AN OPEN-LABEL PHASE IB STUDY OF PALBOCICLIB (ORAL CDK 4/6 INHIBITOR) PLUS ABRAXANE® (NAB-PACLITAXEL) IN PATIENTS WITH METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA

Compound:	PD-0332991
Compound Name:	Palbociclib
United States (US) Investigational New Drug (IND) Number:	122,168
European Clinical Trials Database (EudraCT) Number:	2015-001307-31
Protocol Number:	A5481059
Phase:	Phase 1B

[redacted]

Document History

Document	Version Date	Summary of Changes
Original protocol	20 May 2015	Not applicable (N/A)
Amendment 1	15 September 2016	Major changes include: 1. Addition of modified dose regimen cohorts, resulting in an increased sample size of the overall study. 2. CCI [redacted] 3. Changes to dose modification guidelines for hematologic toxicities and addition of recommendations for growth factor use. 4. Updates to the list of required laboratory tests (amylase/lipase are required where available). 5. Modifications made to prohibited medications and medications not recommended. 6. Meal information nearest PK sampling days will be collected. 7. PK sample processing information was removed and reference to the Study Manual was added. 8. General spelling and grammar corrections throughout the document.
Amendment 2	26 October 2016	1. CCI [redacted] 2. Clarification was added such that the full physical exam including all major body systems should be done if clinically

		indicated. 3. Karnofsky Performance Status and pain VAS are not required on Cycle 1 Day -2 if acceptable screening assessment is performed within 7 days prior to start of investigational product. 4. A statement was included that will permit completion of dose escalation without determining the MTD, based on emerging safety data and upon agreement between the investigators and the sponsor. 5. Clarification of minor discrepancies throughout the document.
Amendment 3	23 August 2018	1. Updated background to include a notification that the palbociclib + nab-paclitaxel combination will not be further developed due to emerging data. 2. Included a provision to allow remaining patients on investigational product to continue until progression, unacceptable toxicity or consent withdrawal, and remaining patients in post-treatment follow up will be considered to have completed the study after 12 months (365 days) have elapsed from the first dose of investigational product. 3. Updated the schedule of activities to allow flexibility for remaining patients on investigational product.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

PROTOCOL SUMMARY

Metastatic pancreatic cancer is one of the most aggressive and highly lethal malignancies, with an estimated 5-year survival rate of less than 5%.[1]

KRAS mutations are a hallmark of pancreatic ductal adenocarcinoma (PDAC) with mutation found in more than 75% and up to 95% of tumors. Important regulatory proteins involved in the cell cycle transition from G1 into S-Phase are cyclin D1 (encoded by CCND1), p16INK4a (thereafter referred to as p16, and encoded by CDKN2A), and cyclin-dependent kinases (CDKs). Deregulation of aspects of the cell-cycle, including CDKs, have been shown to contribute to the development of cancer. Inactivation of p16 occurs in the majority of cases of metastatic PDAC (mPDAC). Genomic characterization of PDAC identified loss of CDKN2A in more than 50% of tumors, most often concurrent with KRAS mutation. In addition, activated MAPK pathway results in the increased expression of cyclin D1.

Palbociclib, (Ibrance®; PD-0332991) is a highly selective, reversible oral inhibitor of cyclin-dependent kinases 4 and 6 (CDK 4/6). This compound prevents cellular deoxyribonucleic acid (DNA) synthesis by inhibiting progression of the cell cycle from G1 into S phase.

CCI

Nab-paclitaxel is indicated for the first-line treatment of patients with metastatic ductal adenocarcinoma of the pancreas (mPDAC), in combination with gemcitabine. Median overall survival (OS) was extended from 6.7 months to 8.5 months when added to gemcitabine as first-line treatment of mPDAC ($p<0.0001$).[2]

Single-agent data for nab-P were generated in a phase 2 clinical study evaluating nab-P (100 mg/m^2) in advanced pancreatic cancer patients who have progressed on gemcitabine-based therapy.[3] Treatment resulted in 58 percent of patients achieving six-month OS, with a median survival of 7.3 months and a median progression-free survival (PFS) of 1.6 months. Five patients remained alive at a median follow-up of 12.7 months, including one patient with stable disease (SD) on cycle 15 of therapy. Safety results were generally consistent with the known safety profile of nab-P. CCI [redacted]

Clinical development of palbociclib in first-line mPDAC builds upon robust pre-clinical data from PDX models. CCI [redacted]

This current study aims to investigate the safety and tolerability, of the combination of palbociclib plus nab-P in patients with mPDAC.

STUDY OBJECTIVES AND ENDPOINTS

Objectives

Primary Objective: To assess the safety and tolerability of palbociclib in combination with nab-paclitaxel (nab-P) in patients with metastatic pancreatic ductal adenocarcinoma in order to estimate the maximum tolerated dose (MTD) and select the recommended Phase 2 dose (RP2D).

Secondary Objectives:

- To evaluate the overall safety profile of palbociclib in combination with nab-P;
- To characterize the multiple-dose pharmacokinetics of palbociclib when administered in combination with nab-P;
- To evaluate the effect of palbociclib on pharmacokinetics of total paclitaxel when nab-P is administered in combination with palbociclib;
- To evaluate the anti-tumor effect of palbociclib in combination with nab-P in patients with mPDAC;
- To evaluate the pharmacodynamic effect of palbociclib and nab-P in patients with mPDAC;

- To characterize candidate biomarkers of sensitivity or resistance in pre-treatment tumor tissue, including Rb1 and p16 expression, that may aid in the identification of patient subpopulations most likely to benefit from treatment.

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted].

Endpoints

Primary Endpoint

- First cycle dose-limiting toxicities (DLTs).

Secondary Endpoints

- Safety;
  - Adverse events (AEs) as characterized by type, frequency, severity [as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.4.03], timing, seriousness, and relationship to study therapy;
  - Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03) and timing;
  - Vital signs;
- Pharmacokinetic parameters of palbociclib and nab-P:

  - For palbociclib PK when given with nab-P: Multiple Dose (MD) (assuming steady-state is achieved) – $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $C_{ss,trough,}$ and CL/F as data permit;
  - For total paclitaxel when nab-P is given alone and in combination with palbociclib: C_{max}, T_{max}, AUC_{last}, AUC_{∞}, $t_{1/2}$, CL, and V_z as data permit;
- Clinical pharmacodynamic (PD) markers associated with mPDAC (eg, Ca19-9);
- Efficacy:
  - Objective tumor response, as assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1;
  - Time-to-event endpoints: eg, Duration of Response (DR), Progression Free Survival (PFS), Six-month progression-free survival rate (6m-PFSR), Overall Survival (OS).
- Biomarker endpoints:
  - Tumor tissue biomarkers (p16 and Rb1 expression by IHC).

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Study Design

This is a Phase 1, open label, multi-center, multiple dose, dose escalation, safety, pharmacokinetic and pharmacodynamic study of palbociclib in combination with nab-P, in sequential cohorts of adult patients with mPDAC, with expansion cohorts. Approximately 60-100 patients are expected to be enrolled in the overall study. The study has several parts:

- **Dose Escalation Cohorts**

  Consecutive cohorts of patients will receive escalating doses of oral palbociclib in combination with intravenous nab-P in 28-day cycles. The starting dose of palbociclib will be 75 mg administered on Days 1-21 of each cycle (3/1 dosing schedule). The starting dose of nab-P is 100 mg/m^2 administered weekly for 3 weeks out of each 28-day cycle. The observation period for dose-limiting toxicities (DLTs) will be from Day 1 until pre-dose Cycle 2 Day 1 (Day -2 and Day -1 will not be included in the DLT observation period). Pharmacokinetic (PK) and pharmacodynamic (PD) properties of palbociclib and nab-P will be assessed. Up to approximately 30 patients will be enrolled.

  The criteria for dose escalation will be based on a modified toxicity probability interval (mTPI) method.

  Alternate dosing schedules for palbociclib may be explored based on emerging PK, PD, and safety data.

- **Modified Dose Regimen Cohorts (Amendment 1):**

  Emerging data from dose levels 1, 2A and 2B have shown only 1 patient meeting the criteria for DLT; however, several patients have required dose reductions. To further evaluate an optimal palbociclib/nab-P combination, an additional 2 cohorts of patients will be enrolled into alternative dose regimens at doses lower than the dose levels tested in dose escalation. The following dose regimens will be tested:

  - Modified Dose Regimen 1 (MDR1)-75 mg palbociclib once daily on Days 1-21 of each 28-day cycle, plus nab-P 125 mg/m^2 biweekly in each 28-day cycle.

  - Modified Dose Regimen 2 (MDR2)-75 mg palbociclib continuous dosing, once daily, plus nab-P 100 mg/m^2 biweekly in each 28-day cycle.

  For patients assigned to a modified dose regimen, the use of granulocyte-colony stimulating factor (G-CSF) is prohibited in the first 3 cycles unless clinically indicated and medically unavoidable. Dose reduction and/or interruption should first be used to manage hematologic toxicities.

  At least 6-9 patients will be enrolled into each MDR cohort.

- **Expansion Cohorts**

  - MTD Expansion Cohort(s).

When the MTD(s) of palbociclib plus nab-P has been estimated with confidence, enrollment will proceed into 1 or 2 MTD expansion cohort(s) of up to 20 patients each at the MTD(s). Patients will receive the same dosing regimen as in the dose escalation cohorts (palbociclib 3/1 schedule and weekly nab-P for 3 weeks in each 28-day cycle).

- **Modified Dose Regimen (MDR) Expansion Cohort (Amendment 3)**

  Based on emerging data from the MDR1 and MDR2 cohorts, enrollment into the MDR Expansion Cohort will be terminated.

Patients will be treated as long as they are clinically benefiting from investigational products (IP) without unacceptable toxicity, objective disease progression, or withdrawal of consent.

Protocol Amendment 3

1. Patients who are continuing to receive IP may continue to do so as long as they are clinically benefiting from IP without unacceptable toxicity, objective disease progression, or withdrawal of consent. Once a patient has completed Cycle 13, only safety data will be collected thereafter. Patients who have completed 13 cycles of IP are not required to enter post-treatment follow-up upon permanent discontinuation of IP. Patients who are ongoing beyond Cycle 13 will be considered to have completed the study upon permanent discontinuation of IP.

2. Patients who have discontinued IP before completing Cycle 13 will remain in post-treatment follow-up (See Schedule of Activities) until 12 months (365 days) have elapsed from the first dose of IP. Once a patient has been followed for 12 months from the first dose, the patient is considered to have completed the study and no further data will be collected.

Statistical Methods:

Dose escalation and de-escalation will follow a 2x3 matrix "Up-and-Down" design, with different dose combinations of palbociclib and nab-P using the modified toxicity probability interval (mTPI) method. Approximately 60-100 patients are expected to be enrolled in the overall study.

SCHEDULE OF ACTIVITIES

The Schedule of Activities (SOA) table provides an overview of the protocol visits and procedures. Refer to the Assessments section of the protocol for detailed information on each assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the Schedule of Activities, in order to conduct evaluations or assessments required to protect the well-being of the patient.

Table 1. SCHEDULE OF ACTIVITIES (up to Cycle 13)

Visit Identifier	Screening	Treatment Phase[1] (1 cycle = 28 days)										End of Treatment/ Withdrawal[2]	Post-Treatment Follow-Up[3]
		Cycle 1							Cycles ≥2-13				
Study Day	**Within 28 days prior to enrollment**	**Day -2[4]**	**Day -1**	**Day 1**	**Day 6[5]**	**Day 13**	**Day 14**	**Day 15**	**Day 1[6]**	**Day 8[5]**	**Day 15**	**Within 56 days of IP discontinuation**	**Monthly**
Visit Time Window		**±1 day**			**±1 day**	**±1 day**			**±7 days**	**±7 days**	**±7 days**	**+7 days**	**±28 days**
Baseline Documentation													
Informed Consent Process[7]	X												
Medical / Oncological History[8]	X												
Baseline Signs / Symptoms[9]		X[4]											
Physical Examination/Vital Signs[10]	X	X[4]		X	X	X			X (C2D1 only, then as clinically indicated)			X	
Serum/Urine Pregnancy Test[11]	X	X							X			X	
Contraception Check[12]		X											
Karnofsky Performance Status[13]	X	X										X	
Laboratory Studies													
Hematology[14]	X	X[4]			X	X			As clinically indicated			X	
Coagulation[14]	X	X[4]			X	X			As clinically indicated				
Blood Chemistry[14]	X	X[4]			X	X			As clinically indicated			X	
Urinalysis[14]	X	X[4]							As clinically indicated			X	
12-Lead ECG (in triplicate)[15]	X	X[4]				X			$X_{(C2D1, C2D15, C4D1, C7D1)}$			X	
Special Laboratory Studies													
Blood Sample for Ca 19-9		X							X			X	
Blood Samples for Pharmacokinetics[16]		X	X	X		X	X	X	X (C2 only)		X (C2 only)		

Visit Identifier	**Screening**	**Treatment Phase[1] (1 cycle = 28 days)**										**End of Treatment/ Withdrawal[2]**	**Post-Treatment Follow-Up[3]**
		Cycle 1							**Cycles ≥2-13**				
Study Day	**Within 28 days prior to enrollment**	**Day -2[4]**	**Day -1**	**Day 1**	**Day 6[5]**	**Day 13**	**Day 14**	**Day 15**	**Day 1[6]**	**Day 8[5]**	**Day 15**	**Within 56 days of IP discontinuation**	**Monthly**
Visit Time Window		**±1 day**			**±1 day**	**±1 day**			**±7 days**	**±7 days**	**±7 days**	**+7 days**	**±28 days**
CCI													
Archival Tumor Tissue Specimen	X												
De Novo Tumor Specimens[19]	X											X	
CCI													
CCI													
Computed Tomography (CT)/ Magnetic Resonance Imaging (MRI); Clinical evaluation of superficial disease[23]	X	As clinically indicated. See Table 2.											
Other Clinical Assessments													
Drug Compliance[24]	X								X			X	
Adverse Events[25]	X	Monitored and Recorded Continuously											X
Concomitant Medications/Treatments[26]	X	X				X			X				X
CCI													
Survival													X
Investigational Products													
Enrollment[29]		X											
Nab-paclitaxel administration (IV)[30] – Dose escalation and MTD expansion cohorts		X			X	X			X	X	X		
Nab-paclitaxel administration (IV)[30] – MDR and MDR expansion cohorts		X				X			X		X		

Visit Identifier	Screening	Treatment Phase[1] (1 cycle = 28 days)										End of Treatment/ Withdrawal[2]	Post-Treatment Follow-Up[3]
		Cycle 1							Cycles ≥2-13				
Study Day	Within 28 days prior to enrollment	Day -2[4]	Day -1	Day 1	Day 6[5]	Day 13	Day 14	Day 15	Day 1[6]	Day 8[5]	Day 15	Within 56 days of IP discontinuation	Monthly
Visit Time Window		±1 day			±1 day	±1 day			±7 days	±7 days	±7 days	+7 days	±28 days
Palbociclib administration (oral) – all patients except Modified Dose Regimen 2 (MDR2)		◄----------► Once daily with food on Days 1-21 of each 28-day cycle											
Palbociclib administration (oral) – Modified Dose Regimen 2 only		◄----------► Once daily (continuous dosing)											

Note: After completion of Cycle 13, only safety data will be collected thereafter. Patients who have completed 13 cycles of IP are not required to enter post-treatment follow-up upon permanent discontinuation of IP. Patients who are ongoing beyond Cycle 13 will be considered to have completed the study upon permanent discontinuation of IP.

Abbreviations: ◄--► = ongoing/continuous event; CxDy = Cycle x Day y; ECG = electrocardiogram; CCI [redacted]; CT = computed tomography; IP=investigational product; IV=intravenous; MDR=Modified Dose Regimen; MRI = magnetic resonance imaging; MTD=Maximum Tolerated Dose; CCI [redacted];

1. All assessments should be performed prior to dosing with IP on the visit day unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers. For the purposes of this trial, 1 cycle is 28 days in length. A cycle could be longer than 28 days if persistent toxicity delays the initiation of the subsequent cycle. Maximum time between visits is 30 days.
2. **End of Treatment/Withdrawal**: End of Treatment/Withdrawal visit will be performed as soon as possible but no later than 8 weeks (ie, 56 days) ±7 days from last dose of IP and prior to the initiation of any new anticancer therapy.
3. **Post Treatment Follow up**: After discontinuation of IP, post study follow-up (including survival status and post study anticancer therapy therapies) will be collected every month (±28 days) from the last dose of IP. Telephone contact is acceptable. Post-treatment follow up is considered complete after 12 months (365 days) have elapsed from the first dose of IP.
4. **Cycle 1/Day -2**: Blood chemistry, hematology, coagulation, urinalysis, 12-lead ECG, physical examination/vital signs, Karnofsky performance status, CCI [redacted] and baseline signs/symptoms are not required if acceptable screening assessment is performed within 7 days prior to start of investigational product.
5. **Day 6/Day 8:** Procedures on Day 6 of Cycle 1 and Day 8 of Cycle 2 are not required for patients assigned to MDR1 and MDR2 cohorts, since nab-P is administered biweekly in these cohorts.
6. **Cycle ≥2, Day 1**: In the event that the start of a new cycle is delayed due to treatment-related toxicity, procedures required on Day 1 of the given cycle will be performed when either investigational product is resumed.
7. **Informed Consent**: Informed consent may be obtained greater than 28 days from start of investigational product; however, it must be obtained prior to any protocol-required assessments being performed.
8. **Medical/Oncological History**: To include information on prior anticancer treatments.

9. **Baseline Signs/Symptoms**: Baseline tumor-related signs and symptoms will be recorded at the C1D-2 visit prior to initiating nab-P and then reported as adverse events during the trial if they worsen in severity or increase in frequency.
10. **Physical Examination/Vital Signs:** A full physical examination including an examination of all major body systems (including general appearance, head, ears, eyes, nose, mouth, throat, neck, thyroid, lungs, heart, breasts, abdomen, and musculoskeletal as clinically indicated), height (at screening only), weight, blood pressure and pulse rate, which may be performed by a physician, registered nurse or other qualified health care provider, will be required at Screening, C1D-2, and C2D1. Thereafter, symptom directed physical examinations, blood pressure and pulse rate assessment will be performed as clinically indicated.
11. **Serum/Urine Pregnancy Test**: For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed on two occasions prior to starting IP, once at the start of screening, and once at the baseline visit immediately before investigational product administration (Cycle 1 Day -2). Pregnancy tests will also be routinely repeated at every treatment cycle during the treatment period, at the End of Treatment visit, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. See Section 7.1.3 for further information.
12. **Contraception Check**: Male patients who are able to father children, and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly, and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.
13. **Karnofsky Performance Status**: See Appendix 2. Karnofsky Performance Status is not required on Cycle 1 Day -2 if acceptable screening assessment is performed within 7 days prior to start of investigational product.
14. **Hematology, Coagulation, Blood Chemistry, and Urinalysis**: Hematology includes hemoglobin, WBC, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, absolute basophils, and platelet count. Coagulation analysis includes PT or INR, aPTT and PTT. Blood chemistry includes AST/ALT, alkaline phosphatase, sodium, potassium, magnesium, chloride, total calcium, total bilirubin, BUN (or urea), serum creatinine, uric acid, phosphorus (or phosphate), albumin, glucose, and amylase/lipase (where available). Additional blood tests should be performed where needed for the purpose of evaluating potential DLTs or other adverse events. -Urinalysis will be conducted via urine dipstick for urine protein: if the result is positive, further diagnostic testing will be performed as clinically indicated.
15. **12-lead ECG**: to be performed pre-dose at Screening, Cycle 1 Day -2, Cycle 1 Day 13, Cycle 2 Day 1, and Cycle 2 Day 15; subsequent ECGs will be performed pre-dose on Day 1 of Cycles 4, and 7. Patients should be fasted for at least 1 hour before ECGs are performed. After Cycle 7, ECGs may be performed as clinically indicated.
16. **Blood Sample for Pharmacokinetics**: Plasma PK samples (4 mL) for total paclitaxel determination will be collected prior to nab-P IV infusion and at 30 min (end of infusion), 1, 2, 4, 6, 8, 24, and 48 hours post the start of nab-P infusion on Day -2 and 13 of Cycle 1. Plasma PK samples (3 mL) for palbociclib determination will be collected on Cycle 1 Day 13 at 0 (pre-dose), 2, 4, 6, 8, and 24 hours post palbociclib dose, and pre-dose on Cycle 2 Days 1 and 15. Meal information (nearest the palbociclib dose) will be collected on Cycle 1 Day 12, Cycle 1 Day 13, Cycle 2 Day 1, Cycle 2 Day 14, and Cycle 2 Day 15.
17. CCI [redacted]

18. **Archival Tumor Tissue Specimen**: A FFPE tissue block that contains sufficient tissue to generate at least 12 (preferably 15) unstained slides, each with tissue sections that are 5 microns thick should be collected. If an FFPE tissue block cannot be provided, at least 12 (preferably 15) unbaked glass slides, each containing an unstained 5 micron FFPE tissue section will be required. If an archival tumor tissue sample is not available, a de novo tumor biopsy specimen must be obtained before IPs are administered (Cycle 1 Day -2). Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted. Specimens will be sent to the sponsor-designated central laboratory. Details for the handling of these specimens, including processing, storage, and shipment will be provided in the Study Manual.
19. **De Novo Tumor Specimens**: Optional de novo tumor biopsy collection at Screening and End of Treatment. If collected, these specimens will be provided in addition to the archival tumor tissue specimen that is required for eligibility purposes. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted. Details for handling of these specimens including processing, storage, and shipment will be provided in the Study Manual.
20. CCI [redacted]
21. CCI [redacted]
23. **Disease Assessments**: Disease Assessments will be performed as clinically indicated. See Table 2 for details and timing of procedures.
24. **Drug Compliance**: Palbociclib bottle(s), including any unused capsules, will be returned to the clinic for drug accountability. Drug accountability will be performed on Day 1 of every cycle prior to dispensing drug supply for the next cycle.
25. **Adverse Events**: For SAEs, the active reporting period begins from the time that the patient provides informed consent through and including 28 calendar days after the last administration of either investigational product. Following the active safety reporting period, other SAEs of which the investigator becomes aware should be reported to Pfizer, unless the SAE is attributed by the investigator to complications of either the underlying malignancy or any subsequent anti cancer therapy or to the patient's participation in a subsequent clinical study. AEs (serious and non-serious) should be recorded on the CRF from the time the patient has taken at least one dose of investigational product through last patient visit.
26. **Concomitant Medications/Treatments**: Concomitant medications and treatments will be recorded from 28 days prior to the start of IP and up to 28 days after the last dose of IP. This includes H1 antagonists pre-medication to alleviate nab-paclitaxel infusion reactions. Only anticancer medications will be collected in the post-treatment follow-up period.
27. CCI [redacted]
28. [redacted]

29. **Enrollment:** A patient is considered enrolled when all screening procedures have been completed, the patient has satisfied the requirements of all inclusion/exclusion criteria, and the completed registration form has been approved by the sponsor.
30. **Nab-Paclitaxel Administration**: Nab-paclitaxel will be administered as an intravenous infusion over 30 minutes. For Cycle 1, nab-P will start on Days -2; for subsequent cycles, nab-paclitaxel will start on Day 1.

Table 2. Tumor Assessment Requirements Flowchart

	Screening[a]	Treatment Period[b]	End of Treatment Visit[c]
CT or MRI of the chest and abdomen (including images of entire liver) and any other sites of disease, as clinically indicated[d]	Required[e]	Required for sites of disease identified at screening	Required for sites of disease identified at screening, unless disease progression has been confirmed elsewhere
Photographs of all superficial lesions as applicable[f]	Required	Required for sites of disease identified at screening	Required for sites of disease identified at screening, unless disease progression has been confirmed elsewhere

a. Screening scans must occur within 4 weeks (ie, 28 days) prior to start of IP unless otherwise specified.

b. Tumor assessment are to be performedas clinically indicated during the treatment period, or until the patient meets criteria for investigational product discontinuation. Tumor assessments are no longer required when the patient meets any of the following criteria: 1. Radiographically confirmed disease progression (PD) as per RECIST v.1.1 (Appendix 5), 2. Initiation of new anticancer therapy, or 3. Discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow up). The same tumor assessment technique MUST be used throughout the study for a given lesion/patient.

c. Patients who have already demonstrated objective disease progression as per RECIST v.1.1 do not need to have scans repeated at the End of Treatment visit or during the post-treatment follow-up period-

d. CT scans, including brain CT scan if applicable, should be performed with IV contrast agents unless contraindicated for medical reasons. If IV contrast is medically contraindicated, the imaging modality to be used to follow the disease (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist. MRI of the abdomen and pelvis can be substituted for CT if MRI adequately depicts the disease. However, MRI of the chest should not be substituted for CT of chest even if IV contrast is contraindicated. In such case CT will be performed without contrast. If MRI is used to follow-up bone lesion(s) it should be performed a few days before any treatment that may affect bone-marrow cellularity (eg, G-CSF).

e. Radiographic assessments obtained per the patient's standard of care prior to consent is obtained do not need to be repeated and are acceptable to use as baseline evaluations, if (1) obtained within 28 days before start of IP, (2) they were performed using the method requirements outlined in RECIST v.1.1, (3) the same technique/modality can be used to follow identified lesions throughout the trial for a given patient, and (4) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes.

f. Clinical assessment of superficial disease should be carried out on the same date as the imaging studies and will include photographs of all superficial metastatic lesions. All lesion measurements must be recorded in the case report form (CRF).

Notes:

Radiographic tumor assessments may be done at any time if there is clinical suspicion of disease progression at the discretion of the investigator.

If progressive disease is confirmed, patients are expected to discontinue IP and begin the follow-up phase of the trial.

Table 3. PK Sampling and CCI Schema

Visit Identifier	Cycle 1																					Cycle 2	
Study Day	-2							-1	1	2-5	6[1]	7-12	13							14	15	15-21	1[1]	15[1]
Hours Pre/Post Dose[2]	**0[1]**	**0.5**	**1**	**2**	**4**	**6**	**8**	**24**	**48**				**0[1]**	**0.5**	**1**	**2**	**4**	**6**	**8**	**24**	**48**			
Nab-paclitaxel Dosing	X										X[3]		X										X[3]	X
Total paclitaxel PK blood sampling	X	X	X	X	X	X	X	X	X				X	X	X	X	X	X	X	X	X			
Palbociclib Dosing									X	X	X	X[4]	X[4,5,6]							X	X	X	X[5]	X[5]
Palbociclib PK blood sampling													X			X	X	X	X	X			X[1]	X[1]
CCI																								

1. Sample to be drawn prior to dosing of both nab-P and palbociclib.
2. Relative to nab-P start of infusion or palbociclib dosing, respectively.
3. MDR and MDR expansion cohorts will not receive nab-P on Day 6/Day 8.
4. Every attempt should be made to ensure the palbociclib was taken for the last 7 consecutive days, and the dose on Cycle 1 Day 12 is at least 20 hours before the pre-dose PK sample on Cycle 1 Day 13. PK, CCI CCI and CCI blood sample should be rescheduled if one or more of these requirements have not been met.
5. Meal information (nearest the palbociclib dose) will be collected on Cycle 1 Day 12, Cycle 1 Day 13, Cycle 2 Day 1, Cycle 2 Day 14, and Cycle 2 Day 15. Information including meal time and type (high fat, low fat, or standard) will be collected.
6. On Cycle 1 Day 13, patients will be instructed to withhold administration of their palbociclib dose and bring it with them to their clinic visit. Patients should be provided a meal within 30 minutes prior to palbociclib dosing. After the meal is eaten, the pre-dose PK samples may be drawn just prior to palbociclib dosing. Palbociclib dosing should be as close as possible to the start of the nab-P infusion.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Palbociclib (Ibrance®) is a highly selective, reversible oral inhibitor of cyclin-dependent kinases 4 and 6 (CDK 4/6). The compound prevents cellular deoxyribonucleic acid (DNA) synthesis by prohibiting progression of the cell cycle from G1 into S phase. Palbociclib is being developed in combination with nanoparticle albumin-bound paclitaxel (nab-paclitaxel or nab-P) (Abraxane®) in patients with metastatic ductal adenocarcinoma of the pancreas (mPDAC).

1.2. Background and Rationale

1.2.1. Pancreatic Ductal Adenocarcinoma

Metastatic pancreatic cancer is one of the most aggressive and highly lethal malignancies, with an estimated 5-year survival rate of less than 5%.[1]

It is estimated that over 280,000 new cases of pancreatic cancer are diagnosed globally each year. In the US and European Union (EU), the crude incidence rate of pancreatic cancer averages 15 cases per 100,000 population, which translates to approximately 38,000 incident cases and 34,000 deaths yearly.[4]

Over 95% of all malignancies of the pancreas are ductal adenocarinomas (PDAC). Primary PDAC spreads and invades locally, affecting the organs of the abdominal cavity including the stomach, colon duodenum, and major blood vessels supplying and draining the intestinal tract and liver. Regional lymph nodes are the most common site of metastasis while the liver is second. Over 80% of patients present with regional or distant metastases at the time of diagnosis (Stage III or Stage IV) and are unsuitable for surgical resection.[5] KRAS mutations are a hallmark of PDAC with mutations found in more than 75% and up to 95% of tumors.

PDAC was the fourth leading cause of death from cancer in Europe and the United States in 2010.[6,7] PDAC carries a grim prognosis with a median overall survival (OS) of only 9-11 months,[8,9] largely due to difficulties associated with diagnosing the disease in its early stages.[7]

Since 1997, gemcitabine (GEM) therapy has been the standard first-line treatment for patients with unresectable locally advanced or metastatic pancreatic cancer. Clinical activity of GEM in metastatic PDAC (mPDAC) is relatively modest, as response rates are low (approximately 20%), and disease control rates and median OS benefits are extremely limited with a median progression-free survival (PFS) of approximately 3 months, and a median OS of 6 to 7 months.[10]

Given the poor response rates seen with single-agent GEM therapy, more recently clinical trial efforts have been undertaken to improve the efficacy of GEM while maintaining an acceptable safety profile.

A small, but statistically significant improvement in survival among patients with advanced pancreatic cancer has been shown for erlotinib, a small-molecule inhibitor of the epidermal growth factor receptor (EGFR).[11] As shown in other studies of agents targeting the EGFR, patients in whom drug-induced rashes developed had a better outcome. However, the high frequency of KRAS-mutations in pancreatic cancer probably limits the benefits of an EGFR inhibitor. As compared with erlotinib alone, the combination of gemcitabine and erlotinib has more toxicity, particularly gastrointestinal symptoms. Together with the rather modest improvement in survival, the toxicity of this combination has limited its wide acceptance as the standard of care.

The FOLFIRINOX regimen (5-fluorouracil, leucovorin, oxaliplatin, irinotecan) has gained favor as a first-line treatment for patients with locally-unresectable or metastatic pancreatic cancer. In a Phase 3 study[8] comparing FOLFIRINOX with single-agent GEM, the FOLFIRINOX regimen showed a median PFS of 6.4 vs. 3.3 months for GEM (HR =0.47; 95% confidence interval [CI], 0.37 to 0.59; P <0.001); a median OS of 11.1 vs. 6.8 months (HR = 0.57, 95% CI, 0.45 to 0.73, P <0.001), and a 1-year survival of 48.4% vs. 20.6%. The Disease Control rate (CR + PR + SD) was 70.2% vs. 50.9% (P <0.001), with a duration of response of 5.9 vs. 4 months (p = NS). However, while survival rates were improved with FOLFIRINOX, the toxicity of the regimen is significantly higher compared to GEM. In this study, nearly half of the patients (45.7%) developed Grade 3/4 neutropenia with respect to 21% in the GEM arm, and febrile neutropenia was noted in 5.4% of patients treated with FOLFIRINOX compared to 1.2% of patients treated with GEM (p = 0.03). Patients on the FOLFIRINOX arm developed Grade 3/4 vomiting, fatigue, sensory neuropathy, and diarrhea at rates of 15%, 23%, 9% and 13%, respectively compared to 8%, 18%, 0% and 2% of patients treated with GEM. This toxicity profile limits the use of FOLFIRINOX to those patients who are in good physical condition, relatively young, and with an excellent performance status.

Compared to FOLFIRINOX, the combination of GEM with a unique formulation of paclitaxel (Abraxane®, nab-paclitaxel) provides a more favorable safety profile while maintaining similar levels of efficacy. A Phase 3 trial confirmed the superiority of the combination of GEM with nab-paclitaxel (nab-P) versus GEM alone with statistically significant and clinically meaningful results across primary and secondary endpoints.[9] Median OS in the combination arm was superior to GEM alone (8.5 vs. 6.7 months, HR = 0.72, p =0.000015). The one-year survival rate was 35% vs. 22% (p<0.001), and the two-year survival rate was 9% vs. 4% (p=0.02). The median PFS was 5.5 vs. 3.7 months (HR = 0.69, p<0.001), and the overall response rate (ORR) was 23% compared to 7% (p<0.001). The safety profile of the doublet was manageable with the most common Grade ≥3 treatment-emergent AEs in the doublet vs. GEM alone being neutropenia (38% vs. 27%), fatigue (17% vs. 7%), and neuropathy (17% vs. 1%). There was no significant difference in life-threatening toxicities between treatment arms.

However, the medical need remains high and the development of novel more efficacious and safe combinations is warranted.

1.2.2. Investigational Agents: Nab-Paclitaxel

Abraxane® (nab-paclitaxel or nab-P) is nanoparticle albumin-bound paclitaxel and therefore a microtubule inhibitor. Nab-P is created by encapsulating paclitaxel within albumin nanoparticles. This encapsulated formulation eliminates the need for Cremophor EL, thereby reducing hypersensitivity reactions during taxane infusion according to the product labeling.

Nab-paclitaxel is indicated for the first-line treatment of patients with metastatic ductal adenocarcinoma of the pancreas (mPDAC), in combination with gemcitabine. Median overall survival (OS) was extended from 6.7 months to 8.5 months when added to gemcitabine as first-line treatment of mPDAC ($p<0.0001$).[2]

Single-agent data for nab-P were generated in a Phase 2 clinical study evaluating nab-P (100 mg/m^2) in advanced pancreatic cancer patients who have progressed on gemcitabine-based therapy.[3] Treatment resulted in 58 percent of patients achieving six-month OS, with a median survival of 7.3 months and a median progression-free survival (PFS) of 1.6 months. Five patients remained alive at a median follow-up of 12.7 months, including one patient with stable disease (SD) on Cycle 15 of therapy. Safety results were generally consistent with the known safety profile of nab-P. Non-hematological toxicities were generally mild with Grade 1 or 2 nausea (63%), anorexia (47%), hypocalcemia (37%) and vomiting (26%) observed. The most common Grade 3 and 4 adverse events that occurred were neutropenia (32%), neutropenic fever (11%) and anemia (11%). There were no cases of Grade 3 or 4 neuropathy. Nab-P was well-tolerated and provided clinical benefit in 37 percent of patients who had previously progressed on gemcitabine-based therapy.[3]

The results of this study demonstrated that single agent nab-paclitaxel is active in pancreatic cancer patients who have previously progressed on gemcitabine-based therapy. However, most of the safety data for single agent nab-P are have been generated in patients with metastatic breast cancer in a Phase 3 trial in comparison to paclitaxel.[12] Mainly based on this study, the following adverse events describe the side effect profile for single agent nab-P:

Hematologic Disorders

Neutropenia was dose dependent and reversible. Among patients with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm^3 (Grade 4) in 9% of the patients treated with a dose of 260 mg/m^2 compared to 22% in patients receiving paclitaxel injection at a dose of 175 mg/m^2. Pancytopenia has been observed in clinical trials.

Infections

Infectious episodes were reported in 24% of the patients treated with nab-P. Oral candidiasis, respiratory tract infections and pneumonia were the most frequently reported infectious complications.

Hypersensitivity Reactions (HSRs)

Grade 1 or 2 HSRs occurred on the day of nab-P administration and consisted of dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmia (all <1%). The use of nab-P in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

Cardiovascular

Hypotension, during the 30-minute infusion, occurred in 5% of patients. Bradycardia, during the 30-minute infusion, occurred in <1% of patients. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation. Severe cardiovascular events possibly related to single-agent nab-P occurred in approximately 3% of patients. These events included cardiac ischemia/infarction, chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension. Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported. Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 60% of patients. Among patients with a normal ECG prior to study entry, 35% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, and sinus tachycardia.

Respiratory

Dyspnea (12%), cough (7%), and pneumothorax (<1%) were reported after treatment with nab-P.

Neurologic

The frequency and severity of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of nab-P discontinuation in 7/229 (3%) patients. Twenty-four patients (10%) treated with nab-P developed Grade 3 peripheral neuropathy; of these patients, 14 had documented improvement after a median of 22 days; 10 patients resumed treatment at a reduced dose of nab-P and 2 discontinued due to peripheral neuropathy. Of the 10 patients without documented improvement, 4 discontinued the study due to peripheral neuropathy. No Grade 4 sensory neuropathies were reported. Only one incident of motor neuropathy (Grade 2) was observed in either arm of the controlled trial.

Vision Disorders

Ocular/visual disturbances occurred in 13% of all patients (n=366) treated with nab-P and 1% were severe. The severe cases (keratitis and blurred vision) were reported in patients who received higher doses than those recommended (300 or 375 mg/m^2). These effects generally have been reversible.

Arthralgia/Myalgia

The symptoms were usually transient, occurred two or three days after nab-P administration, and resolved within a few days.

Hepatic

Grade 3 or 4 elevations in GGT were reported for 14% of patients treated with nab-P and 10% of patients treated with paclitaxel injection in the randomized trial.

Renal

Overall 11% of patients experienced creatinine elevation, 1% severe. No discontinuations, dose reductions, or dose delays were caused by renal toxicities.

Other Clinical Events

Nail changes (changes in pigmentation or discoloration of nail bed) have been reported. Edema occurred in 10% of patients; no patients had severe edema. Dehydration and pyrexia were also reported.

The Single Reference Safety Document (SRSD) for nab-P (Abraxane®) is the most recent version of the Summary of Product Characteristics (SPC).[2]

1.2.3. Investigational Agents: Palbociclib

1.2.3.1. Pre-Clinical Data

Important regulatory proteins involved in the cell cycle transition from G1 into S-Phase are cyclin D1 (encoded by CCND1), p16INK4a (thereafter referred to as p16, and encoded by CDKN2A), and cyclin-dependent kinases (CDKs). Deregulation of aspects of the cell-cycle, including CDKs, have been shown to contribute to the development of cancer. Palbociclib (Molecular Weight: 447.53) is a highly selective inhibitor of CDK4/cyclin D1 kinase activity (IC_{50} = 11 nM; Ki= 2 nM). Palbociclib has selectivity for CDK4/6, with little or no activity against a large panel of 274 other protein kinases including other CDKs and a wide variety of tyrosine and serine/threonine kinases. CDK6, another enzyme that also complexes with cyclin-D subunits, is also commonly expressed in mammalian cells and tumors. CDK6 is highly homologous to CDK4 and can perform the same function by phosphorylating retinoblastoma protein (Rb1), thus potentially creating a redundant mechanism to promote cell cycle progression. Consequently, inhibition of both enzymes is necessary to ensure complete suppression of Rb1 phosphorylation and the greatest possible spectrum of antitumor activity.

Results indicate that palbociclib inhibits CDK6 with equivalent potency to CDK4. Palbociclib showed anti-proliferative effects on Rb1-positive cells in vitro and inhibition of tumor growth in several Rb-positive human breast and colon xenografts. In these models, palbociclib resulted in decreased Rb1 phosphorylation and decreased Ki-67 expression, but did not show activity in Rb1-negative tumor xenografts.[13] Additional information may be found in the Investigator's Brochure (IB) for palbociclib.

CCI

[redacted]

1.2.3.3. Overview of Palbociclib Nonclinical Safety Data

The nonclinical safety profile of palbociclib has been well characterized through the conduct of single- and repeat-dose toxicity studies up to 39 weeks in duration, and safety, pharmacology, genetic toxicity, reproductive and developmental toxicity, and phototoxicity studies.

Detailed information may be found in the IB for palbociclib.

1.2.3.4. Palbociclib Pharmacokinetics in Human

As of 01 September 2015, twenty-five clinical studies have evaluated the PK of palbociclib. Seven of these trials were conducted in patients with advanced malignant disease. Detailed information on the PK properties of palbociclib may be found in the IB.

1.2.4. Palbociclib Clinical Data

Palbociclib has been explored in multiple clinical trials in a variety of malignancies, as single agent and in combination therapy.

Two Phase 1 trials evaluated single agent administration of palbociclib to patients with Rb-positive cancers.[14,15] One of these trials determined that the dose-limiting toxicity (DLT) was neutropenia and the maximum tolerated dose (MTD) was 125 mg once daily when administered for 21 of 28 days (3 weeks on/1 week off schedule). The most common non-hematologic AEs included fatigue, nausea, and diarrhea. The mean half-life of palbociclib was 26.9 hours. Patients were selected for Rb-positive cancers, based on immunohistochemistry (IHC) stain, defined as positive if staining intensity was 1+ or greater above background. Stable disease for ≥4 cycles (16 weeks) occurred in 27% of evaluable patients and in a number of tumor types (liposarcoma, testicular, renal, ovarian, breast, appendiceal, peritoneal, melanoma, thymoma and lung). Another Phase I trial of palbociclib using an alternative dosing plan (21 day cycles; 2 weeks on/1 week off schedule) observed a similar likelihood of disease control in a variety of tumor types.[14] These studies demonstrate that palbociclib has substantial activity in Rb-positive tumors.

A randomized Phase 2 trial was initiated to determine the overall safety and efficacy of palbociclib (125 mg) and letrozole (2.5 mg) versus letrozole in post-menopausal women with ER+ HER2-negative advanced breast cancer.[16] The ORR was 45% for those women who received palbociclib plus letrozole versus 31% for those who received letrozole (statistically significant). Importantly, the median PFS was significantly different (26.2 versus 7.5 months) favoring the combination arm. The most common adverse drug reactions of any grade reported in patients in the palbociclib plus letrozole arm were neutropenia, leukopenia, fatigue, anemia, upper respiratory infection, nausea, stomatitis, alopecia, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, and epistaxis. The most frequently reported serious adverse drug reaction in patients receiving palbociclib plus letrozole was diarrhea (2.4%).

Overall, neutropenia of any grade was reported in 62 (74.7%) patients in the combination arm, with Grade 3 neutropenia being reported in 40 (48.2%) patients, and Grade 4 neutropenia being reported in 5 (6.0%) patients.

In the combination arm, 56.6% of patients had a maximum grade of Grade 3 neutropenia and 4.8% of patients had a maximum grade of Grade 4 neutropenia based on laboratory data. The median time to first episode of neutropenia was 15 days for any grade, Grade ≥2, and Grade 4 neutropenia, and 28 days for Grade ≥3 neutropenia in the palbociclib plus letrozole arm. Median duration of Grade 3 or 4 neutropenia was 7 days. Most episodes of Grade ≥3 neutropenia were managed by dose reduction and/or dose delay or temporary discontinuation and did not require permanent discontinuation of study treatment or addition of supportive therapy. Grade 3-4 fatigue/asthenia, vomiting, diarrhea and peripheral neuropathy rates were 6%, 0%, 4% and 0% respectively.

Based on these data, the US FDA approved palbociclib for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- letrozole as initial endocrine based therapy in postmenopausal women (1), or
- fulvestrant in women with disease progression following endocrine therapy.

The indication in combination with letrozole is approved under accelerated approval based on progression-free survival (PFS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

There are currently no clinical data for palbociclib in pancreatic cancer.

Complete information for palbociclib may be found in the Single Reference Safety Document (SRSD), which for this study is the current IB.

1.2.5. Study Rationale

Currently FOLFIRINOX is the preferred chemotherapy combination in patients with good performance status. Although the combination of GEM/nab-P represents an acceptable and potentially less toxic alternative to FOLFIRINOX in less fit patients, the replacement of GEM with palbociclib in combination with nab-P could provide additional benefits.

Clinical development of palbociclib in mPDAC builds upon robust pre-clinical data from PDX models. CCI

CCI [redacted]

A number of genetic, pre-clinical *in vitro* and *in vivo* data further provide robust rationale for CDK4/6 inhibition in PDAC:

- A recent study examining mutational patterns in PDAC using whole genome sequencing identified a number of alterations in the CyclinD/CDK4/RB pathway leading to an increased cell cycle activity through this pathway.[17]
- PDAC is enriched for oncogenic KRAS mutations, which has been shown to be synthetic lethal with CDK4/6 inhibition,[18] observed in up to 95% of patients.
- Over 50% and up to 90% of cases reveal a loss of the tumor suppressor CDKN2A (p16INK4a), the endogenous inhibitor of CDK4/6.[19,17]
- While loss of Rb1 is uncommon in PDAC,[17] detection of phosphorylated Rb1 is reported at high frequencies suggesting that CDK4/6 signaling may be critical for the dysregulation of cell cycle control in PDAC.
- CCI [redacted]

1.2.6. Rationale for Modified Dose Regimens (Amendment 1)

Emerging data from dose levels 1, 2A and 2B have shown only 1 patient meeting the criteria for DLT; however, several patients have required dose reductions. A lower or modified dose regimen may show better tolerability. Biweekly regimens of the GEM/nab-P combination have shown comparable efficacy with an improved toxicity profile.[23]

1.2.7. Rationale for Amendment 3

The rationale for the study was supported on theoretical and preclinical grounds. However, based on emerging clinical data, the combination of palbociclib and nab-paclitaxel will not be further developed.

1.2.8. Summary of Benefit Risk Assessment

Systemic chemotherapy represents the main treatment option in patients with metastatic pancreatic cancer. However, mPDAC patients treated with current chemotherapy regimens still have a poor prognosis, and more efficacious and tolerable therapies are desirable.

The relevance of CDK 4/6 activity in pancreatic cancer together with the efficacy observed with palbociclib in combination with nab-P in PDAC preclinical models support testing this novel combination in mPDAC patients, with the aim to improve clinical outcomes including survival, progression-free survival, and other health-related outcomes, such as delayed deterioration and/or improvement of global health status and pain. The safety profile of the combination should be manageable. The most likely risk associated with a palbociclib/nab-P treatment regimen is neutropenia which can be managed by dose delay, dose reduction, temporary discontinuation, or growth factors without permanent discontinuation of treatment. Other potentially overlapping toxicities include anemia, neuropathy, nausea, vomiting, fatigue/asthenia, hypertension, and diarrhea. In order to minimize the risk for the patients, safety and tolerability of the proposed combination will be carefully monitored in the proposed clinical protocol by means of medical visits and laboratory tests at predefined time points, and dose modifications for one or both drugs as well as supportive medical treatment may be implemented in case of emerging toxicities.

Taken together, the potential benefits of a palbociclib/nab-P treatment outweigh the potential risks, supporting an overall favorable benefit/risk assessment in the treatment of patients with mPDAC.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objective

- To assess the safety and tolerability of palbociclib in combination with nab-paclitaxel (nab-P) in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) in order to estimate the maximum tolerated dose (MTD) and select the recommended Phase 2 dose (RP2D).

Secondary Objectives

- To evaluate the overall safety profile of palbociclib in combination with nab-P;
- To characterize the multiple-dose pharmacokinetics of palbociclib when administered in combination with nab-P;
- To evaluate the effect of palbociclib on pharmacokinetics of total paclitaxel when nab-P is administered in combination with palbociclib;
- To evaluate the anti-tumor effect of palbociclib in combination with nab-P in patients with mPDAC;

- To evaluate the pharmacodynamic effect of palbociclib and nab-P in patients with mPDAC;

- To characterize candidate biomarkers of sensitivity or resistance in pre-treatment tumor tissue, including Rb1 and p16 expression, that may aid in the identification of patient subpopulations most likely to benefit from treatment.

CCI

[redacted]

2.2. Endpoints

Primary Endpoint

- First cycle dose limiting toxicities (DLTs).

Secondary Endpoints

- Safety:
  - Adverse Events as characterized by type, frequency, severity [as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03], timing, seriousness, and relationship to study therapy;
  - Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing;
  - Vital signs;

- Pharmacokinetic parameters of palbociclib and nab-P:
  - For palbociclib PK when given with nab-P: Multiple Dose (MD) (assuming steady-state is achieved) - $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $C_{ss,trough,}$ and CL/F, as data permit;
  - For total paclitaxel when nab-P is given alone and in combination with palbociclib: C_{max}, T_{max}, AUC_{last}, AUC_{∞}, $t_{1/2}$, CL, and V_z as data permit;
- Clinical pharmacodynamic markers associated with mPDAC (eg, Ca19-9);
- Efficacy:
  - Objective tumor response, as assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1;
  - Time-to-event endpoints: eg, Duration of Response (DR), Progression Free Survival (PFS), Six-month progression-free survival rate (6m-PFSR), Overall Survival (OS);
- Biomarker endpoints:
  - Tumor tissue biomarkers (p16 and Rb1 expression by IHC).

CCI

[redacted]

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1, open label, multi-center, multiple dose, dose escalation, safety, pharmacokinetic and pharmacodynamic study of palbociclib in combination with nab-P, in sequential cohorts of adult patients with mPDAC, with expansion cohorts. Approximately 60-100 patients are expected to be enrolled in the overall study. The study has several parts:

- **Dose-Escalation Cohorts:**

  Consecutive cohorts of patients will receive escalating doses of oral palbociclib in combination with intravenous nab-P in 28-day cycles as illustrated in Figure 2, in order to estimate the MTD(s) of the combination. The starting dose of palbociclib will be 75 mg palbociclib, administered on Days 1-21 of each cycle (3/1 dosing schedule). The starting dose of nab-P is 100 mg/m^2 - administered weekly for 3 weeks out of each 28-day cycle. The observation period for dose-limiting toxicities (DLTs) will be from Day 1 until pre-dose Cycle 2 Day 1 (Day -2 and -1 will not be included in the DLT observation period). Pharmacokinetic (PK) and pharmacodynamic (PD) properties of palbociclib and nab-P will also be assessed. Up to approximately 30 patients will be enrolled.

  The criteria for dose escalation will be based on a modified toxicity probability interval (mTPI) method.

- **Modified Dose Regimen Cohorts:**

  Emerging data from dose levels 1, 2A and 2B have shown only 1 patient meeting the criteria for DLT; however, several patients have required dose reductions. To further evaluate an optimal palbociclib/nab-P combination, an additional 2 cohorts of patients will be enrolled into alternative dose regimens at doses lower than the dose levels tested in dose escalation. The following dose regimens will be tested:

- Modified Dose Regimen 1 (MDR1)-75 mg palbociclib once daily on Days 1-21 of each 28-day cycle, plus nab-P 125 mg/m^2 biweekly in each 28-day cycle.

- Modified Dose Regimen 2 (MDR2)-75 mg palbociclib continuous dosing, once daily, plus nab-P 100 mg/m^2 biweekly in each 28-day cycle.

  For patients assigned to a modified dose regimen, the use of G-CSF is prohibited in the first 3 cycles, unless clinically indicated an medically unavoidable. Dose reduction and/or interruption should first be used to manage hematologic toxicities.

At least 6-9 patients will be enrolled into each MDR cohort. Patients enrolled into MDR cohorts will also be assessed for DLTs. If the number of patients with a DLT falls into the "De-escalate" category (Table 14) in one or both MDR cohorts, the cohort(s) will not move forward into expansion. The MDR cohort with a DLT rate <0.33 in at least 9 DLT evaluable patient will be considered to move forward into expansion.

- **Expansion Cohorts:**

  - MTD Expansion Cohort(s);

  When the MTD(s) of palbociclib plus nab-P has been estimated with confidence, enrollment will proceed into 1 or 2 MTD expansion cohort(s) of up to 20 patients each at the MTD(s). Patients will receive --the same dosing regimen as in the dose escalation cohorts (palbociclib 3/1 schedule and weekly nab-P for 3 weeks in each 28-day cycle).

- **Modified Dose Regimen (MDR) Expansion Cohort (Amendment 3)**

Based on emerging data from the MDR1 and MDR2 cohort, enrollment into the MDR expansion cohort will be terminated.

For all patients, to allow for PK evaluation of nab-P administered alone, nab-P will be administered on Day -2 for Cycle 1 only. Subsequent cycles will administer both nab-P and palbociclib on Day 1. Alternate dosing schedules for palbociclib may be explored based on emerging PK, PD, and safety data.

Patients will be treated as long as they are clinically benefiting from investigational product without unacceptable toxicity, objective disease progression, or withdrawal of consent.

Patients discontinuing the treatment phase will enter a follow-up period during which survival and new anti-cancer therapy information will be collected every month from the last dose of study drug.

Protocol Amendment 3

1. Patients who are continuing to receive IP may continue to do so as long as they are clinically benefiting from IP without unacceptable toxicity, objective disease progression, or withdrawal of consent. Once a patient has completed Cycle 13, only safety data will be collected thereafter. Patients who have completed 13 cycles of IP are not required to enter post-treatment follow-up upon permanent discontinuation of IP. Patients who are ongoing beyond Cycle 13 will be considered to have completed the study upon permanent discontinuation of IP.

2. Patients who have discontinued IP before completing Cycle 13 will remain in post-treatment follow-up (See Schedule of Activities) until 12 months (365 days) have elapsed from the first dose of IP. Once a patient has been followed for 12 months from the first dose, the patient is considered to have completed the study and no further data will be collected. Efficacy analyses will be performed using the local radiologist's/investigator's tumor assessments as the primary data source. Patients will undergo study-related safety, efficacy, and PK assessments as outlined in the Schedule of Activities (Table 1, Table 2, and Table 3).

Blood, tumor biopsies (optional), and/or CCI [redacted] will be taken while on-treatment and at the end of treatment.

CCI [redacted]

[redacted]

3.1.1. Starting Dose Level

The starting dose level (DL) for dose escalation will be 75 mg palbociclib and 100 mg/m^2 nab-P. See Section 5.3.3 for the dosing schedules for MDR and expansion cohorts.

3.1.2. Criteria for Dose Escalation

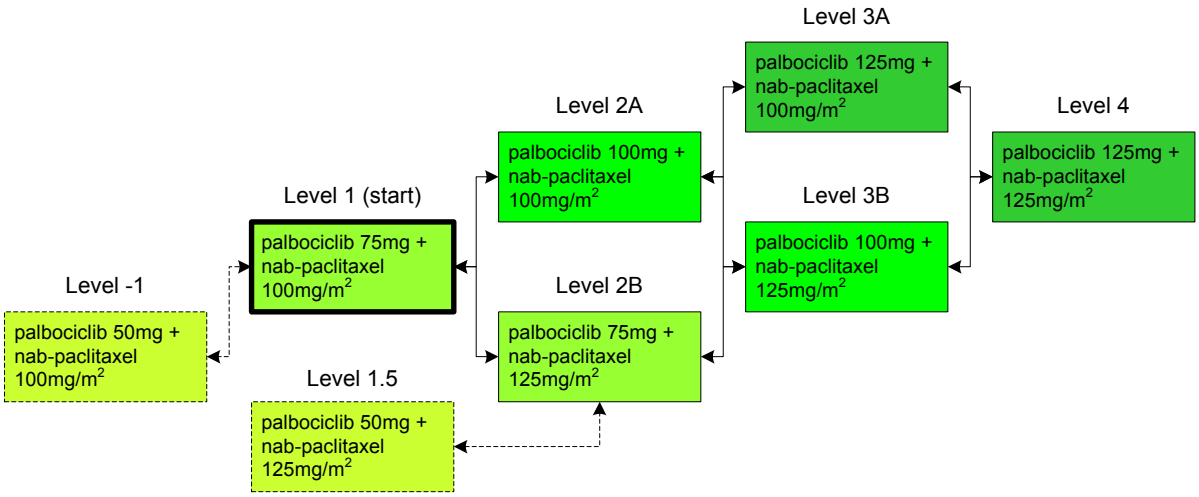
Dose escalation and de-escalation will follow a 2x3 matrix "Up-and-Down" design, using doses of palbociclib and nab-P as shown in Table 4 and Figure 2 below. In this dosing algorithm, there are up to 7 potential dose combinations (excluding DL -1):

Table 4. Potential Palbociclib and Nab-Paclitaxel Dose Combinations

Dose Level	Palbociclib (oral, mg/day) Days 1-21 within a 28-day cycle	Nab-Paclitaxel (IV, mg/m2/day) Weekly dose for 3 weeks within a 28-day cycle
-1	50	100
1 (starting dose level)	**75**	**100**
1.5	50	125
2A	100	100
2B	75	125
3A	125	100
3B	100	125
4	125	125

The 2x3 matrix approach allows for parallel dose level cohorts consisting of different dose combinations. Dose escalations and de-escalations will be called for based upon assessment of DLTs and other adverse events during the first treatment cycle (28 days). See Section 9.2.1 for a detailed description of the mTPI dose-escalation method.

Figure 2. Palbociclib and Nab-Paclitaxel Combination Dose Escalation and De-Escalation Sequence



Dose escalation will start from DL 1. The sequential dose escalation scheme and the rules for determining dose escalation, de-escalation, or 'stay' (ie, enroll an additional group of patients to the current DL) at any given dose level are described in the following paragraph and are illustrated in Figure 3.

Starting from DL 1:

- Once DL 1 has been found to be tolerable, DL 2A and DL 2B will be evaluated in parallel;
- If dose de-escalation is required at DL 1, then DL -1 will be evaluated next.

The following rules apply if escalation to DL 2A and DL 2B will be explored:

- If both DL 2A and DL 2B are tolerated and further dose escalation is considered, then DL 3A and DL 3B will be evaluated in parallel;
- If DL 2A is tolerated and further dose escalation is recommended, but no dose escalation is determined from DL 2B, then only DL 3A will be evaluated as the subsequent dose escalation step;

- If DL 2B is tolerated, but no dose escalation is determined at DL 2A, then no further dose escalation will be performed and the current DL(s) will be expanded to 9 patients, unless already done, in order to enable a dose escalation or de-escalation decision;

- If no dose escalation is determined at DL 2A and DL 2B, then no further dose escalation will be performed and the current DL(s) will be expanded to 9 patients, unless already done, in order to enable a dose escalation or de-escalation decision;

- If dose de-escalation is recommended after DL 2A, then DL 1 will be expanded to 9 patients, unless already done, in order to enable a dose escalation or de-escalation decision;

- If dose de-escalation is recommended after DL 2B, then DL 1.5 will be evaluated.

If dose escalation to DL 3A and DL 3B will be explored:

- If further dose escalations are recommended at both DL 3A and DL 3B, then DL 4 will be evaluated;

- If dose escalation is recommended only at DL 3A or DL 3B, then no further dose escalation will be performed and the current DL(s) will be expanded to 9 patients, unless already done, in order to enable a dose escalation or de-escalation decision;

- If dose de-escalation is recommended after both DL 3A and DL 3B, or after DL 3B only, then DL 2A and DL 2B will be expanded to 9 patients, unless already done, in order to enable a dose escalation or de-escalation decision (the order of the evaluation will be determined based on the toxicities observed from DL 2A and DL 2B);

- If dose de-escalation is only recommended after DL 3A (but not at DL 3B), then DL 2A will be expanded to 9 patients, unless already done, in order to enable a dose escalation or de-escalation decision.

If dose escalation to DL 3A will only be explored:

- DL 4 will not be evaluated regardless of the outcome at DL3A;

- If dose de-escalation is recommended at DL 3A, then DL 2A will be expanded to 9 patients, unless already done, in order to enable a dose escalation or de-escalation decision.

If dose escalation to DL 4:

- Dose escalation will be stopped at this DL;

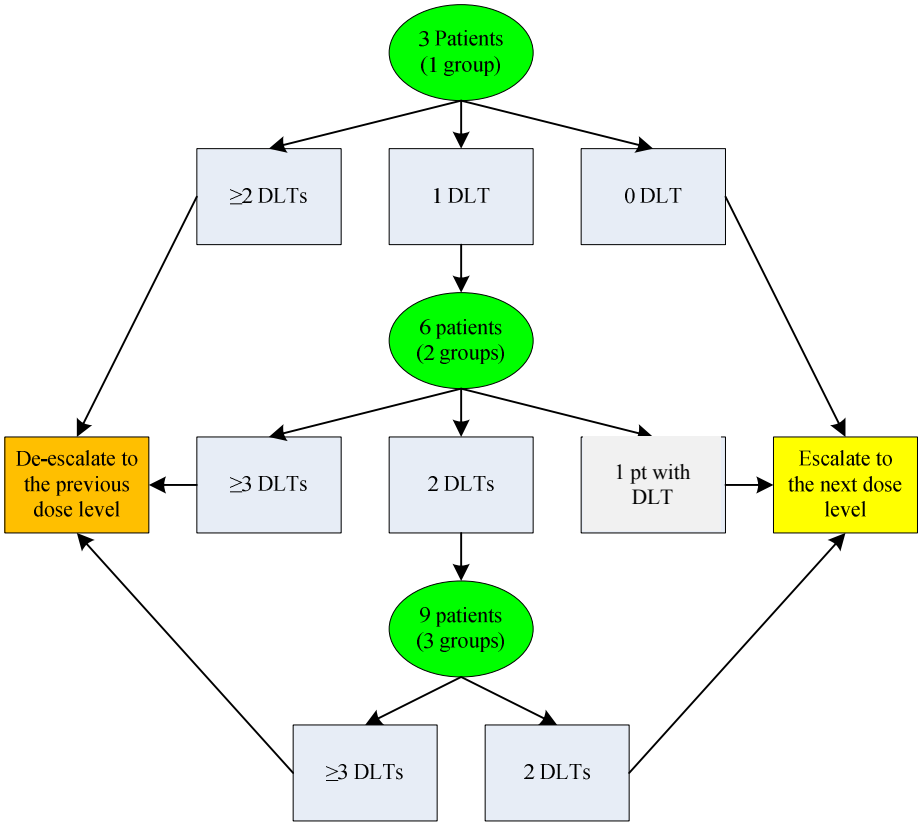
- If dose de-escalation is recommended after DL 4, then DL 3A and DL 3B will be expanded to 9 patients, unless already done, in order to enable a dose escalation or de-escalation decision (the order of the evaluation will be determined based on the toxicities observed at DL 3A and DL 3B).

If de-escalation to DL -1:

- If dose escalation is determined from DL-1, then DL 1 will be re-evaluated;
- If dose de-escalation is determined from DL -1, the study will be terminated.

Three (3) patients per group will be initially treated at any given combination DL. Up to 3 groups for a total of 9 patients can be treated at the same DL. Figure 3 illustrates the general dose escalation and de-escalation schema with a group size of 3 patients for a given DL based on this method. Detailed dose re-escalation and de-escalation schemas for a previous DL are provided in Appendix 7.

Figure 3. The General Dose Escalation and De-Escalation Schema with a Group Size of 3 Patients at a Given Dose Level



Note: In the figure, the term "DLT" means "patients with DLT", not the actual number of DLT events.

Initially a group of 3 patients will be enrolled at the starting DL. When all 3 patients are available for DLT assessment, the number of patients with DLT(s) will inform the decision for the next step:

- If 0 patient with a DLT out of 3 evaluable patients, escalate;
- If 1 patient with a DLT out of 3 evaluable patients, stay;
- If 2 patients with a DLT out of 3 evaluable patients, de-escalate;
- If 3 patients with a DLT out of 3 evaluable patients, stop the dose escalation.

Based on the decision above, a second group of 3 patients will be enrolled at the corresponding DL. Upon completion of the second group, a decision will be made again to escalate, de-escalate, or stay. Table 14 is derived from a generalized approach that extends the current mTPI method and preserves its decision-theoretical properties.

There are two scenarios under the decision of de-escalation: de-escalate and revisit allowed or de-escalate and revisit not allowed. The latter means that the current DL is determined to be unacceptably toxic; this DL and the subsequent higher DLs will be excluded from the study.

The decision-making needs to consider all patients treated at the current DL under evaluation. For example, if the decision is to stay at the starting DL after the first group of 3 patients (ie, there is 1 patient with a DLT), and another group of 3 additional patients is enrolled at the same DL, the next decision will be made based on all 6 patients treated at that DL:

- If 1 patient experiences a DLT out of 6 evaluable patients, escalate;
- If 2 patients experience a DLT out of 6 evaluable patients, stay;
- If ≥3 patients experience a DLT out of 6 evaluable patients, stop the dose escalation.

Dose escalation will continue until at least 9 patients have been treated at any given DL. Doses will not be escalated if the starting DL is deemed overly toxic, or if reaching the maximum sample size of approximately 30 patients is reached (ie, the number of DLT-evaluable patients).

The MTD determination will be based on the observed toxicity rates among all evaluable patients at any given DL. When dose escalation is stopped, the highest DL with an observed DLT rate <33% (in at least 9 DLT-evaluable patients) will be considered the MTD. It is possible that more than one MTD will be determined, in which case a decision will be made to expand one or both MTDs in order to determine the RP2D.

The general approach to dose-finding, using the mTPI method, involves the following:

- The target group size is 3. However, patients can be enrolled in group sizes of 2-4 patients if necessary, depending on the number of potential patients identified at participating sites (see Table 14);
- The next group of patients can be enrolled when all patients at a given DL have been evaluated for 28 days in the first treatment cycle, or any of the patients experience a DLT, whichever comes first;
- If a patient withdraws from the study before having received >80% of the planned first-cycle dose for palbociclib and nab-P for reasons other than investigational product-related toxicity, another patient will be enrolled to replace that patient at the current DL.

The dose escalation portion of the study is completed when at least 9 evaluable patients have been treated at the highest DL associated with a DLT rate <33%. It is estimated that approximately 30 'DLT-evaluable' patients will be enrolled to reach n = 9 'DLT-evaluable' patients at the estimated MTD.

Dose escalation may be completed without determining the MTD based on emerging safety data, and upon agreement between the investigators and the sponsor.

The RP2D will be determined in the dose expansion cohorts, taking into account the MTD(s) from the dose-escalation and modified dose regimen components, and other factors related to safety, efficacy, and PK/PD involving all available data from all tested DLs.

3.1.3. Modified Dose Regimens: Criteria for Opening MDR Expansion Cohort

The modified dose regimen chosen for expansion will take into account factors including frequency of dose reductions and/or interruptions, safety, efficacy, and PK/PD. If the number of patients with a DLT falls into the "De-escalate" category (Table 14) in one or both MDR cohorts, the cohort(s) will not move forward into expansion.

3.2. Dose Limiting Toxicity Definition

Severity of adverse events will be graded according to NCI CTCAE version 4.03. For the purpose of dose escalation, any adverse events occurring in the first cycle of treatment (Day 1 until pre-dose Cycle 2 Day 1) which are attributable to palbociclib, nab-P, or to the combination of palbociclib and nab-P will be classified as DLTs. Adverse events that occur between Cycle 1 Day -2 after nab-P administration and Cycle 1 Day 1 (prior to palbociclib dosing) will not be considered a DLT. The following adverse events will be considered a DLT:

- Hematologic:
  - Grade 4 neutropenia lasting >4 days;

- Febrile neutropenia (defined as neutropenia Grade ≥3 [ANC <1000 cells/mm^3] and a body temperature ≥38.5°C) requiring antibiotic or antifungal treatment;
- Any Grade 4 thrombocytopenia (<25,000/mm^3 or <25.0 x 10^9/L).

- Non-hematologic: Grade ≥3 toxicities, except those that have not been maximally treated (eg, nausea, vomiting, diarrhea).
- Other:
  - Any adverse event that causes a palbociclib treatment interruption of greater than 7 consecutive days; or causes any combination of interruption/reduction for ≥14 days;
  - Any adverse event that causes omission or reduction of at least 2 of the 3 weekly doses of nab-P.

3.3. Maximum Tolerated Dose Definition

The estimated MTD is the DL associated with <33% of 9 patients experiencing a DLT.

3.4. Recommended Phase 2 Dose (RP2D) Definition

The Recommended Phase 2 Dose (RP2D) is the drug regimen and doses chosen for potential future studies based on the results of this Phase 1 study. If the MTD proves to be clinically feasible for long-term administration in a reasonable number of patients, this dose usually becomes the RP2D. Further experience with the MTD may result in an RP2D dose lower than the MTD.

4. PATIENT SELECTION

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom participation in the study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

4.1. Inclusion Criteria

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

Patients must meet all of the following inclusion criteria to be eligible for the study:

1. Histologically or cytologically-confirmed pancreatic ductal adenocarcinoma (mPDAC), with metastatic disease confirmed radiographically.
   - Dose-escalation and MDR cohorts:
     - Prior therapy(ies) for the treatment of metastatic disease is permitted.

- **Expansion cohorts:**
  - No prior anti-cancer therapy for the treatment of metastatic disease;
  - At least one measurable lesion [as defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.1)] that has not been previously irradiated.

2. Availability of a tumor tissue specimen (ie, archived FFPE tissue [block preferred, or at least 12 (preferably 15) unstained slides]), which will be used for centralized, retrospective biomarker analysis. If no archived tumor tissue is available, then a de novo biopsy is required for patient participation.

3. Age ≥18 years.
   - For dose-escalation cohorts, age must also be ≤75 years.

4. Karnofsky Performance Status (PS) 70 or greater (see Appendix 2).

5. Adequate Bone Marrow Function, including:
   a. Absolute Neutrophil Count (ANC) ≥1,500/mm^3 or ≥1.5 x 10^9/L;
   b. Platelets ≥100,000/mm^3 (100 x 10^9/L);
   c. Hemoglobin ≥9 g/dL (90 g/L).

6. Adequate Renal Function, including:
   a. Serum creatinine ≤1.5 x upper limit of normal (ULN) or estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution.

7. Adequate Liver Function, including:
   a. Total serum bilirubin ≤1.5 x ULN unless the patient has documented Gilbert syndrome;
   b. Aspartate and Alanine aminotransferase (AST & ALT) ≤2.5 x ULN; ≤5.0 x ULN if there is liver involvement secondary to tumor;
   c. Alkaline phosphatase ≤2.5 x ULN; (≤5 x ULN in case of bone metastasis).

8. Resolved acute effects of any prior therapy to baseline or Grade ≤1 severity except for AEs not constituting a safety risk by investigator judgment.

9. Serum or urine pregnancy test (for females of childbearing potential) negative at screening.

10. Male patients able to father children and female patients of childbearing potential and at risk for pregnancy must agree to use two highly effective methods of contraception throughout the study and for 1 month after the last dose of assigned treatment.

11. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

12. Patients who are willing and able to comply with scheduled visits, treatment plans, laboratory tests and other procedures.

4.2. Exclusion Criteria

1. Prior treatment with a CDK 4/6 inhibitor.

2. Prior treatment with nab-P for the treatment of metastatic disease (nab-P that was administered in the adjuvant setting is permitted).

3. Patients with known CNS metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth.

4. Major surgery, chemotherapy, radiotherapy, any investigational agents, or other anti-cancer therapy within 2 weeks prior to enrollment. Patients who received prior radiotherapy to ≥25% of bone marrow (Appendix 8) are not eligible independent of when it was received.

5. Diagnosis of any other malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.

6. QTc >480 msec (based on the mean value of the triplicate electrocardiograms (ECGs), family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation, or Torsade de Pointes.

7. Uncontrolled electrolyte disorders (eg, hypocalcemia, hypokalemia, hypomagnesemia).

8. Any of the following within 6 months of enrollment: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism.

9. Known human immunodeficiency virus infection.

10. History of interstitial lung disease or pneumonitis.

11. Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

12. History of allergic reactions attributed to compounds of similar chemical or biologic composition to nab-P.

13. Difficulty swallowing capsules or requirement for a feeding tube.

14. Previous high-dose chemotherapy requiring stem cell rescue.

15. Pregnant female patients; breastfeeding female patients; male patients with partners currently pregnant.

16. Active inflammatory gastrointestinal disease, chronic diarrhea, known diverticular disease or previous gastric resection or lap band. Gastroesophageal reflux disease under treatment with proton pump inhibitors is allowed.

17. Active bleeding disorder, including gastrointestinal bleeding, as evidenced by hematemesis, significant hemoptysis or melena in the past 6 months.

18. Patients treated within the last 7 days prior to the start of IP with:

    - Food or drugs that are known to be strong/moderate **CYP3A4 inhibitors** (ie, amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit or grapefruit juice);

    - Drugs that are known to be strong/moderate **CYP3A4 inducers** (ie, carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort);

    - Drugs that are known to be **CYP2C8 inhibitors:** including but not limited to deferasirox, gemfibrozil, lapatinib, trimethoprim and fluvoxamine;

    - Drugs that are known to be strong/moderate **CYP2C8 inducers:** including but not limited to rifampin;

    - Drugs that are known to prolong the QT interval (see Appendix 9).

19. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.

20. Participation in other studies involving investigational drug(s) within 4 weeks prior to study entry.

4.3. Lifestyle Guidelines

4.3.1. Dietary Restrictions

The following dietary restrictions are necessary during the treatment phase:

- Palbociclib should be taken with food. Patients must be instructed to avoid ingesting grapefruit, grapefruit juice, or grapefruit-containing products while taking palbociclib.

4.3.2. Use of Contraception

In this study, male patients who are able to father children and female patients of childbearing potential and are sexually active and at risk for pregnancy will receive nab-P, which has been associated with teratogenic risk and/or palbociclib, a compound for which the teratogenic risk is currently unknown. Those who, in the opinion of the investigator, are sexually active and at risk for pregnancy must agree to use two (2) methods of highly effective contraception throughout the study and continue to do so for 1 month after the last dose. The investigator or his or her designee, in consultation with the patient, will confirm the patient has selected 2 appropriate methods of contraception for the individual patient and his/her partner from the list of permitted contraception methods (see below) and instruct the patient in their consistent and correct use. Patients need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his/her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly according to the Schedule of Activities (SOA) and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued or if pregnancy is known or suspected in the patient or the patient's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of oral, inserted, injected, or implanted hormonal methods of contraception are allowed provided the patient plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.

5. Bilateral tubal ligation / bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

Female partners who meet the criteria for non-childbearing potential must meet at least one of the following criteria:

- Have undergone a documented hysterectomy and/or bilateral oophorectomy;

- Have medically confirmed ovarian failure; or

- Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.

All other female patients (including females with tubal ligations) will be considered to be of childbearing potential.

All sexually active male patients must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for 1 month after the last dose.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list, located in the coordinator's manual.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study numbers, contact information for the investigational site, and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact

number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

Therefore, for purposes of this study, investigational product refers to both palbociclib and nab-P.

5.1. Allocation to Treatment

Dose level allocation will be performed by the sponsor after patients have given their written informed consent and have completed the necessary baseline assessments. The site staff will email a complete Registration Form to the designated sponsor study team member. The sponsor will assign a patient identification number, which will be used on all Case Report Form (CRF) pages and other study-related documentation or correspondence referencing that patient and email to the site.

No patient shall receive investigational product until the investigator or designee has received the following information in writing from the sponsor:

- Confirmation of the patient's eligibility and permission to start IP;
- Specification of the dose level for that patient and
- Permission to proceed with dosing the patient.

The sponsor or designee will notify the other sites of the inclusion of a new patient, and will inform study sites about the next possible investigational product start date.

5.2. Patient Compliance

Patients will be instructed to record administration of palbociclib in a patient diary provided by the sponsor. Missed or changed doses and dates of all missed doses need to be recorded. In addition, any co-medications, especially those taken for pain, should be recorded.

Patients will be required to return all bottles of palbociclib, including any unused capsules, as well as the completed patient diary at the beginning of each cycle for drug accountability. Drug accountability will be performed on Day 1 of every cycle prior to dispensing drug supply for the next cycle. The number of remaining capsules will be documented and recorded.

5.3. Investigational Product Supplies

5.3.1. Dosage Form(s) and Packaging

5.3.1.1. Palbociclib

Palbociclib will be supplied as capsules containing 25 mg, 75 mg, 100 mg, or 125 mg equivalents of palbociclib free base. The sponsor will supply the oral drug formulation to sites in high-density polyethylene (HDPE) bottles containing 25 mg, 75 mg, 100 mg, or 125 mg capsules. The capsules can be differentiated by their color, as shown in Table 5. Labeling will occur according to local regulatory requirements.

Table 5. Palbociclib Capsule Characteristics

Strength	Capsule color
25 mg	Grey/Caramel
75 mg	Sunset Yellow
100 mg	Sunset Yellow/Caramel
125 mg	Caramel

5.3.1.2. Nab-Paclitaxel

Nab-paclitaxel is commercially available as a lyophilized powder for reconstitution (single-use vials containing 100 mg of paclitaxel and approximately 900 mg of human albumin as a lyophilized powder). Central supply or locally obtained commercial supplies of nab-P will be used in accordance with local regulations. Detailed information about nab-P formulation can be found in the locally approved package insert.

5.3.2. Preparation and Dispensing

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of palbociclib and nab-P. Refer to the Investigational Product Manual (IP Manual) for additional information about the investigational products.

See the locally approved package insert for instructions on how to prepare nab-P for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

5.3.2.1. Palbociclib

Palbociclib will be provided as capsules for oral administration. The 25 mg, 75 mg, 100 mg, and 125 mg capsules will be supplied in separate bottles and labeled according to local regulatory requirements. The patient number must be recorded on the bottle label in the spaces provided by site personnel at the time of assignment to patient. Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given a sufficient supply to last until their next study visit. All bottles must be returned to the site at the next study visit. This includes unopened, empty, or partially used bottles

containing unused drug. Returned, unused investigational product MUST NOT be re-dispensed to the patient.

Palbociclib is an agent that must be handled and administered with care. Patients must be instructed to keep their medication in the bottles provided and not transfer it to any other container. Due to possible unknown hazards associated with topical and environmental exposure to experimental agents, capsules must not be opened and/or emptied into any vehicle for oral ingestion; capsules must be swallowed intact.

Only one capsule strength will be dispensed to the patient at each dispensing visit. In the event of dose modification, request should be made of the patient to return all previously dispensed investigational product to the clinic and new capsules will be dispensed.

5.3.2.2. Nab-Paclitaxel

Nab-paclitaxel must be reconstituted before use. Detailed information about nab-P reconstitution and dispensing can be found in the locally approved package insert for Abraxane®.

Nab-paclitaxel is a cytotoxic drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling it. The use of gloves is recommended. If nab-P (lyophilized cake or reconstituted suspension) contacts the skin, the skin must be washed immediately and thoroughly with soap and water. Following topical exposure to nab-P, events may include tingling, burning and redness. If nab-P contacts mucous membranes, the membranes should be flushed thoroughly with water. Procedures for proper handling and disposal of anticancer drugs should be considered.

The appropriate amount of reconstituted nab-P will be injected into an empty, sterile intravenous bag [plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type intravenous bag]. The use of specialized di-ethylhexylphthalate (DEHP)-free solution containers or administration sets is not necessary to prepare or administer nab-P infusions. The use of an in-line filter is not recommended.

5.3.3. Administration

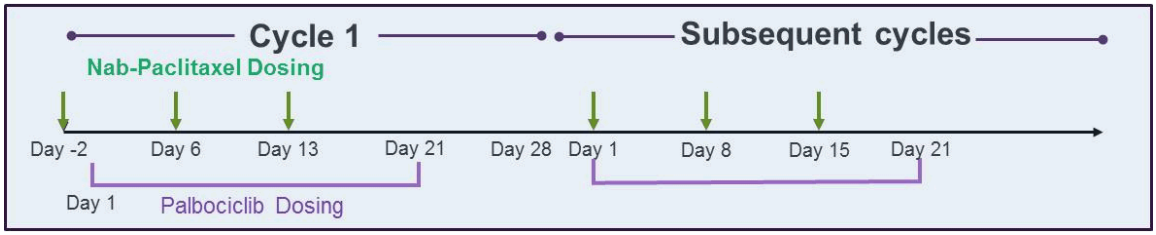
5.3.3.1. Nab-Paclitaxel Administration

Nab-P will be administered in the clinic.

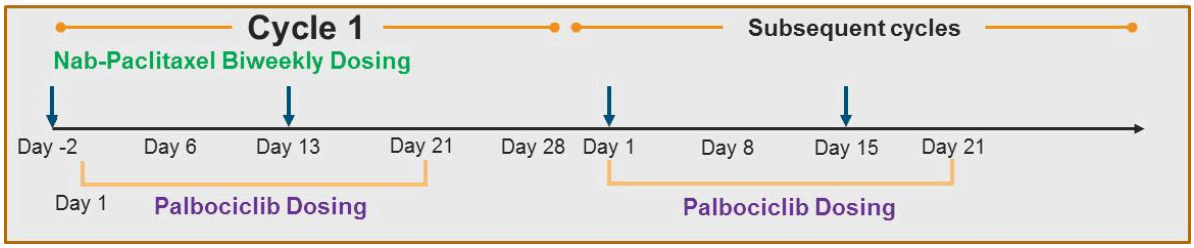
Patients will receive nab-P as an intravenous infusion over 30 minutes. Nab-P will be administered based on the assigned dose regimen (either once weekly for 3 weeks, or biweekly in each 28-day cycle). In Cycle 1, nab-P will start on Day -2 in order to evaluate the pharmacokinetics of nab-P administered alone and in combination with palbociclib (Figure 4). On Day 13, nab-P and palbociclib should be dosed at approximately the same time. For cycles ≥2, both palbociclib and nab-P administration will start on Day 1, and palbociclib dosing should occur as close as possible to the start of infusion of nab-P. Treatment with IP will continue until disease progression, unacceptable toxicity, or consent withdrawal.

Figure 4. Palbociclib and Nab-Paclitaxel Dose Combination Schema

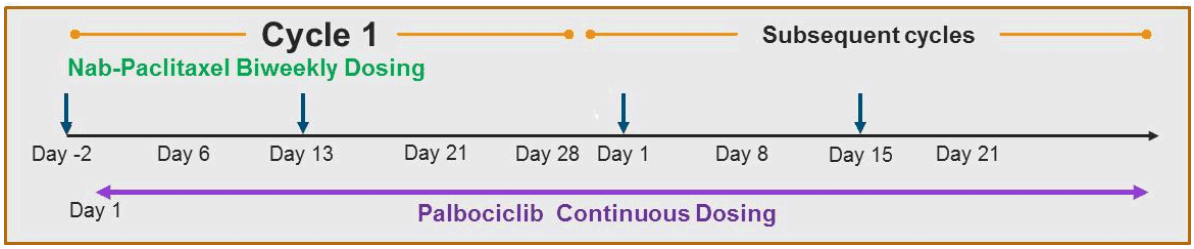
Dose Escalation and MTD Expansion Cohorts



Modified Dose Regimen 1 (palbociclib 3/1 schedule, biweekly nab-P)



Modified Dose Regimen 2 (continuous palbociclib, biweekly nab-P)



5.3.4. Palbociclib Administration

Palbociclib dosing will be administered orally. The palbociclib dosing schedule is determined by cohort assignment, either 3/1 schedule (once a day for 21 consecutive days, followed by 7 days off treatment) or continuous dosing in each 28-day cycle (for MDR2 cohort). Each patient will receive enough palbociclib to support their treatment cycle duration each month. Patients should be instructed to swallow palbociclib capsules whole and not to manipulate or chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact. Patients should be encouraged to take their dose at approximately the same time each day. Patients should be instructed to record daily administration of the investigational product in a patient diary provided by the sponsor.

Patients should take palbociclib with food.

To ensure consistency with PK sample analysis, patients should ensure their palbociclib dose on Cycle 1 Day 12 is taken at least 20 hours before the pre-dose PK sample on Cycle 1 Day 13. Patients must be instructed to withhold their dose of palbociclib Cycle 1 Day 13, Cycle 2 Day 1, and Cycle 2 Day 15 until after the pre-dose PK sample is drawn. Patients

should bring their palbociclib dose with them to the clinic on these days. Once the pre-dose PK sample is drawn, palbociclib may be taken with food.

Patients who miss a day's dose entirely must be instructed NOT to "make it up" the next day. If a palbociclib dose is missed, and the next dose is more than 12 hours away, the patient should take the missed dose as soon as they remember. If the next dose is less than 12 hours away, the patient should skip the missed dose and take palbociclib at the next regularly scheduled time. The patient must not double or take extra doses to make up for a missed dose. Patients who vomit any time after taking a dose must be instructed NOT to take another dose on that day. The patient should resume treatment the next day at their regularly scheduled time.

Patients who inadvertently take 1 extra dose during a day must be instructed to skip the next day's dose. Also refer to Section 8.3 for further details on medication errors and overdose.

Patients experiencing investigational product related toxicity may have their dose modified according to Section 5.3.6 and Section 5.3.7.

5.3.5. Nab-Paclitaxel

Nab-paclitaxel will be prepared and dispensed according to the product labeling information.[2]

5.3.6. General Recommended Dose Modifications

Every effort should be made to administer the investigational products (palbociclib and/or nab-P) at the planned dose. However, in the event of significant treatment-related toxicity, administration of investigational products may need to be adjusted as described in the following sections. Depending on the nature of the toxicity observed, dosing adjustment may be required for just one or both investigational products in the combination.

In the event of significant treatment-related toxicity, palbociclib and/or nab-P dosing may be interrupted or delayed and/or reduced as described below. Except where specified (Section 5.3.7), if one investigational product is delayed, the other may be continued as scheduled. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify investigators at the first occurrence of any adverse sign or symptom.

Dose modifications/interruptions may occur in two ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;

- Between cycles: dosing interruptions until adequate recovery and/or dose reduction, if required, for the next treatment cycle. If both palbociclib and nab-P are interrupted, the start of a new cycle will be delayed until one or both investigational products are re-started.

5.3.6.1. Dosing Interruptions

Patients should have their treatment with the investigational products (nab-P and/or paclitaxel) interrupted if they experience Grade 3 or 4 toxicities, as detailed in Table 8, Table 9, and Table 10.

Appropriate follow up assessments should be done until adequate recovery occurs as assessed by the investigator. Criteria required before treatment can resume are described in Section 5.3.6.2.

Doses may be held as needed until toxicity resolution. Depending on when the adverse event resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

If an adverse event that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in Section 5.3.7 unless expressly agreed otherwise following discussion between the investigator and the sponsor.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, non-cancer related surgery) lasting more than 2 weeks, treatment resumption will be decided in consultation with the sponsor.

Except where specified (Section 5.3.7), if one investigational product is interrupted, the other may continue as scheduled upon agreement by the sponsor and investigator (unless otherwise noted in the dose modification sections).

Dose re-escalation is permitted on this study. If the dose was reduced due to neutropenia, the dose modification guidelines in Table 10 provide additional guidance on dose re-escalation with concomitant administration of granulocyte-colony stimulating factors (G-CSF).

5.3.6.2. Dose Delays and Retreatment Criteria

Retreatment of palbociclib and/or nab-P following treatment interruption for -the start of any new cycle may not occur until all of the parameters in Table 6 have been met:

Table 6. General Criteria for Start of New Cycle

Platelet count ≥100,000/mm^3
ANC ≥1500/mm^3 and without fever
No fever
Other non-hematologic toxicities returned to baseline or Grade ≤1 severity (or, at the investigator discretion, Grade ≤2, if not considered a safety risk for the patient)

If a treatment delay results from decline in hematologic parameters, refer to Table 9 or Table 10. The frequency of blood count assessments should be increased as clinically indicated.

If these parameters are met within 1 week of cycle delay, investigational products may be resumed. Refer to Section 5.3.6 and Section 5.3.7 for adverse events requiring dose reduction at the time of treatment resumption.

If these parameters have not been met after 2 weeks of dosing interruption (including the scheduled 1 week off treatment for patients on a palbociclib 3/1 schedule) or 2 weeks of cycle delay, permanent discontinuation of investigational product(s) should be considered. Treatment resumption for patients recovering from treatment-related toxicity after >2 weeks of treatment interruption or cycle delay but deemed to be deriving obvious clinical benefit per the investigator's best medical judgment is left at the investigator's discretion.

If both investigational products are interrupted and the interruption continues beyond Day 28 of the current cycle, then the day when either investigational product is restarted will be counted as Day 1 of the next cycle.

New cycle Day 1 procedures (ie, physical examination, Karnofsky performance status, ECG, Quality of Life questionnaire, blood chemistry, hematology) that were performed prior to knowing the need to delay the start of the cycle do not need to be repeated (1) if not required to determine whether investigational product may be resumed and (2) if performed within 7 days prior to investigational product resumption.

5.3.6.3. Dose Reductions

Following dosing interruption or cycle delay the palbociclib or nab-P dose may need to be reduced when treatment is resumed.

No specific dose adjustments are recommended for Grade 1/2 treatment-related toxicity. However, investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances.

Step-wise dose reduction of palbociclib and/or nab-P (Table 7) (if needed, up to 3 dose levels) will be allowed depending on the type and severity of toxicity encountered. Patients requiring palbociclib dose reductions below 50 mg or nab-P dose reductions below 60 mg/m^2 should be discontinued from the respective investigational product and entered into the follow-up phase, unless otherwise agreed between the investigator and the sponsor. In addition, if one investigational product is discontinued, the other may continue as scheduled (upon agreement by the sponsor and investigator). All dose modifications/adjustments must be clearly documented in the patient's source notes and investigational product administration CRF. Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation is allowed if the dose was reduced due to hematologic toxicity and can be effectively managed with administration of growth factors (refer to Table 10). Table 7 below shows the available dose levels for palbociclib and nab-P.

Patients experiencing a DLT or any adverse event, laboratory abnormality or severe intercurrent illness presenting a substantial clinical risk to the patient will be discontinued based on the judgment of the investigator.

Table 7. Palbociclib and Nab-Paclitaxel Dose Levels

Palbociclib Dose (mg)	Nab-Paclitaxel (mg/m^2)
125	125
100	100
75	75
50[1]	60[2]

1. Palbociclib dose de-escalation below 50 mg/day is not permitted, unless otherwise agreed between the investigator and the sponsor.
2. Nab-P dose de-escalation below 60 mg/m^2 is not permitted, unless otherwise agreed between the investigator and the sponsor.

Recommended dose modifications for hematologic and non-hematologic treatment-related toxicities requiring treatment interruption/delay or persisting despite optimal medical treatment are described in the following sections.

5.3.7. Recommended Dose Modifications for Specific Toxicities

Recommendations for dose modifications are list in Table 8. Modifications from these guidelines should only occur after discussion between the investigator and the sponsor. Appropriate follow up assessments should be performed until the investigator has determined the patient has adequately recovered.

Table 8. Recommended Dose Modifications for Adverse Events Associated with Palbociclib and/or Nab-Paclitaxel

Toxicity (NCI CTCAE version 4.03)	Proposed Action for:	
	Palbociclib	**Nab-Paclitaxel**
Hematologic		
Neutropenia and/or thrombocytopenia	See Table 9 (dose escalation and MTD expansion cohorts) or Table 10 (MDR cohorts)	
Grade 3 Neutropenia + Fever ≥38.5°C and/or infection	Withhold until fever resolves and ANC ≥1500; resume both drugs at next lower dose level	
Cardiovascular		
QTc prolongation	See Table 11	Monitor patient carefully; no dose modification is required
Gastrointestinal		
Mucositis or Diarrhea, Grade 3	Withhold until symptoms resolve to Grade ≤1; resume at the next lower dose level	
Mucositis or Diarrhea, Grade 4	Permanently discontinue if symptoms uncontrollable by supportive care	
Nausea or Vomiting, Grade 3	Withhold until symptoms resolve to Grade ≤1; resume at the next lower dose level	
Nausea or Vomiting, Grade 4	Permanently discontinue if symptoms uncontrollable by supportive care	
Hepatic		
AST and/or ALT >10 - ≤20 x ULN	Withhold until recovery to or baseline, then resume at next lower dose level or discontinue	
Infection		
Sepsis (with or without neutropenia)	Withhold until resolution and ANC ≥1500; resume at next lower dose level	
Lung		
Pneumonitis	No action required	Permanently discontinue
Uncomplicated Pulmonary Embolism (Grade 3)	Withhold until recovery; then resume at next lower dose level or discontinue as per investigator judgment	
Pulmonary Embolism (Grade 4)	Permanently discontinue	
Nervous System		
Peripheral Neuropathy Grade 3 or 4	No action required	Withhold until improves to ≤ Grade 1; resume at next lower dose level
Immune System		
Hypersensitivity reactions Grade 3 or 4[(a)]	Withhold until symptoms resolve, then resume at the same dose level	Immediately stop infusion, do not re-challenge
Other		
Any other Grade ≥3 non-hematologic toxicity	Withhold palbociclib and/or nab-P treatment until Grade 1 or Grade 2 (if not considered a safety risk), resume investigational products at the next lower dose	

Abbreviations: ANC=Absolute Neutrophil Count

a. Severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy.

5.3.7.1. Dose Modifications for Hematologic Toxicities

The below tables present guidelines for dose modifications for patients who experience hematologic toxicities. For patients in dose escalation and MTD expansion cohorts, the use of G-CSF is permitted; recommendations for use are described in Table 9. Dose re-escalation to the initial dose level should be considered in subsequent cycles as long as the criteria for retreatment are met (See Table 6).

For patients assigned to a modified dose regimen, the use of G-CSF is prohibited in the first 3 cycles unless clinically indicated and medically unavoidable.

Table 9. Recommended Dose Modifications for Neutropenia and/or Thrombocytopenia (Dose Escalation and MTD Expansion Cohorts)

Day 8 Blood Counts	Day 8 Nab-P Dose	Day 8 Palbo Dose	Day 15 Blood Counts	Day 15 Nab-P Dose	Day 15 Palbo dose
ANC >1000 and Platelets ≥75,000	No modification required.		ANC >1000 and Platelets ≥75,000	No modification required.	
			ANC 500-1000; or Platelets 50,000-74,999	Continue at same dose level + G-CSF[1]	Continue at same dose level + G-CSF[1]
			ANC<500; or Platelets <50,000	Withhold dose + G-CSF[1], reduce dose for next cycle	Reduce by 1 dose level from Day 8 + G-CSF[1]
ANC 500-1000; or Platelets 50,000-74,999	Continue dose, but reduce by 1 dose level	Withhold until ANC ≥1000, AND platelet count ≥75,000; then reintroduce at same dose level	ANC>1000 and Platelets ≥75,000	Return to previous dose level + G-CSF[1]	Continue at same dose level + G-CSF[1]
			ANC 500-1000; or Platelets 50,000-74,999	Continue at dose level from Day 8 + G-CSF[1]	Reduce by 1 dose level from Day 8 + G-CSF[1]
			ANC<500; or Platelets <50,000	Withhold dose + G-CSF[1], reduce dose for next cycle	Withhold dose + G-CSF[1] until ANC ≥1000, AND platelet count ≥50,000; then reintroduce at next lower dose level
ANC<500; or Platelets <50,000	Withhold dose	Withhold until ANC ≥1000, AND platelet count ≥50,000; then reintroduce at same dose level	ANC>1000 and Platelets ≥75,000	Reduce by 1 dose level (compared to Day 1) + G-CSF[1]	Reduce dose by 1 dose level + G-CSF[1]
			ANC 500-1000; or Platelets 50,000-74,999	Reduce by 2 dose levels (compared to Day 1+ G-CSF[1]	Withhold dose + G-CSF[1] until ANC ≥1000, AND platelet count ≥75,000; then reintroduce at same at next lower dose level
			ANC<500; or Platelets <50,000	Withhold dose + G-CSF[1]	Withhold dose + G-CSF1 until ANC ≥1000, AND platelet count ≥50,000; then reintroduce at next lower dose level

Abbreviations: ANC=absolute neutrophil count; G-CSF=granulocyte-colony stimulating factor
1. G-CSF should be administered according to the prescribing information until ANC ≥1500 cells/mm^3.

Table 10. Recommended Dose Modifications for Neutropenia and/or Thrombocytopenia (MDR and MDR Expansion Cohorts)

Cycle Day	Absolute Neutrophil Count (ANC) (cells/mm^3)		Platelet count (cells/mm^3)	Proposed Action	
				Nab-Paclitaxel	Palbociclib
Day -2 (Cycle 1) or Day 1 (Cycles ≥2)	<1500	OR	<100,000	Delay dose until recovery (ANC ≥1500 AND platelet count ≥100,000	
Day 13 (Cycle 1) or Day 15 (Cycles ≥2)	500 to <1000	OR	50,000 to <75,000	Continue dose, but reduce by 1 dose level (compared to Day 8)	Withhold dose until ANC ≥1000, then reintroduce at same dose level
	<500	OR	<50,000	Withhold dose	Withhold dose until ANC ≥1000 AND platelet count ≥50,000, then reintroduce at next lower dose level

Abbreviations: ANC=absolute neutrophil count
1. In the first 3 cycles, G-CSF use in the MDR cohorts is prohibited unless clinically indicated and medically unavoidable.

5.3.7.2. Dose Modifications for QTc Prolongation

Patients experiencing QTc prolongation (QTc ≥501 msec on at least two separate ECGs) should have their palbociclib treatment interrupted/delayed.

In the event of QTc prolongation, possible alternative reversible causes such as serum electrolytes abnormalities, or usage of concomitant medications with the potential to prolong the QTc interval should be evaluated.

If such reversible causes are identified, then they should be corrected accordingly (ie, correction of electrolyte abnormalities with supplements to within normal limits and/or discontinuation (if possible) of concomitant medications known to prolong the QT interval).

Recommended dose modifications in the event of QTc prolongation are provided in Table 11.

Table 11. Palbociclib Dose Modifications in the Event of QTc Prolongation

	Toxicity (NCI CTCAE Grade, Version 4.03)		
	Grade 2 QTc prolongation	**Grade 3 QTc prolongation**	**Grade 4 QTc prolongation**
Reversible cause identified	Treat reversible cause Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc ≤480 msec Continue at the same dose level[1]	Treat reversible cause Withhold treatment until QTc <501 msec Resume treatment at the same dose level. Monitor ECG more frequently as per investigator's best medical judgment until QTc ≤480 msec.	Permanently discontinue
No reversible cause identified	Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc ≤480 msec Continue at the same dose level[1]	Withhold treatment until QTc <501 msec Resume treatment at the next lower dose level[2] Monitor ECG more frequently as per investigator's best medical judgment until QTc ≤480 msec.	Permanently discontinue

1. If the QTc remains above 480 msec more than 2 cycles or if Grade 2 QTc prolongation recurs in the absence of other alternative causes or despite correction of alternative causes, then dose adjustment and/or discontinuation should be considered in consultation with a cardiologist and the sponsor, taking into account the emerging safety data from palbociclib trials and the investigator's best medical judgment.
2. If the Grade 3 QTc prolongation occurs again after one DL reduction, further dose adjustment and/or discontinuation should be discussed with the sponsor in consultation with a cardiologist, taking into consideration the emerging safety data from palbociclib trials and the investigator's best medical judgment.

5.4. Investigational Product Storage

The investigator, or an approved representative (eg, pharmacist) will ensure that all IP, including any comparative agents and/or marketed products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product must be stored in its original container and in accordance with the label. See the locally approved package insert for storage conditions of nab-P once it is reconstituted.

Storage conditions stated in the Study Reference Safety Document (SRSD) (ie, IB or SPC) will be superseded by the storage conditions stated in the product label information. The IP Manual must be referenced for any additional guidance on storage conditions and actions to be taken when conditions are outside the specified range.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This must be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be documented. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions must be reported upon discovery. The site must actively pursue options for returning the product to that storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of labeled temperature range are not considered excursions. More specific details will be provided to the sites separately.

Site staff will instruct patients on the storage requirements for take home medications.

5.5. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies.

Medication should be kept in a secured locked area at the study site in accordance with applicable regulatory requirements. Returned medication should be stored separately from medication that needs to be dispensed.

To ensure adequate records, palbociclib capsules will be accounted for as instructed by the sponsor. Patients are requested to return previously dispensed containers as well as their completed patient diary to the clinic at each visit for accountability purposes even if no new investigational product will be issued at that visit.

5.5.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer and all destruction must be adequately documented.

5.6. Concomitant Medications and Treatment(s)

Patients must be instructed not to take any additional medications (over-the-counter or other products) during the study without prior consultation with the investigator. Any medications including herbal supplements, vitamins, or treatment taken by the patient from 28 days prior to the start of IP and up to 28 days following the last dose, including the reason for their administration, must be recorded on the CRF, which includes pre-medications to alleviate nab-P infusion reactions.

Routine postoperative care, such as dressing changes, suture removal, drain removal, or venous access (central or peripheral), does not need to be recorded. Anesthetics used for any surgical procedures performed during the patient's participation in the study must be recorded on the CRF; it is not necessary to list the specific anesthetics. Palliative and supportive care for cancer-related symptoms will be offered to all patients in this study.

5.6.1. Prohibited Medications

The following treatments are prohibited throughout the duration of the treatment phase:

- **Anticancer agents:** No additional investigational or commercial anticancer agents such as chemotherapy, targeted therapy, or biological response modifiers, will be permitted during the treatment phase.

- **Strong/Moderate CYP3A inhibitors:** including but not limited to amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, suboxone, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit, grapefruit juice or any product containing grapefruit.

- **Strong/Moderate CYP3A inducers**: including but not limited to carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifampin, rifabutin, rifapentin, and St. John's wort.

- Dexamethasone is considered a weak to moderate CYP3A inducer depending on the dose regimen. The use of dexamethasone as a premedication is prohibited on days where PK samples are drawn. Sponsor approval must be obtained if dexamethasone is needed to prevent adverse reactions to nab-P.

- **Strong/Moderate CYP2C8 inhibitors:** including but not limited to deferasirox, gemfibrozil, lapatinib, trimethoprim, and fluvoxamine.

- **Strong/Moderate CYP2C8 inducers:** including but not limited to rifampin.

- **Drugs known to cause QT interval prolongation** Refer to Appendix 9 for a list of drugs known to predispose to Torsade de Pointes.

5.6.2. Medications Not Recommended

The following treatments are not recommended throughout the duration of the treatment phase. Alternative therapies should be considered whenever possible. If usage of the following treatments is deemed necessary, consultation and agreement with the sponsor is required prior to treatment initiation.

- The concurrent use of dexamethasone is not recommended.

- **Chronic immunosuppressive therapies** should be avoided, including systemic corticosteroids. Steroids given for physiological replacement, as anti-emetics or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares are allowed.

- The use of **herbal medicine** is not recommended during the treatment phase.

5.6.3. Antacids Agents

Proton-pump inhibitors (PPIs): The concomitant use of PPIs with palbociclib is prohibited 7 days before the scheduled palbociclib PK sample collection (eg, C1D13) until the last palbociclib PK sample is drawn.

H2-receptor antagonists: If H2-receptor antagonists are used, staggered dosing relative to palbociclib dosing is recommended on palbociclib PK sample collection days. The evening dose of H2-receptor antagonist should be given 10 hours before the palbociclib dose, and the morning dose of H2-receptor antagonist should be given 2 hours after the palbociclib dose.

Local antacids: The staggered dosing of local antacid relative to palbociclib dosing is recommended on palbociclib PK sample collection days. Local antacids should be given at least 2 hours before or after palbociclib administration.

5.6.4. Use of Growth Factors

In the dose-escalation and MTD expansion cohorts, the use of G-CSF to manage neutropenia is permitted at the discretion of the investigator. Dose modification guidelines in Table 9 provide recommendations on G-CSF administration. Growth factors should be used in accordance with the prescribing information.

For patients assigned to a modified dose regimen, growth factors should not be used during the first 3 cycles unless clinically indicated and medically unavoidable.

5.7. Other Investigational Agent(s)

While on IP, patients will not be permitted to participate in another study involving investigational drug(s) (Phases 1-4).

5.8. Concomitant Radiotherapy or Surgery

Any concurrent radiotherapy (except palliative radiotherapy as specified below) or cancer-related surgery are prohibited throughout the duration of the treatment phase of the study. Patients requiring any of these procedures will be discontinued from the treatment phase and will enter the follow-up phase.

Palliative radiotherapy is permitted for the treatment of painful bony lesions provided that the lesions were known to be present at the time of study entry and the investigator clearly documents that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of palbociclib with radiotherapy, palbociclib treatment should be interrupted during palliative radiotherapy, stopping 1 day

before and resuming treatment 1 week after. For patients with bone involvement, it is suggested to institute palliative radiotherapy before study initiation if possible and clinically appropriate (eg, lesions at risk for spontaneous micro-fractures or painful lesions). Palliative radiotherapy during the treatment phase will be considered alternative cancer therapy and will result in censoring of the PFS endpoint. The dates on which palliative radiotherapy is administered must be recorded on the appropriate CRFs.

Caution is advised on theoretical grounds for any non-cancer related surgical procedures during the study. The appropriate interval of time between surgery and palbociclib required to minimize the risk of impaired wound healing and bleeding has not been determined. Based on the available pharmacokinetic data, stopping palbociclib is recommended at least 7 days prior to elective surgery. Postoperatively, the decision to reinitiate palbociclib treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6. STUDY PROCEDURES

6.1. Screening

For details on screening/baseline procedures, see the Schedule of Activities tables.

Voluntary, written, dated, and signed informed consent must be obtained before any study specific procedures are performed (with the exception of certain imaging assessments if meeting the criteria defined in this section); however, it may be obtained more than 28 days before enrollment. See Section 4 for detailed inclusion and exclusion criteria.

Medical and oncological history must include information on prior anticancer treatments.

Date of enrollment is defined as the day the patient has satisfied all inclusion and exclusion criteria and is considered eligible for the study.

Baseline tumor related signs and symptoms will be recorded at the C1D-2 visit prior to initiating treatment and then reported as adverse events during the trial if they worsen in severity or increase in frequency.

Radiographic tumor assessments (as documented on the Tumor Assessments flowchart) that were performed before the signing of the informed consent form as routine procedures (but within 28 days prior to the start of IP) do not need to be repeated and may be used as baseline assessments, as long as:

- The tests were performed per the method requirements outlined in the Tumor Assessments flowchart and, Section 7.1.

  and

- Appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes.

6.2. Treatment Period

For details on procedures during the treatment phase, see the Schedule of Activities tables.

On C1D-2, blood chemistry, hematology, coagulation, urinalysis, 12-lead ECG, physical examination/vital signs, and baseline signs/symptoms are not required if acceptable screening assessment is performed within 7 days prior to start of IP.

Patients who are sexually active and at risk for pregnancy must agree to use two methods of highly effective contraception throughout the treatment period and continue for 1 month after the last dose of IP. See Section 4.3 for further information.

The start of a new cycle may be delayed when both palbociclib and nab-P are withheld due to treatment-related toxicity. In the event that the start of a new cycle is delayed, procedures required on Day 1 of the given cycle will be performed when either investigational product is resumed. New cycle Day 1 procedures (ie, physical examination, Karnofsky performance status, ECG, questionnaire, blood chemistry, hematology, coagulation) that were performed prior to knowing the need to delay the start of the cycle do not need to be repeated (1) if not required to determine whether investigational product may be resumed and (2) if performed within 7 days prior to investigational product resumption. Maximum time between visits is 30 days.

Procedures on Day 6 of Cycle 1 and Day 8 of Cycle 2 are not required for patients assigned to MDR1 and MDR2 cohorts, since nab-P is administered biweekly in these cohorts.

If only one investigational product (either palbociclib or nab-P) is delayed, the next cycle may begin as scheduled.

6.3. End of Treatment Visit

For details on procedures to be performed at the End of Treatment visit, see the Schedule of Activities tables.

The End of Treatment visit will be performed as soon as possible but no later than 8 weeks (ie, 56 days) ±7 days from last dose of investigational product and prior to the initiation of any new anticancer therapy.

Patients who are sexually active and at risk for pregnancy must continue to use two methods of highly effective contraception for 1 month after the last dose of investigational product.

Patients who discontinue nab-P treatment due to treatment-related toxicity may continue palbociclib treatment as scheduled. Similarly, patients who discontinue palbociclib treatment due to treatment-related toxicity may continue nab-P therapy as scheduled (agreement by the sponsor and investigator is required in either case).

6.4. Follow-up Visit

For details on follow-up visit procedures, see the Schedule of Activities tables.

Approximately every month (±28 days) after discontinuation of IP, post-treatment follow-up visit procedures will be collected until 12 months (365 days) have elapsed from the first dose of IP. Telephone contact is acceptable. Patients who have discontinued IP within 12 months (365 days) since the first dose will remain in post-treatment follow-up (See Schedule of Activities) until 12 months have elapsed from the first dose of IP. Anticancer medications will be collected in the post-treatment follow-up period.

6.5. Post-Study Patient Interview

Upon implementation of Amendment 3, this assessment is no longer required.

6.6. Patient Withdrawal

6.6.1. Study Treatment Discontinuation

The term "interruption" refers to a patient stopping the investigational products during the course of the study, but then re-starting it at a later time in the study. The reason for dosing interruption will be collected on the appropriate CRF.

The term "discontinuation" refers to a patient's withdrawal from the study treatment. The reason for discontinuation from treatment will be collected on the appropriate CRF.

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given study site.

Reasons for withdrawal of study treatment may include:

- Objective disease progression;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment;
- Study terminated by sponsor;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. Lost to follow-up is defined by the inability to reach the patient after a minimum of three documented phone calls, faxes, or emails as well as lack of response by the patient to one registered mail letter. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use permissible local methods to obtain the date and cause of death. If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the patient's informed consent, then the investigator may use a sponsor retained third-party representative to assist site staff with obtaining patient's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the patient remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the patient's medical records. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the patient return all unused investigational product(s), request that the patient return for a final visit, if applicable, and follow-up with the patient regarding any unresolved AEs.

If the patient refuses further visits, the patient should continue to be followed for survival unless the patient withdraws consent for disclosure of future information or for further contact. In this case, no further study specific evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Patients who request to discontinue IP will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a patient specifically withdraws consent for any further contact with him/her or persons previously authorized by patient to provide this information. Patients should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with investigational product only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the patient is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

6.6.2. Study Discontinuation

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

Patients will be withdrawn from study in the case of:

- Withdrawal of consent (ie, refuses tumor assessments or survival status after end of treatment);
- Lost to follow-up;
- Death;
- Administrative study closure by sponsor.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. If after three unsuccessful attempts to contact the patient, one of which is by registered letter, the patient should be considered "lost to follow-up". Steps taken to contact the patient (eg, dates of telephone calls, registered letters, etc.) must be clearly documented in the source documents. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return all unused investigational product(s), request the patient to return for a final visit, if applicable, and follow-up with the patient regarding any unresolved adverse events (AEs).

If the patient refuses further visits, the patient should continue to be followed for survival unless the patient withdraws consent for disclosure of future information or for further contact. In this case, no further study specific evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

All study procedures are described in the Schedule of Activities table and footnotes. Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

All assessments should be performed prior to dosing with IP on the visit day unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers. For the purposes of this trial, the first cycle is 30 days in length; subsequent cycles are 28 days in length. A cycle could be longer than 28 days if persistent toxicity delays the initiation of the subsequent cycle.

7.1. Efficacy Assessments

7.1.1. Tumor Assessments

The importance of timely and complete disease assessments in this study cannot be understated. Disease assessments must be performed as scheduled according to the calendar, regardless of treatment delays resulting from toxicity, to prevent the introduction of bias into the assessment of efficacy. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point. A series of incomplete disease assessments will result in censoring of the exploratory endpoint of PFS back to the time of the last full assessment that did not show progression. Frequent off schedule or incomplete disease assessments have the potential to weaken the conclusion of this clinical trial.

Objective tumor response will be measured using the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1(Appendix 5). All measurements should be recorded in metric notation using a ruler or calipers.

MRI of the abdomen and pelvis can be substituted for CT if MRI adequately depicts the disease. However, MRI of the chest should not be substituted for CT of chest even if IV contrast is contraindicated. In such case, CT will be performed without contrast. If MRI is used to follow-up bone lesion(s) it should be performed a few days before any treatment that may affect bone-marrow cellularity [eg, granulocyte-colony stimulating factor (G-CSF)].

Refer to Table 2 and the Schedule of Activities for timing of disease assessments.

7.1.1.1. Screening/Baseline Tumor Assessment

Screening/baseline tumor assessment will be carried out within 28 days before start of IP (unless otherwise specified below).

Disease assessment for all patients at baseline will include computed tomography (CT) or magnetic resonance imaging (MRI) scan of all sites of disease as clinically indicated.

Clinical assessment of superficial disease which will include photographs of all superficial metastatic lesions. All lesion measurements must be recorded in the CRF.

7.1.1.2. Post-Baseline Tumor Assessments

Post-baseline tumor assessments will be performed as clinically indicated from start of investigational product until radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v.1.1, initiation of new anticancer therapy, or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up). Imaging assessments are to be scheduled using the investigational product start date (Cycle 1 Day -2) as the reference date for all time points and are NOT to be scheduled based on the date of the previous imaging time point. Imaging assessment delay to conform to treatment delay is not permitted.

Post-baseline tumor assessments will include clinical assessment of sites of superficial disease identified at baseline. Clinical assessment of superficial disease should coincide with the imaging studies and will include photographs of all superficial metastatic lesions. All lesion measurements must be recorded in the CRF.

- CT or MRI scan of any other sites of disease identified at baseline, including brain CT scan if applicable. CTs should be performed with contrast agents unless contraindicated for medical reasons. If IV contrast is medically contraindicated, the imaging modality to be used to follow the disease (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist.

The same method and technique should be used to characterize each lesion identified and reported at baseline, during the study treatment period and during follow-up. The use of plain-film X-rays is discouraged. The use of positron emission tomography (PET) imaging as the only imaging modality is not permitted.

7.1.2. Overall Survival

Following the End of Treatment Visit, survival status will be collected in all patients (telephone contact is acceptable) every 28 days (±28 days) until 12 months (365 days) have elapsed from the first dose of IP. Information on subsequent anticancer therapy will also be collected.

Patients who have completed 13 cycles of IP are not required to enter post-treatment follow-up upon permanent discontinuation of IP. Patients who are ongoing beyond Cycle 13 will be considered to have completed the study upon permanent discontinuation of IP.

Patients who have discontinued IP before completing Cycle 13 will remain in post-treatment follow-up (See Schedule of Activities) until 12 months (365 days) have elapsed from the first dose of IP. Once a patient has been followed for 12 months from the first dose, the patient is considered to have completed the study and no further data will be collected.

7.1.3. Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study treatment, once at the start of screening and once at the baseline visit, immediately before investigational product administration (Cycle 1 Day -2). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and another negative pregnancy test result will then be required at the baseline visit before the patient may receive IP. Pregnancy tests will also be routinely repeated at every treatment cycle during the treatment period, at the end of study treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive hCG test, the patient will be withdrawn from treatment and will be withdrawn from the study. Additional pregnancy tests may also be undertaken if requested by institutional review boards (IRBs)/ethics committees (EC) or if required by local regulations.

7.2. Safety Assessments

Safety assessments will include collection of adverse events (AEs), serious adverse events (SAEs), vital signs and physical examination, electrocardiogram [ECG (12-lead)], laboratory assessments, including pregnancy tests and verification of concomitant treatments.

7.2.1. Adverse Events

Assessment of adverse events will include the type, incidence, severity (graded by the NCI CTCAE version 4.03) timing, seriousness, and relatedness.

Adverse events that occur during the study, including baseline signs and symptoms, will be recorded on the adverse events CRF page.

7.2.2. Laboratory Safety Assessment

Haematology, blood chemistry, coagulation, and urinalysis will be drawn as indicated in the Schedule of Activities and analyzed at local laboratories.

Blood tests will include the following:

Table 12. Laboratory Tests

Hematology	Chemistry	Coagulation	Urinalysis	Pregnancy Test
Hemoglobin Platelets WBC Absolute Neutrophils Absolute Lymphocytes Absolute Monocytes Absolute Eosinophils Absolute Basophils	ALT AST Alk Phosphatase Sodium Potassium Magnesium Chloride Total Calcium Total Bilirubin* BUN or Urea Creatinine Uric Acid Glucose (non-fasted) Albumin Phosphorous or Phosphate Amylase (if available) Lipase (if available)	PT or INR PTT aPTT	Urine dipstick for urine protein: If positive, further diagnostic testing will be performed as clinically indicated - Urine dipstick for urine blood: If positive collect a microscopic (Reflex Testing)	For female patients of childbearing potential, serum or urine

*For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, and alkaline phosphastase. In addition, acetaminophen levels should be considered.

Blood tests will be drawn as described in the Schedule of Activities table, and analyzed at local laboratories. Additional blood tests should be performed where needed for the purpose of evaluating potential DLTs or other adverse events.

Urinalysis will be conducted via urine dipstick for urine protein: if the result is positive, a 24-hour collection and microscopic reflex testing will be conducted.

7.2.3. Vital Signs and Physical Examination

Patients will have a physical exam to include weight, vital signs (pulse rate and blood pressure), assessment of Karnofsky (see Appendix 2) performance status, and height; height will be measured at screening only.

7.2.4. (12-Lead) Electrocardiogram

All ECGs will be performed using a 12-lead (with a 10-second rhythm strip) tracing. ECG measurements will include PR interval, QT interval, RR interval, and QRS complex. It is preferable that the machine used has a capacity to calculate the standard intervals automatically.

ECG interval readings by the ECG recorder's algorithm will be read and interpreted at the investigational site for eligibility determination and patient safety monitoring and documentation stored in the source documents.

Triplicate ECGs will be performed for all patients.

- **All ECGs should be obtained after a fast of at least 1 hour**. When scheduled at the same nominal time/visit, triplicate ECGs should be collected prior to any blood draws for PK, biomarkers, or safety labs and prior to placement of the IV line for nab-P administration.

- Triplicate ECGs will be obtained for safety monitoring at Screening, and 0 hour (pre-dose) on C1D-2, C1D13, C2D1 and C2D15, then on Day 1 of Cycles 4 and 7. ECGs will be obtained at the time of End of Treatment or Withdrawal. ECGs beyond Cycle 7 will be performed as clinically indicated.

Additional ECGs may be performed as clinically indicated at any time.

For the purpose of the study, triplicate ECGs are defined as three consecutive ECGs performed approximately 2 minutes apart but within 10 minutes for all 3 ECGs at the protocol specified timepoints (see Schedule of Activities table for details) to determine the mean QTc interval.

If at any time during the course of treatment, the mean QTc is prolonged (≥501 msec on at least two separate ECGs, ie, CTCAE Grade ≥3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate (and manual calculation of QTcF). If manual reading confirms a QTcF of ≥501 msec, immediate search for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the

potential to prolong the QTc interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTc interval falls below 501 msec.

- If QTcF interval reverts to less than 501 msec, and in the judgment of investigator(s) in consultation with the sponsor the cause is determined to be other than investigational product, treatment may be continued with regular ECG monitoring under hospital supervision.

- If in that timeframe the QTc intervals remain above 501 msec the investigational product (palbociclib) will be held until the QTc interval decreases to <501 msec.

- Patients will then restart investigational product at the next lowest dose level. If the QTcF interval has still not decreased to ≤480 msec after 2 weeks, or if at any time a patient has a QTcF interval >515 msec or becomes symptomatic, the patient will need to discontinue IP. Additional triplicate ECGs may be performed as clinically indicated.

Prior to concluding that an episode of prolongation of the QTc interval is due to investigational product, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

If patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), an ECG (triplicate) should be obtained at the time of the event.

When matched with PK sampling, ECG must be carried out before PK sample drawing such that the PK samples are collected at the nominal time (ie, the timing of the PK collections overrides the timing of the ECG collections.

7.2.5. Other Safety Assessments

A full physical examination including an examination of all major body systems (including general appearance, head, ears, eyes, nose, mouth, throat, neck, thyroid, lungs, heart, breasts, abdomen, and musculoskeletal), height (at Screening only), weight, blood pressure and pulse rate which may be performed by a physician, registered nurse or other qualified health care provider, will be required at screening, and Cycle 1 Day -2 and Cycle 2 Day 1.

Symptom directed physical examinations, blood pressure and pulse rate will be performed at subsequent visits according to the Schedule of Activities.

7.3. Pharmacokinetics Assessments

7.3.1. Palbociclib Pharmacokinetic Assessments

Plasma PK samples for palbociclib determination will be collected on Day 13 of Cycle 1 at 0 (pre-dose), 2, 4, 6, 8 and 24 hours post palbociclib dose, and on Cycle 2 Days 1 and 15 (pre-dose) as described in Schedule of Activities. Patients must have received at least

7 consecutive days of palbociclib before PK assessments on Cycle 1 Day 13 and Cycle 2 Day 15.

Additional instructions for serial PK sampling on Cycle 1 Day 13 include the following:

- The palbociclib dose that is taken on C1D12 should be at least 20 hours from the time the pre-dose PK sample is drawn on C1D13. Patients should record the time of their C1D12 palbociclib dose in the patient diary.

- Patients must not take their palbociclib dose on C1D13 until after the pre-dose PK sample is drawn. Patients must be instructed to bring their palbociclib dose with them to the clinic.

- Because patients must take palbociclib with food, the investigator must provide the patient with a structured meal on C1D13. The total nutritional composition should be approximately 50% carbohydrate, 35% fat and 15% protein. The caloric intake per for the meal should be approximately 500-700 kcal. The meal should be eaten within 30 minutes prior to administration of palbociclib, and the patient should consume at least 80% of the meal provided before palbociclib dosing.

- Palbociclib must be administered as close as possible to the start of infusion of nab-P.

Other PK sampling days (C2D1, C2D15) - On the days where trough PK samples are drawn, patients must not take their palbociclib dose until after the predose PK sample is drawn. Once the predose PK sample is drawn, patients should take their palbociclib dose (with any food the patient prefers) as close as possible to the start of nab-P infusion. The investigator should plan to provide the patient with a meal on these days.

Meal information (nearest the palbociclib dose) will be collected on Cycle 1 Day 12, Cycle 1 Day 13, Cycle 2 Day 1, Cycle 2 Day 14, and Cycle 2 Day 15. Information including meal time and type (high fat, low fat, or standard) will be collected.

In the event nab-P is not dosed on Day 13, PK samples for palbociclib determination can be collected on the day the second or third dose of nab-P is administered as long as there is no dose interruption, reduction or delay of palbociclib dosing within 7 days of the intended nab-P dosing and PK sampling. In the event PK samples cannot be collected (or is not collected) on Day 13 of Cycle 1 or the day of third nab-P dosing, every effort should be made to collect makeup samples on Day 8 or 15 of Cycle 2 or the day when the second or third dose of nab-P in Cycle 2 (or later cycles) is administered using the same criteria. The Day 13, 24-hour PK sample should collected prior to the administration of the Day 14 palbociclib dose. The exact time of the sample collection and the most recent dosing time before and after PK sample collection will be recorded on the CRF. The date of missing dose should also be recorded in the CRF. CCI [redacted] and CCI [redacted] blood sample on Day 13 should also be rescheduled to coincide with PK assessments.

During all study periods, blood samples (3 mL) to provide approximately 1 mL of plasma for pharmacokinetic analysis will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) at times specified in the Study Procedures section of the protocol.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF/DCT).

Refer to the Study Manual for details on PK sample collection, processing and shipping procedures.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures. As part of understanding the PK of the palbociclib, blood samples may be used for metabolite identification and/or evaluation of the bioanalytical method. CCI [redacted]

7.3.2. Nab-Paclitaxel Pharmacokinetic Assessments

Plasma PK samples for total paclitaxel determination will be collected on Days -2 to Day 1 and Days 13 to 15 of Cycle 1 at 0 (pre-dose), 0.5 (end of infusion), 1, 2, 4, 6, 8, 24 and 48 hours post the start of nab-P IV infusion as described in SOA. The pre-dose samples should be collected just before the start of the nab-P infusion. On Day 13, nab-P and palbociclib should be dosed at approximately the same time. The PK samples should be drawn from the opposite arm of the IV infusion. For Day 13 and 14 PK samples, the PK samples will only be collected for patients who have received at least 7 consecutive days of palbociclib dosing. For patients who had a palbociclib dose interruption, reduction or delays within 7 days of the third nab-P dose, PK samples collection can be made up in later cycles. In the event nab-P is not dosed on Day 13, PK samples for total paclitaxel determination can be collected on Day 8 or 15 (the day the second or third nab-P dose is administered), as long as there is no dose interruption, reduction or delay of palbociclib dosing within 7 days of the intended nab-P dosing and PK sampling. The exact date and time of the sample collection and the exact start and stop time of the nab-P infusion will be recorded on the CRF. The date of missing dose(s) should also be recorded in the CRF.

During all study periods, blood samples (4 mL) to provide approximately 1.5 mL of plasma for pharmacokinetic analysis will be collected into appropriately labeled tubes containing sodium heparin at times specified in the Study Procedures section of the protocol.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the

exact time of the sample collection is noted on the source document and data collection tool (eg, CRF/DCT).

Additional blood samples may be requested from patients experiencing unexpected or serious adverse events, or adverse events that lead to discontinuation.

Refer to the Study Manual for detailed PK sample collection, processing and shipping procedures.

As part of understanding the PK of total paclitaxel following nab-P administration, blood samples may be used for evaluation of the bioanalytical method. CCI [redacted]

7.4. Biomarker Assessments

An archival tumor tissue sample (or de novo tumor biopsy tissues) is required from all patients for study participation.

Specifically, an FFPE tissue block that contains sufficient tissue to generate at least 12 (preferably 15) unstained slides, each with tissue sections that are 5 microns thick, should be collected. If an FFPE tissue block cannot be provided, at least 12 (preferably 15) unbaked glass slides, each containing an unstained 5 micron FFPE tissue section, is required. If an archival tumor tissue sample is not available, a de novo tumor biopsy specimen must be obtained before investigational products are administered (Cycle 1 Day -2). Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted. Specimens will be sent to the sponsor-designated central laboratory. Results from the Rb1 and p16 expression testing by IHC will be used for sensitivity analyses. CCI [redacted]

- CCI [redacted]

- CCI [redacted]

Detailed information about biomarker sample collection, preparation, storage, labeling, and shipment is indicated in the Study Manual. Refer to the Schedule of Activities for details pertaining to specific days of sample collection. Table 13 summarizes the biomarker assessments currently planned for the study.

These analyses may also lead to the identification of potential biomarkers of response to the combination treatment, ultimately leading to the development of a patient selection strategy for further clinical investigation.

Table 13. Summary of Biomarker Assessments

Assay	Source
CCI [redacted]	
p16 and Rb1 status	Archival tumor specimen and/or de novo tumor biopsies
CCI [redacted]	

7.4.1. Optional De Novo Tumor Tissue Biopsy for Pharmacodynamic Analysis

For patients who consent, the optional de novo tumor biopsy collection should be collected at Screening and End of Treatment. If collected, these specimens will be provided in addition to the archival tumor tissue specimen that is required for eligibility purposes. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted. Details for handling of these specimens including processing, storage, and shipment will be provided in the Study Manual.

De novo tumor core biopsy collection is strongly encouraged unless it poses a safety risk to the patient, in the opinion of the investigator. The tumor tissue will be used for pharmacodynamic assessment and to further determine possible mechanisms of sensitivity/resistance to study treatment. CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the CRF from the time the patient has taken at least 1 dose of investigational product (either nab-P or palbociclib) through the patient's last visit.

If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;

- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasations;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure;
- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong patient, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AEs are captured on an AE CRF page.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
    - Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTCAE Grade 5 (see the section on Severity Assessment).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

  - For patients with preexisting AST or ALT baseline values above the normal range, AST or ALT value ≥2 times the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller);

  Concurrent with

  - For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 × ULN; **or** if the value reaches ≥3 × ULN (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time, should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. **Such potential Hy's Law cases should be reported as SAEs**.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pre-treatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

GRADE	Clinical Description of Severity
0	No Change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an SAE report form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for the termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE [ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly (in a live-born baby, a terminated fetus, an intrauterine fetal demise or a neonatal death)], the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (see also the section on Patient Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a patient withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Analysis Sets

1. Safety analysis set.

The safety analysis set includes all enrolled patients who receive at least one dose of either investigational product. The safety analysis set will also be used for efficacy analyses.

2. Per protocol analysis set evaluable for MTD.

The per protocol analysis set includes all enrolled patients who receive at least one dose of investigational product and who do not have major treatment deviations during the first cycle of treatment. Patients with major treatment deviations in the first cycle are not evaluable for the MTD assessment and will be replaced as needed to permit MTD estimation. Major treatment deviations include administration of less than 80% of the planned dose of palbociclib, or less than 2 doses of nab-P for reasons other than treatment-related toxicity in Cycle 1.

3. PK analysis sets.

The PK parameter analysis population is defined as all enrolled patients treated who have sufficient information to estimate at least 1 of the PK parameters of interest and have no major protocol deviations affecting PK assessment.

The PK concentration population is defined as all enrolled patients who are treated and have at least 1 analyte concentration.

4. Biomarker analysis sets.

The biomarker analysis set is defined as all patients who have received at least one dose of investigational product and who have at least one baseline biomarker assessment. Analysis sets will be defined separately for serum, plasma, archival tumor tissue, CCI [redacted] and de novo tumor biopsies.

9.2. Statistical Methods and Properties

Due to the exploratory nature of this study, no confirmatory inferential analyses are planned since the primary objectives of this study are to assess the safety and tolerability MTD(s), of palbociclib in combination with nab-P in patients with mPDAC in order to estimate the MTD and select the RP2D.

Dose escalation and de-escalation will follow a 2x3 matrix "Up-and-Down" design, with different dose combinations of palbociclib and nab-P using the modified toxicity probability interval (mTPI) method. Approximately 60-100 patients are expected to be enrolled in the overall study.

9.2.1. Statistical Methods for Dose Escalation/De-Escalation

9.2.1.1. mTPI Method

The rules for dose escalation/de-escalation will follow a modified toxicity probability interval (mTPI) method.[20] The mTPI method relies upon a statistical probability algorithm which is calculated using all patients treated at the same dose level. Upon completion of a group (ie, all patients in that cohort are evaluable for DLT), a decision to escalate, de-escalate, or stay (ie, enroll an additional group at the current dose level) will be made.

Many alternative designs have been proposed to the standard 3+3 design for Phase 1 dose escalation studies that improve its accuracy, efficiency and statistical validity.

The modified toxicity probability interval (mTPI) design uses a Bayesian statistics framework and a beta/binomial hierarchical model to compute the posterior probability of three dosing intervals that reflect the relative difference between the toxicity rate of each dose level to the target rate (pT = 0.28). If the toxicity rate of the currently used dose level is far smaller than pT, the mTPI will recommend escalating the dose level; if it is close to target probability (pT), the mTPI will recommend continuing at the current dose; if it is far greater than pT, the mTPI will recommend de-escalating the dose level. These rules are conceptually similar to those used by the 3+3 design, except the decisions of an mTPI design are based on posterior probabilities calculated under a coherent probability model.

Being a model-based design, mTPI automatically and appropriately tailors dose-escalation and de-escalation decisions for different studies with different toxicity parameters. More importantly, all the dose-escalation decisions for a given study can be pre-calculated under the mTPI design and presented in a two-way table below. Thus, compared to other advanced model-based designs published in the literature, the mTPI design is logistically less complicated and easier to implement. Recently, a Phase 1 study based on the mTPI design has been published.[21]

Table 14. Number of Patients with DLT for Dose Escalation Decisions at a Dose Level

	Total Number of DLT Evaluable Patients								
	2	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Escalate	**0**	**0**	**0**	**0**	**0-1**	**0-1**	**0-1**	**0-2**	**0-2**
Stay	**1**	**1**	**1**	**1-2**	**2**	**2**	**2**		**3**
De-Escalate & revisit allowed		**2**	**2**			**3**	**3-4**	**3-4**	**4-5**
De-Escalate & revisit not allowed	**2**	**3**	**3-4**	**3-4**	**3-5**	**4-5**	**5**	**5**	**6**

Decision rules are based on calculating unit probability mass (UPM) of three dosing intervals corresponding to under, proper, and overdosing in terms of toxicity. Specifically, the underdosing interval is defined as (0; pT-e_1), the overdosing interval (pT+e_2), and the proper-dosing interval (pT- e_1, pT+ e_2), where e_1 and e_2 are small fractions. Based on the safety profile of palbociclib as a single-agent in Study A5481001, e_1 is selected as 0.03, and e_2 is selected as 0.045. Therefore, the target interval for the DLT rate is (0.25, 0.325).

The three dosing intervals are associated with three different dose-escalation decisions. The underdosing interval corresponds to a dose escalation (E), overdosing corresponds to a dose de-escalation (D), and proper-dosing corresponds to remaining at the current dose (R). Given a dosing interval and a probability distribution, the unit probability mass (UPM) of that dosing interval is defined as the probability of a patient belonging to that dosing interval divided by the length of the dosing interval. The mTPI design calculates the UPMs for the three dosing intervals, and the one with the largest UPM informs the corresponding dose-finding decision, which is the dose level to be used for future patients. For example, if the underdosing interval has the largest UPM, the decision will be to escalate, and the next cohort of patients will be treated at the next higher dose level. Ji et al. (2010)[20] have demonstrated that the decision based on UPM is optimal in that it minimizes a posterior expected loss (ie, minimizes the chance of making a wrong dosing decision).

The dose-finding portion of the study is terminated when either approximately 30 DLT evaluable patients have been enrolled or when at least 9 evaluable patients have been treated at the highest dose with DLT rate <33%, whichever comes first.

9.2.2. Statistical Method for Estimating the Maximum Tolerated Dose

As previously described, the estimated MTD is the highest tested dose level with DLT rate <0.33 in at least 9 DLT evaluable patients. It is assumed that higher doses of either palbociclib or nab-P result in higher toxicity rates. But, due to the relatively low number of patients that may be potentially allocated to any dose combination, this assumption may be violated.

For example, at the end of the study, the dose combination palbociclib 100 mg and nab-P 125 mg/m^2 may have a higher proportion of observed toxicities than, say, palbociclib 125 mg, nab-P 125 mg/m^2, and this variability may be simply related to small cohort size alone. To overcome this potential problem, a bivariate isotonic regression is used to smooth the resulting toxicity surface to a monotonically increasing one. The determination of the MTD contour is accomplished using the Dykstra-Roberston algorithm.[22] Once a monotonically increasing toxicity surface is obtained (either observed or smoothed according to the bivariate isotonic regression algorithm), the MTD combinations closest to the targeted DLT rate of 0.28 but still <0.33 are calculated. Clinical judgment will be exercised in taking forward combinations to the expansion cohorts in case no clear choice exists between more than 1 competing MTD combination. While the limited sample size may result in up to 2 dose combinations of equal potential anti-tumor activity, under the circumstances of this study, it is possible that 2 MTD expansion cohorts will be explored. This decision will be based upon the combination of data related to safety, PK, PD, anti-tumor activity, and clinical judgment of the investigators and the sponsor.

9.3. Sample Size Determination

Due to the dynamic nature of the Bayesian allocation procedure, the sample size of the Up-and-Down matrix design using the mTPI approach cannot be determined in advance. It is estimated that approximately 30 DLT evaluable patients will be enrolled in the dose escalation stage in order to have a reliable and accurate estimate of the MTD(s). The expansion cohorts will enroll up to approximately 20 response evaluable patients at the estimated MTD(s).

Based on probability theory, a sample size of approximately 20 patients per expansion cohort at the MTD(s) will ensure the estimates of any binary variable (eg, ORR) have a 95% confidence interval of width ≤0.45. A sample size of approximately 60 patients (at any dose) also enables detection of any unexpected toxicity that occurs at 5% rate (in a non-dose-dependent fashion) with a probability of 0.95, and that occurs at 10% rate with a probability of 0.998.

9.4. Efficacy Analysis

In this study, anti-tumor activity is a secondary objective in the dose-finding component and in the expansion component. The analyses of endpoints dependent on disease assessments will be based on results of the investigator assessment of disease response and progression.

9.4.1. Analysis of Efficacy Endpoint (Expansion Cohorts)

PFS, duration of response (DR), and OS will be summarized using the Kaplan-Meier method and displayed graphically. The median event time and 2-sided 95% confidence interval for the median will be provided for each endpoint. ORR will be reported along with its 2- sided 95% confidence interval. OS will also be summarized based on all treated patients.

Six-month progression-free survival rate (6m-PFSR) will be summarized as a product limit estimator based on the Kaplan-Meier method to account for censored events, together with the corresponding 2-sided 95% confidence interval (CI). The 2-sided 95% CI for the log[-log(6-month PFS probability)] will be calculated using normal approximation and then back transformed to give the CI for the 6m-PFSR itself. Analysis results will be included in the table for the PFS analysis.

9.5. Analysis of Other Endpoints

9.5.1. Analysis of Pharmacokinetics

9.5.1.1. Palbociclib

PK samples for palbociclib determination will be collected on Day 13 of Cycle 1 when palbociclib is given in combination with nab-P for all patients at all dose levels studied. Plasma pharmacokinetic parameters including maximum plasma concentration at steady state ($C_{ss,max}$), time for $C_{ss,max}$ ($T_{ss,max}$), trough plasma concentration at steady state ($C_{ss,trough}$), area under the plasma concentration-time curve for dosing interval τ at steady state ($AUC_{ss,\tau}$), and apparent clearance (CL/F) for palbociclib will be estimated using non-compartmental analysis. The effect of nab-P on steady-state palbociclib exposure will be evaluated by comparing palbociclib PK parameters, including C_{max} and AUC_{τ} obtained on Day 13 of Cycle 1 with historical data.

9.5.1.2. Nab-Paclitaxel

PK samples for total paclitaxel determination will be collected on Days -2 to 1 when nab-P is given alone and on Days 13-15 when nab-P is given in combination with multiple doses of palbociclib. Plasma PK parameters including maximum plasma concentration (C_{max}), time for C_{max} (T_{max}), area under the plasma concentration-time curve from time 0 to last quantifiable concentration (AUC_{last}), area under the plasma concentration-time curve from time 0 extrapolated to infinite time (AUC_{inf}), terminal plasma elimination half-life ($t_{1/2}$), clearance (CL), and volume of distribution (V_z) will be estimated using non-compartmental analysis if data permit. The effect of palbociclib on total paclitaxel PK will be evaluated by determining the ratios of adjusted geometric means (nab-P in combination with palbociclib/nab-P alone) and 90% CIs for the ratios (AUC_{inf} and C_{max}).

9.5.1.3. Statistical Analysis of Pharmacokinetic endpoints

For both palbociclib and nab-P concentrations, concentrations will be summarized descriptively (n, mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by dose/cohort, cycle, day, and nominal time. Individual patient and median profiles of the concentration-time data will be plotted by dose/cohort, cycle, and day (using nominal times. Median profiles will be presented on both linear-linear and log-linear scales.

For both palbociclib and total paclitaxel, PK parameters will be summarized descriptively by treatment day. For total paclitaxel, statistical summary of treatment comparison (nab-P given in combination with palbociclib vs. nab-P given alone) will also be provided.

For both palbociclib and total paclitaxel, dose normalized AUC_{τ} (AUC_{inf} for total paclitaxel), and C_{max} will be plotted against dose (using a logarithmic scale) by day. These plots will include individual patient values and the geometric means for each dose. These plots will be used to help understand the relationship between the PK parameters and dose.

9.5.2. Population Pharmacokinetic Analysis or Pharmacokinetic/Pharmacodynamic Modeling

Pharmacokinetic (PK) and pharmacodynamic (PD) data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between palbociclib exposure and biomarkers or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

CCI [redacted]

[redacted]

9.5.3. Biomarkers

9.5.3.1. Analysis of Biomarker Endpoints

Biomarkers will be assessed separately for serum, plasma, archival tumor tissue, de novo tumor biopsies and CCI . In each case, summaries of baseline levels, changes from baseline (where appropriate), expression and mutation will be reported. For continuous variables, summary statistics may include the mean, ratio to baseline, standard deviation, 25th median, and 75th quartile, % CV, and minimum/maximum levels of biomarker measures; for categorical variables, summary may include number and percentage, odds ratio as appropriate.

For p16 and Rb1 expression, sensitivity analysis may be performed.

Data from biomarker assays will be analyzed using graphical methods and descriptive statistics such as linear regression, t test, and analysis of variance (ANOVA). The statistical approach may examine correlations of biomarker results with pharmacokinetic parameters and measures of anti-tumor efficacy.

CCI

CCI

CCI

9.6. Safety Analysis

Summaries and analyses of safety parameters will include all patients in the Safety Analysis Set.

9.6.1. Analysis of the Primary Endpoint

Dose Limiting Toxicity (DLT) is the primary endpoint of the dose escalation component of the study. The occurrence of DLTs observed in the dosing cohorts is used to estimate the MTD(s) as described in the Study Design section. Adverse Events constituting DLTs will be listed per dose level.

9.6.2. Analysis of Secondary Safety Endpoints

Adverse Events

Adverse Events (AEs) will graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of investigational product. The number and percentage of patients who experienced any AE, serious AE (SAE), treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and cycles beyond 1).

Laboratory Test Abnormalities

The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each lab assay. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and cycles beyond 1). Shift tables will be provided to examine the distribution of laboratory toxicities.

For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal or not done.

9.6.3. Electrocardiogram

The analysis of ECG results will be based on patients in the safety analysis set with baseline and on-treatment ECG data. Baseline is defined as Cycle 1 Day -2.

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for heart rate (QTc) using standard correction factors [ie, Fridericia's (default correction), Bazett's, and possibly a study specific factor, as appropriate]. Data will be summarized and listed for QT, HR, response rate (RR), PR, QRS, QTcF (and other correction factors, eg, QTcB as appropriate), and dose. Individual QT (all evaluated corrections) intervals will be listed by time and dose. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions. Descriptive statistics (n, mean, median, standard

deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment by dose and time point. For each patient and by treatment, the maximum change from baseline will be calculated as well as the maximum post-baseline interval across time points. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post-baseline QT interval.

Shift tables will be provided for baseline vs worst on treatment corrected QT (one or more correction method will be used) using maximum CTCAE Grade. Shift tables will also be provided for ECG abnormality at baseline vs. on treatment (yes, no, not done: (n, %)). Patients experiencing clinically-relevant morphological ECG changes will be summarized (including frequency and percentage).

The effect of drug concentrations on corrected QT change from baseline will be explored graphically. Additional concentration-corrected QT analyses may be performed. Data may be pooled with other study results and/or explored further with PK/PD models.

9.7. Data Safety Monitoring Committee

An external Data Safety Monitoring Committee will not be established for the study. For the purpose of this protocol, Pfizer procedures for periodic safety review will be applied by an internal safety review team with medical and statistical capabilities to review individual and summary data collected in the safety and clinical databases. Procedures include:

- Surveillance for serious adverse events (SAEs) according to regulatory guidelines;
- Discussions between the investigators and the sponsor of AEs and laboratory tests alterations seen at each dose level in an ongoing manner at regular teleconferences and/or meetings to determine the safety profile and risk/benefit ratio and decide if further enrollment is appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigative site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should

be retained by the investigator according to ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 and 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study patients. Note that the use of initials should be avoided in compliance with Pfizer CT08-GSOP. The study site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed. Radiologic assessments performed as standard of care prior to informed consent is obtained may be used for the study provided they were performed within the protocol guidelines. The investigator will retain the original of each patient's signed consent document.

12.4. Patient Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study patients before such materials are used.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union (EU) is defined as the time at which it is deemed that a sufficient number of patients have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as last patient last visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of palbociclib at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within one week of notification. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicentre study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study patients, and the CSA will control as to all other issues.

16. REFERENCES

1. Thota R, Pauff JM, Berlin JD. Treatment of metastatic pancreatic adenocarcinoma: a review. Oncology (Williston Park). 2014;28:70-74.

2. Summary of Product Characteristics for Abraxane ®http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000778/WC500020435.pdf.

3. Hosein PJ, Lopes Jr Gd, Gomes CM, Pastorini VH, Macintyre J, et al. A phase II trial of nab-paclitaxel (NP) in patients with advanced pancreatic cancer (PC) who have progressed on gemcitabine (G)-based therapy. *J Clin Oncol 2010*; 28:15s,(abstr 4120).

4. Jemal A, Siegel R, Ward E, Hao Y, et al. Cancer Statistics, 2008. *CA Cancer J Clin. 2008*; 58: 71-96.

5. De Vita VT et al. (2011) DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology. Philadelphia, PA: Lippincott Williams & Wilkins.

6. Cancer facts and figures 2013. Atlanta: American Cancer Society, 2013.

7. Malvezzi M, Bertuccio P, Levi F, La Vecchia C, Negri E. European cancer mortality predictions for the year 2013. Ann Oncol 2013;24:792-800.

8. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *New Engl J Med. 2011*; 364:1817-25.

9. Von Hoff DD, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. New Engl J Med. 2013; 369:1691-1703.

10. Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreatic cancer: a randomized trial. *J Clin Onc.1997;* 15:2403-2413.

11. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol 2007*; 25:1960-6.

12. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol 2005;23(31):7794-803.

13. Fry D, Harvey PJ, Keller PR, Elliott WL, Meade MA, Trachet E, Albassam M, Zheng XX, Leopold WR, Pryer NK, Toogood PL. Specific Inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. *Mol Cancer Ther 2004*;3:1427-37.

14. Schwartz GK, LoRusso PM, Dickson MA, Randolph SS, Shiak MN, et al. Phase I study of PD 0332991, a cyclin-dependent kinase inhibitor, administered in 3-week cycles (Schedule 2/1). *Brit J Cancer 2011*;104:1862-68.

15. Flaherty KT, LoRusso PM, DeMichele A, Abramson VG, Courtney R, et al. Phase I, Dose-Escalation Trial of the Oral Cyclin-Dependent Kinase 4/6 Inhibitor PD 0332991, Administered Using a 21-Day Schedule in Patients with Advanced Cancer. *Clin Cancer Res 2012*;18(2):568-76.

16. Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol. 2015 Jan*;16(1):25-35. doi: 10.1016/S1470-2045(14)71159-3.

17. Waddell G, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, et al. Whoe genomes redefine the mutational landscape of pancreatic cancer. *Nature 2015*; 518(7540):495-501.

18. Puyol M, Martin A, Dubus P, Mulero F, Pizcueta P, et al. A Synthetic Lethal Interaction between K-Ras Oncogenes and Cdk4 Unveils a Therapeutic Strategy for Non-small Cell Lung Carcinoma. *Cancer Cell, 2010*; 18(1):63-73.

19. Schutte M, Hruban RH, Geradts J, Maynard R, Werner H, et al. Abrogation of the Rb/p16 Tumor-suppressive Pathway in Virtually All Pancreatic Carcinomas. *Cancer Research* 1997; 57:3126-3130.

20. Ji Y, Liu P, Li Y, and Bekele BN. A modified toxicity probability interval method for dose-finding trials. *Clinical Trials 2010*; 7:653 663.

21. Fanale M , Fayad L , Pro B *et al.* Phase I study of bortezomib plus ICE(BICE) for the treatment of relapsed/refractory Hodgkin lymphoma. *Br. J. Hematol. 2011;* 154, 271–286.

22. Dykstra R, Robertson T. An algorithm for isotonic regression for two or more variables. *Annals of Statistics. 1982;* 10(3):708-716.

23. Krishna K,. Blazer MA, Wei L, et al. Modified gemcitabine and nab-paclitaxel in patients with metastatic pancreatic cancer (MPC): A single-institution experience. J Clin Onc 2015; 33 (suppl 3; abstr 366).

17. APPENDICES

Appendix 1. Abbreviations

Abbreviation	Term
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice daily
BP	blood pressure
BUN	blood urea nitrogen
C	Cycle
C	Concentration
°C	degrees Celsius
CHF	congestive heart failure
CI	confidence interval
CL	Clearance
CLIA	Clinical Laboratory Improvement Amendments
CNS	central nervous system
CR	complete response
CRF	case report form
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
D	day
DAI	dosage and administration instructions
DCT	data collection tool
DDI	drug-drug interaction
DEHP	di-ethylhexylphthalate
DL	dose level
DLT	dose limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DR	Duration of Response
EC	ethics committee
ECG	electrocardiogram

Abbreviation	Term
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
eg	for example
CCI	[redacted]
ESoE	Early Signs of Efficacy
etc	'and other things' or 'and so forth'
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
g	gravity
GCP	Good Clinical Practice
GEM	gemcitabine
G-CSF	granulocyte-colony stimulation factor
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high-density polyethylene
HER2	Human epidermal growth factor receptor 2
Hgb	hemoglobin
HIV	human immunodeficiency virus
HR	hazard ratio
IB	investigator's brochure
IC_{50}	concentration of an inhibitor where the response (or binding) is reduced by half
ICH	International Conference on Harmonisation
ID	identification
ie	that is
IHC	immunohistochemistry
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IP	investigational product
IV	intravenous
K_2EDTA	dipotassium ethylene diamine tetraacetic acid
KPS	Karnofsky performance status
KRAS	Kirsten rat sarcoma viral oncogene homolog
LFT	liver function test
mTPI	modified toxicity probability interval
MAPK	Mitogen-activated protein kinase

Abbreviation	Term
MD	multiple dose
MDR	Modified Dose Regimen
MedDRA	Medical Dictionary for Regulatory Activities
MFD	maximum feasible dose
MID	minimally important difference
mPDAC	Metastatic Pancreatic Ductal Adenocarcinoma
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N/A	not applicable
Nab-P	nanoparticle albumin-bound Paclitaxel
NCI	National Cancer Institute
CCI	[redacted]
NS	not significant
ORR	overall response rate
OS	overall survival
pT	target probability
PCD	primary completion date
PD	pharmacodynamics
PD	progressive disease
PDAC	Pancreatic ductal adenocarcinoma
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PPI	Proton-pump inhibitor
PR	partial response
p-Rb1	Phosphorylated retinoblastoma protein
CCI	[redacted]
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
PVC	plasticized polyvinyl chloride
QD	every day
QT	time between the start of the Q wave and the end of the T wave
R	ratio
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Relapse-Free Survival
CCI	[redacted]
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SIB	suicidal ideation and behavior

Abbreviation	Term
SOA	Schedule of Activities
SPC	Summary of Product Characteristics
SRSD	single reference safety document
T	Time
$T_{1/2}$	terminal elimination half-life
TBR	tumor background ratio
TTD	time to deterioration
ULN	upper limit of normal
UPM	unit probability mass
US	United States
USPI	United States Package Insert
V	volume of distribution
V_z/F	
WBC	white blood cell

Appendix 2. Karnofsky Performance Status

KARNOFSKY PERFORMANCE STATUS SCALE
DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; No special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; Minor signs or symptoms of disease.
	80	Normal activity with efforts; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; Requires equivalent of institutional or hospital care; diseases may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; Active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Oxford Textbook of Palliative Medicine, Oxford University Press. 1993;109.

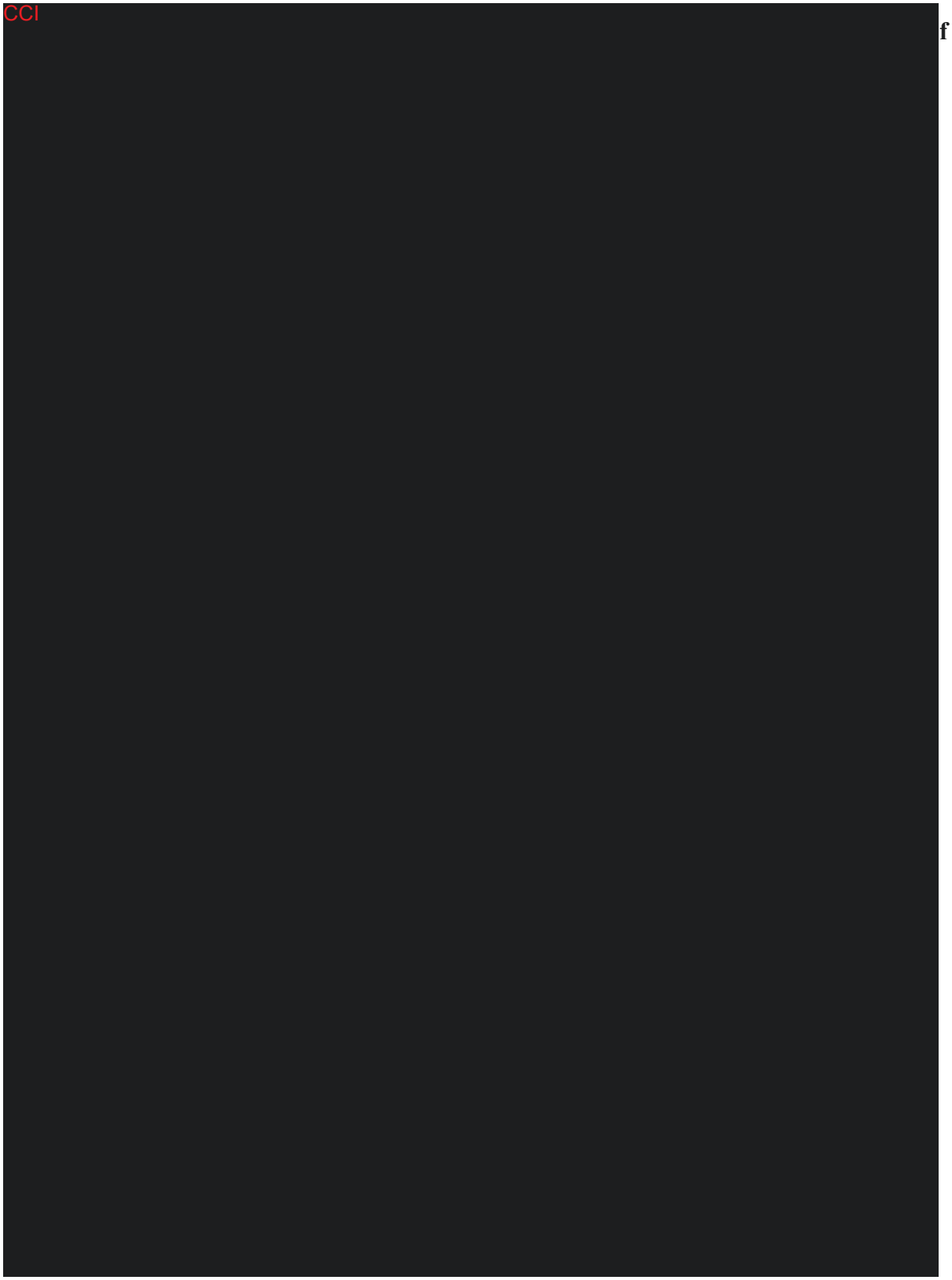
FUNCTIONAL ASSESSMENT STAGING (FAST)
(Check highest consecutive level of disability.)

1. No difficulty either subjectively or objectively.
2. Complains of forgetting location of objects. Subjective work difficulties.
3. Decreased job functioning evident to co-workers. Difficulty in traveling to new locations. Decreased organizational capacity. *
4. Decreased ability to perform complex task, (e.g., planning dinner for guests, handling personal finances, such as forgetting to pay bills, difficulty marketing, etc.)
5. Requires assistance in choosing proper clothing to wear for the day, season or occasion, (e.g. patient may wear the same clothing repeatedly, unless supervised. *)
6. A) Improperly putting on clothes without assistance or cueing (e.g., may put street clothes on over night cloths, or put shoes on wrong feet, or have difficulty buttoning clothing) (Occasionally or more frequently over the past weeks. *)
   B) Unable to bathe properly (e.g., difficulty adjusting bath-water temperature) (Occasionally or more frequently over the past weeks. *)
   C) Inability to handle mechanics of toileting (e.g., forget to flush the toilet, does not wipe properly or properly dispose of toilet tissue) (Occasionally or more frequently over the past weeks. *)
   D) Urinary incontinence (Occasionally or more frequently over the past weeks. *)
   E) Fecal incontinence (Occasionally or more frequently over the past weeks. *)
7. A) Ability to speak limited to approximately a half a dozen intelligible different words or fewer, in the course of an average day or in the course of an intensive interview.
   B) Speech ability is limited to the use of a single intelligible word in an average day or in the course of an intensive interview (the person may repeat the word over and over.)
   C) Ambulatory ability is lost (cannot walk without personal assistance.)
   D) Cannot sit up without assistance (e.g., the individual will fall over if there are not lateral rests [arms] on the chair.)
   E) Loss of ability to smile.
   F) Loss of ability to hold up head independently.

*Scored primarily on the basis of information obtained from acknowledgeable informant and/or category.
Reisberg, B. Functional assessment staging (FAST). Psychopharmacology Bulletin, 1988; 24:653-659.

CCI

f



CCI

[redacted]

CCI

[redacted]

Appendix 5. RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

Lesions that can be accurately measured in at least one dimension.

a. Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).

b. Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.

c. Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.

d. Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.

- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a

single item on the case report form (eg, multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.

- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

- Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

- Indeterminate. Progression has not been documented, and

    - one or more target measurable lesions have not been assessed;

    - or assessment methods used were inconsistent with those used at baseline;

    - or one or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure);

    - or one or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target disease

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

- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Table 1. Objective Response Status at each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

If the protocol allows enrollment of patients with only non-target disease, the following table will be used:

Table 2. Objective Response Status at each Evaluation for Patients with Non-Target Disease Only

Non-target Disease	New Lesions	Objective status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

Appendix 6. Schedule of Activities for Patients on Investigational Product(s) Beyond 2 Years (Not Applicable after implementation of Protocol Amendment 3)

Appendix 7. Dose Re-Escalation and De-Escalation Schemas for a Previous Dose Level (3 patients per group)

Figure A. Dose de-escalation schema to a previous dose level where 3 patients have been treated with 0 DLT

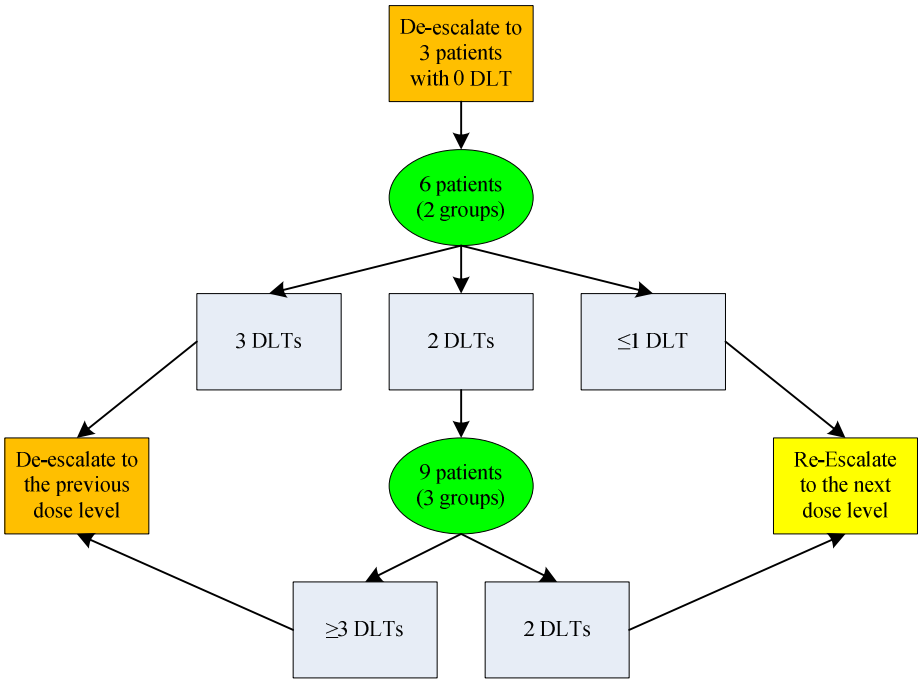


Figure B. Dose de-escalation schema to a previous dose level where 6 patients have been treated with ≤1 DLT

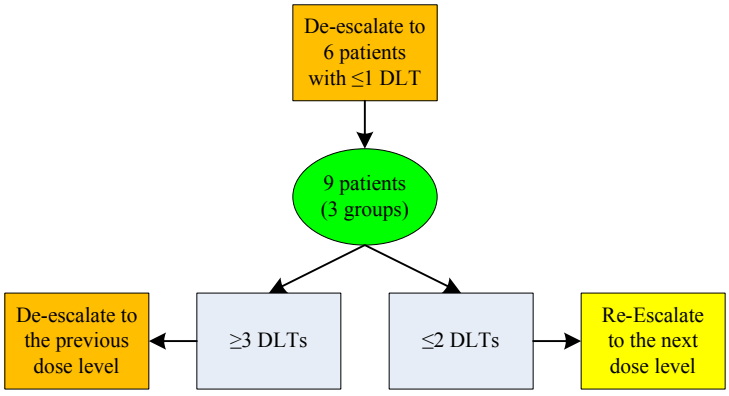


Figure C. Dose re-escalation schema from a previous dose level where 3 patients have been treated with 2 DLTs

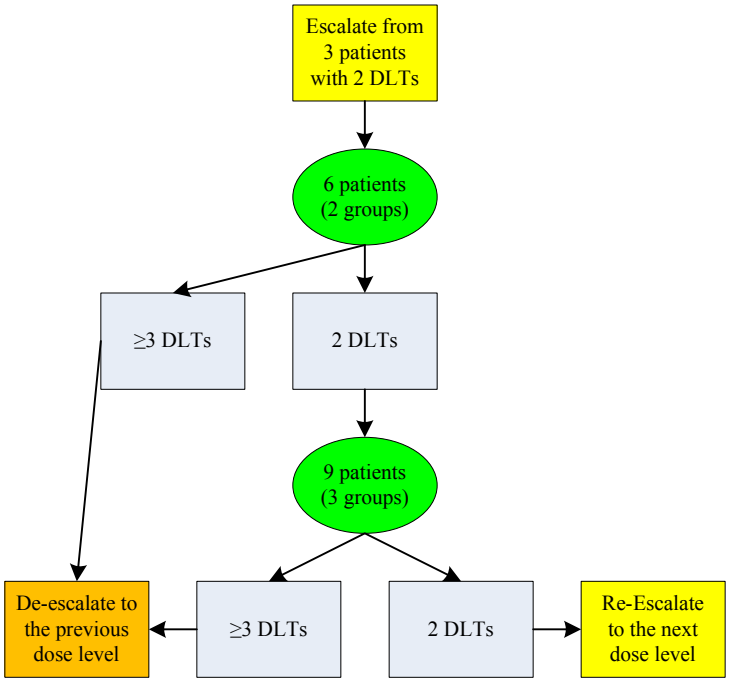
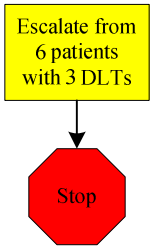


Figure D. Dose re-escalation schema from a previous dose level where 6 patients have been treated with 3 DLTs



Appendix 8. Bone Marrow Reserve in Adults

***Adapted from R.E. ELLIS**: The Distribution of Active Bone Marrow in the Adult, Phy. Med. Biol. 5, 255-258, 1961*

Marrow Distribution of the Adult

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
CRANIUM	Head :			136.6		
AND	Cranium	165.8	0.75	124.3	13.1	**13.1**
MANDIBLE	Mandible	16.4	0.75	12.3		
	Upper Limb Girdle :			86.7		
HUMERI,	2 Humerus, head & neck	26.5	0.75	20.0	8.3	8.3
SCAPULAE,	2 Scapulae	67.4	0.75	50.5		
CLAVICLES	2 Clavicles	21.6	0.75	16.2		
	Sternum	39.0	0.6	23.4	2.3	
	Ribs :			82.6		
	1 pair	10.2	All 0.4	4.1		
	2	12.6		5.0		
	3	16.0		6.4		
STERNUM	4	18.6		7.4		
AND	5	23.8		9.5	7.9	**10.2**
RIBS	6	23.6		9.4		
	7	25.0		10.0		
	8	24.0		9.6		
	9	21.2		8.5		
	10	16.0		6.4		
	11	11.2		4.5		
	12	4.6		1.8		

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
CRANIUM	Head :			136.6		
AND	Cranium	165.8	0.75	124.3	13.1	**13.1**
MANDIBLE	Mandible	16.4	0.75	12.3		
	Upper Limb Girdle :			86.7		
	Sacrum	194.0	0.75	145.6	13.9	
PELVIC BONES	2 os coxae	310.6	0.75	233.0	22.3	**36.2**
FEMUR	2 Femoral head and neck	53.0	0.75	40.0		**3.8**

Marrow Distribution of the Adult (cont'd)

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
	Vertebrae (Cervical):			35.8		
	1	6.6	All 0.75	5.0		
	2	8.4		6.3		
	3	5.4		4.1	3.4	
	4	5.7		4.3		
	5	5.8		4.4		
	6	7.0		5.3		
	7	8.5		6.4		
	Vertebrae (Thoracic):			147.9		
	1 pair	10.8	All 0.75	8.1		
	2	11.7		8.8		
	3	11.4		8.5		
	4	12.2		9.1		
VERTEBRAE	5	13.4		10.1	14.1	**28.4**
	6	15.3		11.5		
	7	16.1		12.1		
	8	18.5		13.9		
	9	19.7		14.8		
	10	21.2		15.9		
	11	21.7		16.3		
	12	25.0		18.8		

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
	Vertebrae (Lumbar) :			114.1		
	1 pair	27.8	All 0.75	20.8		
	2	29.1		21.8	10.9	
	3	31.8		23.8		
	4	32.1		24.1		
	5	31.4		23.6		
TOTAL		**1497.7**		**1045.7**	**100.0**	**100.0**

Appendix 9. List of Drugs Known to Predispose to Torsade de Pointes

Generic Name	Brand Name(s)
Amiodarone	Cordarone®, Pacerone®
Arsenic trioxide	Trisenox®
Astemizole	Hismanal®
Azithromycin	Zithromax®
Bepridil	Vascor®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®
Cisapride	Propulsid®
Citalopram	Celexa®
Clarithromycin	Biaxin®
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Domperidone	Motilium®
Droperidol	Inapsine®
Erythromycin	Erythrocin®, E.E.S. ®
Flecainide	Tambocor®
Halofantrine	Halfan®
Haloperidol	Haldol®
Ibutilide	Corvert®
Levomethadyl	Orlaam®
Mesoridazine	Serentil®
Methadone	Dolophine®, Methadose®
Moxifloxacin	Avelox®
Ondansetron*	Zofran®
Pentamidine	Pentam®, NebuPent®
Pimozide	Orap®
Probucol	Lorelco®
Procainamide	Pronestyl®, Procan®
Quinidine	Cardioquin®, Quinaglute®
Sotalol	Betapace®
Sparfloxacin	Zagam®
Terfenadine	Seldane®
Thioridazine	Mellaril®
Vandetanib	Caprelsa®

*when administered intravenously at high dose (32 mg).

Adapted from the University of Arizona Cancer Center for Education and Research on Therapeutics: "Torsades List: Drugs with a Risk of Torsades de Pointes," drugs that are generally accepted by the QTdrugs.org Advisory Board to carry a risk of Torsades de Pointes on the University of Arizona CERT website: http://www.crediblemeds.org/. This list is not meant to be considered all inclusive. See website for current list.