of disease control rate (DCR; DCR = objective response rate plus stable disease rate at 24 weeks).

Stratum A: Anthracycline-naïve patients will receive the combination of PM01183 and doxorubicin every 21 days for up to a total of 6 cycles; patients who exhibit disease control or objective response after 6 cycles of the combination will continue on single-agent PM01183 until disease progression or unacceptable toxicity.

Stratum B: Patients with prior anthracycline exposure (or a contraindication to anthracyclines) and without prior gemcitabine exposure will receive the combination of PM01183 and gemcitabine on day 1 and the combination of PM01183 and gemcitabine on day 8 of a 21 day cycle until disease progression or unacceptable toxicity. Patients who stop gemcitabine for unacceptable toxicity may continue on single-agent PM01183 (according to the single agent dosing strategy in Stratum C) until disease progression or unacceptable toxicity.

Stratum C: Patients who have received prior anthracycline (or have a contraindication to anthracyclines) AND prior gemcitabine (or have a contraindication to gemcitabine) will receive PM01183 as a single agent every 21 days until disease progression or unacceptable toxicity.

Imaging will be obtained every 6 weeks for the first 8 cycles. Imaging frequency will decrease to every 9 weeks thereafter.

1.2 Primary Objectives

- To determine the Disease Control Rate (DCR = Overall Response Rate [ORR] + Stable Disease [SD] at 24 weeks) of PM01183 alone and DCR of PM01183 in combination with chemotherapy in sarcomas

1.3 Secondary Objectives

- To further characterize the clinical activity of PM01183 alone or with chemotherapy by: ORR, progression free survival (*PFS*) and overall survival (OS) at two years
- To explore the correlation of DCR, ORR, PFS and OS to disease subtype

- To further determine the safety profile of PM01183 alone or with chemotherapy in this patient population

2. BACKGROUND

2.1 Study Disease(s)

Sarcomas represent a complex and heterogeneous group of mesenchymal malignancies arising from connective tissue in bone or soft tissue. There will be approximately 12-15,000 new cases of sarcoma this year in the United States, and 4-5,000 deaths.[1] When localized, many sarcomas are potentially curable with surgical resection with or without radiation and chemotherapy. Unfortunately despite adequate local control metastases are common and, for most patients, advance disease, whether at diagnosis or recurrence, is lethal.

In metastatic soft tissue sarcomas (STS), single agent or combination chemotherapy has led to a median survival of only 12 months across histologies.[2, 3] Standard single agent regimens for STS include doxorubicin (response rates <25%),[4-6] ifosfamide (response rates <25%),[7-10] and other less active therapies including vinorelbine, dacarbazine and platinum compounds. Combination regimens include doxorubicin plus ifosfamide (response rates 20-24%),[5, 11] doxorubicin plus ifosfamide and dacarbazine (response rates 32-49%),[12, 13] and additionally gemcitabine with a second agent such as docetaxel (response rate 18-53%, histology dependent), vinorelbine or dacarbazine (clinical benefit rate =49%).[14-17] In general, combination therapies improve response rates and progression-free survival but have no impact on overall survival. [18]

Pazopanib is a multikinase inhibitor that was recently approved for second line or greater treatment of metastatic STS. In a double-blinded phase III study pazopanib was compared to placebo in 369 patients with STS, excluding adipocytic sarcomas and GIST.[17] Although the response rate was quite low at 6% there was a significant improvement in median progression free survival (4.6 versus 1.6 months). There was no difference in overall survival.

Prior to the pazopanib approval in 2012, there have been no therapies approved by the U.S. FDA for sarcomas other than GIST since doxorubicin in the 1980's. It has been challenging to develop therapies in sarcoma largely due to a combination of small patient numbers and the inherent biological complexity of this heterogeneous group of tumors. Novel therapies with unique mechanisms of action are clearly needed.

2.2 PM01183

PM01183 is produced by chemical synthesis and has the following properties:

Chemical Name	[redacted]

Molecular Formula	[redacted]
Molecular Weight	[redacted]
CAS Number	[redacted]
INN	lurbinectedin

2.2.1 Chemical Structure

PM01183 is a new Chemical Entity that binds the DNA leading to the formation of DNA double strand breaks. The binding to DNA is likely occurring in the minor groove region and induces apoptosis and delayed progression through the phase S/G2. PM01183 also induces the specific degradation of transcribing RNA Pol II in several human tumor cell lines.

2.2.2 In Vitro Anti-neoplastic Activity

As a single agent, PM01183 was evaluated in vitro by a monolayer assay in a set of 36 human tumor cell lines after 96 hours of incubation, as well as in 64 human-derived tumors by a clonogenic assay in which semi-solid agar cell suspensions were incubated with ranging concentrations of PM01183 for up to 18 days. In both systems, strong in vitro cytotoxic activity of PM01183 was reported, with mean IC_{50} varying between 0.074 nM and 0.4 nM. No clear clustering of sensitive cell lines could be identified.

In solid tumor models, two combinations were strongly synergistic: i) PM01183 combined with topotecan (colon HT29, pancreas PANC-1 and glioblastoma U87MG cell lines) and ii) PM01183 combined with erlotinib (lung A-549, gastric HGC-27 and prostate PC-3 cell lines). Some other standard agents (paclitaxel, vinorelbine, vincristine, oxaliplatin, 5-FU, bortezomib and

trabectedin) showed synergistic activity in combination with PM01183 in different cell lines. In hematological cell lines, no significant synergies were identified with 10 standard antineoplastic agents. However, combinations of PM01183 with cytarabine, daunorubicin, methotrexate, gemcitabine or trabectedin showed hints of synergism in specific cell line models.

2.2.3 In Vivo Anti-neoplastic Activity

In vivo, PM01183 also exhibits antitumor activity against different murine models of xenografted human-derived tumor types.

In a panel of 6 human tumor xenografts grown in athymic micea single bolus intravenous (i.v.) injection of PM01183 at the maximum tolerated dose (0.3 mg/kg [0.9 mg/m^2]) demonstrated statistically significant antitumor activity ($p<0.05$) against breast, colon, gastric, and kidney xenografts, but not in ovarian and prostate tumors.

Intravenous administration of PM01183 at a dose of 0.2 mg/kg/day (0.6 mg/m^2/day) for 3 consecutive weeks in the M5076 sarcoma model that spontaneously metastasizes in the liver of C57Bl/6 female tumor bearing mice showed marginal activity on the primary tumor, but statistically significantly reduced the number of liver metastases compared to placebo-treated animals (Median<5 and 124 for PM01183 and placebo groups, respectively).

For additional preclinical PK and safety pharmacology data please refer to the PM01183 Investigator's Brochure (IB).

2.2.4 PM01183 CLINICAL STUDIES

As of 15 January 2014, 366 patients (331 with solid tumors and 35 with advanced acute leukemia) had been treated with PM01183 in clinical trials within the clinical development program of this compound: 198 patients in phase I trials (35 with advanced acute leukemia) and 168 patients in phase II trials.

Only the first-in-human (FiM) phase I trial (PM1183-A-001-08) has been completed. This phase I trial evaluated intravenous (i.v.) PM01183 when infused over 1 hour (h) every three weeks (q3wk) in 31 patients with advanced and refractory solid tumors. Among these, 15 (48.4%) patients were treated at the defined recommended dose (RD). The RD for phase II studies was defined at a PM01183 dose of 4 mg/m^2 q3wk which was found equivalent by pharmacokinetic analysis to 7 mg flat dose (FD) q3wk in this study. Treatment at the RD was generally well tolerated with standard antiemetic prophylaxis. The most relevant toxicity at the RD was reversible, short-lasting myelosuppression. One patient had a grade 4 thrombocytopenia, the only dose-limiting toxicity (DLT) at the RD. No signs of cumulative toxicity were observed. Antitumor activity was observed at the RD. The pharmacokinetic (PK) analysis showed high inter-patient variability (> 50% in the area under the curve [AUC]), and linearity across all explored doses. Linear regression analysis showed correlation between neutropenia and AUC (r2=0.452).

The other six phase I trials are ongoing. Two of them (PM1183-A-005-11 and PM1183-A-004-10) have closed recruitment after planned accrual. In these ongoing phase I trials, PM01183 is being evaluated as single agent in solid tumors (PM1183-A-005-11) and in acute relapsed/refractory adult leukemia (PM1183-A-002-10), as well as in combination with

doxorubicin (PM1183-A-003-10), gemcitabine (PM1183-A-004-10), capecitabine (PM1183-A-006-12), and weekly paclitaxel, with or without bevacizumab (PM1183-A-007-13) in patients with selected solid tumors. Antitumor activity has been consistently observed across all studies as described below.

Four phase II clinical trials are ongoing. Two of them (PM1183-B-001-10 and PM1183-B-002-10) have closed recruitment after planned accrual. In these ongoing phase II trials, PM01183 is being evaluated as second-line treatment in advanced pancreatic cancer (PM1183-B-001-10), platinum-resistant and platinum-refractory ovarian cancer (PM1183-B-002-11), BRCA 1/2-associated or unselected breast cancer (PM1183-B-003-11), and in non-small cell lung cancer, either alone or in combination with gemcitabine (PM1183-B-004-13).

2.2.4.1 Single agent PM1183 Phase I study:

The FiM study (PM1183-A-001-08) was conducted in patients with advanced and refractory solid tumors and evaluated PM01183 intravenously (i.v.) infused over 1 hour every three weeks (q3wk). Thirty-three patients were included and 31 patients received at least one dose of PM01183. Among these, 15 patients were treated at the defined RD: six during escalation and nine in the subsequent cohort expansion using a flat dose (see below).

The study followed an accelerated titration design that allowed the PM01183 dose to be safely increased by 200-fold, from 0.02 mg/m^2 to 5 mg/m^2 q3wk, which was found to be the MTD. Two of three patients had dose-limiting toxicities (DLTs) at the maximum tolerated dose (MTD); both patients had transient grade 4 transaminase increases, and one patient also had multiple toxicities including fatigue, diarrhea, nausea and neutropenia, none of which was individually considered a DLT but overall led to treatment discontinuation. The MTD was then reduced by 20%, to 4 mg/m^2 which was defined as the RD. Overall, only one of 15 evaluable patients treated at the RD (7%) had a DLT: grade 4 thrombocytopenia).

Primary antiemetic prophylaxis was not required for patients treated up to 1.3 mg/m^2 of PM01183. Mild nausea and vomiting were observed in patients treated at a dose of 2.6 mg/m^2. As a result, standard antiemetic prophylaxis was mandatory in all subsequently treated patients, particularly those treated at the MTD and the RD.

The most relevant toxicity found in the FiM was reversible myelosuppression, mainly consisting of grade 3/4 non-febrile neutropenia (FN) in 53.3% of patients. Grade 4 neutropenia was short-lasting (median: 3 days; range, 1-4) with nadir occurring at D13 (median value) (range 10-15 days). Only one of 15 patients (51 cycles) at the RD failed to recover neutrophil counts by D22 and had a PM01183-related dose delay.

Treatment was generally well tolerated in the expansion cohort treated at the RD. No unexpected toxicities occurred in this study, and there were no signs of cumulative toxicity despite six patients (19%) receiving at least six cycles.

Regarding antitumor activity at the RD, there were one confirmed PR in a pancreatic cancer patient, three SD $\geq$ 4 months in two patients with soft tissue sarcoma (STS) and one patient with malignant melanoma.

The patient population in this study was highly selected, particularly at the RD. All patients were <75 years of age, had an ECOG PS score of 0 or 1, and baseline albumin levels >3.3 g/dl, thus reflecting an excellent metabolic and nutritional status for a phase I study population.

Pharmacokinetic analysis of PM01183 showed high inter-patient variability (> 50% in AUC) and linearity across all doses explored. PM01183 clearance was not found to be related to BSA; hence, the RD (originally 4 mg/m^2 q3wk) was then rounded to a FD of 7 mg in the RD expansion cohort (n=9). Linear regression analysis showed a strong correlation between neutropenia and systemic exposure (AUC) (r^2=0.452).

2.2.4.2 PM1183-A-003-10 (PM01183/Doxorubicin Combination):

The primary objective of this ongoing clinical study is to determine a safe RD for phase II studies with this combination. Secondary objectives include to assess safety, to analyze possible PK drug-drug interactions, and to evaluate the antitumor activity observed in patients with selected advanced solid tumors. The dose of DOX remains fixed at 50 mg/m^2 q3wk, up to a maximum cumulative dose (MCD) of 450 mg/m^2 throughout the study. Once this MCD is reached, PM01183 administration may continue alone at its full single-agent RD (7 mg FD q3wk) as long as sustained clinical benefit is observed. The DOX dose calculation is capped at 2 m^2 of BSA. An amendment to the original protocol set a maximum age of 75 years and allowed the addition of primary growth factor prophylaxis to a prospective cohort of patients.

At data cutoff (January 15, 2014), 45 patients have been included and treated with the combination across four different dose levels. Data from 41 patients (13 with CSF prophylaxis and 28 without CSF prophylaxis) are available for analysis, including nine treated with single-agent PM01183. As of cutoff, 10 patients have continued treatment with PM01183 alone after DOX discontinuation.

The MTD is defined at 5 mg of PM01183 combined with the fixed DOX dose (50 mg/m^2) both on D1 q3wk regardless of CSF support. At this dose level, three of seven patients (43%) with CSF and two of five (40%) without CSF had DLTs: FN (n=3), grade 3 diarrhea with grade 3 colitis (n=1), and neutropenic septic shock with grade 4 thrombocytopenia (n=1). The immediately lower DL (PM01183 4 mg and DOX) was then expanded. DLTs were found in none of three patients with CSF at this dose level, and in one of ten (10%) patients without CSF (FN); as a result, PM01183 4 mg FD and DOX 50 mg/m^2 was defined as the RD for this combination.

Primary CSF prophylaxis did not allow further dose escalation in this study. FN was delayed to Cycle 2 in some patients, instead of Cycle 1 without CSF prophylaxis, but the incidence of FN did not seem to have been significantly prevented. DLTs occurring at the MTD regardless of CSF prophylaxis were not exclusively related to neutropenia and also included non-hematological toxicities (grade 3 diarrhea) and grade 4 thrombocytopenia. Thus, RD was not further expanded with primary CSF prophylaxis. As of cutoff, the RD is being expanded for selected tumor types due to the promising antitumor activity observed in small cell lung cancer (SCLC) as second line, endometrial cancer and neuroendocrine tumors (NET). According to established guidelines, primary CSF prophylaxis should be administered when at least a 20% risk of FN is associated with any particular regimen. At cutoff, FN was observed at the RD in two of ten patients in the cohort without CSF prophylaxis, but in one of three patients in the cohort with CSF prophylaxis; hence, more data are needed to draw definitive conclusions regarding primary CSF prophylaxis requirements at this point.

As mentioned above, a protocol amendment established the maximum age limit in 75 years old.

Among the initial five patients treated before the protocol amendment in study PM1183-A-003-10 at DL1 (PM01183 3.5 mg FD and DOX 50 mg/m^2), two DLTs (both FN) occurred in the only two patients older than 75 years.

Most non-hematological treatment-related AEs observed at the RD for the PM01183 + DOX combination were mild or moderate. The most frequently reported were fatigue, nausea, constipation and alopecia. No non-hematological grade 4 events occurred at the RD. Severe related AEs at the RD only reached grade 3 and comprised febrile neutropenia and mucosal inflammation (mucositis).

Grade 3/4 neutropenia was the most common hematological toxicity at the RD, regardless of CSF prophylaxis. Although it occurred slightly less frequently with CSF prophylaxis, this approach was not preventive enough to allow dose escalation to continue safely. Other toxicities at the RD were less common and occurred irrespectively of CSF prophylaxis, as expected: grade 3 anemia was found in two patients with CSF and one without CSF, and grade 3 thrombocytopenia in only one patient with CSF. Nevertheless, as one of the DLTs (grade 4 thrombocytopenia) observed at the MTD in the cohort without CSF was not associated to neutropenia, the RD with CSF prophylaxis was not further expanded. Most biochemical abnormalities were unremarkable in most patients and were mild or moderate.

Preliminary efficacy results from 33 patients are available at cutoff. An ORR of 39% (95% CI, 23-58%), including four patients with CR and nine with PR, was achieved. Additionally, SD lasting ≥ 4 months was observed in six (18%) patients with STS (n=2), SCLC, bladder, endometrial and HCC (n=1 each). Therefore, preliminarily results available at cutoff showed that 58% of patients experienced either response or prolonged disease stabilization as clinical benefit to treatment with the PM01183/DOX combination in this study.

At cutoff, at least 10 patients had continued treatment with PM01183 alone after DOX discontinuation.

Best tumor response as per RECIST v.1.1 with PM01183 + DOX in study PM1183-A-003-10.

	Tumor type																		Total	
	SCLC		Bladder		STS		Ovarian		Gastric		Endometrial		Breast		NET		Other			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
CR	.	.	.	.	1	17	1	100	.	.	1	33	1	50	.	.	.	.	4	12
PR	5	42	1	25	.	.	.	.	.	.	1	33	1	50	1	50	.	.	9	27
SD ≥ 4 months	1	8	1	25	2	33	.	.	.	.	1	33	.	.	.	.	1	50	6	18
SD < 4 months	.	.	.	.	.	.	.	.	1	100	.	.	.	.	1	50	.	.	2	6
PD	6	50	2	50	3	50	.	.	.	.	.	.	.	.	.	.	1	50	12	36
Total	12	100	4	100	6	100	1	100	1	100	3	100	2	100	2	100	2	100	33	100

All SCLC patients who achieved PR received PM01183 + DOX as second-line treatment.
CR, complete response; DOX, doxorubicin; NET, neuroendocrine tumor; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SCLC, small cell lung cancer; SD, stable disease; STS, soft tissue sarcoma.

2.2.4.3 PM1183-A-004-10 (PM01183 + Gemcitabine Combination)

This study aimed to define a safe RD for phase II studies for this drug combination, and to explore its tolerability, feasibility and antitumor activity, in patients with specific solid tumors up to 75-years-old of age and with ECOG PS 0-1. The starting dose was PM01183 2.5 mg FD and GEM 800 mg/m^2/day, both on D1 and D8 q3wk. The GEM dose calculation was capped at a

BSA of 2 m^2.

Recruitment is closed prior to cutoff (January 15, 2014). A total of 47 patients were included, 45 were treated and are available for analysis.

DL4 (PM01183 3.5 mg FD + GEM 1000 mg/m^2/day) was the highest DL explored in this study. Nine patients were included at this DL, and seven were evaluable for DLTs. Four of these patients had DLTs during Cycle 1. These consisted of neutropenic infection; FN; treatment-related dose omission due to myelosuppression; and neutropenic sepsis with grade 4 thrombocytopenia that resulted in death. Consequently, DL3 (PM01183 3.5 mg FD + GEM 800 mg/m^2/day) was initially expanded to nine patients; there were two DLTs (both FN), and the cohort was further expanded in order to confirm feasibility of this dose. Finally, five of 21 patients (24%) had DLTs: FN alone (n=3); FN and grade 4 thrombocytopenia (n=1); and neutropenic sepsis and grade 4 thrombocytopenia that resulted in death (n=1). After discussion with the Investigators, this dose level was considered not feasible for phase II studies; the observed rate of neutropenic fever would have required primary CSF prophylaxis in accordance with current guidelines, which would have not prevented the severe thrombocytopenia observed in some cases. Therefore, DL3 was defined as the MTD and the next lower dose level (DL2, PM01183 3 mg FD + GEM 800 mg/m^2/day) was further expanded to 10 evaluable patients. None of these patients had DLTs; therefore, this DL was defined as the RD for this combination.

Most treatment-related AEs observed at the RD were mild or moderate. The most frequent were fatigue (n=8, 72.7%), gastrointestinal disorders such as nausea (n=6, 54.5%) and vomiting (n=4, 36.4%), decreased appetite (n=3, 27.3%) and rash (n=3, 27.3%). No grade 4 events occurred at the RD; grade 3 events comprised two episodes of fatigue and one of rash. No alopecia related to the PM01183 + GEM combination was reported.

Myelosuppression, particularly grade 3/4 neutropenia, was the most remarkable hematological toxicity at the RD. It reached grade 4 in five patients (45.5%). Of note, in contrast to what happened at the MTD, no grade 4 thrombocytopenia occurred at the RD: grade 3 events only occurred in two patients (18.2%). Another severe hematological toxicity was grade 3 anemia (n=5, 45.5%). One of 11 patients treated at the RD (9.1%) experienced a single episode of FN.

Most biochemical abnormalities were mild or moderate. No grade 4 abnormalities occurred. Of note, mild grade ALT/AST increases were observed in all patients at the RD, in contrast to the findings with other combinations being tested. Only one patient at the RD (9.1%) showed grade 3 ALT increase.

At cutoff, 38 of 45 treated patients were evaluable for efficacy. The best response achieved with the PM01183 + GEM combination in this study is shown in the table below. Overall, nine of 38 evaluable patients responded to the combination, for an ORR of 24% (95% CI, 11.4%-40.2%). Five of the nine responses occurred in patients with NSCLC, including one CR. In addition, prolonged SD (≥ 4 months) was achieved in 10 patients (26%); tumor types comprised NSCLC (n=4), breast cancer (n=3), pancreas cancer, ovarian cancer, and mesothelioma (n=1 each).

Best tumor response as per RECIST v.1.1 with PM01183 + GEM in study PM1183-A-004-10.

	Tumor type												Total	
	NSCLC		Pancreas		Breast		Ovarian		Mesothelioma		Biliary tract			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
CR	1	6	.	.	.	.	.	.	.	.	.	.	1	3
PR	4	24	1	17	1	17	2	40	.	.	.	.	8	21

	Tumor type												Total	
	NSCLC		Pancreas		Breast		Ovarian		Mesothelioma		Biliary tract			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
SD ≥ 4 months	4	24	1	17	3	50	1	20	1	50	.	.	10	26
SD < 4 months	4	24	1	17	1	17	.	.	1	50	2	100	9	24
PD	4	24	3	50	1	17	2	40	.	.	.	.	10	26
Total	17	100	6	100	6	100	5	100	2	100	2	100	38	100

CR, complete response; GEM, gemcitabine; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

2.2.5 Safety Data:

Available data from ongoing phase II trials suggest that, besides myelosuppression, other toxicities of PM01183 are mild to moderate gastrointestinal (GI) AEs, in particular nausea and vomiting, constipation, diarrhea and abdominal pain. Gastrointestinal AEs occasionally reach grade 3, but no PM01183-related grade 4 episodes have occurred. Severe nausea and/or vomiting seem to have occurred to date more frequently in PRROC patients than in MBC or pancreatic cancer patients.

The higher than expected severity of nausea/vomiting observed in some patients in the PRROC study (PM1183-B-002-11) could be in some cases associated to the disease under study (intestinal sub-occlusion is usually observed in these patients). This event probably led to the use of aprepitant during Cycle 2, particularly in those more severely affected in Cycle 1 (when use of aprepitant was forbidden). This resulted in unusually prolonged and severe myelosuppression (particularly, neutropenia and thrombocytopenia) in at least four patients. A PK analysis that compared systemic exposure to PM01183 during Cycle 1 (without aprepitant) and Cycle 2 (after receiving aprepitant) showed a 50% decrease in PM01183 clearance during Cycle 2, which in turn resulted in nearly double PM01183 AUC values. This was likely due to the concomitant aprepitant administration. Therefore, aprepitant administration is currently excluded in almost all ongoing clinical trials, unless explicitly and specifically authorized.

General disorders related to PM01183 treatment mainly consisted of fatigue/asthenia, in about two thirds of all patients treated in phase II trials. Other AEs that occurred at lower frequencies were pyrexia, mucosal inflammation and peripheral edema. Fatigue/asthenia is relatively prevalent in cancer patients, and is sometimes related to the nearly ubiquitous anemia caused either by prior therapies, the disease itself, or most frequently has a multifactorial etiology. These general disorders, with the exception of asthenia, were rarely severe and seemed to have relatively spared the MBC patients.

Potentially serious or life-threatening AEs related to PM01183 were rare and occurred in less than three patients in each phase II trial. Of note, severe respiratory disorders (dyspnea, pneumonitis, respiratory failure and tachypnea) occurred mainly among MBC patients so far.

Myelosuppression is by far the most frequent toxicity observed in phase II trials. The incidence of grade 3/4 neutropenia increased from over 50% of patients in phase I studies to 72.5% in all phase II studies, yet the overall incidence of FN remains just below the 20% threshold in all phase II studies as of cutoff (while in some specific settings, such as ovarian cancer, it is just above this threshold). Therefore, the need for primary CSF prophylaxis at the RD for single-agent PM01183 q3wk needs to be adequately individualized at present. Grade 3/4 thrombocytopenia also seems to have increased in frequency to nearly one third of patients, as compared to the highly selected phase I patient population.

Pooled analysis of the first three Phase 2 studies, including more than 100 patients, identified that body surface area statistically correlated to thrombocytopenia. There was also variability in the incidence of neutropenia and febrile neutropenia depending on the population of the different studies. For example, in the platinum-resistant ovarian cancer study, 23% of the patients had febrile neutropenia. However, in the Phase 2 in breast cancer, less than 5% of the patients had febrile neutropenia.

2.3 *Other Agent(s)*

Doxorubicin:
Doxorubicin (Adriamycin®, Rubex®, and Doxil®) is an anthracycline antibiotic that exerts its effects on cancer cells via two primary mechanisms. (1) Intercalation: In its role as an intercalating agent the drug wedges between the bases of DNA and blocks DNA synthesis and transcription. (2) Enzyme inhibition: The drug inhibits the activity of an enzyme, topoisomerase type II. This leads to breaks in the genomic DNA. Both of these mechanisms result in DNA disruption that ultimately can lead to the death of the cell. Single agent doxorubicin is the standard treatment in patients with advanced soft tissue sarcoma.[19] Typical institutional dosing is up to 75 mg/m^2 given by bolus over 1-3 days with maximum life-time dose at 450 mg/m^2.

Gemcitabine:
Gemcitabine is a nucleoside analogue that is FDA approved for several malignancies including but not limited to lung cancer, breast cancer, pancreas/biliary tumors and sarcomas. Gemcitabine is a pyrimidine antimetabolite.[20] It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and blocking the progression through the Gl/S-phase boundary. The cytotoxic effect of gemcitabine is attributed to a combination of two actions, as follows. First, gemcitabine disphosphate inhibits ribonuclease reductase, which is responsible for catalyzing the reactions that generate deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme causes a reduction in the concentrations of deoxynucleotides, including dCTP. Secondly, gemcitabine triphosphate competes with dCTP for incorporation into DNA. Reduction in the intracellular concentration of dCTP by the diphosphate enhances incorporation of gemcitabine triphosphate into DNA. After the gemcitabine nucleotide is incorporated into DNA only one additional nucleotide is added to the growing DNA strands and there is inhibition of further DNA synthesis. Gemcitabine induces intranucleosomal DNA fragmentation characteristic of programmed cell death.

The use of Gemcitabine in patients with locally advanced or metastatic sarcoma, either as a single agent or in combination with other cytotoxic agents, has been evaluated in several clinical trials. A seminal study performed at MD Anderson showed that intracellular accumulation of gemcitabine triphosphate is saturated at plasma gemcitabine levels of 10-25 uM.[21] Cytotoxic activity was thought to be more active with longer exposure to drug, which maximizes the intracellular accumulation of gemcitabine. This hypothesis was tested in pancreatic cancer, where subjects were randomized to receive gemcitabine at 10 mg/m2/min vs. a 30 minute bolus.[22] The infusional treatment arm had a median survival time of 8 months versus 5 months in the control arm (p=.013). Dr. Shreyas Patel further evaluated infusional gemcitabine in patients with advanced soft tissue sarcomas in a phase II study where patients received two

different dose rates.[23] 56 patients received gemcitabine at 1g/m2 over 30 minutes. 9 patients received standard bolus dosing in week 1 and infusional dosing over 150 minutes on week 2 to evaluate GTP levels in PBMCs. A 1.4 fold increase in the concentration of GTP was seen in the infusional treatment arm. Several other phase II and retrospective studies have also demonstrated safety and efficacy of infusional gemcitabine, including a SARC study that tested infusional gemcitabine as a single agent (1200 mg/m2 over 120 min) versus in combination with docetaxel (gemcitabine infused at 900 mg/m2 over 90 minutes).[24]

Myelosuppression (anemia, leucopenia, neutropenia) is the dose-limiting toxicity associated with Gemcitabine. Common toxicities include nausea and vomiting usually of mild to moderate severity, transient elevations of serum transaminases (serious hepatotoxicty including liver failure and death have been reported rarely in patients receiving Gemcitabine alone or in combination with other potentially hepatotoxic drugs), fever, and rash. A comprehensive review of gemcitabine therapy in metastatic sarcoma can be seen at Maki et al.[25]
In sarcomas, gemcitabine is most active in combination with docetaxel, dacarbazine and vinorelbine.[14-17] Institutional dosing standards vary by regimen from 800 mg/m^2 to 1000 mg/m^2 administered by weekly bolus (e.g. days 1 and 8 of a 21 day cycle).

2.4 Rationale

The sarcomas are a heterogenous group of malignancies encompassing almost 50 different subtypes of cancer. Despite advances in surgical and radiation techniques, when sarcomas recur or metastasize, they are almost universally lethal. Single agent or combination chemotherapy regimens, that are doxorubicin or gemcitabine-based, are the standard of care for STS. However, response rates are consistently less than 50% and median progression-free and overall survival remain poor at 3 and 12 months, respectively, and as such, novel therapies for sarcomas are needed. PM01183 (*Lurbinectedin*), is a synthetically derived novel chemical entity that induces double-strand DNA breaks through binding to the DNA minor grove. Though PM01183 is an analogue of trabectedin in certain aspects, novel structural features have improved its toxicity profile, potency and pharmacokinetics such that ~4-fold higher doses and ~15-fold higher plasma exposure are achieved relative to trabectedin. Additionally, PM01183 can be administered as a one-hour outpatient infusion and appears to have less risk of increasing serum transaminase levels. Recent phase I and II data of PM01183 either alone or in combination with doxorubicin or gemcitabine chemotherapy have shown promising early clinical activity and excellent clinical tolerability. The potential activity of PM01183 in sarcomas remains poorly defined, but very early and limited experience suggests clinical activity. Given the advantages of the easier dosing administration and the early activity signals, we believe this agent warrants further investigation as efficiently as possible in sarcoma patients.

3. PARTICIPANT SELECTION

Laboratory tests required for eligibility must be completed within 15 days prior to day 1 of treatment. Baseline measurements must be documented from tests within 15 days of day 1 of treatment. Diagnostic tests, such as MRIs and CT scans, must be performed within 30 days of day 1 of treatment.

3.1 Eligibility Criteria

3.1.1 Participants must have pathologically confirmed soft-tissue sarcoma, which is metastatic or unresectable, sarcoma with no curative multimodality options (pathology review required for patients with pathology not previously reviewed at DFCI, BWH or MGH)

3.1.2 Participants must have measurable disease by RECIST 1.1. See Section 11 for the evaluation of measurable disease.

3.1.3 No more than two prior lines of chemotherapy for metastatic sarcoma are allowed; Neo-adjuvant/adjuvant chemotherapy with definitive therapy (radiation, surgery or radiation and surgery) will not be counted as one of these prior lines of therapy. Non-cytotoxic therapies will not be counted as one of these prior lines of therapy.

3.1.4 Age $\geq$ 18 and $\leq$ 75 years.

3.1.5 ECOG performance status $\leq$1 (see Appendix A)

3.1.6 Life expectancy of greater than 3 months

3.1.7 Participants must have normal organ and marrow function as defined below:

– Hemoglobin	$\geq$ 9 g/dl
– absolute neutrophil count	$\geq$ 1,500/mcL
– platelets	$\geq$ 100,000/mcL
– total bilirubin	$\leq$ 1.5 X ULN
– AST(SGOT)/ALT(SGPT)	$\leq$3 X ULN (including patients with liver metastases)
– creatinine	$\leq$1.5 X ULN
– CPK	< 2.5 X ULN
– Albumin	$\geq$ 3 g/dl

3.1.8 Women of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to receiving study agents.

3.1.9 For patients in stratum A, an ECHO or MUGA demonstrating EF > 50% is required within 28 days prior to study drug administration.

3.1.10 Participants must be willing and able to comply with the study scheduled visits, laboratory tests, and other procedures outlined in the protocol.

3.1.11 Pre-menopausal women must have a negative pregnancy test before study entry. Both women and men must agree to use a medically acceptable method of contraception throughout the treatment period and for at least six weeks after treatment discontinuation. Acceptable methods of contraception include intrauterine device (IUD), oral contraceptive, subdermal implant, double barrier and/or complete abstinence (non-periodic).

3.1.12 Washout period prior to Day 1 Cycle 1:

- ≥ 3 weeks since last chemotherapy or therapeutic radiation therapy
- ≥ 4 weeks or 3 half-lives since prior antibody-based therapy, whichever is shorter
- ≥ 2 weeks since any oral anti-neoplastic or oral investigational agent
- Resolution of treatment-related toxicity to ≤ grade 1; alopecia and cutaneous toxicity are allowed ≤ grade 2.
- ≥1 week since palliative RT

3.1.13 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Prior exposure to PM01183

3.2.2 Patients who have received trabectedin (Yondelis, ET-743) or participated in the phase III clinical study of trabectedin NCT01343277 previously will not be eligible.

3.2.3 For stratum A, patients must not have received prior anthracycline-based therapy (prior treatment with non-anthracyclines is permitted).

3.2.4 For stratum B patients must have received prior anthracycline-based therapy (or have a contraindication to receiving this treatment) and must not have received prior gemcitabine

3.2.5 For stratum C, patients must have received prior anthracycline (or have a contraindication to anthracycline) AND gemcitabine-based therapy (or have a contraindication to gemcitabine).

3.2.6 Prior radiation treatment of >45 Gy to the pelvis

3.2.7 Previously untreated Ewing Sarcoma and rhabdomyosarcoma

3.2.8 Non-soft tissue sarcomas, such as osteosarcoma and chondrosarcoma are excluded

3.2.9 Participants who are receiving any other investigational agents.

3.2.10 Active hepatopathy of any origin including active hepatitis B and hepatitis C

3.2.11 Participants with known uncontrolled brain metastases will be excluded from this clinical.

3.2.12 History of allergic reactions attributed to compounds of similar chemical or biologic composition to PM01183 or trabectedin (Yondelis, ET-743).

3.2.13 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, chronic indwelling drains, history of interstitial pneumonitis or pulmonary fibrosis or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.14 Actively breastfeeding women unless it is interrupted during treatment and at least 6 weeks after treatment discontinuation.

3.2.15 Known myopathy or persistent CPK elevations >2.5 ULN in two different determinations performed one week apart.

3.2.16 Immunocompromised patients, including those with HIV.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the QACT protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Notify the QACT Registrar of registration cancellations as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin protocol therapy during off-hours or holidays, call the QACT registration line at [redacted] and follow the instructions for registering participants after hours.

The registration procedures are as follows:

- Obtain written informed consent from the participant prior to the performance of any protocol specific procedures or assessments.

- Complete the QACT protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. **To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.**

- Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at [redacted] For Phase I protocols, attach participant dose level assignment confirmation from the sponsor.

- The QACT Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable.

- An email confirmation of the registration and/or randomization will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

5. TREATMENT PLAN

5.1 Treatment Regimen

Stratum A: (Anthracycline-naïve patients, unless a contraindication to doxorubicin exists)

- **Cycles 1-6:** Doxorubicin followed by PM01183 will be administered on an outpatient basis on day 1 of a 21-day cycle.

  Treatment will continue for a total of 6 cycles unless PD or unacceptable toxicity.

- **Cycles 7 and beyond**; patients who exhibit disease control or response after 6 cycles may continue on PM01183 single-agent on day 1 of a 21-day cycle

Stratum B: (Patients with prior anthracycline treatment or contraindication, but with no prior treatment with gemcitabine)

- Gemcitabine followed by PM01183 will be administered on an outpatient basis on day 1 and gemcitabine followed by PM01183 will be administered 8 of a 21-day cycle.

Stratum C: (Patients who have received both prior anthracycline and prior gemcitabine, unless a contraindication to either anthracyclines or gemcitabine exists, as outlined in the inclusion/exclusion criteria in sections 3.1/3.2)

- PM01183 as a single agent will be administered on an outpatient basis on day 1 of a 21-day cycle.

Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Prophylactic GCSF will be administered according to the guidelines in section 6.4 . Dosing and formulation will be per institution standard.

Body surface area (BSA) will be calculated using the Dubois formula on day 1 of each cycle or per institution standard of care.

5.2 Pre-Treatment Criteria

Prior to any study related testing, patients will sign the informed consent form and undergo medical evaluation to establish their baseline condition and determine eligibility. The following studies will be obtained within 30 days of enrollment for the purpose of baseline assessment:

Complete medical history and physical examination including:

- Complete medical history
- Documentation status of disease
- Documentation of prior therapies
- Documentation of current medications
- Complete physical examination, including vital signs and assessment of ECOG performance status
- Pre-existing conditions will be assessed and evaluated according to the NCI CTCAE v4.03 to establish the patient's baseline condition

Disease-Specific Laboratory Tests- Pathology and Tumor Imaging

- Confirm institutional review of diagnostic pathologic material
- Baseline tumor imaging studies will be either CT or MRI. The modality chosen for any individual patient will be the same throughout the duration of the study.

The following screening tests will be performed within 15 days prior to Day 1 of treatment:

- CBC with differential
- Chemistries: sodium, potassium, glucose, creatinine, total bilirubin, alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea or blood urea nitrogen [BUN], total protein, albumin, CPK
- INR and APTT
- LDH
- Urinalysis
- Urine or serum pregnancy test (for premenopausal women)
- ECG if clinically indicated

For Stratum A a pre-treatment echocardiogram or MUGA must be completed within 28 days prior to day 1.

5.2.1 Stratum A: PM01183 and Doxorubicin

Cycle 1, Day 1:
Patients who have signed the informed consent form, completed the screening process, and met

the criteria for enrollment will be entered into the trial and assigned an identification number. In addition the following will be performed:

- Certification that patient meets all inclusion and exclusion criteria and is able to comply with all requirements of the clinical trial
- Review concomitant medications since screening
- Perform physical examination with vital signs (temperature, heart rate, blood pressure, oxygen saturation, respiratory rate, height and weight) and ECOG performance status
- Laboratory testing – to be done if screening labs were done more than 7 days prior to Day 1. Patient will wait for the lab results on this day to re-confirm lab parameters for eligibility.
    - CBC with differential
    - Chemistries: sodium, potassium, calcium, phosphorus, glucose, creatinine, total bilirubin, alkaline phosphatase, AST, ALT, BUN, total protein, albumin, CPK, LDH
    - Urine or serum pregnancy test (for premenopausal women) if not performed within 7 days of cycle 1 day 1
- Treatment: Doxorubicin 50 mg/m^2 followed by PM01183 2 mg/m^2

Cycles 2-6, Day 1:

- Please see section 6 for Criteria for Treatment Continuation and dosing delays/modifications.
- Review concomitant medications
- Perform physical examination with vital signs (temperature, heart rate, blood pressure, oxygen saturation, respiratory rate, height and weight) and ECOG performance status
- Laboratory testing
    - CBC with differential
    - Chemistries: sodium, potassium, calcium, phosphorus, glucose, creatinine, total bilirubin, alkaline phosphatase, AST, ALT, BUN, total protein, albumin, CPK, LDH
- Treatment: Doxorubicin 50 mg/m^2 followed by PM01183 2 mg/m^2

Cycles 7 and subsequent, Day 1:

- Please see section 6 for Criteria for Treatment Continuation and dosing delays/modifications.
- Review concomitant medications
- Perform physical examination with vital signs (temperature, heart rate, blood pressure, oxygen saturation, respiratory rate, height and weight) and ECOG performance status
- Laboratory testing
    - CBC with differential
    - Chemistries: sodium, potassium, calcium, phosphorus, glucose, creatinine, total bilirubin, alkaline phosphatase, AST, ALT, BUN, total protein, albumin, CPK, LDH
- Treatment:
    - PM01183:

- 3.2 mg/m^2

5.2.2 Stratum B: PM01183 and Gemcitabine

Cycle 1 Day 1

Patients who have signed the informed consent form, completed the screening process, and met the criteria for enrollment will be entered into the trial and assigned an identification number. In addition the following will be performed:

- Certification that patient meets all inclusion and exclusion criteria and is able to comply with all requirements of the clinical trial
- Review concomitant medications since screening
- Perform physical examination with vital signs (temperature, heart rate, blood pressure, oxygen saturation, respiratory rate, height and weight) and ECOG performance status
- Laboratory testing – to be done if screening labs were done more than 7 days prior to Day 1. Patient will wait for the lab results on this day to re-confirm lab parameters for eligibility.
    - CBC with differential
    - Chemistries: sodium, potassium, calcium, phosphorus, glucose, creatinine, total bilirubin, alkaline phosphatase, AST, ALT, BUN, total protein, albumin, CPK, LDH
    - Urine or serum pregnancy test (for premenopausal women) if not performed within 7 days of cycle 1 day 1
- Treatment: Gemcitabine 800 mg/m^2 followed by PM01183 1.6 mg/m^2

Cycle 1 Day 8:

- Please see section 6 for Criteria for Treatment Continuation and dosing delays/modifications.
- Review concomitant medications
- Perform physical examination with vital signs (temperature, heart rate, blood pressure, oxygen saturation, respiratory rate, height and weight) and ECOG performance status
- Laboratory testing
    - CBC with differential
    - Chemistries: sodium, potassium, calcium, phosphorus, glucose, creatinine, total bilirubin, alkaline phosphatase, AST, ALT, BUN, total protein, albumin, CPK, LDH
- Treatment: Gemcitabine 800 mg/m^2 followed by PM01183 1.6 mg/m^2

Subsequent cycles, Day 1

- Please see section 6 for Criteria for Treatment Continuation and dosing delays/modifications.
- Review concomitant medications
- Perform physical examination with vital signs (temperature, heart rate, blood pressure, oxygen saturation, respiratory rate, height and weight) and ECOG performance status
- Laboratory testing

  - CBC with differential
  - Chemistries: sodium, potassium, calcium, phosphorus, glucose, creatinine, total bilirubin, alkaline phosphatase, AST, ALT, BUN, total protein, albumin, CPK, LDH
- Treatment: Gemcitabine 800 mg/m^2 followed by 1.6 mg/m^2

Subsequent cycles, Day 8:

- Please see section 6 for Criteria for Treatment Continuation and dosing delays/modifications.
- Review concomitant medications
- Perform physical examination with vital signs (temperature, heart rate, blood pressure, oxygen saturation, respiratory rate, height and weight) and ECOG performance status
- Laboratory testing
  - CBC with differential
  - Chemistries: sodium, potassium, calcium, phosphorus, glucose, creatinine, total bilirubin, alkaline phosphatase, AST, ALT, BUN, total protein, albumin, CPK, LDH
- Treatment: Gemcitabine 800 mg/m^2 followed by PM01183 1.6 mg/m^2

Subsequent cycles, Day 1, if gemcitabine is discontinued:

- If gemcitabine is discontinued for gemcitabine-related toxicity the patient may continue PM01183 Monotherapy provided they meet criteria for treatment continuation and dosing delays/modification rules.
- Treatment of PM01183 will follow the *Subsequent Cycle Day 1* guidelines for Stratum C PMO1183 Monotherapy in section 5.2.3

5.2.3 Stratum C: PM01183 Monotherapy

Cycle 1 Day 1

Patients who have signed the informed consent form, completed the screening process, and met the criteria for enrollment will be entered into the trial and assigned an identification number. In addition the following will be performed:

- Certification that patient meets all inclusion and exclusion criteria and is able to comply with all requirements of the clinical trial
- Review concomitant medications since screening
- Perform physical examination with vital signs (temperature, heart rate, blood pressure, oxygen saturation, respiratory rate, height and weight) and ECOG performance status
- Laboratory testing – to be done if screening labs were done more than 7 days prior to Day 1. Patient will wait for the lab results on this day to re-confirm lab parameters for eligibility.
  - CBC with differential
  - Chemistries: sodium, potassium, calcium, glucose, creatinine, total bilirubin, alkaline phosphatase, AST, ALT, BUN, total protein, albumin, CPK, LDH
  - Urine or serum pregnancy test (for premenopausal women) if not performed

within 7 days of cycle 1 day 1

- Treatment: PM01183
  - 3.2 mg/m^2

Subsequent cycles, Day 1

- Please see section 6 for Criteria for Treatment Continuation and dosing delays/modifications.
- Review concomitant medications
- Perform physical examination with vital signs (temperature, heart rate, blood pressure, oxygen saturation, respiratory rate, height and weight) and ECOG performance status
- Laboratory testing
  - CBC with differential
  - Chemistries: sodium, potassium, calcium, glucose, creatinine, total bilirubin, alkaline phosphatase, AST, ALT, BUN, total protein, albumin, CPK, LDH
- Treatment:
  - PM01183
    - 3.2 mg/m^2

5.3 Agent Administration

5.3.1 PM01183

PM01183 drug product (DP) is supplied as a lyophilized powder in one strength: 4 mg/vial.

Before use, the 4-mg vial should be reconstituted with 8 ml of water for injection, to give a solution containing 0.5 mg/ml PM01183. For administration to patients as i.v. infusion, reconstituted vials should be diluted with glucose 5% solution for infusion or 0.9% NS for infusion. PM01183 should be reconstituted in 100 ml (either 5% glucose or 0.9% sodium chloride) for infusion through a central catheter or a minimum volume of 250 ml if through a peripheral line. Infusion should be given at a fixed infusion rate over at least 60-minutes.

The full composition of the PM01183 vials and the reconstituted solution per ml is as follows:

Component	PM01183 4 mg	Concentration per vial after reconstitution
PM01183	4.00 mg	0.50 mg/ml
Sucrose	800 mg	100 mg/ml
Lactic acid	22.08 mg	2.76 mg/ml
Sodium hydroxide	5.12 mg	0.64 mg/ml

Dosing will be capped at 2 m^2.

5.3.2 Doxorubicin

Doxorubicin will be administered slowly by push/infusion over 5 to 30 minutes into the tubing of a freely running IV infusion (0.9% normal saline or 5% dextrose), or per institutional guidelines.

Unless otherwise specified by institution standard of care, dosing by mg/m^2 should be re-calculated on day 1 of each scheduled doxorubicin push/infusion.

Dosing will be capped at 2 m^2.

Care is to be taken when administering doxorubicin due to its strong vesicant properties. The use of veins over joints, or in extremities with compromised venous and/or lymphatic drainage must be avoided, and use of a central venous catheter is recommended in subjects with difficult venous access. Doxorubicin must not be mixed with other drugs, or with heparin. Doxorubicin must be protected from sunlight (normal room light allowed).

In case of suspected extravasation, the infusion must be stopped and immediate measures must be taken according to institutional guidelines. Tissue necrosis resulting from extravasation may occur days to weeks after the incident. Subjects must be observed for delayed reactions, and prior injection sites carefully inspected. In severe cases, a plastic surgeon may be consulted. Erythematous streaking (a histamine release phenomenon) along the vein proximal to the injection site must be differentiated from an extravasation event. This "doxorubicin flare" reaction usually subsides within 30 minutes. The injection may be continued at a slower pace in the same site, or it may be changed to another site. Administration of diphenhydramine 25-50 mg IV and hydrocortisone 100 mg IV into the same IV line may accelerate clearing of the reaction.

5.3.3 Gemcitabine

Gemcitabine will be given via IV at a fixed rate of approximately 10 mg/m^2/min.

Unless otherwise specified by institution standard of care, dosing by mg/m^2 should be re-calculated on day 1 and day 8 of each scheduled gemcitabine treatment.

Dosing will be capped at 2 m^2.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Prophylactic Medication

Patients must receive standard antiemetic prophylactic medications at least 30 minutes before administration of PM01183 as follows:

- Corticosteroid (dexamethasone IV/po or equivalent as per institutional standards)
- Serotonin (5-HT3) antagonists
    - Stratum A: ondansetron 16 mg IV/po or equivalent
    - Stratum B and C: ondansetron 8 mg IV/po or equivalent
- If necessary extended dosing or additional antiemetics are allowed
- Aprepitant and fosaprepitant are prohibited
- Secondary prophylaxis GCSF is only allowed according to the guidelines in

section 6.4.

5.4.2 Allowed Medications/Therapies

Any medications, with the exceptions noted below, which are considered necessary for the patient's welfare, and which are not known to interact with the study medication, may be given at the discretion of the Investigator, providing the medications, the doses, dates and reasons for administration are recorded in the eCRF.

In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded in the eCRF.

All medications (prescriptions or over-the-counter medications) continued at the start of the trial or started during the study or until 30 days from the end of the last protocol treatment and different from the study medication must be documented.

Contraception
Patients of child bearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception throughout their participation in the study and for 3 months after last dose of study drug(s).

- Condom with spermicide and one of the following:
- Oral contraceptive or hormonal therapy (e.g. hormone implants)
- Placement of an intra-uterine device

Acceptable non-hormonal birth control methods include:

- Total sexual abstinence. Abstinence must be for the total duration of the study and the drug washout period.
- Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia
- Tubal occlusion plus male condom with spermicide
- Intrauterine Device (IUD) plus male condom+spermicide. Provided coils are copper-banded

Acceptable hormonal methods:

- Etonogestrel implants (eg, Implanon, Norplan)+male condom with spermicide
- Normal and low dose combined oral pills+male condom with spermicide
- Norelgestromin/ethinyl estradiol (EE) transdermal system+male condom with spermicide
- Intravaginal device+male condom with spermicide (eg, EE and etonogestrel)
- Cerazette (desogestrel)+male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill.

5.4.3 Prohibited Medications/Therapies

Because there is a potential for interaction of PM01183 with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use

of all other drugs, over-the-counter medications, or alternative therapies. The Overall PI should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes (notably CYP2C8 and CYP3A4). Appendix B presents guidelines for identifying medications/substances that could potentially interact with the study agent(s).

Aprepitant and related compounds are prohibited.

The plasma protein binding of PM01183 ranged from 88-98% in all species tested. In humans, 97% of PM01183 was bound to plasma proteins independent of drug concentration. There for caution is recommended when concomitant medications known to be highly protein-bound are administered with PM01183.

Palliative radiation will be permitted after cycle 2 only for localized pain control and not due to unequivocal radiological or clinically progressive disease. Study drug, doxorubicin and gemcitabine should be temporarily held during this period. Dosing should resume with the next scheduled cycle that is at least 7 days after radiation is complete.

Administration of other anti-cancer agents
Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment. Full details of all of these treatments are recorded in the patient's notes and appropriate section of the eCRF

5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s) despite dose-reduction.
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

A QACT Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the QACT website or obtained from the QACT registration staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Gregory M. Cote MD PhD at [redacted].

5.6 Duration of Follow Up

Participants will be followed every 6 months +/- 1 month after removal from protocol therapy until death for overall survival for 2 years after discontinuing study drug(s). This may include office visits or phone call inquiries if the patient is not available. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event and/or death.

5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

A QACT Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the QACT website or obtained from the QACT registration staff.

6. CRITERIA FOR TREATMENT CONTINUATION AND DOSING DELAYS/DOSE MODIFICATIONS

Criteria for treatment continuation and dose delays and modifications will be made as indicated in the following table(s). Dosing can be reduced based on the clinical judgment of the treating investigator if it is thought to be in the interest of the patient.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.03 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

6.1 Stratum A Day 1(cycles 2-6) and Stratum B Day 1 (cycle 2 and beyond): Criteria for Treatment Continuation

- ECOG — PS $\leq$ 1
- absolute neutrophil count — $\geq$ 1,500/mcL
- Hb — $\geq$ 9 g/dL (transfusion is permitted)
- platelets — $\geq$ 100,000/mcL (transfusion is not permitted)
- total bilirubin — $\leq$ 1.5X ULN

- AST/ALT ≤ 3 X institutional upper limit of normal
- Albumin ≥ 3.0 g/dl
- creatinine ≤ 1.5X ULN
- CPK ≤ Grade 1
- Other non-hematologic, clinically significant, drug-related AE's ≤ Grade 1
- If the above criteria are not met on day 1 of any following treatment cycle, regardless of the reason, re-assessment for treatment continuation eligibility will be performed every 48-72 hours at the discretion of the treating investigator. Treatment will be delayed up to a maximum of three weeks beyond its due date until appropriate recovery. Patients not meeting re-treatment criteria after a maximum of three-week delay will be withdrawn from the study. Exceptions are permitted in the case of objective clinical benefit upon the agreement of the overall PI.
- See section 6.4 Table 1 for dose modification for hematologic and non-hematologic toxicities.
- Delays for non-clinical reasons OR not clinically significant AEs which are unrelated or unlikely related, will be permitted upon agreement with the overall PI.

6.2 Stratum B Day 8 (Cycle 1 and subsequent cycles): Criteria for Treatment Continuation,

- ECOG PS ≤ 2
- absolute neutrophil count ≥ 1,000/mcL
- Hb ≥ 8 g/dL (transfusion is permitted)
- platelets ≥ 75,000/mcL (transfusion is not permitted)
- total bilirubin ≤ 1.5X ULN
- AST/ALT ≤ 5 X institutional upper limit of normal (≤grade 2 by CTCAE4)
- creatinine ≤ 1.5X ULN
- Albumin ≥ 3.0 g/dl
- CPK ≤ Grade 1
- Other non-hematologic, clinically significant, drug-related AE's ≤ Grade 2
- If the above criteria are not met on day 8, the patient should be reassessed for eligibility within 72 hours. If at this point the patient still does not meet treatment criteria, regardless of the reason, the patient will not receive the day 8 infusion and resume treatment with dose reduction on schedule for the subsequent cycle day 1 provided treatment criteria in section 6.1 are met. Day 8 treatment delays will not change the next cycle day 1 schedule, provided the treatment criteria in section 6.1 are met.
- See section 6.4 Table 1 for dose modification for hematologic and non-hematologic toxicities.
- Delays for non-clinical reasons OR not clinically significant AEs which are unrelated or unlikely related, will be permitted upon agreement with the overall PI.

6.3 Stratum C, or Strata A and B if on PM01183 Monotherapy at any point, Day 1: Criteria for Treatment Continuation

- ECOG PS ≤ 1
- absolute neutrophil count ≥ 1,500/mcL
- Hb ≥ 9 g/dL (transfusion is permitted)

- platelets ≥ 100,000/mcL (transfusion is not permitted)
- total bilirubin ≤ 1.5X ULN
- AST/ALT ≤ 3 X institutional upper limit of normal
- creatinine ≤ 1.5X ULN
- Albumin ≥ 3.0 g/dl
- CPK ≤ Grade 1
- Other non-hematologic, clinically significant, drug-related AE's ≤ Grade 2
- If the above criteria are not met on day 1 of any following treatment cycle, regardless of the reason, re-assessment for treatment continuation eligibility will be performed every 48-72 hours at the discretion of the treating investigator. Treatment will be delayed up to a maximum of three weeks beyond its due date until appropriate recovery. Patients not meeting re-treatment criteria after a maximum of three-week delay will be withdrawn from the study. Exceptions are permitted in the case of objective clinical benefit upon the agreement of the overall PI.
- See section 6.4 Table 1 for dose modification for hematologic and non-hematologic.
- Delays for non-clinical reasons OR not clinically significant AEs which are unrelated or unlikely related, will be permitted upon agreement with the overall PI.

6.4 Dose Modification

Non-hematologic toxicities:

- For any cycle day 1 delay lasting more than one week, or strata B day 8 delay lasting more than 72 hours, due to treatment-related toxicity dose reduction must be implemented according to the strategy below in Table 1.
- For any treatment-related, clinical significant, non-hematologic grade ≥3 toxicity, dose reduction must be implemented according to the strategy in Table 1.

Hematologic toxicities:

- For any cycle day 1 delay lasting more than one week, or stratum B day 8 delay lasting more than 72 hours, due to a treatment-related hematologic toxicity, dose reduction must be implemented
- Neutropenia:
  - Asymptomatic grade 4 neutropenia: the investigator may either add GCSF prophylaxis per institution standards or dose-reduce according to Table 1.
  - Febrile Neutropenia: requires dose reduction according to Table 1 and at the investigator's discretion GCSF prophylaxis may be added
- Other treatment-related, clinically significant, Grade 4 hematologic toxicities or Grade 3 thrombocytopenia with clinically significant bleeding:
  - Dose reduction is required according to Table 1

TABLE 1. Dose Modification Guidelines

	PM01183	PM01183 and Doxorubicin		PM01183 and Gemcitabine	
		PM01183	Doxorubicin	PM01183	Gemcitabine
Initial Dose	3.2 mg/m²	2 mg/m²	50 mg/m²	1.6 mg/m²	800 mg/m²
1st Dose Reduction	2.6 mg/m²	2 mg/m²	40 mg/m²	1 mg/m²	800 mg/m²
2nd Dose Reduction	2 mg/m²	1.25 mg/m²	40 mg/m²	1 mg/m²	600 mg/m²

- Two dose reductions are allowed per patient for the duration of treatment
- No dose escalations are allowed
- If in Strata A or B a participant develops a specific toxicity or intolerance felt to be related to doxorubicin or to gemcitabine, the participant may continue on single agent PM01183, provided other treatment criteria are met. Criteria for Treatment Continuation in these patients should subsequently be followed according to Stratum C. The patient should receive the Stratum C PM01183 dose level that correlates with the previous dose level of Strata A or B. For example if the participant completes 6 cycles of doxorubicin at the 1st dose reduction level or stops doxorubicin at the 1st dose reduction level they should start PM01183 monotherapy at the 1st dose reduction level of Stratum C (e.g 2.6 mg/m^2)
- Treatment delay is permitted up to a maximum of three weeks beyond its due date until appropriate recovery of AE's listed in sections 6.1, 6.2 and 6.3. Patients not meeting re-treatment criteria after a maximum of three-week delay will be withdrawn from the study. Exceptions are permitted in the case of objective clinical benefit upon the agreement of the overall PI.
- Delays for non-clinical reasons OR not clinically significant AEs which are unrelated or unlikely related, will be permitted upon agreement with the overall PI.

7. ADVERSE EVENTS REPORTING REQUIREMENTS:

7.1 Definitions

7.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign, (e.g., an abnormal laboratory finding), or a disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Illnesses with onset during the study or exacerbations of pre-existing illnesses, including but not

limited to clinically significant changes in physical examination findings and abnormal objective tests/procedures findings (e.g., X-ray, ECG) should be recorded. The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- The test result is associated with clinically significant symptoms, and/or
- The test result leads to a change in the study dosing or discontinuation from the clinical trial, significant additional concomitant drug treatment or other therapy, and/or
- The test result leads to any of the outcomes included in the definition of a SAE (see definition below), and/or
- The test result is considered to be clinically relevant by the Investigator.

"Disease progression" will not be reported as an AE, as this information will be used for efficacy assessment.

7.1.2 Serious Adverse Event (SAE)

A SAE is any adverse experience occurring at any dose that:

- Results in death (is fatal),
- Is life-threatening,
- Requires or prolongs inpatient hospitalization,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly or birth defect,
- Is medically significant, or
- Is any suspected transmission of an infectious agent via a medicinal product.

Medical and scientific judgment should be exercised in deciding medically significant events; this criterion should be applied to AEs that may not be immediately life-threatening or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the above definition.
"Disease progression" as a term will not be reported as a SAE.

7.1.3 Death

Death as such is the outcome of a SAE and should not be used as the SAE term itself. The cause of death should be recorded as the SAE term instead. When available, the autopsy report will be provided to the Sponsor.
Grade 5 should be used for events which lead immediately and directly to death, and grade 4 should be used with outcome death for events which lead to death after a longer time period, and that may also be linked to additional morbidities.

7.1.4 Life-threatening Event

Any event in which the patient was at risk of death at the time of the event is considered life-threatening; it does not refer to an event which hypothetically might have caused death if it were more severe.

7.1.5 Hospitalization or Prolongation of Hospitalization

Any AE requiring hospitalization (or prolongation of hospitalization) that occurs or worsens during the course of a patient's participation in a clinical trial must be reported as a SAE unless exempted from SAE reporting. Prolongation of hospitalization is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required for the initial admission, as determined by the Investigator or treating physician.

Hospitalizations that do not meet criteria for SAE reporting are:

a. Reasons described in protocol [e.g., investigational medicinal product (IMP) administration, protocol-required intervention/investigations, etc.]. However, events requiring hospitalizations or prolongation of hospitalization as a result of a complication of therapy administration or clinical trial procedures will be reported as SAEs.
b. Hospitalization or prolonged hospitalization for technical, practical or social reasons, in absence of an AE.
c. Pre-planned hospitalizations: any pre-planned surgery or procedure must be documented in the source documentation. Only if the pre-planned surgery needs to be performed earlier due to a worsening of the condition, should this event (worsened condition) be reported as a SAE.

Other situations that MUST NOT be considered as hospitalizations are the following:

d. An emergency visit due to an accident where the patient is treated and discharged.
e. When the patient is held 24 hours for observation and finally is not admitted.
f. Planned treatments at sites not associated to a hospital and generally considered as minor surgical procedures (i.e., laser eye surgery, arthroscopy, etc.).

7.1.6 Unlisted/Unexpected Adverse Event

An AE, the nature or severity of which is not consistent with the applicable reference safety information.
The Sponsor and the Sponsor designee will use as the reference safety information for the evaluation of listedness/expectedness the IB for lurbinectedin (PM01183) and the Summary of Product Characteristics (SmPC) for doxorubicin and gemcitabine as described in the FDA package insert.

7.1.7 Adverse Reactions

All untoward and unintended responses to an investigational medicinal product related to any dose administered. This definition covers also medication errors and uses outside what is foreseen in the protocol, including overdose, lack of efficacy, misuse and abuse of the product.

7.1.8 Adverse Events Related to the Study Drug

An AE is considered related to a study drug/IMP if the Investigator's assessment of causal relationship to the IMP(s) is "Y (yes)" (see Section 7.1.10).

The Investigator will assess the causal relationship of the IMP(s) to the SAE.

The Sponsor may also consider related to the study drug(s)/IMP(s) those events for which the Investigator assesses the causal relationship with the IMP(s) as "Uk (unknown)" when it cannot rule out a role of the IMP(s) in the event.

7.1.9 Expedited Reporting

The Sponsor is responsible for the appropriate expedited reporting according to the applicable legislation.

7.1.10 Assessment of Causal Relationship to the Study Drug

The Investigator must provide an assessment of the causal relationship of each SAE to the clinical trial IMP(s) according to the following scale:

Y There is a reasonable possibility that the IMP(s) caused the SAE.

N There is no reasonable possibility that the IMP(s) caused the SAE and other causes are more probable.

Uk (Unknown). Only to be used in special situations where the Investigator has insufficient information (i.e., the patient was not seen at his/her center) if none of the above can be used.

7.2 Adverse Events Reporting Procedures

7.2.1 Reporting Adverse Events

The Sponsor will collect AEs until 30 days after administration of the last dose of study drug(s)/IMP(s) or until the start of a new antitumor therapy or until the date of death, whichever occurs first. All AEs suspected to be related to the study drug/IMP must be followed-up after the time of therapy discontinuation until the event or its sequelae resolve or stabilize at an acceptable level to the Investigator and the Sponsor.

All AEs, including misuse, overdose and abuse, must be recorded in English using medical terminology in the source document and the CRF. Whenever possible, the Investigator will record the main diagnosis instead of the signs and symptoms normally included in the diagnoses.

Investigators must assess severity (grade) of the event following the NCI-CTCAE v. 4 and assign a relationship to each study drug(s)/IMP(s); and pursue and obtain information adequate both to determine the outcome and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to the Sponsor and the Sponsor designee. The Investigator must provide any relevant information as requested by the Sponsor or the Sponsor designee in addition to that on the CRF.

Abnormal laboratory tests occurring during the study should only be recorded in the AE section of the CRF if the disorder:

- Is associated with clinically significant symptoms, and/or
- Leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or

- Leads to any of the outcomes included in the definition of a SAE.

Otherwise laboratory results should be reported in the corresponding section of the CRF (e.g. biochemistry, hematology).

All episodes of febrile neutropenia must always be reported within 24 hours following the same procedure for reporting SAEs (see Section 7.2.2), including episodes that occurred in patients without seriousness criteria. For these cases, the seriousness criterion should be reported as a medically significant event.

7.2.2 Reporting Serious Adverse Events

The Sponsor will collect SAEs from the time of signing of the informed consent form (ICF) until 30 days after administration of the last dose of study drug(s)/IMP(s) or until the start of a new antitumor therapy or until the date of death, whichever occurs first. Beyond this period of time, only those SAEs suspected to be related to the IMP will be collected. Nonetheless, the Sponsor will evaluate any safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

All SAEs (as defined above) occurred after patient registration regardless of relationship to the study drug(s)/IMP(s) must be reported immediately and always within 24 hours to the Sponsor, and the Sponsor designee, PharmaMar.

SAEs will be reported within 24 hours to the Sponsor Dr. Gregory Cote by email (gcote @mgh.harvard.edu) or telephone [redacted] and the Sponsor designee (PharmaMar) using the paper SAE form by fax [redacted] e-mail [redacted] or telephone [redacted]

The Sponsor will report to the FDA any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment. Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information. All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information. Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800-FDA-0178) using Form FDA 3500A (Mandatory Reporting Form for investigational agents) or FDA Form 3500 (Voluntary Reporting Form for commercial agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

All SAEs suspected to be related to the IMP(s) must be followed until the event or its sequelae resolves or stabilizes at an acceptable level by the Investigator.

7.2.3 Reporting Pregnancy Cases Occurred within the Clinical Trial

National regulations require that clinical trial Sponsors collect information on pregnancies occurring during clinical trials, in which exposure to the IMP(s) at any time during pregnancy, via either maternal or paternal exposure, is suspected.

Therefore, pregnancy and suspected pregnancy (including a positive pregnancy test regardless of age or disease state) of patient occurring while the patient is on study drug, or within 30 days after the administration of the last dose of the study drug(s)/IMP(s), are considered immediately reportable events. Beyond this timeframe, the investigator will report any pregnancy if there is any suspicion that the study drug(s)/IMP(s) might have an impact on the occurrence of the pregnancy.

The Investigator will report the following events immediately and always within 24 hours from first knowledge:

- Any occurrence of a pregnancy where any kind of exposure to the IMP(s) is suspected.
- Possible exposure of a pregnant woman.
- All reports of elevated/questionable or indeterminate beta human chorionic gonadotropins (β-hCGs).

Immediately after detecting a case of suspected pregnancy in a patient, the decision on her continued participation in the clinical trial will be jointly taken by the patient, the Investigator and the Sponsor, with the patient's best interest in mind. A decision to continue the pregnancy will require immediate withdrawal from the trial.

Any pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Sponsor and the Sponsor designee immediately using the Pregnancy Report form.

The Investigator will follow the pregnancy until its outcome, and must notify the Sponsor and the Sponsor designee the outcome of the pregnancy within 24 hours of first knowledge as a follow-up to the initial report.

For any event during the pregnancy which meets a seriousness criterion (including fetal or neonatal death or congenital anomaly) the Investigator will also follow the procedures for reporting SAEs (complete and send the SAE form to the Sponsor and the Sponsor designee within 24 hours of the Investigator's knowledge of the event).

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death at any time thereafter that the Investigator suspects is related to the exposure to the study drug(s)/IMP(s) should also be reported to the Sponsor and the Sponsor designee by facsimile within 24 hours of the Investigators' knowledge of the event.

7.3 Adverse Events Monitoring

Safety review will be performed by the Sponsor designee once SAE forms have been received and the CRFs electronically completed by the Investigator.

At every monitoring visit performed by the designed clinical research monitor in charge of the study, the consistency between the CRF/SAE data reported to the Sponsor / Sponsor designee and the patient's source data will be reviewed. When a discrepancy is found during the review,

data will be amended/updated in the CRF and the SAE form/information reported to the Sponsor and the Sponsor designee (when applicable), according to source data.

SAEs will be continuously collected, assessed and reported throughout all the study as per the applicable legislation by the Sponsor designee. Periodic safety reviews of SAE reports including events of special interest (e.g., neutropenia and thrombocytopenia) are to be conducted and documented by the Sponsor designee.

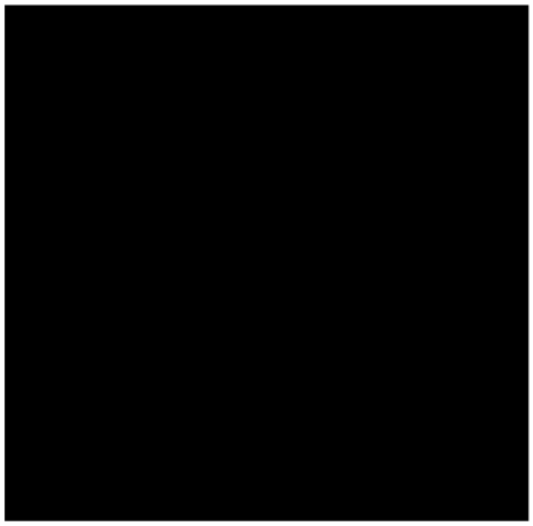
Non-serious AEs will be verified during monitoring visits by the clinical trial monitor, who will discuss them with the Investigators, if applicable. Periodic safety review of safety data from the clinical database, i.e. AEs and laboratory data, will be performed along the study by the Sponsor Pharmacovigilance, Clinical Oncology and Data Management departments.

8. PHARMACEUTICAL INFORMATION

[redacted]

INN	lurbinectedin

Structural Formula



Chirality/Stereochemistry [redacted]

8.1.2 **Form**

PM01183 DP is currently presented as a lyophilized powder for concentrate for solution for infusion in strength of 4 mg/vial.

Before use, the vials are reconstituted with water for injection (2 ml or 8 ml) to give a solution containing 0.5 mg/ml of PM01183. For administration to patients as intravenous infusion, the reconstituted vials are diluted with glucose 5% solution for infusion or 0.9% NS for infusion.

8.1.3 **Storage and Stability**

Until more information is available from on-going stability studies, PM01183 DP 4 mg) should be stored at +5ºC ± 3ºC with a shelf life of 36 months.

8.1.4 **Compatibility**

Reservoirs made of Polyethylene (PE), polyvinylchloride (PVC) and mixtures of polyethylene/polypropylene are compatible with the product and can be used for infusion.

PE, PVC, polyurethane (PU) or polypropylene (PP) infusion lines are recommended.

Implantable reservoirs with plastic (acetal resin) or titanium portals and silicone or polyurethane catheters are also compatible with PM01183.

8.1.5 **Handling**

PM01183 is a cytotoxic anticancer medicinal product, and like other potentially toxic

compounds, caution should be exercised during its handling. Thus, procedures for proper handling and disposal of cytotoxic medicinal products should be followed. Personnel should be trained to reconstitute the drug. Personnel handling this active substance during reconstitution should wear protective clothing including mask, goggles, and gloves.

Accidental contact with the skin, eyes, or mucous membranes should be treated immediately with copious amounts of water. Pregnant staff members should be excluded from working with this drug.

Any unused product or waste materials should be disposed of in accordance with local requirements for high-risk materials.

8.1.6 **Preparation**

8.1.7 **Administration**

PM01183 should be reconstituted in at least 100 ml (either 5% glucose or 0.9% sodium chloride) for infusion through a central catheter or a minimum volume of 250 ml if through a peripheral line. Infusion should be always given at a fixed infusion rate over at least 60-minutes.

8.1.8 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form.

(See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.9 **Destruction and Return**
All unused drug supplied by the PharmaMar will be properly destroyed at the study site. Documentation of this procedure must be provided to PharmaMar by the clinical trial monitor.

8.2 Doxorubicin

8.2.1 Form: Doxorubicin is a commercially available chemotherapy agent.
8.2.2 Storage, dosage form and preparation will be according to institutional standards.

8.3 Gemcitabine

8.3.1 Form: Gemcitabine HCl is a commercially available nucleoside analog that exhibits antitumor activity.
8.3.2 Storage, dosage form and preparation will be according to institutional standards

9. STUDY CALENDAR

Baseline evaluations are to be conducted within 15 days prior to cycle 1 day 1. Baseline CT scans, or MRIs or x-rays must be done $\leq$30 days prior to cycle 1 day 1. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments must be performed prior to administration of any study agent. Study assessments should be within $\pm$3 days of the protocol-specified date, unless otherwise noted. For all strata, day 1 of a given cycle can start -1 to +2 days to allow for scheduling. For Stratum B, Day 8 of a given cycle can start up to +2 days late to allow for scheduling.

Stratum A											
		Cycle 1			Cycles 2-6[f]			Cycles 7 and subsequent cycles[f]			
	Pre-Study[k]	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	Off Study[c]
PM01183		X			X			X			
Doxorubicin		X			X						
Informed consent	X										
Demographics	X										
Medical history	X										
Concurrent meds	X	X----------X									
Physical exam	X	X	X		X	X[i]		X			X
Vital signs[m]	X	X	X		X	X[i]		X			X
Height	X										
Weight	X	X			X			X			X
ECOG Performance status	X	X			X			X			X
CBC w/diff, plts[d]	X	X	X	X	X	X[i]	X[i]	X	X[l]	X[l]	X
Serum chemistry[a, d]	X	X	X		X			X	X[l]		X
Urinalysis	X										
PT, aPTT	X										
ECG (as indicated) [j]	X										
Adverse event evaluation		X----------X									X
Radiologic evaluation[g]	X	Repeated every 6 weeks for the first 8 cycles and then every 9 weeks thereafter. Documentation (radiologic) must be provided for participants removed from study for progressive disease.									
Urine or serum pregnancy testing	X[b]										
Review of Pathology[h]	X										
Echocardiogram or MUGA[j]	X				X			X			X

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, CPK.
b: Serum or urine pregnancy test (women of childbearing potential). Must be repeated if not within 7 days of c1d1.
c: Off-study evaluation to be completed 30 + 7 days from last study drug dose.
d: laboratory testing can be performed up to 48h prior to scheduled visit (excluding screening laboratory testing)
f: day 1 of a given cycle can start -1 to +2 days to allow for scheduling
g: scan window is +/- 7 days
h: only required for patients with pathology not previously reviewed at DFCI, BWH or MGH
i: during the combination of doxorubicin and PM01183 day 8 and day 15 (+/- 3 days) CBC/diff required for cycles 1 and 2, optional thereafter. During the combination of doxorubicin and PM01183 day 8 (+/- 3 days) vital signs and physical exam is required for cycles 1 and 2, optional thereafter. Please see footnote L for PM01183 monotherapy.
j: 28 days window for the echocardiogram or MUGA before treatment day 1; ECG required only as clinically indicated; LV ejection fraction assessment will be repeated before cycle 4 and before cycle 7 and then at end of study

k: screening data to be obtained within 15 days of treatment day 1; baseline radiological evaluations within 30 days of treatment day 1
l: for the first cycle after doxorubicin is discontinued (PM01183 monotherapy) day 8 and day 15 (+/- 3 days) cbc/dif is required and day 8 (+/- 3 days) chemistries are required; these laboratory values are optional for further cycles
m: on days where labs are optional, vital signs are also optional

Stratum B

		Cycle 1			Cycle 2 and subsequent cycles[f]			
	Pre-Study[j]	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	Off Study[c]
PM01183		X	X		X	X		
Gemcitabine		X	X		X	X		
Informed consent	X							
Demographics	X							
Medical history	X							
Concurrent meds	X	X----------X						
Physical exam	X	X	X		X	X		X
Vital signs	X	X	X		X	X		X
Height	X							
Weight	X	X	X		X	X		X
ECOG Performance status	X	X	X		X	X		X
CBC w/diff, plts[d,k]	X	X	X	X	X	X	X[i]	X
Serum chemistry[a,d,k]	X	X	X	X	X	X	X[i]	X
Urinalysis	X							
PT, aPTT	X							
ECG (as indicated)	X							
Adverse event evaluation		X----------X						
Radiologic evaluation[g]	X	Repeated every 6 weeks for the first 8 cycles and then every 9 weeks thereafter. Documentation (radiologic) must be provided for participants removed from study for progressive disease.						
Urine or serum pregnancy testing	X[b]							
Review of Pathology[h]	X							

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, CPK.
b: Serum or urine pregnancy test (women of childbearing potential). Must be repeated if not within 7 days of c1d1.
c: Off-study evaluation to be completed 30 + 7 days from last study drug dose
d: laboratory testing can be performed up to 48h prior to scheduled visit (excluding screening

laboratory testing)
f: day 1 of a given cycle can start -1 to +2 days to allow for scheduling. Day 8 of a given cycle can start up to +2 days late to allow for scheduling.
g: scan window is +/- 7 days
h: only required for patients with pathology not previously reviewed at DFCI, BWH or MGH
i day 15 +/- 3 days blood tests required for cycles 1 and 2, optional thereafter
j: screening data to be obtained within 15 days of treatment day 1; baseline radiological evaluations within 30 days of treatment day 1
k: if gemcitabine is discontinued: for the first cycle after gemcitabine is discontinued (PM01183 monotherapy) day 8 and day 15 (+/- 3 days) cbc/dif is required and day 8 (+/- 3 days) chemistries are required; these laboratory values are optional for further cycles

Stratum C

		Cycle 1			Cycle 2 and subsequent cycles[f]			
	Pre-Study[j]	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	Off Study[e]
PM01183		X			X			
Informed consent	X							
Demographics	X							
Medical history	X							
Concurrent meds	X	X----------X						
Physical exam	X	X	X		X	X[i]		X
Vital signs	X	X	X		X	X[i]		X
Height	X							
Weight	X	X			X			X
ECOG Performance status	X	X			X			X
CBC w/diff, plts[d]	X	X	X	X	X	X[i]	X[i]	X
Serum chemistry[a,d]	X	X	X		X			X
Urinalysis	X							
PT, aPTT	X							
ECG (as indicated)	X							
Adverse event evaluation		X----------X						X
Radiologic evaluation[g]	X	Repeated every 6 weeks for the first 8 cycles and then every 9 weeks thereafter. Documentation (radiologic) must be provided for participants removed from study for progressive disease.						
Urine or serum pregnancy testing	X[b]							
Review of Pathology[h]	X							

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT

[ALT], sodium, CPK.
b: Serum or urine pregnancy test (women of childbearing potential). Must be repeated if not within 7 days of c1d1.
c: Off-study evaluation to be completed 30 + 7 days from last study drug dose.
d: laboratory testing can be performed up to 48h prior to scheduled visit (excluding screening laboratory testing)
f: day 1 of a given cycle can start -1 to +2 days to allow for scheduling
g: scan window is +/- 7 days
h: only required for patients with pathology not previously reviewed at DFCI, BWH or MGH
i: day 8 (+/- 3 days) physical exam and day 8 (+/- 3 days) and 15 (+/- 3 days) CBC/diff required for cycles 1 and 2, optional thereafter.
j: screening data to be obtained within 15 days of treatment day 1; baseline radiological evaluations within 30 days of treatment day 1

10. MEASUREMENT OF EFFECT

10.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 6 weeks for the first 8 cycles and then every 9 weeks thereafter.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

10.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

10.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

10.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

(a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

(b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

MIBG (meta-iodobenzylguanidine).The following is recommended, to assure high quality images are obtained.

Patient preparation: Iodides, usually SSKI (saturated solution of potassium iodide), are administered to reduce thyroidal accumulation of free radioiodine, preferably beginning the day prior to injection and continuing for 3 additional days (4 days total). For infants and children, one drop t.i.d. is sufficient, for adolescents 2 drops t.i.d., and for adults 3 drops t.i.d. Participants and/or parents are asked about exposure to potential interfering agents. If none is noted, an indwelling intravenous line is established. The dose of MIBG is administered by slow intravenous injection over 90 seconds.

Images from the head to the distal lower extremities should be obtained.

I-123MIBG scintigraphy is performed to obtain both planar and tomographic images.

Planar: Anterior and posterior views from the top of the head to the proximal lower extremities are obtained for 10 minutes at 24 hours and occasionally at 48 hours following injection of 10 mCi/1.7 square meters of body surface area (~150 μCi/kg, maximum 10 mCi). Anterior views of the distal lower extremities are adequate. A large field of view dual head gamma camera with low energy collimators is preferred.

SPECT: Most participants receiving I-123 MIBG also undergo SPECT at 24 hours, using a single or multi-headed camera with a low energy collimator. The camera is rotated through 360 degrees, 120 projections at 25 seconds per stop. Data are reconstructed using filtered back projections with a Butterworth filter and a cut off frequency of 0.2-0.5. SPECT/CT may be performed at institutions with this capacity.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later data and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

10.1.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

10.1.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or

unequivocal progression of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

10.1.3.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

10.1.3.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

*	See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
**	Only for non-randomized trials with response as primary endpoint.
***	In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

10.1.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

10.1.5 Progression-Free and Overall Survival

Overall Survival: Overall Survival (OS) is defined as the time from cycle 1 day 1 to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from cycle 1 day 1 to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from cycle 1 day 1 to progression, or censored at date of last disease evaluation for those without progression reported.

11. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

11.1 Data Reporting

11.1.1 Method

The QACT will collect, manage, and perform quality checks on the data for this study.

Note: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS.

11.1.2 Responsibility for Data Submission

Please use the appropriate text below, which can be modified as necessary.

For non-CDUS/CTMS submissions: Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the QACT according to the schedule set by the QACT.

For CDUS and CMTS submissions:

Participant institutions are responsible for submitting CDUS data and/or data forms to either the Coordinating Center or to the Lead Organization on the study quarterly. The date for submission to the Coordinating Center or to the Lead Organization will be set by them. CDUS does not accept data submissions from the participant institutions on the study. When setting the dates, allow time for Coordinating Center compilation, Overall PI review, and timely submission to CTEP by the quarterly deadlines (see Section 12.1.1). For trials monitored by CTMS, a quarterly report of data will be provided by Theradex to the Coordinating Center.

Either the Coordinating Center or the Lead Organization is responsible for compiling and

submitting CDUS data to CTEP for all participant institutions and for providing the data to the Overall PI for review.

11.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12. STATISTICAL CONSIDERATIONS

We have designed an exploratory phase II, three-stratum study for the primary endpoint of DCR greater than 24 weeks. Patients will be stratified among the three strata based upon history of prior therapy. Stratum A will consist of anthracycline-naïve patients and will receive the combination regimen of PM01183 plus doxorubicin (with maintenance of PM001183 if long-term benefit occurs after maximal cumulative doxorubicin is reached). Stratum B will consist of patients with prior anthracycline therapy who are gemcitabine naïve and will receive the combination regiment of PM01183 plus gemcitabine. Stratum C will consist of patients who will receive PM01183 as a single agent. The true disease control rate is defined as achievement of confirmed objective response (complete response or partial response), or stable disease that is confirmed at least 24 weeks from start of study drug administration. Patients without stable disease, disease progression within 24 weeks, deaths within 24 weeks, or without confirmatory scans at 24 weeks post-start of study drug will be counted as failures.

We will enroll 20 evaluable patients by intention to treat in each stratum following a two-stage approach; however, we will enroll patients to the second stage by performing a concurrent interim analysis. Patients who do not receive drug for any reason (e.g. withdrawal of consent) will be replaced.

12.1 Study Design/Endpoints

- Primary Endpoint:
  - The true disease control rate is defined as achievement of confirmed objective response (complete response or partial response), or stable disease that is confirmed at least 24 weeks from start of study drug administration

- Secondary Endpoints:
  - Overall response rate (ORR), progression free survival (*PFS*) at 24 weeks, overall survival (*OS*) at 24 months
  - Toxicity profile of PM01183 alone or with chemotherapy in this patient population

Stratum A (PM01183 plus doxorubicin, followed by PM01183 maintenance)

At the first stage analysis we will assess disease control rate (null: 21%, alternative: 50%); we will need to observe at least 3 responses (as measured by DCR at 24 weeks) out of 10 patients to continue through the second stage. At the second stage, we will assess disease control rate again, and we will need to observe at least 7 responses out of 20 patients to accept the combination treatment as highly promising. The overall power for true disease control rate at 24 weeks is 91%. The overall type I error, the chance of incorrectly rejecting the null hypothesis, is 9%. The probability of stopping at the first stage under the null hypothesis is 65%. The operating characteristics of this design are calculated using the exact binomial distribution.

Overall objective response rate is also of interest in this trial, but the overall objective response rate is likely less than 50% for stratum A. If there are 7 or more patients with complete or partial response, the treatment will also be considered promising. There is at least 58% probability of observing 7 or more responses in 20 treated patients if the true known response rate is 40%.

Stratum B (PM01183 plus gemcitabine)

At the first stage analysis we will assess disease control rate (null: 21%, alternative: 50%); we will need to observe at least 3 responses (as measured by DCR at 24 weeks) out of 10 patients to continue through the second stage. At the second stage, we will assess disease control rate again, and we will need to observe at least 7 responses out of 20 patients to accept the combination treatment as highly promising. The overall power for true disease control rate at 24 weeks is 91%. The overall type I error, the chance of incorrectly rejecting the null hypothesis is 9%. The probability of stopping at the first stage under the null hypothesis is 65%. The operating characteristics of this design are calculated using the exact binomial distribution.

Overall response rate is also an interest of this trial, but the overall response rate is likely less

than 50% for stratum B. If there are 7 or more patients with complete or partial response, the treatment will also be considered promising. There is at least 58% probability of observing 7 or more responses in 20 treated patients if the true known response rate is 40%.

Stratum C (PM01183 monotherapy)

At the first stage analysis we will assess disease control rate (null: 10%, alternative: 30%). We will need to observe at least 2 responses (as measured by DCR at 24 weeks) out of 12 patients to continue through the second stage. At the second stage, we will assess disease control rate again, and we will need to observe at least 4 responses out of 20 patients to accept the combination treatment as highly promising. The overall power for true disease control rate at 24 weeks is 86%. The overall type I error, the chance of incorrectly rejecting the null hypothesis is 12%. The probability of stopping at the first stage under the null hypothesis is 66%. The operating characteristics of this design are calculated using the exact binomial distribution.

Overall response rate is also an interest of this trial, but the overall response rate is likely less than 30% for stratum C. If there are 4 or more patients with complete or partial response, the treatment will also be considered promising. There is at least 37% probability of observing 4 or more responses in 20 treated patients if the true known response rate is 20%.

Progression-free and overall survival of patients receiving combination PM01183 plus Doxorubicin, combination PM01183 plus Gemcitabine, or single agent PM01183 will be described using the method of Kaplan and Meier, and Greenwood's formula for 90% confidence intervals for PFS and OS at 24 weeks will be reported. Separate analyses will be conducted based on study stratum.

12.2 Sample Size, Accrual Rate and Study Duration

Sample size: 20 patients will be enrolled to each stratum for a total of 60 patients.

Accrual Rate: It is estimated accrual will be 2-5 patients per stratum per month. This broad study design will allow for eligibility of nearly every patient in clinic to participate.

Study Duration: 24 months

12.3 Monitoring Plan

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Principal Investigator or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements. All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

12.4 Confidentiality

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. Patient names are not included in data sets that are transmitted outside of the clinical team.
Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form.

12.5 Evaluation of Toxicity

Toxicity is an important secondary endpoint. With 20 patients in each stratum, there is at least 71% probability of observing one or more toxicities with a true rate as low as 6%. With 20 treated patients in each stratum, the maximum width of a 90% two-sided confidence interval for any estimated adverse event proportion ± 20%.

13. PUBLICATION PLAN

The investigators plan to publish within two years of the last patient enrolled on study.

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B INFORMATION ON POSSIBLE DRUG INTERACTIONS

MEDICATION/THERAPY ALLOWED	• Therapies for pre-existing and treatment-emergent medical conditions, including pain management. • Blood products and transfusions, as clinically indicated. • Bisphosphonates. • Erythropoietin according to ASCO guidelines. • Secondary GCSF prophylaxis will be administered according to the guidelines in section 6.4. Dosing and formulation will be per institution standard. Dose timing must be at least 48 hours since last study drug infusion • Anticoagulation therapy for the treatment or secondary prophylaxis of deep vein thrombosis. • Luteinizing hormone-releasing hormone (LHRH) agonists, in pre-menopausal women. • Megestrol acetate for appetite stimulation if appropriate for management of emerging wasting syndrome.
MEDICATION/THERAPY PROHIBITED	• Concomitant administration of any other antineoplastic therapy • Any other investigational agents. • Immunosuppressive therapies other than corticosteroids. • *In vitro* studies have shown that PM01183 has the potential to inhibit cytochromes CYP2C8, CYP2B6 and CYP3A4. The clinical relevance of this potential interaction is unknown at present. Therefore, caution should be exercised when PM01183 is administered concomitantly with CYP2C8, CYP2B6 and CYP3A4 substrates, particularly those with a narrow therapeutic index . • Aprepitant or related compounds. • Radiotherapy, is excluded from the clinical trial at this time. Palliative radiation will be permitted after cycle 2 only for localized pain control and not due to unequivocal radiological or clinically progressive disease. Study drug, doxorubicin and gemcitabine should be temporarily held during this period. Dosing should resume with the next scheduled cycle that is at least 7 days after radiation is complete.

In vitro studies using human liver microsomes have shown that PM01183 has the potential to inhibit cytochrome CYP2B6, CYP2C8 and CYP3A4. Moreover, the Ki values compared with the achieved maximum plasma concentration (C_{max}) values at relevant doses indicate that the likelihood of a clinically relevant inhibition of PM01183 is possible for CYP2C8 ([I]/Ki>0.1) and likely for CYP3A4 ([I]/Ki>1). The magnitude of the interaction is unknown at present. Therefore, caution should be exercised when PM01183 is administered concomitantly with CYP2B6, CYP2C8 and CYP3A4 substrates.

Additionally, *in vitro* studies with human microsomes have shown that isoforms CYP2D6, CYP2E1, CYP3A4, CYP2C9 and CYP2C19 participate in PM01183 metabolism. Therefore, concomitant drugs which induce or inhibit any of these cytochromes, especially CYP3A4 and CYP2C19, should be avoided whenever is possible. A list of commonly prescribed drugs that are inhibitors, inducers and substrates for these enzymes can be found at this website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

A potentially significant interaction with aprepitant is suggested by available data in patients with platinum-resistant/refractory ovarian cancer. Patients treated with aprepitant in Cycle 2 had PM01183 clearance reduced by 50%, approximately, compared to Cycle 1 exposure.

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