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CLINICAL TRIAL PROTOCOL

Phase I Multicenter, Open-label, Clinical and Pharmacokinetic Study of PM060184 in Combination with Gemcitabine in Selected Patients with Advanced Solid Tumors

INVESTIGATIONAL MEDICINAL PRODUCTS: PM060184 and Gemcitabine

Protocol No.: PM60184-A-003-14

EudraCT No.: 2014-002943-16

NCT Code: 02533674

Protocol final version 3.0 including amendment #1 dated 14 August 2015, nonsubstantial amendment #1 dated 17 Nov 2016, non-substantial amendment #2 dated 18 Oct 2017 and substantial amendment #2 dated 8 May 2018.

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This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

Confidentiality statement

STUDY CONTACTS	NAME AND ADDRESS	PHONE, FAX NUMBER, AND E-MAIL ADDRESS
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PRINCIPAL INVESTIGATORS

A full list of Investigators will be available as a separate document.

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SYNOPSIS

TITLE	Phase I Multicenter, Open-label, Clinical and Pharmacokinetic Study of PM060184 in Combination with Gemcitabine in Selected Patients with Advanced Solid Tumors.
PROTOCOL CODE	PM60184-A-003-14
INVESTIGATORS	A full list of investigators will be available as a separate document.
NUMBER OF SITES/ TRIAL LOCATION	Three sites are expected to participate in this study: two in Spain and one in the U.S.
STUDY OBJECTIVES	**Primary:** • To determine the maximum tolerated dose (MTD) and the recommended dose (RD) of PM060184 in combination with gemcitabine in selected patients with advanced solid tumors. **Secondary:** • To characterize the safety profile and feasibility of this combination in this study population. • To characterize the pharmacokinetics (PK) of this combination and to detect major drug-drug PK interactions. • To obtain preliminary information on the clinical antitumor activity of this combination.
STUDY DESIGN	Prospective, open-label, dose-ranging, uncontrolled phase I study with escalating doses of PM060184 in combination with gemcitabine in selected patients with advanced solid tumors. Following a classical 3+3 design, successive cohorts of patients will receive escalating doses of intravenous (i.v.) gemcitabine over 30 minutes (min), followed by i.v. PM060184 over 10 min on Day 1 and Day 8 every three weeks (q3wk), until the RD is reached. All evaluable patients within a dose level (DL) must be followed for at least one full cycle (i.e., three weeks) before dose escalation may proceed to the next DL. The MTD will be the lowest DL explored during dose escalation at which more than one third of evaluable patients experienced a DLT during Cycle 1. The RD will be the highest DL explored at which less than one third of evaluable patients experienced a DLT during Cycle 1. Dose escalation will cease immediately once the MTD is reached. Intermediate DLs can be tested, if deemed appropriate upon the Sponsor's and Investigators' agreement. At least nine evaluable patients will be treated in an expansion

	cohort at the RD in order to confirm its tolerability and feasibility. Once the RD is confirmed, exploratory cohorts of at least 12 patients each will be expanded at RD in selected tumor type(s) and/or target subpopulations, chosen according to the preliminary efficacy observed among patients treated during dose escalation, discussed and agreed between the Investigators and the Sponsor, as appropriate.
STUDY POPULATION **Inclusion criteria**	1) Voluntarily signed and dated written informed consent prior to any specific study procedure. 2) Age ≥ 18 years. 3) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 1. 4) Life expectancy ≥ 3 months. 5) Patients with a histologically/cytologically confirmed diagnosis of advanced disease of any of the following tumors that progressed to standard therapy or for whom no standard therapy exists (with the exception of neuroendocrine, carcinoid, small cell and sarcoma histology subtypes, which are not allowed): a) Breast cancer non-candidate for hormone therapy alone. b) Epithelial ovarian cancer (including primary peritoneal disease and/or fallopian tube carcinomas and/or endometrial adenocarcinomas). c) Locally advanced or metastatic head and neck cancer. d) Non-small cell lung cancer (NSCLC). e) Germ cell tumors (GCTs). f) Biliary tract adenocarcinoma. g) Adenocarcinoma or carcinoma of unknown primary site (UKPS). h) Cervix carcinoma. i) Gastrointestinal stromal tumor (GIST). j) Urothelial cancer. 6) **Expansion cohort at the RD and tumor-specific cohorts:** All patients must have: a) Measurable disease according to Response Evaluation Criteria In Solid Tumors (RECIST) v.1.1 [or Choi criteria and/or European Organization for Research and Treatment of Cancer (EORTC) metabolic response criteria for solid tumors, in the case of GIST]; or b) Evaluable disease by serum markers in the case of ovarian cancer [Gynecologic Cancer Intergroup (GCIG) specific criteria]; and c) Documented disease progression during or immediately after last therapy according to any of the aforementioned criteria.

	7) Wash-out periods: at least three weeks since the last administration of an anticancer therapy, including radiation therapy (RT) or a biological/investigational therapy [excluding monoclonal antibodies (MAbs)]; at least four weeks since the last MAb-containing therapy; and at least six weeks since nitrosoureas and mitomycin C (systemic). In the case of hormone-sensitive breast cancer progressing while on hormone therapy, the latter must be either stopped up to one week before or continued without changes during the trial. 8) Adequate bone marrow, renal, hepatic, and metabolic function (assessed ≤ 7 days before inclusion in the study): a) Platelet count ≥ 100 x 10^9/l, hemoglobin ≥ 9.0 g/dl and absolute neutrophil count (ANC) ≥ 1.0 x 10^9/l. b) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x upper limit of normal (ULN), independently of the presence of liver metastases. c) Alkaline phosphatase (AP) ≤ 2.5 x ULN (≤ 5 x ULN if disease-related). d) Total bilirubin ≤ 1.5 x ULN. e) International Normalized Ratio (INR) < 1.5 (except if patient is on oral anticoagulation therapy). f) Calculated creatinine clearance (CrCl) ≥ 50 ml/min (using Cockcroft and Gault's formula). g) Albumin ≥ 2.5 g/dl. 9) Recovery to grade ≤ 1 from any adverse event (AE) derived from previous treatment (excluding alopecia and/or cutaneous toxicity and/or asthenia). 10) Left ventricular ejection fraction (LVEF) by echocardiography (ECHO) or multiple-gated acquisition (MUGA) within normal range (according to institutional standards). 11) Women of childbearing potential must have a negative serum or urine pregnancy test before study entry. Both women and men must agree to use a medially acceptable method of contraception throughout the treatment period and for six months after discontinuation of treatment. Acceptable methods of contraception include intrauterine device (IUD), oral contraceptive, subdermal implant and/or double barrier.
Exclusion criteria	1) Concomitant diseases/conditions: a) History or presence of unstable angina, myocardial infarction, congestive heart failure, or clinically significant valvular heart disease within last year. b) Symptomatic arrhythmia or any uncontrolled arrhythmia requiring ongoing treatment. c) Known chronic active hepatitis or cirrhosis. d) Active uncontrolled infection [i.e., antibiotic,

	antifungal or antiviral intervention indicated or surgical procedure (i.e., pleural or deep abscess drainage) conducted within 15 days prior to inclusion]. e) Known human immunodeficiency virus (HIV) infection. f) Current or prior history of grade ≥ 2 peripheral sensory and/or motor neuropathy. g) Prior treatment with oxaliplatin. h) Limitation of the patient's ability to comply with the treatment or follow-up protocol. i) Any other major illness that, in the Investigator's judgment, will substantially increase the risk associated with the patient's participation in this study. 2) Symptomatic, progressive or corticosteroids-requiring documented brain metastases or leptomeningeal disease involvement. 3) Men or women of childbearing potential who are not using an effective method of contraception as previously described; women who are pregnant or breast feeding. 4) Patients who have had RT in more than 35% of the bone marrow. 5) Prior treatment with PM060184. 6) Prior treatment with gemcitabine-containing therapy for advanced disease (adjuvant therapy is allowed, provided not more than six cycles were administered and relapse occurred more than six months after the last drug administration), and/or: **a)** Patients who have previously discontinued gemcitabine-containing regimens due to gemcitabine-related toxicity. 7) Known hypersensitivity to gemcitabine or any component of the formulation.
EXPECTED NUMBER OF PATIENTS	The number of patients may vary depending both on the tolerability of PM060184 combined with gemcitabine and the number of dose levels required to identify the MTD. Approximately between six and 72 evaluable patients are planned to be included in this study.
STUDY DRUGS FORMULATION	**Gemcitabine:** Commercially available presentations of vials containing gemcitabine will be provided as appropriate. Gemcitabine will be prepared in accordance with the applicable Summary of Product Characteristics (SmPC). Medication preparation records will be kept by the site. **PM060184:** The drug substance PM060184-CD is a mixture of PM060184

<table>
<tr><td></td><td>and 2-hydroxypropyl-β-cyclodextrin.
PM060184 drug product (DP) is provided as a sterile lyophilized powder for concentrate for solution for infusion with a strength of 15 mg of the active moiety PM060184.
Before use, the vials should be reconstituted with 6 ml of water for injection to give a solution containing 2.5 mg/ml of PM060184. PM060184 15-mg DP was developed for administration by the i.v. route. Prior to administration, the reconstituted vials should be further diluted with dextrose 5% solution for infusion. Each 15-mg vial of PM060184 is a single-use vial. PM060184 reconstitution/dilution records will be kept by the site.
The full composition of the reconstituted solution per ml is as follows:
<table>
<tr><th>Component</th><th>Concentration (per ml)</th><th>Function</th></tr>
<tr><td>PM060184</td><td>2.5 mg/ml</td><td>Active moiety</td></tr>
<tr><td>2-Hydroxypropyl-β cyclodextrin (DS 4-5)*</td><td>200 mg/ml</td><td>Solubilizing agent</td></tr>
<tr><td>Water for injection</td><td>1 ml</td><td>Solvent</td></tr>
</table>
* DS = Degree of substitution.</td></tr>
<tr><td>TREATMENT SCHEDULE</td><td>Gemcitabine will be administered as a 30-min i.v. infusion, followed by PM060184 as a 10-min i.v. infusion, both on Day 1 and Day 8 q3wk.</td></tr>
<tr><td>ADMINISTRATION ROUTE AND STARTING DOSE</td><td>Patients will consecutively receive the following on Day 1 and Day 8 q3wk (three weeks = one treatment cycle):
• Gemcitabine: i.v. infusion over 30 min (± 10 min) at a starting dose of 800 mg/m^2 via a central or peripheral venous catheter through a pump device, followed by:
• PM060184: i.v. infusion over 10 min (± 3 min) at a starting dose of 6.0 mg/m^2 via a central or peripheral venous catheter through a pump device.
During PK sampling, PM060184 infusion should start no more than 5 min after end of gemcitabine administration.</td></tr>
<tr><td>PROPHYLACTIC MEDICATION</td><td>Primary antiemetic prophylaxis is compulsory prior to all PM060184 infusions. Standard treatment [according to the American Society of Clinical Oncology (ASCO) guidelines] will be administered:
• 5-HT$_3$ antagonists (ondansetron 8 mg i.v. or equivalent).
• Steroids (dexamethasone 8 mg i.v. or equivalent).
If necessary, addition of metoclopramide or extension of treatment with 5-HT$_3$ antagonists and/or dexamethasone could be considered (according to the Investigator’s own criteria).</td></tr>
</table>

ALLOWED MEDICATIONS/ THERAPIES	• Therapies for pre-existing and treatment-emergent medical conditions, including pain management. • Blood products and transfusions, as clinically indicated. • Bisphosphonates. • In case of nausea or vomiting, secondary prophylaxis and/or symptomatic treatment for emesis according to ASCO guidelines. • Erythropoietin use according to ASCO guidelines. • Hormone-responsive breast cancer patients [i.e., those whose tumors express estrogen receptor (ER) and/or progesterone receptor (PrR)] may continue receiving their same prior hormonal therapy without interruption throughout their study participation. • Treatment with granulocyte colony-stimulating factor (G-CSF) in the event of grade 4 neutropenia lasting > 3 days, neutropenic sepsis or febrile neutropenia according to ASCO guidelines. Secondary prophylaxis could be considered after Cycle 1, if it is in the best interest of the patient. • Luteinizing hormone-releasing hormone (LHRH) agonists, in women of reproductive age. • Megestrol acetate for appetite stimulation.
PROHIBITED MEDICATIONS/ THERAPIES	• Concomitant administration of any other antineoplastic therapy is prohibited, other than the aforementioned hormonal therapy for breast cancer. • Patients who require RT within three weeks after the first infusion may remain on the study after being discussed and agreed between the Investigator and the Sponsor, but will not be evaluable for the analysis of the primary endpoint (DLT) and consequently need to be replaced. • Primary prophylaxis with G-CSF in Cycle 1. • Other investigational agents. • Concomitant RT while on gemcitabine treatment. • Immunosuppressive therapies other than corticosteroids.
EVALUABILITY OF PATIENTS	An evaluable patient for the main objective of the study (i.e., determination of the MTD and RD) should have received at least one complete cycle (including the observation period). Patients who are discontinued early or miss/delay doses and/or assessments will be evaluable if these events are the consequence of treatment-related toxicity (excluding hypersensitivity reactions and/or extravasations).
EVALUATION CRITERIA **Primary endpoint**	• **<u>Determination of MTD and RD.</u>** o The MTD will be the lowest DL explored during dose escalation at which more than one third of evaluable patients experienced a DLT during Cycle 1. o The RD will be the highest DL explored at which less than one third of evaluable patients experienced

	a DLT during Cycle 1.
Dose-limiting toxicities	DLTs are defined as AEs and laboratory abnormalities related to the study treatment that occurred during Cycle 1 and fulfilled at least one of the following criteria: • Grade 4 neutropenia (ANC < 0.5 x 10^9/l) lasting > 3 days. • Grade ≥ 3 febrile neutropenia of any duration or neutropenic sepsis. • Grade 4 thrombocytopenia (platelet count < 25 x 10^9/l) or grade 3 with any major bleeding episode requiring a platelet transfusion. • Grade 4 ALT and/or AST increase, or grade 3 lasting > 7 days. • Treatment-related grade ≥ 2 ALT or AST increase concomitantly with ≥ 2 x ULN total bilirubin increase and normal AP. • Any other grade 3/4 non-hematological AE that is suspected to be related to study drug(s), except nausea/vomiting (unless the patient is receiving an optimal anti-emetic regimen), hypersensitivity reactions, extravasations, grade 3 asthenia lasting less than one week, anorexia, and non-clinically relevant isolated biochemical abnormalities [e.g., isolated increase in gamma-glutamyltransferase (GGT)]. In any case, the clinical relevance should be discussed between the Investigators and the Sponsor's representatives. • Delay in the administration of Cycle 2 of the combination exceeding seven (+1) days of the treatment due date (i.e., Day 22), due to any AEs related to study drug(s). • The following circumstances will be discussed between the Principal Investigator and the Sponsor, and the final consensus will be documented: o DLTs with delayed onset (i.e., that occur after Cycle 1). o Non-compliance with the intended dose intensity (DI) in more than half of patients at any dose level (i.e., missing infusions on Day 8 or frequent dose delays due to treatment-related toxicity despite not conforming to a formal DLT definition).
Secondary endpoints	• **Safety:** patients will be evaluable for safety if they have received at least one partial or complete infusion of PM060184 and one partial or complete infusion of gemcitabine. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.4. • **Pharmacokinetics:** PK analyses will be evaluated in plasma by standard non-compartmental analysis (NCA) (compartmental modeling may be performed if appropriate).

	• **<u>Efficacy:</u>** although it is not the main objective of this study, antitumor activity will be evaluated according to RECIST v.1.1 in all patients with measurable disease, according to Choi criteria and/or EORTC metabolic response criteria for solid tumors, in GIST patients, or by evaluation of serum tumor markers if applicable (e.g., ovarian cancer), every two cycles (i.e., approximately every six weeks) ± one week after treatment initiation until Cycle 4. Patients continuing treatment after Cycle 4 will have the assessments performed every three cycles (i.e., approximately every nine weeks) ± one week from Cycle 4 while on treatment, unless otherwise is clinically indicated. Patients included in the expansion cohort at the RD and in the tumor-specific cohorts must be evaluable as per RECIST v.1.1 (or Choi criteria and/or EORTC metabolic response criteria for solid tumors, in GIST patients) or by tumor markers. • **<u>Pharmacogenetics:</u>** a blood sample will be collected to evaluate the presence or absence of known polymorphisms that may explain individual variability in main PK parameters.
REPLACEMENT OF PATIENTS	Patients must be replaced if they are not evaluable for the assessment of the primary endpoint, i.e. if: • They are withdrawn from the study before receiving at least one evaluable cycle for any reason other than treatment-related toxicity (excluding hypersensitivity and/or extravasations reactions). An evaluable cycle is defined as: gemcitabine followed by PM060184 on Day 1 and Day 8, with the corresponding 2-week observation period during the first cycle. • They require RT or other therapeutic procedure within three weeks after the first study drug dose, unless they previously had another treatment-related AE included in the definition of DLT. • There is a protocol violation resulting in an impossibility of concluding anything regarding the safety of the study therapy. All replaced patients will be included in the general safety analysis and in the efficacy analysis (if appropriate).
DOSE ESCALATION SCHEDULE	The starting dose (DL1) for gemcitabine will be 800 mg/m^2. This corresponds to a dose intensity (DI) of 533.33 mg/m^2/week, and is equivalent to 80% of the RD with this schedule. This is the minimal gemcitabine dose accepted in clinical practice. The DL1 for PM060184 will be 6.0 mg/m^2. This corresponds to a DI of 4.0 mg/m^2/week, and is equivalent to 64% of the RD determined for PM060184 given as single agent with this schedule.

The dose escalation scheme will follow pre-defined dose levels, starting at DL1, as summarized in the following table:

DL	No. of patients	Relative DI (%) of gemcitabine / PM060184	Gemcitabine dose (mg/m^2) on Day 1 and Day 8 q3wk	PM060184 dose (mg/m^2) on Day 1 and Day 8 q3wk
DL-1	0-6	80/53	800	5.0
DL1	3-6	80/64	800	6.0
DL2	3-6	80/74	800	7.0
DL3	3-6	100/74	1000	7.0
DL4 and beyond	3-6		No further dose increases beyond 1000 mg/m^2	Further dose increases of 0.5 or 1.0 mg/m^2, according to observed toxicities

DI, dose intensity; DL, dose level; MTD, maximum tolerated dose.

- Cohorts of at least **three** fully evaluable patients will be treated at each cohort.
- The second and third patients of a cohort may be included simultaneously after the first patient has completed the first cycle, except if a DLT is reported in the first patient, in which case the third patient of the cohort will be included once the second patient has received a complete treatment cycle with no reported DLTs. All patients will have to be fully evaluable (3-week period) prior to any further dose escalation. Patients not fully evaluable will be replaced.
- Dose escalation will continue if no DLT is observed.
- Subsequent dose levels will enroll three patients, and up to six fully evaluable patients if one DLT is observed in any of the first three fully evaluable patients.
- Once a DLT is observed, further patients will be included up to **six** fully evaluable patients in this dose cohort.

No. of patients evaluable for DLT	No. of patients with DLTs in Cycle 1	Action
3	0	Escalate DL
	1	Add 3 patients
	>1	MTD
6	1	Escalate DL
	>1	MTD

DL, dose level; DLT, dose-limiting toxicities; MTD, maximum tolerated dose.

- **For gemcitabine**: two doses (800 mg/m^2 and 1000 mg/m^2) will be initially tested. If the toxicity observed during dose escalation is clearly related to gemcitabine (i.e. neutropenia and/or thrombocytopenia), intermediate gemcitabine doses might be tested after agreement between the Investigators and the Sponsor.
- **For PM060184:** pre-established PM060184 doses have been set for the first three DLs. After DL3, dose increments of 1.0 mg/m^2 will be tested if toxicity at each previous DL is acceptable. These dose increments may be

of 0.5 mg/m^2, according to the toxicity observed. In the event of toxicities specifically related with PM060184 (i.e. peripheral neuropathy, post-infusion abdominal pain and/or diarrhea), intermediate PM060184 doses might be tested after agreement between the Investigators and the Sponsor.

Both the PM060184 and the gemcitabine doses may be rounded to the first decimal.

If more than one of three or six evaluable patients at any DL experience a DLT during Cycle 1, dose escalation will be terminated. The MTD will be the lowest level at which more than one third of evaluable patients experienced a DLT in Cycle 1. The RD will be the highest DL explored with less than one third of evaluable patients experiencing a DLT during Cycle 1.

If two or more evaluable patients (of 3-6 patients) at any DL experience a dose delay > 7 (+1) days from the theoretical due date (conforming or not to DLT criteria) and/or dose omissions exclusively related to PM060184 toxicity during Cycle 1, the cohort should be expanded as shown in the table below. If more than 50% of evaluable patients in a cohort experience dose delays and/or omissions, dose escalation will be terminated and this DL will be considered the MTD. An alternative schedule could then be explored after discussion between the Investigators and with the Sponsor's agreement. The starting dose of the new schedule will be the DL immediately below the MTD.

Dose delays	Dose omissions	Action
1	-	None
-	1	None
1	1	Add 3 more patients
≥ 2	-	Add 3 more patients
-	≥ 2	Add 3 more patients
If more than 50% evaluable patients in a cohort have dose delays and/or omissions		MTD

DLT, dose-limiting toxicities; MTD, maximum tolerated dose.

An expansion cohort of a minimum of nine evaluable patients will be treated at the RD once it has been determined; this is to confirm its feasibility and tolerability. Once the RD is confirmed, exploratory cohorts of at least 12 patients each will be expanded at RD in selected tumor type(s) and/or target subpopulations, chosen according to the preliminary efficacy observed among those previously treated during dose escalation, discussed and agreed between the Investigators and the Sponsor.

Intra-patient dose escalation will not be allowed under any circumstances.

CRITERIA FOR TREATMENT CONTINUATION	Patients will be treated with additional cycles of PM060184 combined with gemcitabine as long as no unacceptable toxicity and/or progression of the disease and/or withdrawal of consent occurs. The administration of a new cycle should be delayed if the criteria in the table below are not met on the corresponding Day 1. Parameters will be reevaluated at minimum intervals of 48 hours. The new cycle will be started upon recovery of these parameters. A maximum delay of 7 (+1) days from theoretical due date will be allowed for recovery from treatment-related adverse events. If recovery has not occurred after that period, the patient should discontinue the treatment, except in case of obvious patient benefit at the criteria of the Investigator and upon agreement with the Sponsor. If the re-treatment criteria are not met on Day 8 (±1 day), administration of the corresponding drugs should be omitted instead of delayed. After skipping and/or delaying doses due to treatment-related toxicity (except for neutropenia exclusively), or in patients who experience a DLT, treatment may only continue after appropriate dose reduction.

	Day 1	**Day 8**
ANC	≥ 1.0 x 10^9/l	≥ 1.0 x 10^9/l
Platelets	≥ 100 x 10^9/l	≥ 75 x 10^9/l
Hemoglobin	≥ 9 g/dl	≥ 8 g/dl
Total bilirubin	≤ 1.5 x ULN	
AST/ALT	Grade ≤ 1	Grade ≤ 2
Calculated CrCl (Cockcroft and Gault's formula)	≥ 50 ml/min	≥ 30 ml/min
Peripheral sensory / motor neuropathy	Grade ≤ 1	Grade ≤ 2
Other non-hematological drug-related AEs (except increased GGT, alopecia, nausea, anorexia, and/or asthenia) [a]	Grade ≤ 1	Grade ≤ 2

If a patient does not meet the requirements for treatment continuation on Day 1 of further cycles, the corresponding drug (PM060184 and gemcitabine) infusion will be withheld until recovery for a maximum of 7 days after the theoretical treatment date. If recovery has not occurred after a delay of > 7 (+1) days, the patient must be withdrawn from the trial, except in case of perceived clinical benefit from the Investigator and upon agreement with the Sponsor.

If the above criteria are not met on Day 8 of any cycle, the scheduled infusion will be omitted instead of delayed.

a Any grade accepted for increased GGT. Up to grade 2 for alopecia, nausea, anorexia, and asthenia. Non-symptomatic grade 2-4 metabolic abnormalities (e.g. sodium, magnesium, potassium, calcium) will be allowed for treatment continuation.

AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AP: alkaline phosphatase; AST, aspartate aminotransferase; CrCl, creatinine clearance; GGT, gamma-glutamyltransferase; ULN, upper limit of normal.

DOSE REDUCTION	Treatment after DLT, treatment-related dose delay for > 7 days from theoretical due date and/or toxicity considered as unacceptable by the investigators may continue, after appropriate dose reduction, only if there is clear evidence of objective patient benefit. This will always be discussed with the Sponsor. Under this circumstance, and following recovery to pre-specified re-treatment criteria, patients will be re-treated at the immediately lowest DL. If dose reduction beyond DL-1 is required, the PM060184 dose may be reduced by an additional 1.0 mg/m^2. Up to two individual dose reductions will be allowed per patient; any patients requiring more than two dose reductions will be withdrawn from the study. Once dose has been reduced for an individual patient, it will not be re-escalated again under any circumstances. No individual dose reductions will be allowed during Cycle 1. Patients requiring dose reduction exclusively due to febrile neutropenia or grade 4 neutropenia during the preceding cycle may receive secondary prophylaxis with G-CSF instead of a dose reduction. If toxicity re-occurs despite G-CSF use, dose reduction will then be implemented. Patients who require limited field RT for pain palliation after Cycle 1 may continue treatment with PM060184 alone and without any dose adjustments if patient benefit is perceived; these patients do not need to be replaced. Gemcitabine re-introduction may be considered in patients without progressing disease at least four weeks after the end of RT.
DRUG-DRUG INTERACTIONS	*In vitro* studies using human liver microsomes have pointed to CYP2C19 and CYP3A4 as the predominant cytochrome (CYP) enzymes responsible for the hepatic metabolism of PM060184. Therefore, concomitant drugs which induce or inhibit any of these cytochromes in a significant extent should be avoided whenever possible.
PHARMACOKINETICS	The plasma PK of PM060184, gemcitabine and gemcitabine 2,2 -difluorodeoxyuridine (dFdU) will be evaluated during Days 1 and 2 of Cycle 1 with a schedule of ten samples in all patients (see Table below). Additionally, patients treated in the expanded cohort at RD and in the tumor-specific cohorts will be sampled for PM060184 analysis on Days 1 and 2 of Cycle 2 at the same time points. The sampling schedule for both compounds will be as follows, taking as reference the gemcitabine infusion on Day 1.

	<table><tr><th>Sample number</th><th>Day</th><th>Time relative to gemcitabine infusion (h)</th><th>Sampling times for gemcitabine and dFdU</th><th>Sampling times for PM060184</th><th>Sampling Windows</th></tr><tr><td>#1</td><td>1</td><td>0</td><td>Pre-dose</td><td>Pre-dose</td><td>-</td></tr><tr><td>#2</td><td>1</td><td>0.5</td><td>Just before EOI</td><td>--</td><td>- 2 min</td></tr><tr><td>#3</td><td>1</td><td>0.67</td><td>10 min EOI</td><td>Just before EOI</td><td>- 2 min</td></tr><tr><td>#4</td><td>1</td><td>0.92</td><td>25 min EOI</td><td>15 min EOI</td><td>± 5 min</td></tr><tr><td>#5</td><td>1</td><td>1.17</td><td>40 min EOI</td><td>30 min EOI</td><td>± 5 min</td></tr><tr><td>#6</td><td>1</td><td>1.67</td><td>1 h 10 min EOI</td><td>1 h EOI</td><td>± 10 min</td></tr><tr><td>#7</td><td>1</td><td>2.67</td><td>2 h 10 min EOI</td><td>2 h EOI</td><td>± 10 min</td></tr><tr><td>#8</td><td>1</td><td>3.67</td><td>3 h 10 min EOI</td><td>3h EOI</td><td>± 10 min</td></tr><tr><td>#9</td><td>1</td><td>5.67</td><td>5 h 10 min EOI</td><td>5 h EOI</td><td>± 30 min</td></tr><tr><td>#10</td><td>2</td><td>24 *</td><td>24 h EOI</td><td>24 h EOI</td><td>± 2 h</td></tr></table> dFdU, 2,2-difluorodeoxyuridine; EOI, end of infusion; h, hours; min, minutes. Pharmacokinetic parameters will be calculated using NCA and population methods, after pooling data from this study with data obtained during other studies.
PHARMACOGENETIC EVALUATIONS	In order to explore factors that may help explain individual variability in main PK parameters, the presence or absence of germline mutations or polymorphisms will be analyzed in leukocyte DNA extracted from a blood sample obtained at any time during the study, but ideally before treatment start along with PK sample #1 on Day 1 of Cycle 1.
STATISTICAL METHODS	The main endpoint of the study is the determination of the MTD and the RD of PM060184 in combination with gemcitabine in this study population for future trials. Descriptive statistics (mean, median, standard deviation and 95% confidence interval, range of value, frequencies and percentages) will be used as appropriate. **Safety:** Descriptive statistics will be used to characterize DLTs occurring at the RD and/or at DLs above/below it. The profiles of AEs, deaths, serious adverse events (SAEs), treatment-related delays, dose reductions, dose omissions and/or treatment discontinuations will also be displayed as appropriate. **Efficacy:** Response rates as per RECIST v.1.1 (and as per Choi criteria and/or EORTC metabolic response criteria, for GIST patients) [percentage of patients with any response [partial response (PR), complete response (CR) or the sum of both being the overall response rate (ORR)], percentage of patients with clinical benefit [i.e., patients with any response, or with stable disease (SD) ≥ 4 months], will be characterized using descriptive statistics (95% exact binomial confidence interval) and according to primary tumor type. Time-related parameters [e.g., progression-free survival (PFS), overall survival (OS)] will also be analyzed according to the Kaplan-Meier method, if appropriate. If any specific tumor type

	subset is adequately represented, exploratory subgroup analyses will be performed. The characteristics of the patients achieving an objective response or SD ≥ 4 months by RECIST v.1.1 will be displayed. **Pharmacokinetics:** The PK parameters will be tabulated and selected parameters will be graphically displayed per DL. The dose-exposure relationships for maximum plasma concentration (C_{max}) and area under the curve (AUC) will be evaluated, and any potential PK interaction between gemcitabine, dFdU and PM060184 will also be explored. The potential influence on selected PK parameters of selected demographic and clinical dichotomous variables (gender, laboratory test results above/below selected cutoff values, etc.) will be evaluated by Student's t test or Mann-Whitney's U test as appropriate. For multinomial variables, analysis of variance will be used. For selected continuous demographic and clinical variables, relationship with selected PK parameters will be graphically explored and assessed using correlation and regression methods. **Pharmacogenetics:** The influence of known polymorphisms on main PK parameters will be assessed by Student's test or Mann-Whitney's U test as appropriate.
PLANNED TRIAL PERIODS (individually per patient)	Patients will be evaluated at scheduled visits in three study periods: • **Pre-treatment:** from signature of informed consent form (ICF) to the day of first infusion of study drugs. • **Treatment:** from first infusion of study drugs to the end of treatment (EOT). • **Follow-up**: after EOT, patients will be followed every four weeks until resolution or stabilization of relevant (grade > 1) related toxicities, if any. Patients who discontinued treatment without disease progression will be followed every three months until disease progression, other antitumor therapy, death or until the date of study termination (clinical cutoff), whichever occurs first. Patients will be considered to be **on-study** from the signature of the IC to the end of the follow-up period. Patients will be considered to be **on-treatment** for the duration of their treatment and until the EOT. The EOT is defined as 30 days (±15 days) after the day of the last study drug dose administration. An EOT visit will be performed within 30 days (± 15 days) after the last study drug dose administration, unless the patient starts any subsequent antitumor therapy (in which case the EOT visit should be performed before the start of the new therapy, whenever possible). If the patient dies while on treatment, the date of death will be considered the EOT date. Patients will receive the study drugs while it is considered to

	be in their best interest. Specifically, treatment will continue until: • Disease progression. • Unacceptable toxicity. • Intercurrent illness of sufficient magnitude to preclude fulfillment of appropriate re-treatment criteria and/or safe continuation of the study. • Patient refusal and/or non-compliance with study requirements. • Treatment delay > 7 (+1) days from the theoretical due date due to toxicity (except in case of patient's clear clinical benefit, with the Sponsor's approval). • Requirement of > 2 dose reductions.
PLANNED TRIAL PERIODS (for the whole study)	The total duration of the study will be approximately 69 months, including approximately a 60-month enrolment period. **Planned start date** (first patient on study): 4Q2014. **Planned enrolment period**: approximately 60 months. **Planned end-of-study date** (clinical cutoff): six months after the last patient's treatment discontinuation (last patient-last visit), or nine months after accrual of the last evaluable patient, whichever occurs first.

SCHEDULE OF ASSESSMENTS AND PROCEDURES

Assessments and procedures	Screening	Treatment							Follow-up
		Cycle 1			Further cycles			End of treatment	
		D1	D8	D15	D22*	D8	D15**		
Written informed consent	Before any study procedures	-	-	-	-	-	-	-	-
Pharmacogenetics informed consent (optional)	At any time during the study, but always prior to pharmacogenetic sample collection								-
Demographic data including height	-28 to 0	-	-	-	-	-	-	-	-
Medical and cancer history	-28 to 0	-	-	-	-	-	-	-	-
Primary diagnosis /prior treatment(s)	-28 to 0	-	-	-	-	-	-	-	-
Assessment of signs and symptoms	-28 to 0	-	-	-	-	-	-	-	-
Gemcitabine administration (1)	-	•	•	-	•	•	-	-	-
PM060184 administration (1)	-	•	•	-	•	•	-	-	-
Complete physical examination, weight and BSA	-7 to 0	•†	-	-	•ᵒ	-	-	**• (2)**	-
Performance status (ECOG)	-7 to 0	•†	•	•	•	•	•	**• (2)**	-
Vital signs (heart rate, blood pressure, temperature)	-7 to 0	•†	•	•	•	•	•	**• (2)**	-
Hematology (3)	-7 to 0	•†	•	•	•	•	•	**• (2)**	-
Biochemistry-A (3)	-7 to 0	•†	•	•	•	•	•	**• (2)**	-
Biochemistry-B and coagulation.	-7 to 0	•†	-	-	•	-	-	**• (2)**	-
Pregnancy test (if premenopausal woman) (4)	-7 to 0	Repeat if clinically indicated							-
ECG (5)	-28 to 0	Repeat if clinically indicated							-
LVEF (6)	-28 to 0	Every other cycle						**• (6)**	
Radiological tumor assessment as per RECIST v.1.1 (7)	-28 to 0	Every two cycles (every six weeks ± one week) until Cycle 4, and then every three cycles (every nine weeks ± one week) while on treatment						-	- **(8)**
Pharmacokinetics (9)	One blood sample collected immediately before treatment	Cycle 1 Nine blood samples collected from Day 1 to Day 2 for PK						-	
Pharmacogenetics (polymorphisms), if consented	One blood sample collected at any time during the study							-	
Concomitant therapies	-14 to 0	← Throughout the "on-treatment" period →							
Adverse events	- §	← Throughout the "on-treatment" period →							• **(10)**

Day 0 = Day 1 of Cycle 1.

*****Day 22 = Day 1 of the following cycle. Administration could be delayed up to 7 (+1) days; further delay is only acceptable under the Sponsor's approval of documented clinical benefit.

§ Only information on SAEs that occurred after signature of ICF is required. Grading should be as per NCI-CTCAE v.4.

† If performed at screening, the assessment does not need to be repeated on Day 1 of Cycle 1.

ᵒ Before treatment administration of subsequent cycles, BSA will have to be recalculated for patients showing a ≥10

% variation in total body weight from baseline or from last dose adjustment; otherwise the same BSA and dose calculated for the previous cycle could be used. The same BSA calculation method should be used throughout the study.
**From Cycle 5 onwards day 15 visit will not be done unless it is clinically indicated.

Allowed windows for assessments and procedures:

- **A -24-hour window for clinical assessments (ECOG PS, vital signs, weight, BSA, etc.). Additionally, for D15 a +24 hour window will also be allowed.**
- **A -24-hour window for laboratory procedures (a -48-hour window on infusion days, excluding Day 1 of Cycle 1). Additionally, for D15 a +24 hour window will also be allowed.**
- **A ±15-day window for the assessments at EOT.**
- **A ±1-week window for radiological procedures.**
- **A ±24-hour window for administration of gemcitabine (but only if at least six days have passed since the last infusion) and of PM060184.**

1. Gemcitabine will be administered as a 30-min (±10 min) i.v. infusion, followed by PM060184 as a 10-min (±3 min) i.v. infusion. During PK sampling, PM060184 infusion should start no more than 5 min after end of gemcitabine administration.
2. To be repeated only for those parameters for which no measurement is available within 15 (-3) days before the end-of-treatment visit, or for those parameters with values that were out of range in the last assessment (grade > 1 according to NCI-CTCAE v.4).
3. During the first four cycles, hematology and biochemistry-A analyses will be repeated on Days 1, 8 and 15. If any clinically relevant treatment-related NCI-CTCAE grade ≥ 3 toxicity occurs during the first four cycles, the abnormal test(s) should be re-assessed at least every 2-3 days until recovery to at least grade 2. In the event of febrile neutropenia, grade 4 neutropenia and/or grade 4 thrombocytopenia, re-assessment should be performed daily until recovery to at least grade 3 or until fever resolution, if applicable, and then every 2-3 days thereafter until recovery to at least grade 2. From Cycle 5 onwards, any treatment-related NCI-CTCAE grade ≥ 3 toxicity not considered a major risk for the patient is to be re-evaluated according to Investigator's criteria.
4. Beta subunit-human chorionic gonadotropin (ß-hCG) (urine or serum).
5. It should allow rhythm definition and should include assessment of:
    - PR interval.
    - Heart rate.
    - QT interval (raw).
    - QRS complex duration.
6. LVEF assessment: at screening (within 28 days prior to Day 1 of Cycle 1) and then every other cycle. In the event of LVEF decrease to grade ≥ 2 by MUGA, an ECHO should be done to confirm this decrease and also to rule out any heart injures. Major efforts must be done to find the main cause of this AE (cardiac enzymes, troponin I and or T, cardiologist assessment, etc.). LVEF by ECHO should be performed at least every four weeks until recovery or stabilization.
7. Helical contrast-enhanced CT-scan and/or gadolinium-enhanced MRI as appropriate every two cycles ± one week until Cycle 4, and then every three cycles ± one week from Cycle 4 while on treatment (the same method should be used throughout the study for each individual patient). PET-CT scan might be used, if appropriate, on individual cases upon the Sponsor's agreement. (**Patients with GIST should always be assessed with fusion or integrated PET-CT scans, and will be assessed according to Choi criteria and/or EORTC metabolic response criteria for solid tumors**). Anonymized copies of the images showing objective response or meaningful tumor shrinkage must be submitted to the Sponsor.
8. Patients who discontinued treatment without disease progression will be followed every three months until disease progression, other antitumor therapy, death or until the date of study termination (clinical cutoff), whichever occurs first.
9. Additionally, patients treated in the expanded cohort at the RD and in the tumor-specific cohorts will be sampled for PM060184 PK analysis on Day 1 and Day 2 of Cycle 2 at the same time points.
10. Patients withdrawn from the study with an ongoing relevant (grade > 1) drug-related AE should be followed until resolution or stabilization (i.e., to grade 1) or until start of a new therapy. Beyond 30 days (± 15 days) after the last administration of study drugs, only those procedures to assess any remaining relevant treatment-related AEs need to be performed.

Hematology: Differential WBC (neutrophils, lymphocytes), hemoglobin and platelets.
Biochemistry A: AST, ALT, total bilirubin, AP, LDH, creatinine, glucose, and serum electrolytes (Na^+, K^+, Cl^-, total calcium).
Biochemistry B and coagulation: total proteins, albumin and coagulation tests (PT, aPTT, INR).
Exploratory serum tumor markers will be measured as appropriate according to primary tumor type only if elevated at baseline (≥2 x ULN).
AE, adverse event; ALT, alanine aminotransferase; AP, alkaline phosphatase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BSA, body surface area; CT, computed tomography; ECG,

electrocardiogram; ECHO, echocardiography; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; EOT, end of treatment; GIST, gastrointestinal stromal tumor; ICF, informed consent form; INR, international normalized ratio; LDH, lactic dehydrogenase; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition scan; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PET, positron emission tomography; PK, pharmacokinetics; PS, performance status; PT, prothrombin time; RD, recommended dose; RECIST, Response Evaluation Criteria In Solid Tumors; SAE, serious adverse event; ULN, upper limit of normal; WBC, white blood cells.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

5-HT$_3$	Serotonin (5-hydroxytryptamine 3)
AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
aPTT	Activated Plasma Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area Under The Concentration vs. Time Curve
AUKPS	Adenocarcinoma of Unknown Primary Site
β-hCGs	Beta Subunit of Human Chorionic Gonadotropins
BSA	Body Surface Area
CI	Combination Index
CL	Clearance
C_{max}	Maximum Plasma Concentration
CR	Complete Response
CRA	Clinical Research Associate
CrCl	Creatinine Clearance
CT-scan	Computed Tomography Scan
CYP	Cytochrome P450
d/D	Day(s)
dFdC	2,2-difluorodeoxycytidine
dFdCDP	dFdC 5'-diphosphate
dFdCTP	dFdC 5'-triphosphate
dFdU	2,2-difluorodeoxyuridine
DI	Dose Intensity
DL	Dose Level
DLT	Dose-limiting Toxicity
DNA	Deoxyribonucleic Acid
DP	Drug Product
DS	Degree of Substitution
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
e-CRF	Electronic Case Report Form
EOI	End of Infusion
EORTC	European Organization for Research and Treatment of Cancer

EOT	End of Treatment
ER	Estrogen Receptor
FUP	Follow-up
G-CSF	Granulocyte Colony-stimulating Factor
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
GCT	Germ Cell Tumor
GGT	Gamma-glutamyltransferase
GI50	50% Growth Inhibition
GIST	Gastrointestinal Stromal Tumor
GMT	Greenwich Meridian Time
hCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HPβCD	2-hydroxypropyl-β-cyclodextrin
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IEC	Independent Ethics Committees
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine Device (Contraceptive)
i.v.	Intravenous (intravenously)
LDH	Lactate Dehydrogenase
LHRH	Luteinizing Hormone-releasing Hormone
LVEF	Left Ventricular Ejection Fraction
MAb	Monoclonal Antibody
min	Minute(s)
ml	Milliliter
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated Acquisition Scan
NCA	Non-compartmental Analysis
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSCLC	Non-small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival

PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-free Survival
PhV	Pharmacovigilance
PK	Pharmacokinetic(s)
PR	Partial Response
PRE TT	Pre-treatment
PrP	Progesterone Receptor
PS	Performance Status
PT	Prothrombin Time
Q	Quarter
q3wk	Every Three Weeks
q4wk	Every Four Weeks
RD	Recommended Dose
RECIST	Response Evaluation Criteria In Solid Tumors
RT	Radiotherapy
SAE(s)	Serious Adverse Event(s)
SD	Stable Disease
SPC	Summary of Product Characteristics
SUSAR/SUA	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal Elimination Half-life
TGD	Tumor Growth Delay
TT	Treatment
TTP	Time To Progression
Uk	Unknown
UKPS	Adenocarcinoma or Carcinoma of Unknown Primary Site
ULN	Upper Limit of Normal
V_{ss}	Volume of Distribution at Steady State
WBC	White Blood Cells
WHO	World Health Organization
wk/wks	Week/weeks
WMA	World Medical Association

1. INTRODUCTION

1.1 BACKGROUND

Despite recent advances in the treatment of cancer, metastatic disease remains mostly incurable and there is an urgent need for developing new therapeutic options for these patients, particularly including investigational drugs with novel mechanisms of action. The introduction of new combination regimens of non-cross-resistant chemotherapy agents with acceptable safety profiles is a way to try to improve the outcome of patients with advanced solid tumors.

1.2 INFORMATION ON STUDY DRUGS: PM060184

Please refer to the Investigator's Brochure (IB) for full information on PM060184.

1.2.1 Name and Chemical Information

The Drug Substance PM060184-CD is a mixture of PM060184 and 2-hydroxypropyl-β-cyclodextrin (HPβCD).

Chemical name	(1Z,4S,6Z)-1-(N-[(2Z,4Z,6E,8S)-8-((2S)-5-methoxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)-6-methylnona-2,4,6-trienoyl]-3-methyl-L-valyl}amino)octa-1,6-dien-4-yl carbamate	
	2-Hydroxypropyl-β-cyclodextrin (DS 4 – 5)	
Other name	PM060184	
	HPβCD	
Molecular formula	PM060184	$C_{31}H_{45}N_3O_7$
	HPβCD	$(C_6H_9O_5)_7(C_3H_7O)_n$ n=4-5
Molecular weight	PM060184	571.7049
	HPβCD	About 1400
Proportion (w/w)	PM060184	1
	HPβCD	10

The structural and molecular formula of PM060184 and HPβCD are shown in Figure 1:

Figure 1. Molecular formula of PM060184: $C_{31}H_{45}N_3O_7$.

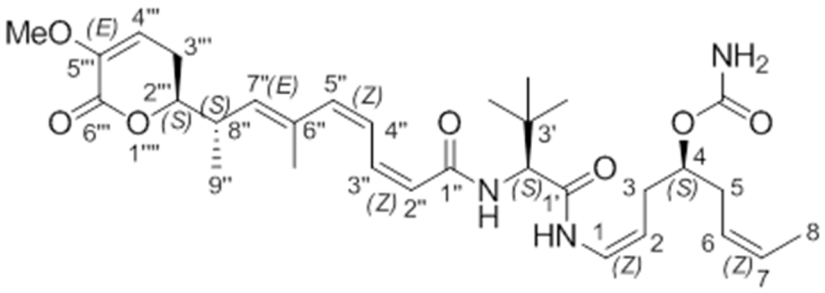
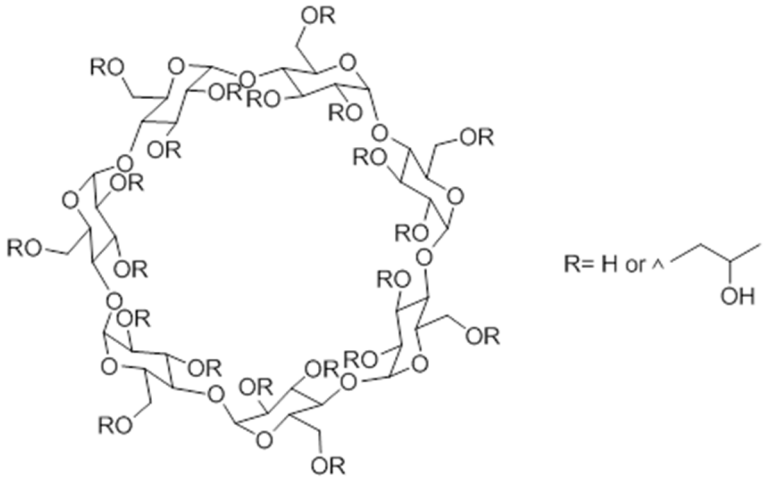


Figure 2. Molecular formula of 2-Hydroxypropyl-β-cyclodextrin: $(C_6H_9O_5)_7(C_3H_7O)_n$ n=4-5.



1.2.2 Non-clinical Data

PM060184 is a new chemical entity that depolimerizes tubulin fibers and causes a disorganization and fragmentation of the microtubule network leading to multipolar mitosis, prometaphase arrest, induction of caspase-dependent apoptosis and/or the appearance of cells in a multinucleated interphase-like state. These effects correlate with induction of cell death.

In vitro, PM060184 demonstrated cytotoxicity against a broad panel of solid human tumor types, with 50% growth inhibition (GI50) values ranging from 40 pM to 5 nM, with the highest activity against representatives of breast (BT-474), colon (HT-29), gastric (HGC-27), lung (A549), prostate (22Rv1), renal (RFX-393) and ovarian (IGROV-1) tumors. *In vivo*, intravenous (i.v.) administration of PM060184 induced strong antitumor activity in different murine models of xenografted human-derived tumor types, such as breast (MAXF401), colon (HCT-116), gastric (HGC-27), non-small cell lung cancer (NSCLC) (H460), prostate (22RV1), renal (Caki-1 or MRI-H-121) and ovarian cancer (A2780 or OVXF 899).

After i.v. administration in CD1 mice, Sprague-Dawley rats, Beagle dogs, *Cynomolgus* monkeys, New Zealand rabbits and Göttingen mini-pigs, PM060184 pharmacokinetics displayed a multi-compartmental distribution, moderate (ranging from ca. 2 to 8 hours) terminal elimination half-lives ($t_{1/2}$) and thus, relatively high plasma clearance (CL). Furthermore, volume of distribution at steady state (V_{ss}) and area under the concentration *vs.* time curves (AUCs) were similar in males and females in all species, except for rat.

The *in vitro* plasma protein binding of PM060184 was higher than 97% in all species tested, including humans (98.7%). *In vitro*, PM060184 underwent extensive turnover by microsomes, with a similar metabolic profile from any of the above mentioned species, humans included. PM060184 showed a limited potential to inhibit or induce cytochrome P450 (CYP) isoforms.

Following single and repeated (three consecutive weekly doses) intravenous administration in rats and dogs, the most toxicologically relevant findings were observed in hematology/bone marrow (leukopenia, thrombocytopenia and

reticulopenia), clinical chemistry (changes in liver function markers), in the gastrointestinal tract (diarrhea and vomiting) and in testes (atrophy). All of them fully recovered by the end of the observation period (Day 29), except for the findings in testes. The more severe, death-causing toxicities were identified as immunosuppression, necrosis, hemorrhages and thrombosis in several organs. As part of the evaluations performed in the general toxicology, heart rate and lead II electrocardiogram-derived variables monitoring was included. The results showed decreases in heart rate and increases in RR and QT intervals that reached a maximal effect at 1 hour post-dose. Furthermore, QTc increases were observed at 6 hours (both genders), and they were still present at 24 hours in the highly dosed groups. In the repeat-dose study, no variations were recorded for any parameter after the third consecutive weekly dose.

No significant gross behavioral or physiological changes were induced by the administration of PM060184 at 8 mg/kg in male rats, although slight changes in the respiratory function (i.e., decreased inspiration time and enhanced pause; increased peak inspiratory flow, respiration rate and minute volume) were observed at one hour post-dose, followed by increased expiration time and decreased respiration rate and minute volume (at 2.5 hours post-dose).

In vitro studies (1) resulted in the identification of CYP isoenzymes involved in phase I-mediated PM060184 metabolism. Incubation of PM060184 (1 µM, 37 ºC, 30 min) with recombinant microsomes expressing CYP isoforms 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and 3A4, suggested that CYP2C19 and CYP3A4 are the two major cytochrome isoforms involved in PM060184 CYP-mediated metabolism (94% and 85%, respectively). CYP2D6 and CYP2C9 also showed involvement to a lesser extent (30% of PM060184 was metabolized). No major contribution of CYP2E1, CYP1A2, CYP2B6 or CYP2A6 isoforms to PM060184 metabolism was seen.

The results gathered from the mechanism of action, *in vitro* and *in vivo* experiments justify the clinical development of PM060184.

1.2.3 Clinical Data

Based on the promising preclinical results described above, the clinical development program of PM060184 was started in January 2011. As of 2014, this clinical development program comprised two phase I single-agent studies in patients with advanced solid tumors, both of which are still ongoing. As of 30th June 2014, 94 patients had been treated with PM060184 in clinical studies.

The first trial (PM060184-A-001-10) evaluated PM060184 administered as a 10-minute (min) infusion on Days 1, 8 and 15 every four weeks (q4wk). The recommended dose (RD) for this schedule was established at 12.0 mg/m^2. The expansion cohort in selected tumors is currently ongoing. The second trial (PM60184-A-002-10) first evaluated PM060184 as a 10-min infusion on Days 1 and 8 q3wk, and determined its RD to be 9.3 mg/m^2. Preclinical studies suggested a similar antitumor effect when a PM060184 dose was split into several daily doses compared to a single administration. Based on these findings, trial PM60184-A-002-10 was amended to determine the safety and efficacy of a new schedule (PM060184 as 10-min infusions on three consecutive days every two weeks in a 28-day cycle. Patient accrual is still ongoing (2, 3).

Similar toxicity profiles were found in all PM060184 schedules evaluated to date. The most frequent dose-limiting toxicity (DLT) observed was grade 3 peripheral sensory neuropathy, with transient symptoms that involved hands and feet. Most episodes of this

adverse event occurred in patients pretreated with oxaliplatin, and some had grade 1 peripheral neuropathy at baseline. As a result, patients pretreated with oxaliplatin or with a previous episode of grade ≥ 2 peripheral neuropathy due to any chemotherapeutic or investigational agents are currently excluded from all clinical trials with PM060184. A rare but potentially life-threatening heart failure was reported in one patient. Common PM060184-related adverse events (AEs) were mild or moderate, and comprised alopecia, fatigue, nausea, vomiting, abdominal pain and peripheral sensory neuropathy. Owing to the finding of PM060184-related nausea or vomiting in > 60% of patients, primary antiemetic prophylaxis with serotonin ($5\text{-}HT_3$) antagonists and steroids is currently compulsory in clinical trials with PM060184. Most hematological and non-hematological laboratory abnormalities reported to date were mild or moderate at all dose levels. Severe abnormalities were transient and generally did not require dose adjustment.

Evidence of objective antitumor activity has been observed in both PM060184 clinical trials. This activity consisted of partial response (PR) in three patients: one with cervix carcinoma, one with breast cancer and one with non-small cell lung cancer (NSCLC). In addition, tumor shrinkage that did not achieve PR criteria was observed in three breast cancer patients (shrinkage of 20-28%), and meaningful disease stabilization in 13 patients with different tumor types (13.8%). One of these disease stabilizations was found in a gastrointestinal stromal tumor (GIST) patient with liver metastases, and was considered to be a PR as per Choi criteria; the patient had a time to progression (TTP) of 20.6 months.

1.3 INFORMATION ON STUDY DRUGS: GEMCITABINE

Gemcitabine (2,2-difluorodeoxycytidine, dFdC) is an antimetabolite and the most important cytidine analog currently used in solid tumors. Alone or in combinations, gemcitabine is commonly used to treat a variety of advanced malignancies, including lymphomas (4) and solid tumors such as breast cancer (5), ovarian cancer (6), stromal uterine sarcomas (7), non-small cell lung cancer (8), exocrine pancreatic carcinoma (9), biliary tract carcinoma (10), relapsed/refractory germ cell tumors (GCTs) (11) and adenocarcinoma of unknown primary site (AUKPS) (12).

Gemcitabine inhibits DNA synthesis. It is actively transported through the cell membrane, and in the cytoplasm it is phosphorylated to its active form, the dFdC 5'-triphosphate (dFdCTP), which is incorporated into the DNA and inhibits the DNA polymerase (13). This potent DNA polymerase inhibition is explained at least in part by the intracellular depletion of deoxyribonucleotide pools through inhibition of the ribonucleotide reductase by the dFdC 5'-diphosphate (dFdCDP) (14). Intracellular conversion of gemcitabine into 2,2-difluorodeoxyuridine (dFdU) by the enzyme cytidine deaminase represents the main catabolic pathway (15). The mechanisms of tumor resistance to gemcitabine are not fully understood. Cells deficient in deoxycitidine kinase (the rate-limiting enzyme in the activation pathway) are resistant to gemcitabine and so are cells overexpressing cytidine deaminase, although overexpression of P-glycoprotein (which also confers resistance to many other drugs) has not been associated with gemcitabine resistance (16).

The main DLT of gemcitabine is myelosuppression, which is mainly characterized by thrombocytopenia and anemia, with a relative sparing of neutrophils (17). Common non-hematological toxicities include flu-like symptoms (fever, headache, back pain and myalgia) and asthenia in approximately 45% and 42% of the patients, respectively. Mild

and transient transaminases elevations [i.e., World Health Organization (WHO) grade 1 or 2 alanine aminotransferase (ALT) increase] were observed in up to 40% of cycles (18). Several rare but potentially life-threatening syndromes have also been described, such as a hemolytic-uremic syndrome or an acute respiratory distress syndrome, possibly in relation with capillary-leaking toxicity.

Weekly (two, three or seven weeks on - one week off) gemcitabine doses of up to 2200 mg/m^2 as a 30-min infusion have been given to non-heavily pretreated cancer patients (19), although due to deoxycitidine kinase saturation (which is the rate-limiting enzyme in the process of activation) at infusion rates of approximately 10 mg/m^2 per min (20), the higher doses resulted in no efficacy improvement. Despite the results of the constant dose-rate-infusion presented by Tempero *et al.* (21), a more practical short i.v. infusion, over 30 min of 800-1000 mg/m^2 weekly was rapidly extended in the clinical practice (18).

For all information related to gemcitabine, please refer to the Summary of Product Characteristics (SPC).

1.4 Information on the Combination of PM060184 and Gemcitabine

The *in vivo* antitumor activity of PM060184 administered alone and in combination with gemcitabine was investigated in a pancreatic cancer model of mice bearing SW1990 xenografted tumors. Treatments administered were: i) placebo; ii) PM060184 at four different dose levels, i.e. maximum tolerated dose (MTD) (16 mg/kg), 0.75•MTD, 0.5•MTD and 0.25•MTD; iii) gemcitabine at four different dose levels, MTD (180 mg/kg), 0.75•MTD, 0.5•MTD and 0.25•MTD; and, iv) PM060184 plus gemcitabine combination, administered at 0.75+0.75, 0.50+0.50, and 0.25+0.25 of their respective MTDs. The highest feasible dose for the PM060184-gemcitabine combination was 0.75+0.75 of their respective MTDs. PM060184 at the MTD resulted in antitumor activity, as reflected by significantly ($p < 0.05$) smaller tumors than in placebo-treated animals. In contrast, gemcitabine at the MTD resulted in marginal antitumor activity ($p < 0.1$) compared to placebo–treated animals. Animals treated with the PM060184-gemcitabine combination at (0.75+0.75)•MTD or (0.50+0.50)•MTD showed a highly significant ($p < 0.01$) reduction of tumor volume compared to placebo-treated animals. In addition, both groups treated with the highest doses [i.e. (0.75+0.75)•MTD and (0.50+0.50)•MTD] showed tumor growth delays (TGD) of 123% and 182%, respectively; these values were longer than those seen with single-agent gemcitabine or PM060184 at their respective MTDs. The analysis by the median-effect principle of the antitumor effect induced by treatments resulted in a combination index (CI) value ≤ 0.1, which suggested a very strong synergistic effect for the combination of both drugs.

1.5 Study Rationale

Because curative therapy has not been established for many solid tumors, there is a need for clinical research to effectively assess new therapeutic proposals including investigational drugs.

PM060184 has been selected for clinical development because *in vitro* demonstrated cytotoxicity against a broad panel of tumor types (breast, colon, renal and ovarian tumors) and *in vivo* induced strong antitumor activity in different murine models of xenografted human-derived tumor types, such as breast, colon, gastric, NSCLC, prostate, renal and ovarian. In addition, PM060184 *in vivo* studies showed a good

tolerability profiling, with no significant signs of systemic and/or local toxicity when given up to 16 mg/kg in a weekly schedule. Evidence of synergistic antitumor activity has been observed *in vivo* when PM060184 was combined with gemcitabine. The clinical toxicity of each compound does not seem to overlap completely, according to currently available data. Therefore, it is feasible to evaluate the safety and efficacy of a combination of PM060184 and gemcitabine in selected patients with advanced solid tumors.

Previous phase I data have shown that an administration schedule on Days 1 and 8 q3wk is feasible for single-agent PM060184, with an RD of 9.3 mg/m^2. In this study, no DLTs occurred among patients treated at or below this RD. Based on these results, a dose of 6.0 mg/m^2, which is equivalent to 64% of the RD for this schedule, was chosen as a safe starting dose level of PM060184 for its combination with gemcitabine in the present study.

The starting dose for gemcitabine will be 800 mg/m^2. This is equivalent to 80% of the RD with this schedule, and is also the minimal gemcitabine dose accepted in clinical practice.

2. STUDY OBJECTIVES

2.1 PRIMARY

- To determine the MTD and the RD of PM060184 in combination with gemcitabine in selected patients with advanced solid tumors.

2.2 SECONDARY

- To characterize the safety profile and feasibility of this combination in this study population.
- To characterize the pharmacokinetics (PK) of this combination and to detect major drug-drug PK interactions.
- To obtain preliminary information on the clinical antitumor activity of this combination.

3. OVERALL STUDY DESIGN

Prospective, open-label, dose-ranging, uncontrolled phase I study with escalating doses of PM060184 in combination with gemcitabine in selected patients with advanced solid tumors.

Following a classical 3+3 design, successive cohorts of patients will receive escalating doses of i.v. gemcitabine over 30 minutes (min), followed by i.v. PM060184 over 10 min on Day 1 and Day 8 q3wk, until the RD is reached. All evaluable patients within a dose level (DL) must be followed for at least one full cycle (i.e., three weeks) before dose escalation may proceed to the next DL.

The MTD will be the lowest DL explored during dose escalation at which more than one third of evaluable patients experienced a DLT during Cycle 1. The RD will be the highest DL explored at which less than one third of evaluable patients experienced a DLT during Cycle 1. Dose escalation will cease immediately once the MTD is reached. Intermediate DLs can be tested, if deemed appropriate upon the Sponsor's and Investigators' agreement.

At least nine evaluable patients will be treated in an expansion cohort at the RD in order to confirm its tolerability and feasibility. Once the RD is confirmed, exploratory cohorts of at least 12 patients each will be expanded at RD in selected tumor type(s) and/or target subpopulations, chosen according to the preliminary efficacy observed among patients treated during dose escalation, discussed and agreed between the Investigators and the Sponsor, as appropriate.

Safety will be evaluated continuously during study participation, and AEs will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), v.4.

Antitumor response will be assessed using the Response Evaluation Criteria In Solid Tumors (RECIST) v.1.1 (or Choi criteria and/or EORTC metabolic response criteria for solid tumors, for GIST patients).

Patients will be evaluated at scheduled visits on three study periods: Pre-treatment, Treatment and Follow-up (see Section 5.2).

3.1 PRIMARY ENDPOINT

3.1.1 Determination of the Maximum Tolerated Dose and the Recommended Dose

The MTD will be the lowest DL explored during dose escalation at which more than one third of evaluable patients experienced a DLT during Cycle 1.

The RD will be the highest DL explored at which less than one third of evaluable patients experience a DLT during Cycle 1. This RD will be confirmed if less than one third of the first nine evaluable patients treated during expansion have DLTs during their Cycle 1.

A patient evaluable for the primary endpoint should have received at least one complete cycle (including the observation period). Patients who are discontinued early or miss/delay doses and/or assessments will be evaluable if these events are the consequence of treatment-related toxicity (excluding hypersensitivity reactions and/or extravasations).

3.1.2 Definition of Dose-limiting Toxicities

DLTs are defined as AEs and laboratory abnormalities related to the study treatment that occurred in an evaluable patient during Cycle 1 and fulfilled at least one of the following criteria:

- Grade 4 neutropenia [absolute neutrophil count (ANC) $< 0.5 \times 10^9$/l] lasting > 3 days.
- Grade ≥ 3 febrile neutropenia of any duration or neutropenic sepsis.
- Grade 4 thrombocytopenia (platelet count $< 25 \times 10^9$/l) or grade 3 with any major bleeding episode requiring a platelet transfusion.
- Grade 4 ALT and/or aspartate aminotransferase (AST) increase, or grade 3 lasting > 7 days.
- Treatment-related grade ≥ 2 ALT or AST increase concomitantly with ≥ 2 x upper limit of normal (ULN) total bilirubin increase and normal alkaline phosphatase (AP).
- Any other grade ≥ 3 non-hematological AE that is suspected to be related to study drug(s), except nausea/vomiting (unless the patient is receiving an optimal anti-emetic regimen), hypersensitivity reactions, extravasations, grade 3 asthenia

lasting less than one week, anorexia, and non-clinically relevant isolated biochemical abnormalities [e.g., isolated increase in gamma-glutamyltransferase (GGT)]. In any case, the clinical relevance should be discussed between the Investigators and the Sponsor's representatives.

- Delay in the administration of Cycle 2 of the combination exceeding seven (+1) days of the treatment due date (i.e., Day 22) due to any AEs related to study drug(s).
- The following circumstances will be discussed between the Principal Investigator and the Sponsor, and the final consensus will be documented:
  - DLTs with delayed onset (i.e., that occur after Cycle 1).
  - Non-compliance with the intended dose intensity (DI) in more than half of patients at any dose level (i.e., missing infusions on Day 8 or frequent dose delays due to treatment-related toxicity despite not conforming to a formal DLT definition).

3.2 SECONDARY ENDPOINTS

3.2.1 Safety

Patients will be evaluable for safety if they have received at least one partial or complete infusion of PM060184 and one partial or complete infusion of gemcitabine. AEs will be graded according to the NCI-CTCAE v.4. For further details on safety evaluation see Section 9.2.

3.2.2 Pharmacokinetics

Pharmacokinetic analyses will be evaluated in plasma by standard non-compartmental analysis (NCA) (compartmental modeling may be performed if appropriate). Samples for PK analysis will be obtained during Cycle 1 (see Section 9.7).

3.2.3 Efficacy

Although it is not the main objective of this study, antitumor activity will be evaluated according to the RECIST v.1.1 in all patients with measurable disease, according to Choi criteria and/or EORTC metabolic response criteria for solid tumors in GIST patients, or by evaluation of serum tumor markers if applicable (e.g., ovarian cancer) every two cycles (i.e., approximately every six weeks) ± one week after treatment initiation until Cycle 4. Patients continuing treatment after Cycle 4 will have the assessments performed every three cycles (i.e., approximately every nine weeks) ± one week from Cycle 4 while on treatment, unless otherwise is clinically indicated. Patients included in the expansion cohort at the RD and in the tumor-specific cohorts must be evaluable as per RECIST v.1.1 (or Choi criteria and/or EORTC metabolic response criteria for solid tumors, in the case of GIST), or by tumor markers (see Section 9.6).

3.2.4 Pharmacogenetics

This analysis will be performed in those patients who signed the ICF for the pharmacogenetic substudy. A blood sample will be collected at any time during the study, but ideally along with the pre-treatment PK sample on Day 1 of Cycle 1, to evaluate the presence or absence of known polymorphisms that may explain individual variability in main PK parameters.

3.3 DOSE ESCALATION SCHEME

The starting dose (DL1) for gemcitabine will be 800 mg/m^2. This corresponds to a DI of 533.33 mg/m^2/week, and is equivalent to 80% of the RD with this schedule. This is the minimal gemcitabine dose accepted in clinical practice.

The DL1 for PM060184 will be 6.0 mg/m^2. This corresponds to a DI of 4.0 mg/m^2/week, and is equivalent to 64% of the RD determined for PM060184 given as single agent with this schedule.

The dose escalation scheme will follow pre-defined dose levels, starting at DL1, as summarized in Table 1.

Table 1. Dose escalation scheme.

DL	No. of patients	Relative DI (%) of gemcitabine / PM060184	Gemcitabine dose (mg/m^2) on Day 1 and Day 8 q3wk	PM060184 dose (mg/m^2) on Day 1 and Day 8 q3wk
DL-1	0-6	80/53	800	5.0
DL1	3-6	80/64	800	6.0
DL2	3-6	80/74	800	7.0
DL3	3-6	100/74	1000	7.0
DL4 and beyond	3-6		No further dose increases beyond 1000 mg/m^2	Further dose increases of 0.5 or 1.0 mg/m^2, according to observed toxicities

DI, dose intensity; DL, dose level; MTD, maximum tolerated dose.

- Cohorts of at least **three** fully evaluable patients will be treated at each cohort.
- The second and third patients of a cohort may be included simultaneously after the first patient has completed the first cycle, except if a DLT is reported in the first patient, in which case the third patient of the cohort will be included once the second patient has received a complete treatment cycle with no reported DLTs. All patients will have to be fully evaluable (3-week period) prior to any further dose escalation. Patients not fully evaluable will be replaced.
- Dose escalation will continue if no DLT is observed.
- Subsequent dose levels will enroll three patients, and up to six fully evaluable patients if one DLT is observed in any of the first three fully evaluable patients.
- Once a DLT is observed, further patients will be included up to **six** fully evaluable patients in this dose cohort.
- **For gemcitabine**: two doses (800 mg/m^2 and 1000 mg/m^2) will be initially tested. If the toxicity observed during dose escalation is clearly related to gemcitabine (i.e. neutropenia and/or thrombocytopenia), intermediate gemcitabine doses might be tested after agreement between the Investigators and the Sponsor.
- **For PM060184:** pre-established PM060184 doses have been set for the first three DLs. After DL3, dose increments of 1.0 mg/m^2 will be tested if toxicity at each previous DL is acceptable. These dose increments may be of 0.5 mg/m^2, according to the toxicity observed. In the event of toxicities specifically related with PM060184 (i.e. peripheral neuropathy, post-infusion abdominal pain and/or diarrhea), intermediate PM060184 doses might be tested after agreement between the Investigators and the Sponsor.

Both the PM060184 and the gemcitabine doses may be rounded to the first decimal.

If more than one of three or six evaluable patients at any DL experience a DLT during Cycle 1, dose escalation will be terminated. The MTD will be the lowest level at which more than one third of evaluable patients experienced a DLT in Cycle 1 (Table 2). The RD will be the highest DL explored with less than one third of evaluable patients experiencing a DLT during Cycle 1.

Table 2. Determination of the maximum tolerated dose.

No. of patients evaluable for DLT	No. of patients with DLTs in Cycle 1	Action
3	0	Escalate DL
	1	Add 3 patients
	>1	MTD
6	1	Escalate DL
	>1	MTD

DL, dose level; DLT, dose-limiting toxicities; MTD, maximum tolerated dose.

If two or more evaluable patients (of 3-6 patients) at any DL experience a dose delay > 7 (+1) days from the theoretical due date (conforming or not to DLT criteria) and/or dose omissions exclusively related to PM060184 toxicity during Cycle 1, the cohort should be expanded as shown in the table below. If more than 50% of evaluable patients in a cohort experience dose delays and/or omissions, dose escalation will be terminated and this DL will be considered the MTD. An alternative schedule could then be explored after discussion between the Investigators and with the Sponsor's agreement. The starting dose of the new schedule will be the DL immediately below the MTD.

Table 3. Cohort expansion and determination of the maximum tolerated dose in the event of dose delays/omissions in Cycle 1.

Dose delays	Dose omissions	Action
1	-	None
-	1	None
1	1	Add 3 more patients
≥ 2	-	Add 3 more patients
-	≥ 2	Add 3 more patients
If more than 50% evaluable patients in a cohort have dose delays and/or omissions		MTD

DLT, dose-limiting toxicities; MTD, maximum tolerated dose.

An expansion cohort of a minimum of nine evaluable patients will be treated at the RD once it has been determined; this is to confirm its feasibility and tolerability. Once the RD is confirmed, exploratory cohorts of at least 12 patients each will be expanded at RD in selected tumor type(s) and/or target subpopulations, chosen according to the preliminary efficacy observed among those previously treated during dose escalation, discussed and agreed between the Investigators and the Sponsor.

Intra-patient dose escalation will not be allowed under any circumstances.

3.3.1 Dose Escalation Meetings

The Sponsor will organize raw data review and discussion (e.g., a teleconference) with the investigators on a regular basis as needed according to study course (e.g., after the first patient enrolled at a given DL has completed the first cycle or when a DL cohort has been completed).

Prior to the meeting, all relevant safety and laboratory non-monitored data must be made accessible by the Investigators to the Sponsor's responsible, preferably using the electronic Case Report Form (e-CRF). Investigators must guarantee the accuracy of the information provided against the source documents.

At the dose escalation discussions, all available clinical data (safety information, including all events that might be considered DLTs, and all grade ≥ 2 toxicity data at least during Cycle 1, as well as available PK data) of each treated patient will be described and discussed in detail. Updated safety data from prior patients, including prior treatment cycles and serious adverse events (SAEs), will also be discussed, if appropriate. The Sponsor will document the final agreement or decision adopted, and will keep the information and all support documents in the trial master file.

Finally, available slot assignment for the next cohort of patients will also be updated during these discussions. Whenever possible, the slot assignment will be similarly distributed among participating centers and according to the number of identified candidates. However, in order not to slow down the recruitment a maximal 2-week period is allowed to effectively start treatment after slot assignment. Failure to do so, in the presence of waiting candidates in another participating center, will result in competitive slot re-allocation. The Investigators will be responsible for informing the Sponsor of any potential candidates on screening at that time. The Sponsor will immediately update all other investigators on slot availability as soon as a screening failure is notified; these slots will be allocated by competitive enrolment.

4. SELECTION OF PATIENTS

Patients must fulfill all the following inclusion criteria and none of the exclusion criteria to be eligible to participate in the study.

4.1 INCLUSION CRITERIA

1) Voluntarily signed and dated written informed consent prior to any specific study procedure.

2) Age ≥ 18 years.

3) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 1 (see APPENDIX 1).

4) Life expectancy ≥ 3 months.

5) Patients with a histologically/cytologically confirmed diagnosis of advanced disease of any of the following tumors that progressed to standard therapy or for whom no standard therapy exists (with the exception of neuroendocrine, carcinoid, small cell and sarcoma histology subtypes, which are not allowed):

a) Breast cancer non-candidate for hormone therapy alone.

b) Epithelial ovarian cancer (including primary peritoneal disease and/or fallopian tube carcinomas and/or endometrial adenocarcinomas).

c) Locally advanced or metastatic head and neck cancer.

d) Non-small cell lung cancer (NSCLC).

e) Germ cell tumors (GCTs).

f) Biliary tract adenocarcinoma.

g) Adenocarcinoma or carcinoma of unknown primary site (UKPS).
h) Cervix carcinoma.
i) Gastrointestinal stromal tumor (GIST).
j) Urothelial cancer.

6) Expansion cohort at the RD and tumor-specific cohorts:

All patients must have:

a) Measurable disease according to RECIST v.1.1 (or Choi criteria and/or EORTC metabolic response criteria for solid tumors, in the case of GIST); or
b) Evaluable disease by serum markers in the case of ovarian cancer [Gynecologic Cancer Intergroup (GCIG) specific criteria]; and
c) Documented disease progression during or immediately after last therapy according to any of the aforementioned criteria.

7) Wash-out periods: at least three weeks since the last administration of an anticancer therapy, including radiation therapy (RT) or a biological/investigational therapy [excluding monoclonal antibodies (MAbs)]; at least four weeks since the last MAb-containing therapy; and at least six weeks since nitrosoureas and mitomycin C (systemic). In the case of hormone-sensitive breast cancer progressing while on hormone therapy, the latter must be either stopped up to one week before or continued without changes during the trial.

8) Adequate bone marrow, renal, hepatic, and metabolic function (assessed ≤ 7 days before inclusion in the study):

a) Platelet count ≥ 100 x 10^9/l, hemoglobin ≥ 9.0 g/dl and ANC ≥ 1.0 x 10^9/l.
b) AST and ALT ≤ 3.0 x ULN, independently of the presence of liver metastases.
c) AP ≤ 2.5 x ULN (≤ 5 x ULN if disease-related).
d) Total bilirubin ≤ 1.5 x ULN.
e) International Normalized Ratio (INR) < 1.5 (except if patient is on oral anticoagulation therapy).
f) Calculated creatinine clearance (CrCl) ≥ 50 ml/min (using Cockcroft and Gault's formula; see APPENDIX 2).
g) Albumin ≥ 2.5 g/dl.

9) Recovery to grade ≤ 1 from any AE derived from previous treatment (excluding alopecia and/or cutaneous toxicity and/or asthenia).

10) Left ventricular ejection fraction (LVEF) by echocardiography (ECHO) or multiple-gated acquisition (MUGA) within normal range (according to institutional standards).

11) Women of childbearing potential must have a negative serum or urine pregnancy test before study entry. Both women and men must agree to use a medially acceptable method of contraception throughout the treatment period and for six months after discontinuation of treatment. Acceptable methods of contraception include intrauterine device (IUD), oral contraceptive, subdermal implant and/or double barrier.

4.2 EXCLUSION CRITERIA

1) Concomitant diseases/conditions:

a) History or presence of unstable angina, myocardial infarction, congestive heart failure, or clinically significant valvular heart disease within last year.
b) Symptomatic arrhythmia or any uncontrolled arrhythmia requiring ongoing treatment.
c) Known chronic active hepatitis or cirrhosis.
d) Active uncontrolled infection [i.e., antibiotic, antifungal or antiviral intervention indicated or surgical procedure (i.e., pleural or deep abscess drainage) conducted within 15 days prior to inclusion].
e) Known human immunodeficiency virus (HIV) infection.
f) Current or prior history of grade ≥ 2 peripheral sensory and/or motor neuropathy.
g) Prior treatment with oxaliplatin.
h) Limitation of the patient's ability to comply with the treatment or follow-up protocol.
i) Any other major illness that, in the Investigator's judgment, will substantially increase the risk associated with the patient's participation in this study.

2) Symptomatic, progressive or corticosteroids-requiring documented brain metastases or leptomeningeal disease involvement.

3) Men or women of childbearing potential who are not using an effective method of contraception as previously described; women who are pregnant or breast feeding.

4) Patients who have had RT in more than 35% of the bone marrow (see APPENDIX 3).

5) Prior treatment with PM060184.

6) Prior treatment with gemcitabine-containing therapy for advanced disease (adjuvant therapy is allowed, provided not more than six cycles were administered and relapse occurred more than six months after the last drug administration), and/or:
a) Patients who have previously discontinued gemcitabine-containing regimens due to gemcitabine-related toxicity.

7) Known hypersensitivity to gemcitabine or any component of the formulation.

4.3 PATIENTS FOR THE PHARMACOGENETIC EVALUATIONS

1) Only patients who voluntarily give their consent and sign the ICF for the pharmacogenetic substudy will participate. Refusal to participate will not affect patient participation in the clinical study PM60184-A-003-14.

5. PLAN OF THE STUDY

5.1 PLANNED TRIAL PERIODS (FOR THE WHOLE STUDY)

The total duration of the study will be approximately 69 months, including approximately a 60-month enrolment period.

Planned start date (first patient on study): 4Q2014.

Planned enrolment period: approximately 60 months.

Planned end-of-study date (clinical cutoff): six months after the last patient's treatment discontinuation (last patient-last visit), or nine months after accrual of the last evaluable patient, whichever occurs first.

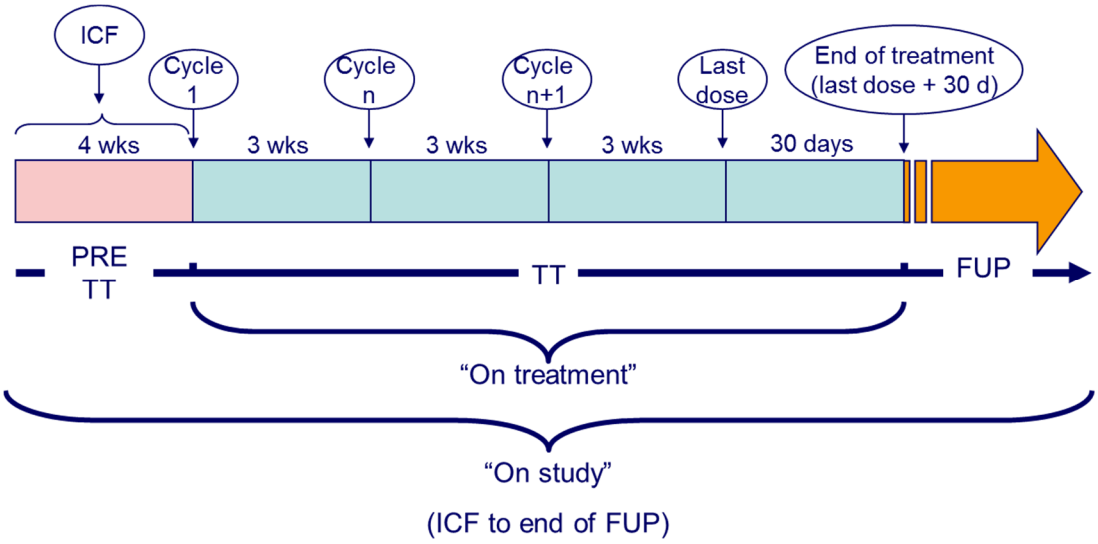
5.2 PLANNED TRIAL PERIODS (INDIVIDUALLY PER PATIENT)

Patients will be evaluated at scheduled visits in three study periods:

- **Pre-treatment:** from signature of IC to the day of first infusion of study drugs.
- **Treatment:** from first infusion of study drugs to the *end of treatment* (EOT) (see Section 5.2.1).
- **Follow-up**: after EOT, patients will be followed every four weeks until resolution or stabilization of relevant related (i.e., grade > 1) toxicities if any. Patients who discontinued treatment without disease progression will be followed every three months until disease progression, other antitumor therapy, death or until the date of study termination (clinical cutoff), whichever occurs first.

Patients will be considered to be **on-study** from the signature of the IC to the end of the follow-up period. Patients will be considered to be **on-treatment** for the duration of their treatment and until the EOT. This EOT is defined as 30 days (±15 days) after the day of the last study drug dose administration (see Figure 3). An EOT visit will be performed within 30 days (± 15 days) after the last study drug dose administration, unless the patient starts any subsequent antitumor therapy (in which case the EOT visit should be performed before the start of the new therapy, whenever possible). If the patient dies while on treatment, the date of death will be considered the EOT date

Figure 3. Study periods.



d, day; FUP, follow-up; ICF, informed consent form; PRE TT, pre-treatment; TT, treatment; wk, week.

Patients may withdraw their consent at any time; under this circumstance, no further study activities will be conducted on them.

5.2.1 Discontinuations

5.2.1.1 *End of Treatment*

Treatment discontinuation occurs when an enrolled patient ceases to receive PM060184 and gemcitabine regardless of the circumstances. The primary reason for any treatment discontinuation will be recorded on the patient's e-CRF.

An *end-of-treatment visit* (*EOT visit*) will be performed within 30 days (± 15 days) after the last study drug dose administration, unless the patient starts any subsequent new antitumor therapy outside this clinical trial (in which case the EOT visit should be performed immediately before the start of the new therapy, whenever possible).

If a patient discontinues treatment, every effort should be made to complete the scheduled assessments as appropriate, whenever possible.

5.2.1.2 *Reasons for End of Treatment*

Patients will receive the study drugs while it is considered to be in their best interest. Specifically, treatment will continue until:

- Disease progression.
- Unacceptable toxicity.
- Intercurrent illness of sufficient magnitude to preclude fulfillment of appropriate re-treatment criteria and/or safe continuation of the study.
- Patient refusal and/or non-compliance with study requirements.
- Treatment delay > 7 (+1) days from the theoretical due date due to toxicity (except in case of patient's clear clinical benefit, with the Sponsor's approval).
- Requirement of > 2 dose reductions.

Patients who are withdrawn for any reasons must not be re-treated in the context of this study at any time. For follow-up activities, please refer to Section 5.9.

5.2.1.3 *Study Discontinuation*

Study discontinuation occurs when an enrolled patient ceases to participate in the study, regardless of the reason (as detailed under "Follow-up" in Section 5.2). Patients have the right to withdraw consent at any time; if this is the case, no further study procedures should be performed, and no further data should be collected from the date of consent withdrawal.

The date and reason for study discontinuation will be clearly documented on the patient's e-CRF.

5.2.2 Protocol Deviations

A protocol deviation is defined as any departure from what is described in the protocol of a clinical trial approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and Competent Authorities. Therefore, it applies to deviations related to patient inclusion and clinical procedures (e.g., assessments to be conducted or parameters to be determined), and also to other procedures described in the protocol that concern the Good Clinical Practice (GCP) guidelines or ethical issues (e.g., issues related to obtaining the patients' Informed Consent, data reporting, the responsibilities of the Investigator, etc.).

Deviations with no effects on the risk/benefit ratio of the clinical trial (such as minimal delays in assessments or visits) will be distinguished from those that might have an effect on this risk/benefit ratio, such as:

- Deviations that might affect the clinical trial objectives, such as those involving the inclusion/exclusion criteria (which could mean that the patient is not eligible for the trial) and those having an effect on patient evaluability.
- Deviations that might affect the patient's well-being and/or safety, such as an incorrect dosing of the investigational medicinal product due to not following dose adjustment specifications or an incorrect preparation of the medication.
- Deviations related to the following of GCP guidelines as described in the protocol and regulations in force, such as deviations when obtaining the IC or not following the terms established for reporting SAEs, etc.

As a general rule, NO deviations that may have an effect on the risk/benefit ratio of the clinical trial will be authorized. All protocol deviations detected during the study will be appropriately documented, and those considered particularly relevant (i.e., those related to ethical issues, to fulfillment of GCP guidelines and with an effect on the risk/benefit ratio) will be notified to the pertinent IEC/IRB and, if applicable, to the Competent Authorities as established by local regulations.

5.3 REPLACEMENT OF PATIENTS

Patients must be replaced if they are not fully evaluable for the assessment of the primary endpoint, i.e. if:

- They are withdrawn from the study before receiving at least one evaluable cycle for any reason other than treatment-related toxicity (excluding hypersensitivity and/or extravasations reactions). An evaluable cycle is defined as: gemcitabine followed by PM060184 on Day 1 and Day 8, with the corresponding 2-week observation period during the first cycle.
- They require RT or other therapeutic procedure within three weeks after the first study drug dose, unless they previously had another treatment-related AE included in the definition of DLT.
- There is a protocol violation resulting in an impossibility of concluding anything regarding the safety of the study therapy.

All replaced patients will be included in the general safety analysis and in the efficacy analysis (if appropriate).

5.4 PRE-TREATMENT ASSESSMENTS

During the pre-treatment period, following signature of the IC form, the Investigator will confirm the patient's eligibility for the study by conducting the assessments summarized in Table 4.

Table 4. Screening period: pre-treatment assessments.

	ASSESSMENT	TIME
1. Written informed consent		Before any study procedures.
2. Pharmacogenetics informed consent (optional)		Before any study procedures.
3. Medical and	◆ Demographic data (race/ethnicity, age, gender,	Within 28 days before the start of

	ASSESSMENT	TIME
cancer history/ clinical examination	height). ◆ Medical and cancer history/baseline condition: ○ Date of diagnosis of the primary disease. ○ Prior treatments (surgery, radiotherapy, chemotherapy, biological/targeted agents), specifying best response and date of PD, when available.	treatment. *
	◆ Assessment of signs and symptoms.	Within 28 days before the start of treatment. *
	◆ Complete physical examination, including weight and BSA. ◆ Performance status (ECOG PS; see APPENDIX 1). ◆ Vital signs: heart rate, blood pressure and body temperature.	Within seven days before the start of treatment. *
	◆ Concomitant therapies.	Within 14 days before the start of treatment. *
4. Laboratory tests	◆ **Hematology:** differential WBC (neutrophils, lymphocytes), hemoglobin and platelets. ◆ **Biochemistry-A:** AST, ALT, total bilirubin, AP, LDH, creatinine, glucose and serum electrolytes (Na^+, K^+, Cl^-, total calcium). ◆ **Biochemistry-B and coagulation:** ○ Total proteins, albumin. ○ Coagulation tests: PT, aPTT, INR. ○ Exploratory serum tumor markers as appropriate, according to primary tumor type.	Within seven days before the start of treatment. *
5. Pregnancy test (if premenopausal woman of childbearing potential)	Assessment of β-hCG (urine or serum).	Within seven days before the start of treatment. *
6. Cardiac assessment	ECG **	Within 28 days before the start of treatment. *
	LVEF by ECHO or MUGA.	Within 28 days before the start of treatment. *
7. Radiological tumor assessment	Helical contrast-enhanced CT-scan and/or gadolinium-enhanced MRI of all measurable/evaluable sites as per RECIST v.1.1, Choi criteria and/or EORTC metabolic response criteria, as applicable (see APPENDIX 4 and APPENDIX 5). ***	Within 28 days before the start of treatment. *
8. PK	One blood sample (as in Section 6).	Immediately before the start of treatment.
9. Pharmacogenetics	One blood sample. ****	At any time during the study, but ideally immediately before the start of treatment (always after the specific optional consent has been given).
10. Adverse events	Only information on SAEs that occurred after signature of the ICF is required before treatment start. Grading should be as per the NCI-CTCAE v.4.	-

* A -24-hour window will be allowed for clinical assessments (ECOG PS, vital signs, weight, BSA, etc.), a -24-hour window for laboratory procedures, and a ±1-week window for radiological procedures.
** ECG should allow rhythm definition, and should include assessment of PR interval, heart rate, QT interval (raw) and QRS complex duration.
*** PET-CT scan might be used, if appropriate additionally, on individual cases upon the Sponsor's agreement. **Patients with GIST should always be assessed with PET-CT scans, and efficacy will be evaluated according to Choi criteria and/or EORTC metabolic response criteria for solid tumors.**
**** One blood sample will be collected to evaluate the presence or absence of known polymorphisms.

ALT, alanine aminotransferase; AP, alkaline phosphatase; aPTT, activated plasma thromboplastin time; AST, aspartate aminotransferase; BSA, body surface area; CT-scan, computed tomography scan; ECG, electrocardiogram; ECHO, echocardiography; ECOG, Eastern Cooperative Oncology Group; EORTC, European

	ASSESSMENT	TIME

Organization for Research and Treatment of Cancer; β-hCG, beta subunit of human chorionic gonadotropin; ICF, informed consent form; INR, international normalized ratio; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition scan; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PD, progressive disease; PET, positron emission tomography; PK, pharmacokinetics; PS, performance status; PT, prothrombin time; RECIST, Response Evaluation Criteria In Solid Tumors; SAE, serious adverse event; WBC, white blood cells.

5.5 PATIENT REGISTRATION

Once the screening period testing has been done in order to confirm that the consenting candidate meets all eligibility criteria, the patient can be registered into the study by completing the electronic screening form. This form will be checked and eligibility confirmed by the Sponsor. An identification number will be automatically assigned (by the system) to the patient during registration; this number should be used on all future documentation and correspondence referring this patient. Regardless of circumstances, the Investigators will not be allowed to treat any patient before appropriate receipt of the Sponsor's agreement.

For patients registered but never treated, only baseline and off-study visits modules of the e-CRF should be completed.

5.6 PATIENT RANDOMIZATION

Not applicable.

5.7 EVALUATIONS DURING TREATMENT

The following assessments will be done while the patient is on treatment (Table 5).

Table 5. Evaluations during treatment.

	ASSESSMENT	TIME
1. Clinical examination	◆ Complete physical examination, including weight and BSA.	Cycle 1: Day 1 (always prior to treatment administration), **but only if not done at screening.** Cycle 2 and further: Day 1 (always prior to treatment administration). * BSA will have to be recalculated before treatment administration in subsequent cycles for patients showing a ≥10 % variation in total body weight from baseline or from last dose adjustment; otherwise the BSA and dose calculated for the previous cycle could be used. The same BSA calculation method should be used throughout the study.
	◆ Performance status (ECOG PS; see APPENDIX 1). ◆ Vital signs**:** heart rate, blood pressure and body temperature.	Cycle 1: Day 8 (always prior to treatment administration) and Day 15. Also on Day 1 prior to treatment administration, **but only if not done at screening.** Cycle 2, 3 and 4: Days 1 and 8 (always prior to treatment administration) and Day 15. * Cycle 5 and further: Days 1 and 8 (always prior to treatment administration), unless otherwise is clinically indicated. *
	◆ Concomitant therapies.	Throughout the "on treatment" period. **
2. Laboratory tests	◆ **Hematology:** differential WBC (neutrophils, lymphocytes), hemoglobin and platelets.	Cycle 1: Day 8 (always prior to treatment administration) and Day 15. * Also on Day 1 prior to treatment

	ASSESSMENT	TIME
		administration, **but only if not done at screening.** Cycles 2, 3 and 4: Days 1 and 8 (always prior to treatment administration) and Day 15. * Cycle 5 and further: Days 1 and 8 (always prior to treatment administration), unless otherwise is clinically indicated. * During the first four cycles, if any clinically relevant **treatment-related NCI-CTCAE grade ≥ 3 toxicity** occurs, the abnormal test(s) should be re-assessed **at least every 2-3 days until recovery to at least grade 2**. In the event of **febrile neutropenia, grade 4 neutropenia and/or grade 4 thrombocytopenia, re-assessment should be performed daily until recovery to at least grade 3** or until fever resolution, if applicable, and then every 2-3 days thereafter until recovery to at least grade 2. From Cycle 5 onwards, any treatment-related NCI-CTCAE grade ≥ 3 toxicity not considered a major risk for the patient is to be re-evaluated according to Investigator's criteria.
	◆ **Biochemistry-A:** AST, ALT, total bilirubin, AP, LDH, creatinine, glucose and serum electrolytes (Na^+, K^+, Cl^-, total calcium).	Cycle 1: Day 8 (always prior to treatment administration) and Day 15. * Also on Day 1 prior to treatment administration, **but only if not done at screening.** Cycles 2, 3 and 4: Days 1 and 8 (always prior to treatment administration) and Day 15. * Cycle 5 and further: Days 1 and 8 (always prior to treatment administration), unless otherwise is clinically indicated. * During the first four cycles, if any clinically relevant **treatment-related NCI-CTCAE grade ≥ 3 toxicity** occurs, the abnormal test(s) should be re-assessed **at least every 2-3 days until recovery to at least grade 2**. From Cycle 5 onwards, any treatment-related NCI-CTCAE grade ≥ 3 toxicity not considered a major risk for the patient is to be re-evaluated according to Investigator's criteria.
	◆ **Biochemistry-B and coagulation:** o Total proteins, albumin. o Coagulation tests: PT, aPTT, INR. o Repeat only the same serum tumor marker that was abnormally elevated at baseline (≥2 x ULN), if applicable.	Cycle 1: Day 1 (always prior to treatment administration), **but only if not done at screening**. Cycle 2 and further: Day 1 (always prior to treatment administration). *
3. Pregnancy test (if premenopausal woman of childbearing potential)	Assessment of β-hCG (urine or serum).	Repeat if clinically indicated.
4. Cardiac assessment	ECG. ***	Repeat if clinically indicated (reason should be specified in the e-CRF). **
	LVEF by ECHO or MUGA. ****	Every other cycle.

	ASSESSMENT	TIME
5. Radiological tumor assessment	Helical contrast-enhanced CT-scan and/or gadolinium-enhanced MRI of all measurable/evaluable sites as per RECIST v.1.1, Choi criteria and/or EORTC metabolic response criteria for solid tumors, as applicable (see APPENDIX 4 and APPENDIX 5). *****	Every two cycles ± one week until Cycle 4, and then every three cycles ± one week from Cycle 4 while on treatment, unless otherwise is clinically indicated. The same method should always be used for each individual patient throughout the study.
6. PK	As in Section 6.	Nine blood samples collected from Day 1 to Day 2 of Cycle 1. Patients treated in the expanded cohort at the RD will also be sampled for PK analysis on Day 1 and Day 2 of Cycle 2 at the same time points.
7. Pharmacogenetics	One blood sample.	At any time during the study (always after the specific optional consent has been given).
8. Adverse events	As per NCI-CTCAE v.4.	Throughout the "on treatment" period. **

* A -24-hour window will be allowed for clinical assessments (ECOG PS, vital signs, weight, BSA, etc.), a -24-hour window for laboratory procedures (a -48-hour window on infusion days, excluding Day 1 of Cycle 1), and a ±1-week window for radiological procedures. Additionally, for D15 a +24 hour window will also be allowed for clinical assessments and laboratory procedures.
** "On treatment period" = from first study drug administration to EOT. The EOT visit will be performed within 30 days (± 15 days) after the last study drug dose administration, unless the patient starts any subsequent antitumor therapy (in which case the EOT visit should be performed before the start of the new therapy, whenever possible).
*** ECG should allow rhythm definition, and should include assessment of PR interval, heart rate, QT interval (raw) and QRS complex duration.
**** In the event of LVEF decrease to grade ≥ 2 by MUGA, an ECHO should be done to confirm this decrease and also to rule out any heart injures. Major efforts must be done to find the main cause of this AE (cardiac enzymes, troponin I and or T, cardiologist assessment, etc.). LVEF by ECHO should be performed at least every four weeks until recovery or stabilization.
***** PET-CT scan must be used, if appropriate, on individual cases upon Sponsor's agreement. **Patients with GIST should always be assessed with fusion or integrated PET-CT scans, and efficacy will be evaluated by Choi criteria and/or EORTC metabolic response criteria for solid tumors.** Anonymized copies of the images showing objective response or meaningful tumor shrinkage must be submitted to the Sponsor.

AE, adverse event; ALT, alanine aminotransferase; AP, alkaline phosphatase; aPTT, activated plasma thromboplastin time; AST, aspartate aminotransferase; BSA, body surface area; CT-scan, computed tomography scan; ECG, electrocardiogram; ECHO, echocardiography; ECOG, Eastern Cooperative Oncology Group; e-CRF, electronic case report form; EORTC, European Organization for Research and Treatment of Cancer; EOT, end of treatment; GIST, gastrointestinal stromal tumor; β-hCG, beta subunit of human chorionic gonadotropin; INR, international normalized ratio; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition scan; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PET, positron emission tomography; PK, pharmacokinetics; PS, performance status; PT, prothrombin time; RD, recommended dose; RECIST, Response Evaluation Criteria In Solid Tumors; ULN, upper limit of normal; WBC, white blood cells.

5.8 EVALUATIONS AT END OF TREATMENT

The *EOT visit* will be scheduled within 30 days (± 15 days) after the last study drug dose administration, unless the patient starts any subsequent antitumor therapy, in which case the EOT visit should be performed immediately before the start of the new therapy, whenever possible.

Evaluable patients, regardless of the reason for ending the treatment, will have to undergo the following assessments at the EOT visit (with a ± 15-day window to conduct them):

- Complete physical examination [including weight and body surface area (BSA)].
- ECOG PS.
- Vital signs (heart rate, blood pressure, body temperature).

- Hematology.
- Biochemistry-A.
- Biochemistry-B and coagulation.
- LVEF.
- Concomitant therapies.
- Adverse events.

On individual patients and if clinically indicated according to the Investigator's criteria, it might also include the following:

- Pregnancy test.
- Electrocardiogram (ECG).
- Other tests as appropriate.

All these evaluations will only have to be repeated for those parameters for which no measurement is available within 15 (-3) days before the EOT visit, or for those parameters with values that were out of range in the last assessment (grade > 1 according to NCI-CTCAE v.4).

Adverse events must be reported for 30 days after the last study treatment administration. All SAEs occurring within 30 days of the last study drugs administration will be reported. Beyond this period of time, only those suspected to be treatment-related SAEs will be reported (Section 9.4.2).

The Sponsor will evaluate all safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

5.9 FOLLOW-UP AFTER END-OF-TREATMENT VISIT

The date and reason of the study discontinuation will be recorded on the patient's e-CRF (see Section 5.2.1.1).

Patients who discontinue treatment without disease progression will be followed every three months until disease progression, other antitumor therapy, death or until the date of study termination (clinical cutoff), whichever occurs first.

The end-of-study date (clinical cutoff) is defined as six months after the last patient's treatment discontinuation (last patient-last visit), or nine months after accrual of the last evaluable patient, whichever occurs first.

All relevant AEs (grade > 1) suspected to be related to study drugs must be followed after the end of treatment until the event resolve or stabilize (i.e., to grade 1), or until start of a new therapy. After the end of treatment, patients will be followed every four weeks until resolution or stabilization of toxicities, if any, or until onset of new therapy.

Patients who withdraw consent will not be followed with any study procedures, and no additional data will be collected after consent withdrawal.

Additional parameters and/or increased frequency of observations should be performed at the Investigator's discretion and according to the nature of the observed AEs. In case of death, when available, autopsy data should be provided.

6. PHARMACOKINETICS

The plasma PK of PM060184, gemcitabine and 2,2-difluorodeoxyuridine (dFdU) will be evaluated during Days 1 and 2 of Cycle 1 with a schedule of ten samples in all patients. Additionally, patients treated in the expanded cohort at RD and in the tumor-specific cohorts will be sampled for PM060184 analysis on Days 1 and 2 of Cycle 2 at the same time points.

The sampling schedule for both compounds is described in Table 6, taking as reference the gemcitabine infusion on Day 1.

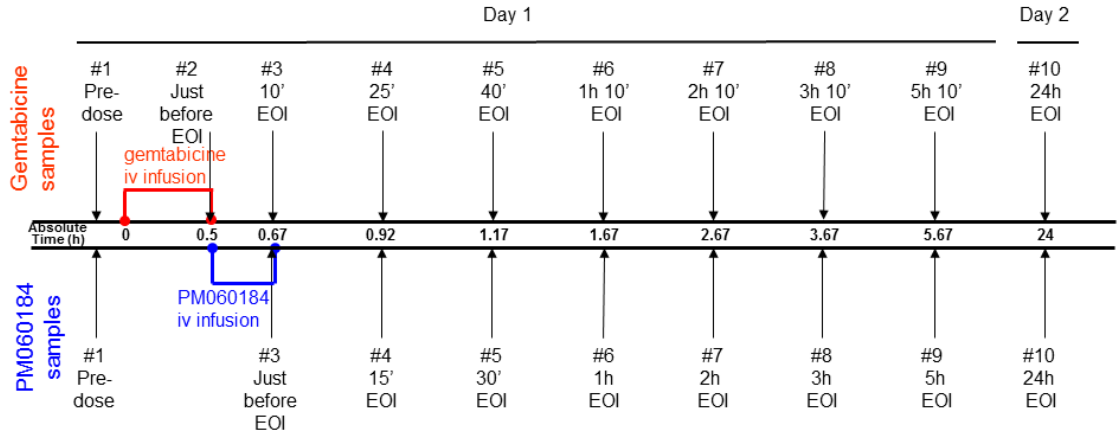
Table 6. Sampling schedule for the determination of gemcitabine, dFdU and PM060184.

Sample number	Day	Time relative to gemcitabine infusion (h)	Sampling times for gemcitabine and dFdU	Sampling times for PM060184	Sampling Windows
#1	1	0	Pre-dose	Pre-dose	-
#2	1	0.5	Just before EOI	--	- 2 min
#3	1	0.67	10 min EOI	Just before EOI	- 2 min
#4	1	0.92	25 min EOI	15 min EOI	± 5 min
#5	1	1.17	40 min EOI	30 min EOI	± 5 min
#6	1	1.67	1 h 10 min EOI	1 h EOI	± 10 min
#7	1	2.67	2 h 10 min EOI	2 h EOI	± 10 min
#8	1	3.67	3 h 10 min EOI	3h EOI	± 10 min
#9	1	5.67	5 h 10 min EOI	5 h EOI	± 30 min
#10	2	24	24 h EOI	24 h EOI	± 2 h

dFdU, 2,2-difluorodeoxyuridine; EOI, end of infusion; h, hours; min, minutes.

Drug administration on Day 1 (i.e., on the same day in which most PK samples are to be collected) should be as follows: after the pre-dose PK sample, gemcitabine will be administered as a 30-min (± 10-min) i.v. infusion. The 10-min (± 3-min) i.v. infusion of PM060184 will start immediately (+5 min window) after completion of the gemcitabine infusion. Figure 4 summarizes the PK sampling schedule.

Figure 4. Pharmacokinetic sampling schedule.



EOI, end of infusion.

Note: the temporal scale is not uniform, but depends on sample density.

The exact recording of the time of drug administration and sampling times during infusions is crucial. The infusion rate will be established to ensure that the whole dose

of each compound is infused over the established time, i.e. 30 min (± 10-min) for gemcitabine and 10 min (± 3-min) for PM060184. The drugs will be infused at a constant rate throughout the corresponding period. In order to obtain reliable PK information, the infusion rate should not be modified once the infusion begins.

Blood samples for PK analysis will be obtained through a peripheral vein located in the contralateral side to that of the infusion. In any case, the sampling vein has to be different to that in which the drugs are infused. Even the last sample **must never be collected from** the **catheter used for drug infusion**.

If the blood sample is obtained from a catheter, the first milliliter (ml) of blood will be discarded to avoid dilution of the sample with the solution used to keep it clean. Heparin (10 U/ml in normal saline solution) or a slow drip of normal saline solution (10 ml/h) can be used to keep the catheter permeable between extractions.

The Instruction Manual for the Collection, Labeling, Storage and Shipment of Pharmacokinetic Samples describes in detail the procedures. Please, read carefully all the procedures before PK days.

In summary, after the collection of each sample (8 ml, whole blood), the sample will be centrifuged and the plasma layer transferred into new tubes for the determination of gemcitabine, dFdU or PM060184. The plasma tubes will be stored under frozen conditions until the shipment to the analysis laboratory. All the PK material will be provided by Pharma Mar S.A.

Once all samples from a patient have been collected, they should be shipped to the central laboratories for PK analysis as soon as possible, ideally on the next shipping day. If the same center has samples from several patients, samples can be sent in the same shipment. However, the time span between the moment the last PK sample for a patient has been collected and ***the shipment of all samples from this patient to the central laboratory should not exceed one month***.

Support PK forms should be sent at the same time, but never in contact with dry ice. Samples will be identified with the following data: study reference, IMP, patient number, sample number, date and time of collection. The confidentiality of patients' data will be maintained at all times. Samples will be destroyed following the appropriate laboratory procedures, after the approval of the final analytical study report by the Sponsor.

7. PHARMACOGENETIC EVALUATIONS

In order to explore factors that may help explain individual variability in main PK parameters, the presence or absence of germline mutations or polymorphisms will be analyzed in leukocyte DNA extracted from a blood sample obtained at any time during the study, but ideally before treatment start along with PK sample #1 on Day 1 of Cycle 1.

The collection and management of the polymorphisms samples are quite different than those for PK assessment. Please follow carefully the instructions detailed in the Instruction Manual for Collection, Labeling, Storage and Shipment of Pharmacogenetic Samples. The assessment of polymorphisms is not affected by treatment. Therefore, the Sponsor may require the collection of additional polymorphisms samples later on, if the sample has not been drawn/processed adequately, thus making the sample not analyzable.

Only patients who voluntarily give their informed consent and sign the ICF for the pharmacogenetic substudy will participate in these evaluations. Refusal will not affect patient participation in the clinical study PM60184-A-003-14.

8. TREATMENT

8.1 DESCRIPTION OF TREATMENT

8.1.1 Drug Formulation and Supply

8.1.1.1 *Gemcitabine*

Commercially available presentations of vials containing gemcitabine will be provided as appropriate. Gemcitabine will be prepared in accordance with the applicable Summary of Product Characteristics (SmPC). Medication preparation records will be kept by the site.

8.1.1.2 *PM060184*

The drug substance PM060184-CD is a mixture of PM060184 and 2-hydroxypropyl-β-cyclodextrin.

PM060184 drug product (DP) is provided as a sterile lyophilized powder for concentrate for solution for infusion with a strength of 15 mg of the active moiety PM060184.

Before use, the vials should be reconstituted with 6 ml of water for injection to give a solution containing 2.5 mg/ml of PM060184. PM060184 15-mg DP was developed for administration by the i.v. route. Prior to administration, the reconstituted vials should be further diluted with dextrose 5% solution for infusion. Each 15-mg vial of PM060184 is a single-use vial. PM060184 reconstitution/dilution records will be kept by the site.

The full composition of the reconstituted solution per ml is shown in Table 7.

Table 7. Composition of PM060184 vials.

Component	Concentration (per ml)	Function
PM060184	2.5 mg/ml	Active moiety
2-Hydroxypropyl-β cyclodextrin (DS 4-5)*	200 mg/ml	Solubilizing agent
Water for injection	1 ml	Solvent

* DS = Degree of substitution.

For instructions regarding drug inventory, handling, reconstitution, dilution, storage, accountability and disposal, please refer to the Preparation Guide for Infusion provided as a separate document.

8.2 ADMINISTRATION OF THE STUDY MEDICATION

Patients will consecutively receive the following on Day 1 and Day 8 q3wk (three weeks = one treatment cycle):

- Gemcitabine: i.v. infusion over 30 min (± 10 min) at a starting dose of 800 mg/m^2 via a central or peripheral venous catheter through a pump device, followed by:

- PM060184: i.v. infusion over 10 min (± 3 min) at a starting dose of 6.0 mg/m^2 via a central or peripheral venous catheter through a pump device.

During PK sampling, PM060184 infusion should start no more than 5 min after end of gemcitabine administration.

More information on dose escalation may be found in Section 3.3.

8.3 CRITERIA FOR TREATMENT CONTINUATION

Patients will be treated with additional cycles of PM060184 combined with gemcitabine as long as no unacceptable toxicity and/or progression of the disease and/or withdrawal of consent occurs.

The administration of a new cycle should be delayed if the criteria in the table below are not met on the corresponding Day 1. Parameters will be reevaluated at minimum intervals of 48 hours. The new cycle will be started upon recovery of these parameters. A maximum delay of 7 (+1) days from theoretical due date will be allowed for recovery from treatment-related adverse events. If recovery has not occurred after that period, the patient should discontinue the treatment, except in case of obvious patient benefit at the criteria of the Investigator and upon agreement with the Sponsor.

If the re-treatment criteria are not met on Day 8 (±1 day), administration of the corresponding drugs should be omitted instead of delayed.

After skipping and/or delaying doses due to treatment-related toxicity (except for neutropenia exclusively), or in patients who experience a DLT, treatment may only continue after appropriate dose reduction (see Section 8.4).

Table 8. Criteria for treatment continuation.

	Day 1	**Day 8**
ANC	≥ 1.0 x 10^9/l	≥ 1.0 x 10^9/l
Platelets	≥ 100 x 10^9/l	≥ 75 x 10^9/l
Hemoglobin	≥ 9 g/dl	≥ 8 g/dl
Total bilirubin	≤ 1.5 x ULN	
AST/ALT	Grade ≤ 1	Grade ≤ 2
Calculated CrCl (Cockcroft and Gault's formula)	≥ 50 ml/min	≥ 30 ml/min
Peripheral sensory / motor neuropathy	Grade ≤ 1	Grade ≤ 2
Other non-hematological drug-related AEs (except increased GGT, alopecia, nausea, anorexia, and/or asthenia) [a]	Grade ≤ 1	Grade ≤ 2

If a patient does not meet the requirements for treatment continuation on Day 1 of further cycles, the corresponding drug (PM060184 and gemcitabine) infusion will be withheld until recovery for a maximum of 7 days after the theoretical treatment date. If recovery has not occurred after a delay of > 7 (+1) days, the patient must be withdrawn from the trial, except in case of perceived clinical benefit from the Investigator and upon agreement with the Sponsor.

If the above criteria are not met on Day 8 of any cycle, the scheduled infusion will be omitted instead of delayed.

a Any grade accepted for increased GGT. Up to grade 2 for alopecia, nausea, anorexia, and asthenia. Non-symptomatic grade 2-4 metabolic abnormalities (e.g. sodium, magnesium, potassium, calcium) will be allowed for treatment continuation.

AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AP: alkaline phosphatase; AST, aspartate aminotransferase; CrCl, creatinine clearance; GGT, gamma-glutamyltransferase; ULN, upper limit of normal.

8.4 DOSE REDUCTION

Treatment after DLT, treatment-related dose delay for > 7 days from theoretical due date and/or toxicity considered as unacceptable by the investigators may continue, after appropriate dose reduction, only if there is clear evidence of objective patient benefit. This will always be discussed with the Sponsor. Under this circumstance, and following recovery to pre-specified re-treatment criteria, patients will be re-treated at the immediately lowest DL. If dose reduction beyond DL-1 is required, the PM060184 dose may be reduced by an additional 1.0 mg/m2.

Up to two individual dose reductions will be allowed per patient; any patients requiring more than two dose reductions will be withdrawn from the study. Once dose has been reduced for an individual patient, it will not be re-escalated again under any circumstances.

No individual dose reductions will be allowed during Cycle 1.

Patients requiring dose reduction exclusively due to febrile neutropenia or grade 4 neutropenia during the preceding cycle may receive secondary prophylaxis with granulocyte colony-stimulating factor (G-CSF) instead of a dose reduction. If toxicity re-occurs despite G-CSF use, dose reduction will then be implemented.

Patients who require limited field RT for pain palliation after Cycle 1 may continue treatment with PM060184 alone and without any dose adjustments if patient benefit is perceived; these patients do not need to be replaced. Gemcitabine re-introduction may be considered in patients without progressing disease at least four weeks after the end of RT.

8.5 CONCOMITANT MEDICATION

All treatments received by the patient during the on-treatment period of the trial must be documented in the e-CRF.

8.5.1 Prophylactic Medication

Primary antiemetic prophylaxis is compulsory prior to all PM060184 infusions. Standard treatment [according to the American Society of Clinical Oncology (ASCO) guidelines] will be administered:

- 5-HT_3 antagonists (ondansetron 8 mg i.v. or equivalent).
- Steroids (dexamethasone 8 mg i.v. or equivalent).

If necessary, addition of metoclopramide or extension of treatment with 5-HT_3 antagonists and/or dexamethasone could be considered (according to the Investigator's own criteria).

8.5.2 Allowed Medications/Therapies

- Therapies for pre-existing and treatment-emergent medical conditions, including pain management.
- Blood products and transfusions, as clinically indicated.
- Bisphosphonates.
- In case of nausea or vomiting, secondary prophylaxis and/or symptomatic treatment for emesis according to ASCO guidelines.
- Erythropoietin use according to ASCO guidelines.

- Hormone-responsive breast cancer patients [i.e., those whose tumors express estrogen receptor (ER) and/or progesterone receptor (PrR)] may continue receiving their same prior hormonal therapy without interruption throughout their study participation.
- Treatment with G-CSF in the event of grade 4 neutropenia lasting > 3 days, neutropenic sepsis or febrile neutropenia according to ASCO guidelines. Secondary prophylaxis could be considered after Cycle 1, if it is in the best interest of the patient.
- Luteinizing hormone-releasing hormone (LHRH) agonists, in women of reproductive age.
- Megestrol acetate for appetite stimulation.

8.5.3 Prohibited Medications/Therapies

- Concomitant administration of any other antineoplastic therapy is prohibited, other than the aforementioned hormonal therapy for breast cancer.
- Patients who require RT within three weeks after the first infusion may remain on the study after being discussed and agreed between the Investigator and the Sponsor, but will not be evaluable for the analysis of the primary endpoint (DLT) and consequently need to be replaced.
- Primary prophylaxis with G-CSF in Cycle 1.
- Other investigational agents.
- Concomitant RT while on gemcitabine treatment.
- Immunosuppressive therapies other than corticosteroids.

8.5.4 Drug-drug Interactions

In vitro studies using human liver microsomes have pointed to CYP2C19 and CYP3A4 as the predominant cytochrome (CYP) enzymes responsible for the hepatic metabolism of PM060184. Therefore, concomitant drugs which induce or inhibit any of these cytochromes in a significant extent should be avoided whenever possible.

A list of commonly prescribed drugs that are inhibitors, inducers and substrates for these enzymes is provided in APPENDIX 6.

8.5.5 Drug Accountability

Proper drug accountability of all investigational medicinal products (IMPs) will be done by appropriate trained study personnel. Each study site will keep records to allow a comparison of quantities of drug received and used at each site for monitoring purposes. The Investigator at each study site will be the person ultimately responsible for drug accountability at the site.

All unused drug supplied by the Sponsor will be properly destroyed at the study site. Documentation of this procedure must be provided to the clinical trial monitor. If the Sponsor agrees, unused drug supplies may be returned to the drug repository.

8.6 TREATMENT COMPLIANCE

The Investigator is ultimately responsible for supervising compliance with the instructions described in this study protocol.

9. STUDY EVALUATIONS

9.1 DETERMINATION OF THE MTD AND THE RD

The definition of the MTD and the RD may be found in Section 3.1.1.

9.2 SAFETY

Patients will be evaluable for safety if they have received at least one partial or complete infusion of PM060184 and one partial or complete infusion of gemcitabine. AEs will be graded according to the NCI-CTCAE v.4.

The evaluation period for individual patients should include observations since start of the treatment until 30 days after the last study drug dose administration, death or until the start of a new antitumor therapy, whichever occurs first. After end of treatment, any ongoing relevant (grade > 1) drug-related AEs must be followed until resolution or stabilization (i.e., to grade 1), or until start of a new therapy.

9.3 ADVERSE EVENTS DEFINITIONS

9.3.1 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 test 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.

9.3.2 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; these criteria 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.

9.3.3 Death

Death as such is the outcome of a SAE and should not be used as the SAE term itself, whenever possible. The cause of death should be recorded as the SAE term instead. When available, the autopsy report will be provided by the Sponsor.

9.3.4 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 had been more severe.

9.3.5 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 (see Section 9.4.2). 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., 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.).

9.3.6 Unlisted/Unexpected Adverse Event

An AE, the nature or severity of which is not consistent with the applicable reference safety information.

The Sponsor will use as the reference safety information for the evaluation of listedness/expectedness the IB for PM060184 and the SPC for gemcitabine.

9.3.7 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.

9.3.8 Adverse Events Related to the Study Drugs

An AE is considered related to a study drug/investigational medicinal product (IMP) if the Investigator's assessment of causal relationship to the IMP(s) is "Y (yes)" (see Section 9.3.10).

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.

9.3.9 Expedited Reporting

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

9.3.10 Assessment of Causal Relationship to the Study Drugs

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.

9.4 ADVERSE EVENTS REPORTING PROCEDURES

9.4.1 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, whichever occurs first. All relevant (grade > 1) AEs suspected to be related to the study drug/IMP must be followed-up after the time of therapy discontinuation until the event resolves or stabilizes (i.e., to grade 1), or until start of a new therapy.

All AEs, including misuse, overdose, abuse and medication error, must be recorded in English using medical terminology in the source document and the e-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 Pharma Mar S.A. or its designated representative. The Investigator must provide any relevant information as requested by the Sponsor in addition to that on the e-CRF.

Abnormal laboratory tests occurring during the study should only be recorded in the AE section of the e-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.
- Leads to a DLT.
- The test result is considered to be clinically relevant by the Investigator.

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

9.4.2 Reporting Serious Adverse Events

The Sponsor will collect SAEs from the time of signing of the 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, 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) that occur after patient registration, regardless of relationship to the study drug(s)/IMP(s) must be reported immediately and always within 24 hours to the Pharma Mar S.A. Pharmacovigilance Department electronically by completing the applicable e-CRF sections. Only in the event of electronic system failure, SAEs can be reported using a paper "SAE form" by fax (+34 91 846 6004), e-mail (phv@pharmamar.com), or telephone (+ 34 91 846 6147). Out of office hours [Greenwich Meridian Time (GMT)], assistance on SAE reporting can be obtained by calling the Pharmacovigilance Department at +34 91 823 4742. SAEs initially reported by alternative (i.e., not electronic) methods must be followed by a completed electronic SAE reporting on e-CRF from the investigational staff within one working day.

Those SAEs occurring during the screening phase (from ICF signature to registration) and after off-study will be reported using a paper "SAE Form" that must be forwarded as mentioned above always within 24 hours to the Pharmacovigilance Department by fax or e-mail.

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.

9.4.3 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 a female patient or the female partner of a male patient occurring while the patient is on study drugs, or within six months of the patient's discontinuation visit, are considered immediately reportable events.

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 [this could involve a partner of a male patient or a pregnant female who came in contact with the clinical trial IMP(s)].

- All reports of elevated/questionable or indeterminate beta human chorionic gonadotropins (β-hCGs).

Immediately after detecting a case of suspected pregnancy in a female clinical trial patient, the decision on her continued participation in the clinical trial will be jointly taken by the trial 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 Pharma Mar S.A. Pharmacovigilance Department immediately using the Pregnancy Report form. In the case of pregnancy of the female partner of a trial patient, the Investigator will obtain her informed consent to provide the information by using the applicable form provided by the Sponsor who will also advise the Investigator in these situations.

The Investigator will follow the pregnancy until its outcome, and must notify Pharma Mar S.A. Pharmacovigilance Department 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 Pharma Mar S.A. Pharmacovigilance Department 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 Pharma Mar S.A. Pharmacovigilance Department within 24 hours of the Investigators' knowledge of the event.

9.5 ADVERSE EVENTS MONITORING

Safety review will be performed at Pharma Mar S.A. once SAE forms have been received and the e-CRFs electronically completed by the Investigator.

At every monitoring visit performed by the clinical research associate (CRA)/monitor in charge of the study, the consistency between the e-CRF/SAE data reported to the Pharmacovigilance department and the patient's medical records (source data) will be reviewed. Whenever a discrepancy is found during the review, data will be amended/updated in the e-CRF and the SAE form/information reported to the Pharmacovigilance department (when applicable), according to source data (medical history and annexes, such as nurse records, lab reports, image reports, others). An update (Follow-up) with changes arisen will be signed by the Principal Investigator (or his/her designee) and then reported/provided to the Pharmacovigilance department within 24 hours, with the e-CRF updated on the same dates.

Periodic safety review of clinical data will be performed; however, no formal Data Safety Monitoring Board has been appointed for this trial. AEs will be monitored by the Investigators and by the study team at Pharma Mar S.A. The personnel in charge of this process are defined in the section "*Study Contacts*" of this protocol. In general, a clinical oncologist, together with a member of the Pharma Mar S.A. Pharmacovigilance Department will review the safety data of this trial on an ongoing basis.

SAEs will be collected, assessed and reported as per the applicable Regulations by the Pharmacovigilance Department. Periodic safety reviews of SAE reports are to be conducted by the clinical oncologist every 3-6 months, depending on recruitment.

Non-serious AEs will be verified during monitoring visits by the monitor, who will discuss them with the Investigators, if applicable.

Any protocol deviation will also be discussed with the Investigator during monitoring visits.

9.6 EFFICACY

Antitumor activity will be evaluated according to the RECIST v.1.1 (see details in APPENDIX 4) in all patients with measurable disease, according to Choi criteria and/or EORTC metabolic response criteria for solid tumors in GIST patients (APPENDIX 5), or by evaluation of tumor markers if applicable (e.g., ovarian cancer), every two cycles (i.e., approximately every six weeks) ± one week after treatment initiation until Cycle 4. Patients continuing treatment after Cycle 4 will have the assessments performed every three cycles (i.e., approximately every nine weeks) ± one week from Cycle 4 while on treatment, unless otherwise is clinically indicated. Anonymized copies of the images showing objective response or meaningful tumor shrinkage must be submitted to the Sponsor.

In patients with disease evaluable by serum markers, tumor assessments will also be obtained every two cycles ± one week until Cycle 4, and every three cycles ± one week from Cycle 4 while on treatment. Tumor response will be evaluated by GCIG specific criteria in patients with ovarian cancer (see details in APPENDIX 7).

Analysis of other clinically routinely employed serum markers will be performed for individual patients in an exploratory fashion, as clinically indicated. This will include baseline measurements of:

- CA19-9: for patients diagnosed with non-neuroendocrine pancreatic cancer or biliary tract cancer.
- CA15-3: for patients diagnosed with breast cancer.
- Alpha-fetoprotein: for patients diagnosed with hepatocellular carcinoma and/or non-seminoma germ cell tumors.
- Beta-hCG: for patients diagnosed with a germ cell tumor.
- CA-125: for patients diagnosed with ovarian cancer.

Patients for whom disease diagnostic applies and are found to have elevated baseline values, according to the institution reference (which will be also provided), will be assessed before treatment at Day 1 of each subsequent cycle.

Since formal response criteria are still pending, the analysis of these markers will be only descriptive in nature. Consequently, formal disease evaluation will be performed according only to RECIST v.1.1, Choi criteria and/or EORTC metabolic response criteria for solid tumors, as stated above, and by GCIG criteria, when applicable.

9.6.1 Progression-free Survival

Progression-free survival (PFS) is defined as the time from the date of first infusion of study treatment to the date of progression or death (due to any cause). If progression or

death has not occurred at the time of the analysis, the PFS will be censored on the date of last tumor evaluation.

9.6.2 Overall Survival

Overall survival (OS) is defined as the time from the date of first infusion of study treatment to the date of death (due to any cause). Patients with no documented death will be censored at the last date they are known to be alive.

9.7 Evaluation Of Pharmacokinetics

PK parameters will be evaluated by standard NCA analysis (compartmental modeling may be performed if appropriate).

9.8 Evaluation of Pharmacogenetics

The presence or absence of known polymorphisms that may explain individual variability in main PK parameters will be evaluated using a blood sample collected before treatment start along with PK sample #1 on Day 1 of Cycle 1.

10. STATISTICAL METHODS

10.1 Sample Size

The number of patients may vary depending both on the tolerability of PM060184 combined with gemcitabine and the number of dose levels required to identify the MTD. Approximately between six and 72 evaluable patients are planned to be included in this study.

10.2 Statistical Analysis

Descriptive statistics (mean, median, standard deviation and 95% confidence interval, range of value, frequencies and percentages) will be used as appropriate.

10.2.1 Safety

Descriptive statistics will be used to characterize DLTs occurring at the RD and/or at DLs above/below it. The profiles of AEs, deaths, SAEs, treatment-related delays, dose reductions, dose omissions and/or treatment discontinuations will also be displayed by group as appropriate. All AEs will be graded according to the NCI-CTCAE v.4.

10.2.2 Efficacy

Response rates as per RECIST v.1.1 (and as per Choi criteria and/or EORTC metabolic response criteria, for GIST patients) [percentage of patients with any response [PR, CR or the sum of both being the overall response rate (ORR)], percentage of patients with clinical benefit [i.e., patients with any response, or with stable disease (SD) $\geq$ 4 months], will be characterized using descriptive statistics (95% exact binomial confidence interval) and according to primary tumor type. Time-related parameters (e.g., PFS, OS) will also be analyzed according to the Kaplan-Meier method, if appropriate. If any specific tumor type subset is adequately represented, exploratory subgroup analyses will be performed. The characteristics of the patients achieving an objective response or SD $\geq$ 4 months by RECIST v.1.1 will be displayed.

10.2.3 Pharmacokinetics

The PK parameters will be tabulated and selected parameters will be graphically displayed per DL. The dose-exposure relationships for maximum plasma concentration (C_{max}) and AUC will be evaluated, and any potential PK interaction between gemcitabine, dFdU and PM060184 will also be explored.

The potential influence on selected PK parameters of selected demographic and clinical dichotomous variables (gender, laboratory test results above/below selected cutoff values, etc.) will be evaluated by Student's t test or Mann-Whitney's U test as appropriate.

For multinomial variables, analysis of variance will be used. For selected continuous demographic and clinical variables, relationship with selected PK parameters will be graphically explored and assessed using correlation and regression methods.

Other tests may be applied if the results of the above evaluations suggest that they may yield additional relevant information.

10.2.4 Pharmacogenetics

The influence of known polymorphisms on main PK parameters will be assessed by Student's test or Mann-Whitney's U test as appropriate.

10.3 INTERIM ANALYSIS

The patient's safety will be assessed on a regular basis prior to each dose escalation upon completion of a cohort. No formal interim analyses are planned.

11. ADMINISTRATIVE SECTION

11.1 ETHICS

This clinical trial will be conducted in accordance with the ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki (see APPENDIX 8) and will be consistent with GCP guidelines and pertinent regulatory requirements.

The study personnel involved in conducting this trial will be qualified by education, training and experience to perform their respective task(s).

The study will be conducted in compliance with the protocol. The protocol, any amendments and the patient informed consent will receive IEC/IRB approval/favorable opinion prior to initiation, according to pertinent regulations.

The decision of the IEC/IRB concerning the conduct of the study will be made in writing to the Investigator, and a copy of this decision will be provided to the Sponsor before the beginning of the study.

The Investigator and/or the Sponsor is/are responsible for keeping the IEC/IRB informed of any significant new information about the study drugs.

All protocol amendments will be agreed upon by the Sponsor and the Investigator.

Administrative changes of the protocol are minor corrections and/or clarifications that have no impact on the way the study is to be conducted.

11.2 MONITORING, AUDITING AND INSPECTING

The study will be monitored by regular site visits and telephone calls to the Investigator by the clinical trial monitor designated by Pharma Mar S.A.

During site visits, the trial monitor should revise original patient records, drug records and document retention (study file). Additionally, the trial monitor should observe study procedures and will discuss any problems with the Investigator.

Adequate time for these visits should be allocated by the Investigator. The Investigator should also ensure that the monitor is given direct access [as per International Conference on Harmonization (ICH) Topic E6 Guideline for Good Clinical Practice, Sections 4.9.7 and 6.10] to source documents (i.e., hospital or private charts, original laboratory records, appointment books, etc.) of the patient which support data entered in the case report forms, as defined in the ICH Topic E6 Guideline for Good Clinical Practice, Sections 1.51 and 1.52.

Systems and procedures will be implemented to ensure the quality of every aspect of the trial.

During the course of the trial, the Clinical Quality Assurance Department of Pharma Mar S.A. or external auditors contracted by the Sponsor may conduct an onsite audit visit (ICH Topic E6 Guideline for GCP, Section 1.6).

Participation in this trial implies acceptance of potential inspection by national or foreign Competent Authorities.

11.3 PATIENT INFORMED CONSENT

The rights, safety and well-being of the trial patients are the most important considerations and should prevail over interests of science and society.

The Informed Consent Forms (ICFs) will include all elements required by ICH, GCP and applicable regulatory requirements.

Prior to inclusion into the trial, the Investigator or a person designated by the Investigator, must provide the patient with one copy of the ICF for the clinical trial and one copy of the ICF for the pharmacogenetic sub-study, if applicable. Both copies must provide written full information about the clinical trial and the sub-study, in a language that is non-technical and easily understood. The Investigator should allow the necessary time for the patient or his/her legally acceptable representative to inquire about the details of the clinical trial and the sub-study; then, both ICFs must be freely signed and personally dated by the patient and by the person who conducted the Informed Consent discussion before the beginning of the study. In addition, the patient should receive a copy of any other written information provided to study patients prior to participation in the trial.

During a patient's participation in the trial, any updates to the consent forms and any updates to the written information will be provided to him/her.

If there is a need to obtain new consent from the patients, the Investigator or a person designated by the Investigator should inform the patients of any new information relevant to the patients' willingness to continue participation in the study, before obtaining the written consent.

11.4 CONFIDENTIALITY/ PATIENTS IDENTIFICATION

The collection and processing of personal data from the patients enrolled in this clinical trial will be limited to those data that are necessary to investigate the efficacy, safety, quality and usefulness of the study drugs used in this trial.

It is the Investigator's responsibility that sufficient information on the identity of the patients will be retained.

The trial monitor, the Sponsor's auditor, the IECs/IRBs and the Competent Authorities should have direct access to all requested trial-related records, and agree to keep the identity of study patients confidential.

The data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

Explicit consent for the processing of personal data will be obtained from the participating patient before data collection, if applicable, and this consent should also address the transfer of the data to other entities and countries.

Pharma Mar S.A. shall comply with the Directive 95/46/EEC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

11.5 CASE REPORT FORMS

e-CRFs will be used to record all data for each patient. It is the responsibility of the Investigator to ensure that the e-CRFs are properly and completely filled in, in English. e-CRFs must be completed for all patients who have given their informed consent and have been enrolled into the study. For patients who gave their informed consent, received an automatic patient number, and for whom registration was not confirmed, the screening form will be sufficient.

A patient's source documentation is the patient's records (including but not limited to physician/hospital notes, nurses notes, IMP preparation records including reconstitution and dilution, IMP administration records, etc.) and any original document, and as such they should be maintained at the study site.

The data collected in the e-CRF will be entered into Pharma Mar S.A. databases, which comply with the Spanish Act implementing the Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data.

11.6 INSURANCE

The Sponsor will provide insurance or indemnity in accordance with the applicable regulatory requirements.

11.7 RETENTION OF RECORDS

The Investigator/Institution should maintain trial documents according to Section 8 of the ICH Topic E6 Guideline for Good Clinical Practice and as required by applicable regulatory requirements.

Essential documents should be retained as per the aforementioned ICH guideline or for a longer period of time, if required by the applicable regulations.

11.8 USE OF INFORMATION AND PUBLICATION

Before the investigators of this study submit a paper or abstract for publication or otherwise publicly disclose information concerning the study drugs or products, Pharma Mar S.A. must be provided with at least 60 days to revise and approve the proposed publication or disclosure to ensure that confidential and proprietary data are protected.

If Pharma Mar S.A. determines that patentable patient matter is disclosed in the proposed publication or disclosure, the publication or disclosure will be withheld for a period of time considered convenient. If the study is part of a multicenter study, the first publication of the study shall be made in conjunction with the presentation of a joint, multicenter publication of the study results with the investigators and the institutions from all appropriate sites that are contributing data, analysis and comments. However, if such a multicenter publication is not submitted within 12 months after conclusion, abandonment or termination of the study at all sites, the present study may be published individually in accordance with the procedure established above.

The order of the coauthors will reflect the relative contribution of each one to study development and analysis. In general, the first author will be the investigator who recruits the highest number of patients with information finally available for data analysis. Relevant Pharma Mar S.A. personnel who have fully participated in the study must be considered for co-authorship of the publication.

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13. APPENDICES

APPENDIX 1: ECOG PERFORMANCE STATUS ASSESSMENT SCALE

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

*As published in Am. J. Clin. Oncol *5:649-655, 1982*: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group.*

APPENDIX 2: COCKCROFT AND GAULT'S FORMULA

For calculating creatinine clearance:

$$\text{Creatinine clearance (ml/min)} = \frac{[(140\text{-age (years)}) \times \text{weight (Kg)}]}{72 \times \text{serum creatinine (mg/dl)}} \times G^{1}$$

$$\text{Creatinine clearance (ml/min)} = \frac{[(140\text{-age (years)}) \times \text{weight (Kg)}]}{72 \times \text{serum creatinine (}\mu\text{mol/l)} \times 0.0113} \times G^{1}$$

[1]G(Gender)= 0.85 if Female; 1 if Male.

Reference:

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

APPENDIX 3: PERCENTAGE OF ACTIVE BONE MARROW AT RISK DUE TO RADIOTHERAPY IN VARIOUS SKELETAL SITES

Skeletal Sites (and Quantities) Used for Spongiosa Volume Estimation

Skeletal site (number of bones)	Percentage of total body active marrow
Cranium (1)	7.6
Mandible (1)	0.8
Humeral heads (2)	2.3
Clavicles (2)	0.8
Scapulae (2)	2.8
Sternum (1)	3.1
Ribs (12)	16.1
Cervical vertebrae (7)	3.9
Thoracic vertebrae (12)	16.1
Lumbar vertebrae (5)	12.3
Sacrum (1)	9.9
Proximal femora (2)	6.7
Ossa coxae (2)	17.5

This table is adapted from Table 9-4 in International Commission on Radiological Protection. Basic Anatomical and Physiological Data for Use in Radiological Protection: Reference Values. New York, NY: International Commission on Radiological Protection; 2002. ICRP Publication 89. Copyright 2002, International Commission on Radiological Protection.

Further details can be found in the original article: Brindle JM., Trindade AA., Shah, AP., Jokisch DW., Patton PW,. Pichardo JC. and Bolch WE. Linear Regression Model for Predicting Patient-Specific Total Skeletal spongiosa volume for use in molecular radiotherapy dosimetry. J Nucl Med 2006; 47:1875–1883.

APPENDIX 4: EVALUATION OF RESPONSE. THE RECIST v.1.1.

This document summarizes the main information contained in RECIST version 1.1.

Further details can be found in the original article: Eisenhauer EA, Therasse P, Bogaerts J, et al.: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45(2): 228-247.[1]

LIST OF ABBREVIATIONS

CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
MRI	Magnetic Resonance Imaging
NE	Not Evaluable
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-free Survival
PR	Partial Response
PSA	Prostate-specific Antigen
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable Disease
TTP	Time to Progression

LIST OF TABLES

1. MEASURABILITY OF TUMOR LESIONS AT BASELINE

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1 Measurable

Tumor Lesions:

Must be accurately measured in at least one dimension (*longest* diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by computed tomography (CT) scan (irrespective of scanner type) and magnetic resonance imaging (MRI) (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical exam (when superficial).

[1] A summary of major changes from RECIST 1.0 to RECIST 1.1 can be found at the beginning of this document (**Table 1**).

- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung).

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 (see Schwartz *et al.* Eur J Cancer. 2009; 45(2):261-267). See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

1.1.2 Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as lesions considered truly non-measurable. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.1.3 Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone Lesions:

- Bone scan, positron emission tomography (PET) scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- 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 patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2. Specifications by Methods of Measurement

1.2.1 Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than four weeks before the beginning of the treatment.

1.2.2 Method of Assessment

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 should always be done rather than 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 and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-Ray:

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. See original article, Appendix II, for more details.

Computed Tomography (CT), Magnetic Resonance Imaging (MRI):

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in original article (Appendix II), when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans). More details concerning the use of both CT and MRI for assessment of objective tumor response evaluation are provided in the original article, Appendix II.

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 date 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 (described in greater detail in the original article, Appendix II). 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 at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy:

The use of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

2. TUMOR RESPONSE EVALUATION

2.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall *tumor burden at baseline* and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 1. Measurability of tumor at baseline). In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

2.2 Baseline Documentation of "Target" and "Non-target" Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as ***target lesions*** and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved that a *maximum* of two and four lesions will be recorded, respectively). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts *et al.* Eur J Cancer 2009;45:248–260.

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. To illustrate this point see the example in the original article, Figure 3 of Appendix II.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted in the previous section, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement (see also the example in the original article, Figure 4 of Appendix II). All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

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 as noted above, 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.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.3 Response Criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

2.3.1 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 diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of 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 progression).

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.

2.3.2 Special Notes on the Assessment of Target Lesions

Lymph Nodes:

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms (CRFs) or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target Lesions that Become 'Too Small to Measure':

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the CRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement

should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that Split or Coalesce on Treatment:

As noted in the original article, Appendix II, when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3 Evaluation of Non-target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

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).
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):	Unequivocal progression (see comments below) of existing non-target lesions (Note: the appearance of one or more new lesions is also considered progression).

2.3.4 Special Notes on Assessment of Progression of Non-target Disease

The concept of progression of non-target disease requires additional explanation as follows:

When the Patient Also Has Measurable Disease:

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see examples in the original article, Appendix II and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has only Non-measurable Disease:

This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. Some illustrative examples are shown in the original article, Figures 5 and 6 of Appendix II. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

2.3.5 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in 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). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

2.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may

also require confirmatory measurement (see Section 2.6. Confirmatory Measurement/Duration of Response). Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

2.4.1 Time Point Response

It is assumed that at each protocol specified time point, a response assessment occurs. **Table 2** provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 2. Time point response: patients with target (+/–non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non- PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR, complete response; NE, inevaluable; PD, progressive disease; PR, partial response; SD, stable disease.

When patients have non-measurable (therefore non-target) disease only, **Table 3** is to be used.

Table 3. Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR, complete response, NE, inevaluable; PD, progressive disease.

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

2.4.2 Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with

three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3 Best Overall Response: All Time Points

The best overall response is determined once all the data for the patient is known.

Best Response Determination in Trials Where Confirmation of Complete or Partial Response IS NOT Required:

Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best Response Determination in Trials Where Confirmation of Complete or Partial Response IS Required:

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally four weeks later). In this circumstance, the best overall response can be interpreted as in **Table 4**.

Table 4. Best overall response when confirmation of complete response (CR) and partial response (PR) is required.

Overall response. First time point	Overall response. Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR, complete response; NE, inevaluable; PD, progressive disease; PR, partial response; SD, stable disease.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

APPENDIX 5: CHOI RESPONSE EVALUATION CRITERIA AND EORTC METABOLIC RESPONSE CRITERIA FOR SOLID TUMORS

Choi Response Evaluation Criteria

Response	Definition
CR	Disappearance of all lesions. No new lesions.
PR	A decrease in size ≥10% or a decrease in tumor attenuation (HU) ≥15% on CT. No new lesions. No obvious progression of non-measurable disease.
SD	Does not meet criteria for CR, PR or PD. No symptomatic deterioration attributed to tumor progression.
PD	An increase in tumor size ≥10% and does not meet criteria of PR by tumor attenuation on CT. New lesions. New intratumoral nodules or increase in the size of the existing intratumoral nodules.

CR, complete response; CT, computed tomography; HU, Hounsfield unit; PD, progressive disease; PR, partial response.

Source: Choi H, Charnsangavej C, Faria SC, Macapinlac HA, Burgess MA, Patel SR, Chen LL, Podoloff DA, Benjamin RS. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. *J Clin Oncol* 2007, 25(13): 1753-9.

European Organization for Research and Treatment of Cancer (EORTC) Metabolic Response Criteria for Solid Tumors

Response	Definition
CMR	Complete resolution of [^{18}F]-FDG uptake within the tumor volume, so that it is indistinguishable from surrounding normal tissue.
PMR	Decrease of 15-25% in [^{18}F]-FDG SUV after one cycle of chemotherapy, and decrease greater than 25% after more than one cycle of chemotherapy. Reduction in extent of [^{18}F]-FDG tumor uptake is not required.
SMD	Increase in [^{18}F]-FDG SUV <25%, or decrease <15% and no visible increase in extent of [^{18}F]-FDG tumor uptake (i.e., <20% in the longest dimension).
PMD	Increase in [^{18}F]-FDG SUV >25% within the tumor region defined on the baseline scan, visible increase in the extent of [^{18}F]-FDG tumor uptake (i.e., >20% in the longest dimension), or appearance of new [^{18}F]-FDG uptake in metastatic lesions.

CMR, complete metabolic response; FDG, fluorodeoxyglucose; PMD, progressive metabolic disease; PMR, partial metabolic response; SMD, stable metabolic disease; SUV, standardized uptake value.

Source: Young H, Baum R, Cremerius U, Herholz K, Hoekstra O, Lammertsma AA, Pruim J, Price P. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. *Eur J Cancer* 1999, 35(13): 1773-82.

APPENDIX 6: CYP1, CYP2 AND CYP3 INHIBITORS, INDUCERS AND SUBSTRATES

Table 1. Classification of *In Vivo* Inhibitors of CYP Enzymes (1).

CYP enzymes	Strong Inhibitors (2) ≥ 5-fold increase in AUC or > 80% decrease in CL	Moderate inhibitors (3) ≥ 2 but < 5-fold increase in AUC or 50-80% decrease in CL	Weak inhibitors (4) ≥ 1.25 but < 2-fold increase in AUC or 20-50% decrease in CL
CYP1A2	Ciprofloxacin, enoxacin, fluvoxamine	Methoxsalen, mexiletine, oral contraceptives, phenylpropanolamine, thiabendazole, zileuton	Acyclovir, allopurinol, caffeine, cimetidine, Daidzein (5), disulfiram, Echinacea (5), famotidine, norfloxacin, propafenone, propranolol, terbinafine, ticlopidine, verapamil
CYP2B6			Clopidogrel, ticlopidine prasugrel
CYP2C8	Gemfibrozil (6)		Fluvoxamine, ketoconazole, trimethoprim
CYP2C9		Amiodarone, fluconazole, miconazole, oxandrolone	Capecitabine, cotrimoxazole, etravirine, fluvastatin, fluvoxamine, metronidazole, sulfinpyrazone, tigecycline, voriconazole, zafirlukast
CYP2C19	Fluconazole (7), Fluvoxamine (8), ticlopidine (9)	Esomeprazole, fluoxetine, moclobemide, omeprazole, voriconazole	Allicin (garlic derivative), armodafinil, carbamazepine, cimetidine, etravirine, human growth hormone (rhGH), felbamate, ketoconazole, oral contraceptives (10)
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice (11), indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, (12) nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice (11), imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo (5), goldenseal (5), isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton
CYP2D6	Bupropion, fluoxetine, paroxetine, quinidine	Cinacalcet, duloxetine, terbinafine	Amiodarone, celecoxib, cimetidine, desvenlafaxine, diltiazem, diphenhydramine, Echinacea (5), escitalopram, febuxostat, gefitinib, hydralazine, hydroxychloroquine, imatinib, methadone, oral contraceptives, propafenone, ranitidine, ritonavir, sertraline, telithromycin, verapamil

1. Please note the following: This is not an exhaustive list. For an updated list, see the following link http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
2. A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold.
3. A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.

4. A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 5-fold.
5. Herbal product.
6. Gemfibrozil also inhibits OATP1B1.
7. Fluconazole is listed as a strong CYP2C19 inhibitor based on the AUC ratio of omeprazole, which is also metabolized by CYP3A; fluconazole is a moderate CYP3A inhibitor.
8. Fluvoxamine strongly inhibits CYP1A2 and CYP2C19, but also inhibits CYP2C8/2C9 and CYP3A;
9. Ticlopidine strongly inhibits CYP2C19, but also inhibits CYP3A, CYP2B6, and CYP1A2.
10. Effect seems to be due to CYP2C19 inhibition by ethinyl estradiol.
11. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).
12. Withdrawn from the United States market because of safety reasons.

Table 2. Classification of *In Vivo* Inducers of CYP Enzymes (1).

CYP enzymes	Strong Inducers ≥ 80% decrease in AUC	Moderate Inducers 50-80% decrease in AUC	Weak Inducers 20-50% decrease in AUC
CYP1A2		Montelukast, phenytoin, smokers versus non-smokers (2)	Moricizine, omeprazole, phenobarbital,
CYP2B6		Efavirenz, rifampin	Nevirapine
CYP2C8		Rifampin	
CYP2C9		Carbamazepine, rifampin	Aprepitant, bosentan, phenobarbital, St. John's wort (3,4)
CYP2C19		Rifampin	Artemisinin
CYP3A	Avasimibe, (5) carbamazepine, phenytoin, rifampin, St. John's wort (3)	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, echinacea,(4) pioglitazone, prednisone, rufinamide
CYP2D6	None known	None known	None known

1. Please note the following: This is not an exhaustive list. For an updated list, see the following link:
2. For a drug that is a substrate of CYP1A2, the evaluation of the effect of induction of CYP1A2 can be carried out by comparative PK studies in smokers vs. non-smokers.
3. The effect of St. John's wort varies widely and is preparation-dependent.
4. Herbal product.
5. Not a marketed drug.

Table 3. Examples (1) of Sensitive *In Vivo* CYP Substrates and CYP Substrates with Narrow Therapeutic Range.

CYP enzymes	Sensitive substrates (2)	Substrates with narrow therapeutic range (3)
CYP1A2	Alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine	Theophylline, tizanidine
CYP2B6 (4)	Bupropion, efavirenz	
CYP2C8	Repaglinide (5)	Paclitaxel
CYP2C9	Celecoxib	Warfarin, phenytoin
CYP2C19	Lansoprazole, omeprazole, S-mephenytoin	S-mephenytoin
CYP3A (6)	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin,	Alfentanil, astemizole (7), cisapride (7), cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus,

CYP enzymes	Sensitive substrates (2)	Substrates with narrow therapeutic range (3)
	sirolimus, tolvaptan, tipranavir, triazolam, vardenafil	terfenadine (7)
CYP2D6	Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine	Thioridazine

1. Note that this is not an exhaustive list. For an updated list, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
2. Sensitive CYP substrates refers to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor.
3. CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).
4. The AUC of these substrates were not increased by 5-fold or more with a CYP2B6 inhibitor, but they represent the most sensitive substrates studied with available inhibitors evaluated to date.
5. Repaglinide is also a substrate for OATP1B1, and it is only suitable as a CYP2C8 substrate if the inhibition of OATP1B1 by the investigational drug has been ruled out.
6. Because a number of CYP3A substrates (e.g., darunavir, maraviroc) are also substrates of P-gp, the observed increase in exposure could be due to inhibition of both CYP3A and P-gp.
7. Withdrawn from the United States market because of safety reasons.

APPENDIX 7: GCIG SPECIFIC CRITERIA

GCIC-Rustin-modified Criteria for CA-125 Response[1]

Patients will be scored as having attained a CA-125 response if they meet the GCIG-Rustin-modified criteria which require that there is at least a 50% reduction in CA-125 levels from a pre-treatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA-125 only if they have a pre-treatment sample that is at least twice the upper limit of normal and within two weeks prior to starting treatment. In addition, CA-125 levels in samples obtained after administration of mouse antibodies or within four weeks after surgery or paracentesis should not be taken into account.

Definition of Progression free survival and duration of response by CA-125

PFS based on CA-125 will be defined as the time from first study drug infusion until the GCIC-Rustin-modified criteria of progression are met, or until the date of death (with or without disease progression).Duration of CA-125 response will be defined as the time between when the CA-125 was first documented to have decreased by 50% in a patient who meets all the GCIG-Rustin-modified criteria for a CA-125 response, and the time the CA-125 is first documented to have risen to the point where the patient meets GCIG criteria of disease progression.

GCIC-Rustin-modified definition of progressive disease according to CA-125 criteria		
	Definition of progression	Date of progression
Patients with elevated CA-125 before treatment and normalization of CA-125 during treatment	CA-125 ≥ 2 X ULN documented on 2 occasions*	Date CA-125 is first elevated to ≥ 2 X ULN
Patients with elevated CA-125 pretreatment that never normalizes	CA-125 ≥ 2 X nadir value on 2 occasions*	Date CA-125 is first elevated to ≥ 2 X nadir value
Patients with CA-125 in normal range pretreatment	CA-125 ≥ 2 X ULN documented on 2 occasions*	Date CA-125 is first elevated to ≥ 2 X ULN
*Repeat CA-125 anytime but normally not less than one week after the first elevated CA-125 level. CA-125 levels in samples obtained after administration of mouse antibodies or within four weeks after surgery or paracentesis should not be taken into account.		

In patients for whom response to treatment is evaluated by both RECIST and CA-125 criteria, the date of response and progression will be the earliest date of the two methods.

[1] Rustin GJ, Quinn M, Thigpen T, du Bois A, Pujade-Lauraine E, Jakobsen A, *et al.* Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). *J Natl Cancer Inst* 2004;96(6):487-8.

APPENDIX 8: DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential

preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary

characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.