Protocol A5481059

An Open-Label Phase 1B Study of Palbociclib (Oral CDK 4/6 Inhibitor) plus Abraxane® (Nab-paclitaxel) in Patients with Metastatic Pancreatic Ductal Adenocarcinoma

Statistical Analysis Plan (SAP)

Version: 4

Author: PPD

Date: December 6, 2018

[redacted]

Document History

Document Version	Date	Summary of Changes
Original SAP	**July 29, 2015**	Not applicable (N/A)
Version 2	**Nov 27, 2017**	Incorporate the changes from protocol Amendment 1 and Amendment 2. Major changes include: 1. Addition of modified dose regimen cohorts, resulting in an increased sample size of the overall study. 2. 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. 3. Adding BOR detail definition. 4. Modify RDI detail definition. 5. Add in subgroup analysis for Ca19a-9. 6. Add in endpoint - Clinical Benefit Response 7. Add in RDI calculation rules for MDR1 and MDR2. 8. Provide details for dosing RDI calculation 9. Clarification of minor discrepancies throughout the document. 10. Modifications on Biomarkers, PRO, PK
Version 3	**May 8, 2018**	**1. Revise Biomarker population** **2. Add analysis on endpoint-CBR** **3. Add analysis on combined treatment group - DL3B (MTD cohort) + MTD** **4. Remove QTcS**
Version 4	**December 6 2018**	**1. Remove MDR expansion cohort, per Protocol Amendment 3** **2. Remover 3-tier AE summary**

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[redacted]

1. AMENDMENTS FROM PREVIOUS VERSION(S)

The SAP was amended based on the Amendment #3 (August 23, 2018). Remove MDR expansion cohort.

2. INTRODUCTION

This document describes the planned statistical analyses for Protocol A5481059 dated May 20, 2015. This analysis plan is meant to supplement the study protocol. Any deviations from this analysis plan will be described in the Clinical Study Report.

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-paclitaxel in patients with mPDAC.

2.1. 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-paclitaxel, in sequential cohorts of adult patients with mPDAC, with maximum tolerated dose (MTD) expansion cohort(s). Approximately 60-100 patients are expected to be enrolled in the overall study. The study has several parts:

2.1.1. Dose Escalation Cohorts

Consecutive cohorts of patients will receive escalating doses of oral palbociclib in combination with intravenous nab-paclitaxel in 28-day cycles. The starting doses of palbociclib will be 75 mg, administered on Day 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-paclitaxel will be assessed. Up to approximately 30 patients will be enrolled.

Dose escalation and de-escalation will follow a 2x3 matrix “Up-and-Down” design based on a modified toxicity probability interval (mTPI) method, using doses of palbociclib and nab-paclitaxel as shown in the Table 2.1 and Figure 2.1 below. In this dosing algorithm, there are up to 7 potential dose combinations (excluding DL -1):

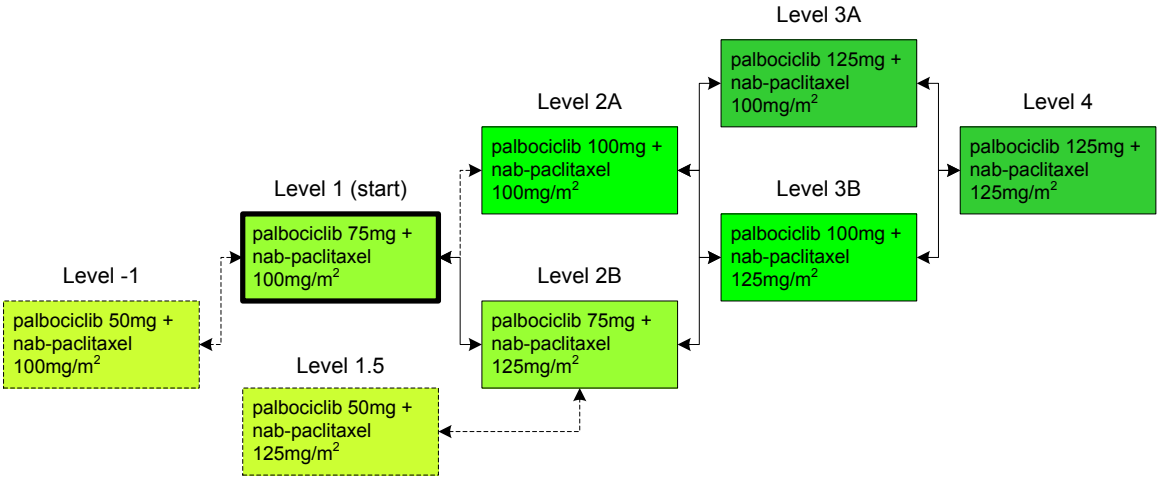
Table 2.1 Potential Palbociclib and Nab-Paclitaxel Dose Combinations

Dose Level	Palbociclib (oral, mg/day) Days 1-21 within a 28-day cycle	Nab-Paclitaxel (IV, mg/m^2/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

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

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 8.1.1. for a detailed description of the mTPI dose-escalation method.

Figure 2.1 Palbociclib and Nab-Paclitaxel Combination Dose Escalation and De-Escalation Sequence



The sequential dose escalation scheme and the rules for determining dose escalation, de-escalation, or 'stay' (i.e. enroll an additional group of patients to the current DL) at any given dose level are described in Appendix 10.2.

2.1.2. Modified Dose Regimen (MDR) Cohort(s)

Per Protocol Amendment 1, 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/m2 biweekly in each 28-day cycle.
- Modified Dose Regimen 2 (MDR2)-75 mg palbociclib continuous dosing, once daily, plus nab-P 100 mg/m2 biweekly in each 28-day cycle.

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 mTPI "De-escalateescalate," category for one or both MDR cohorts, cohort(s) will not move forward into expansion. The MDR cohort with a DLT rate <0.33 in at least 9 DLT evaluable patientspatients will be considered to move forward into expansion.

2.1.3. Expansion Cohort(s)

- MTD Expansion Cohort(s)

When the MTD(s) of palbociclib plus nab-paclitaxel 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).

The objective of the expansion cohort(s) are to provide additional information on safety, tolerability, biomarkers, PD activity and PK/PD relationship for the combination regimen in order to determine the recommended phase 2 dose (RP2D). The expansion cohort(s) will only enroll patients who have not received previous treatment for their metastatic disease in order to evaluate preliminary activity of the combination in patients in the target patient population.

2.1.4. Study Treatments

All patients will receive nab-paclitaxel and palbociclib.

2.1.4.1. Nab-Paclitaxel Administration

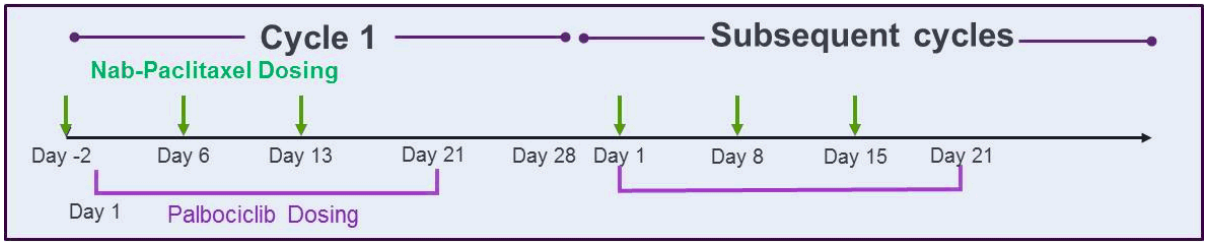
To allow for PK evaluation of nab-paclitaxel administered alone, nab-paclitaxel will be administered on Day -2 for Cycle 1 only. Subsequent cycles will administer both nab-paclitaxel and palbociclib on Day 1. Alternate dosing schedules for palbociclib may be explored based on emerging PK, PD, and safety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

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

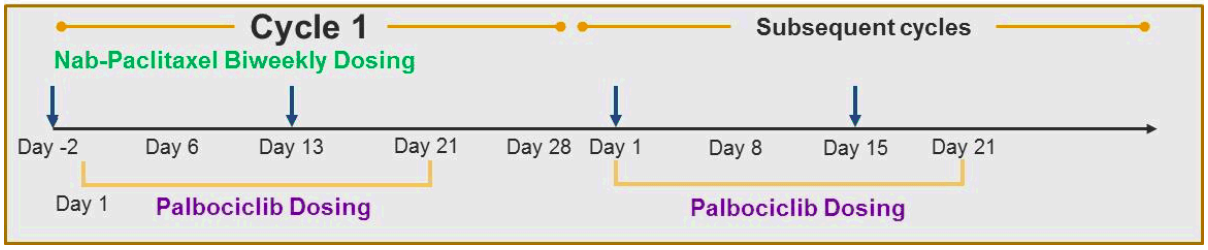
start on Day -2 in order to evaluate the pharmacokinetics of nab-P administered alone and in combination with palbociclib (Figure 2.2). On Day 13, nab-P and palbociclib should be dosed at approximately the same time. For cycle ≥2, both palbociclib and nab-P administration will start on Day 1, and palbociclib 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 2.2 Palbociclib and Nab-Paclitaxel Dose Combination Schema

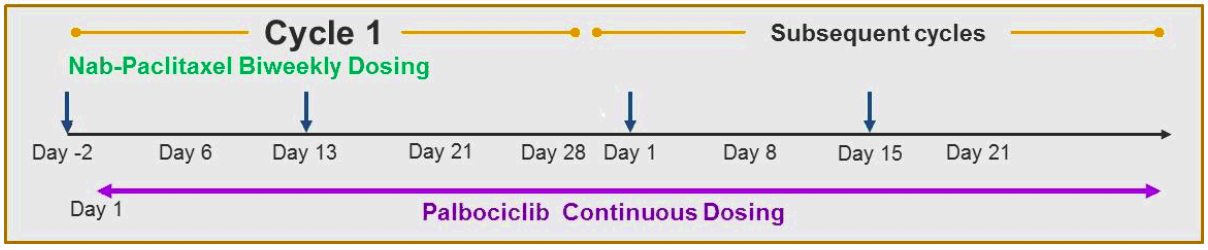
Dose Escalation and MTD Expansion Cohorts



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



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



2.1.4.2. 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 before starting the next 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.

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. A modified visit schedule will be implemented for patients who are on investigational product (IP) for more than 2 years (see Schedule Activities in Appendix 10.2).

Patients who discontinue investigational product (IP) for reasons other than radiographically and/or clinically (i.e. for photographed or palpable lesions) documented PD as per RECIST v.1.1 will continue to have tumor assessment performed during the follow-up visits every 8 weeks until RECIST-defined disease progression, initiation of new anticancer therapy or discontinuation of patient from overall study participation (e.g., death, patient's request, lost to follow-up), whichever occurs first. 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.

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 CCI [redacted]

Blood, tumor biopsies (optional), and/CCI [redacted] (optional for dose escalation and MDR1MDR1 and MDR2 cohorts) will be taken while on-treatment and at the end of treatment.

CCI [redacted]

[redacted]

2.2. Study Objectives

Primary Objective:

- To assess the safety and tolerability of palbociclib in combination with nab-paclitaxel 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-paclitaxel;
- To characterize the multiple-dose pharmacokinetics of palbociclib when administered in combination with nab-paclitaxel;

- To evaluate the effect of palbociclib on pharmacokinetics of total paclitaxel when nab-paclitaxel is administered in combination with palbociclib;
- To evaluate the anti-tumor effect of palbociclib in combination with nab-paclitaxel in patients with mPDAC;
- To evaluate the pharmacodynamic effect of palbociclib and nab-paclitaxel 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

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

This is an open label, single-arm trial for which no formal interim analysis is planned. The final analysis will be performed after the last patient last visit; however, earlier analyses of the data may be performed for publication and regulatory reporting purposes.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

The emphasis of the final analyses will not be on hypothesis testing but rather on estimation of key summary statistics.

4.2. Sample Size Determination and Statistical Decision Rules

4.2.1. 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 MTD expansion cohort(s) 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 have a 95% confidence interval of maximum 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.

4.2.2. Statistical Decision Rules

Dose Escalation Cohorts

The dose escalation/de-escalation rules will follow the mTPI method (see Section 8.1 for a detailed description). Briefly, the mTPI method relies upon a statistical probability algorithm, calculated using data from all patients treated at the same dose level (and not simply those in the current cohort) to determine whether future cohorts should involve dose escalation, no change in dose, or dose de-escalation.

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 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.

Modified Dose Regimen Cohorts

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 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):

Once the MTD for the combination has been defined in the dose-escalation cohorts, up to 20 patients who have not received previous treatment for their metastatic disease will be enrolled and treated in the MTD expansion cohort. 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).

The objectives of the expansion cohorts are to provide additional information on safety, tolerability, biomarkers, PD activity, and PK/PD relationship for the combination regimen in order to determine the RP2D

5. ANALYSIS SETS

5.1. Safety Analysis Set (Full 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.

5.2. 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-paclitaxel for reasons other than treatment-related toxicity in Cycle 1.

5.3. Per Protocol Analysis Set Evaluable for Anti-Tumor Activities

All enrolled patients who are eligible, receive study treatment, have adequate baseline assessments and at least 1 on-study tumor assessment prior to any new anti-cancer therapies will be considered evaluable for anti-tumor activities. Patients who are treated and discontinued from treatment prior to the first on-study tumor assessment because of disease progression will be considered evaluable for efficacy and counted as failures. (Definition for adequate baseline tumor assessment is reported in Appendix 10.4).

5.4. Pharmacokinetic 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.

5.5. 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.

CCI [redacted]

[redacted]

5.7. Treatment Misallocations

Not applicable.

5.8. Protocol Deviations

All deviations will be described when they appear and relate to the statistical analyses or analysis populations.

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

6.1.1. Primary Endpoint

First cycle DLTs

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-paclitaxel, or to the combination of palbociclib and nab-paclitaxel will be classified as DLTs. Adverse events that occur between Cycle 1 Day -2 after nab-paclitaxel 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 (e.g., 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

6.1.2. Secondary Endpoints

6.1.2.1. Safety

Safety assessment will consist of monitoring of all AEs, including SAEs, regular monitoring of hematology, serum chemistry, and routine monitoring of ECGs, physical examinations, vital signs, and ECOG performance status.

Overall safety profile as characterized by type, frequency, severity of adverse events as graded by NCI Common Toxicity Criteria for Adverse Events version 4 (NCI CTCAE

v.4.03), timing, seriousness, and relationship to study therapy, and laboratory abnormalities observed.

Baseline signs and symptoms will be recorded at baseline and then reported as adverse events during the trial if they worsen in severity or increase in frequency.

Adverse events (AEs), hematology, blood chemistry will be assessed as described in the Schedule of Activities of the protocol.

Adverse events will be classified using the MedDRA classification system. The severity of the toxicities will be graded according to the NCI CTCAE version 4.03. For labs without CTCAE grade definitions, results are summarized as normal, abnormal (per Pfizer Data Standards (PDS)) or not done. For other AEs without specific CTCAE definitions, results are identified according to CTCAE "other" categories.

Adverse events leading to death or discontinuation of trial treatment, events classified as NCI CTCAE v.4.03 Grade 3 or higher, trial drug related events, and serious adverse events will be considered with special attention.

The hematologic and chemistry laboratory results will be graded according to the NCI CTCAE v.4.03 severity grade. For parameters for which an NCI CTCAE v.4.03 scale does not exist, the frequency of patients with values below, within, and above the normal range for the local lab will be summarized.

Patients who start treatment are assessed for toxicities up to 28 days after the final dose of treatment or start of new treatment (whichever comes first). Toxicities observed beyond 28 days and recorded in the database per Sponsor's agreement will be included in the summaries.

6.1.2.1.1. Treatment Emergent Adverse Event

An adverse event is considered treatment emergent if:

- The event occurs for the first time after the start of study treatment and before 28 days after final dose of study treatment and was not seen prior to the start of treatment or
- The event was seen prior to the start of treatment but increased in NCI CTCAE v.4.0 grade during study treatment.
- Disease progression is not considered a treatment emergent adverse event unless the patient dies of disease prior to 28 days after discontinuation of treatment.

6.1.2.1.2. Treatment Related Adverse Event

Adverse events defined as treatment emergent adverse events with cause possibly, probably or definitely related to treatment as judged by the investigator are defined as treatment related adverse events. Events that are continuation of baseline abnormalities are not considered treatment related unless there is an increase in grade, or if there is an increase following a decrease, and the increase is judged by the investigator to be caused by the treatment.

6.1.2.2. Laboratory Safety

Laboratory assessment will be assigned to cycles based on the collection date of the sample relative to the start dates of cycles from the study drug administration as described in the Schedule of Activities table in Appendix 10.1.

Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing;

Baseline evaluations for laboratory are those collected

- Within 28 days prior to or on first day of study drug and
- If there is more than one baseline evaluation, closest to but any time prior to the 1st dosing on the first day of study treatment.

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

Additional blood tests should be performed where needed for the purpose of evaluating potential DLTs or other adverse events. In particular, if a patient has Grade 3 neutropenia, complete blood count (CBC) should be performed every 24-48 hours.

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.

Special blood sample for CA19-9 will also be collected.

Blood tests will include the following:

Table 6.1 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	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

	Amylase (if available) Lipase (if available)			

*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.

6.1.2.3. Vital Signs

Patients will have a physical exam to include, weight, vital signs (pulse rate and blood pressure), assessment of Karnofsky (see Appendix 10.8) performance status, and height; height will be measured at screening only.

6.1.2.4. Electrocardiogram (ECG)

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-paclitaxel 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 Section 10.1. for details) to determine the mean QTc interval.

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 (i.e. the timing of the PK collections overrides the timing of the ECG collections.

6.1.2.5. 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.

6.1.2.6. Efficacy

Objective Response (OR) is defined as the overall complete response (CR) or partial response (PR) according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1; Appendix 10.4). **Objective Response Rate (ORR)** is defined as the proportion of patients with a best overall response (BOR based on confirmed responses as described in Appendix 10.4) of CR or PR relative to all anti-tumor evaluable patients. Patients who do not have on-study radiographic tumor re-evaluation, who receive anti-tumor treatment other than the study medication prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of ORR. Clinical Benefit Response (CBR) is defined as a patient with a BOR of CR or PR at any time, or non-CR/non-PD or SD for at least 16 weeks from start date.

Tumor response will be determined from tumor assessment data (as described in Appendix 10.4).

Duration of Response (DR) is defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of disease progression or to death due to any cause, whichever occurs first. If tumor progression data include more than 1 date, the first date will be used. DR will be calculated as [the date response ended (i.e. date of PD or death) – first CR or PR date + 1)]/30.4. DR will only be calculated for the subgroup of patients with an objective tumor response.

Patients last known to be 1) alive and 2) progression-free, are censored at the date of the last objective disease assessment that verified lack of disease progression. In addition,

- If a new anti-cancer treatment is started prior to progression and prior to 28 days after discontinuation of treatment, then censorship is at the date of the last objective disease assessment that verified lack of disease progression prior to the new treatment.
- If patients are removed from the study (withdrew the consent, lost to follow up, etc.) prior to progression and death, then censorship is at the date of the last objective disease assessment that verified lack of disease progression.
- Patients with documentation of progression or death after an unacceptably long interval (>2 consecutive assessments) since the last tumor assessment will be censored at the time of last objective assessment documenting no progression.

Progression Free Survival (PFS) is defined as the time from the date of first dose to the date of the first documentation of objective tumor progression as per RECIST v.1.1 or death due to any cause in the absence of documented PD, whichever occurs first. If tumor progression data include more than 1 date, the first date will be used. PFS (in months) will be calculated as (first event date – first dose date +1)/30.4.

Tumor assessments will be performed every 8 weeks (± 7 days) (12 weeks (± 7 days) for Cycles ≥ 6) from first dose until radiographically and/or clinically (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 (e.g., death, patient's request, lost to follow up).

Imaging assessments are to be scheduled using the first dose date as the reference date for all time-points and are NOT to be scheduled based on the date of the previous imaging time-point. Patients who discontinue study treatment for reasons other than radiographically and/or clinically (for photographed or palpable lesions) documented disease progression as per RECIST definitions will continue to have tumor assessment performed during the follow-up visits every 8 weeks (± 7 days) (12 weeks (± 7 days) for Cycles ≥ 6) until documented disease progression, initiation of new anticancer therapy or discontinuation of patient from overall study participation (e.g., death, patient's request, lost to follow-up), whichever occurs first. Every effort should be made to perform a last tumor assessment before starting a new anticancer therapy. Additional unscheduled tumor assessments may be performed as clinically indicated at any time.

Patients last known to be 1) alive and 2) progression-free, are censored at the date of the last objective disease assessment that verified lack of disease progression (see Appendix 10.4 for determining the date in details). In addition,

- Patients with no baseline tumor assessment (including patients with an inadequate baseline assessment) within 18 weeks after the randomization date will be censored on the randomization date, unless the patient dies within 18 weeks of the randomization date, in which case, death will be an event on date of death.

- Patients with no adequate post-baseline tumor assessments within 18 weeks after the randomization date will be censored on the randomization date, unless the patient dies within 18 weeks of the randomization date, in which case, death will be an event on date of death.
- If a new anti-cancer treatment is started prior to progression and death, then censorship is at the date of the last objective disease assessment that verified lack of disease progression prior to the new treatment.
- If patients are removed from the study (withdrew the consent, lost to follow up, etc.) prior to progression and death, then censorship is at the date of the last objective disease assessment that verified lack of disease progression.
- Patients with documentation of progression or death after an unacceptably long interval (>2 consecutive assessments) since the last tumor assessment will be censored at the time of last objective assessment documenting no progression.

Six-month progression-free survival (6m-PFS) is defined as the PFS status (progression free and alive, or not) at 6-months. The 6-month PFS rate is summarized as a product limit estimator based on the Kaplan-Meier method to account for censored events.

Overall Survival (OS) is defined as the time from the date of first dose to the date of death due to any cause. OS (in months) is calculated as (date of death – first dose date +1)/30.4. For patients lacking survival data beyond the date of their last follow-up, the OS time will be censored on the last date they were known to be alive. Patients lacking survival data beyond first dose will have their OS times be censored at first dose.

Following the End of Treatment visit, survival status will be collected in all patients every month (±7 days) from the last dose of study treatment. Information on subsequent anticancer therapy will also be collected.

The unacceptably long intervals (>2 consecutive assessments) are defined as following: 1) PD occurs during Cycle 4 to 7 or death occurs during Cycle 3 to 6, the unacceptable interval is greater than 18 weeks. 2) PD occurs at Cycle 8 or death occurs during Cycle 7, the unacceptable interval is greater than 22 weeks. 3) PD occurs at/after Cycle 9 or death occurs at/after Cycle 8, the unacceptable interval is greater than 26 weeks.

6.1.2.7. Pharmacokinetics

Pharmacokinetic parameters of palbociclib and nab-paclitaxel:

- For palbociclib PK when given with nab-paclitaxel: 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-paclitaxel 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.

6.1.2.7.1. 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-paclitaxel.

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-paclitaxel infusion. The investigator should plan to provide the patient with a meal on these days.

In the event nab-paclitaxel is not dosed on Day 13, PK samples for palbociclib determination can be collected on the day the third dose of nab-paclitaxel is administered as long as there is no dose interruption, reduction or delay of palbociclib dosing within 7 days of the intended nab-paclitaxel 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-paclitaxel dosing, every effort should be made to collect makeup samples on Day 15 of Cycle 2 or the day when the third dose of nab-paclitaxel in Cycle 2 (or later cycles) is administered using the same criteria. The Day 13, 24-hour PK sample should be 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.

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 CCI [redacted]

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 (e.g., 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 (e.g., CRF/DCT).

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]

6.1.2.7.2. 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-paclitaxel IV infusion as described in SOA. The pre-dose samples should be collected just before the start of the nab-paclitaxel infusion. On Day 13, Nab-paclitaxel 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-paclitaxel dose, PK samples collection can be made up in later cycles. In the event of nab-paclitaxel is not dosed on Day 13, PK samples for total paclitaxel determination can be collected on the day the third nab-paclitaxel dose is administered as long as there is no dose interruption, reduction or delay of palbociclib dosing within 7 days of the intended nab-paclitaxel 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-paclitaxel dosing, every effort should be made to collect makeup samples on Day 15 of Cycle 2 or the day when the third dose of nab-paclitaxel in Cycle 2 (or later cycles) is administered using the same criteria. The exact date and time of the sample collection and the exact start and stop time of the nab-paclitaxel 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 CCI [redacted]

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 (e.g., 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 (e.g., CRF/DCT).

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

6.1.2.8. Biomarkers

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 (e.g., 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

- CCI
-

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.

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 6.2 Summary of Biomarker Assessments

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

6.1.2.8.1. 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 (e.g., 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. Examples of such biomarkers may include phospho-Rb1, p-ERK, FoxM1, Ki67, and TUNEL/apoptosis markers.

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

CCI

[redacted]

CCI

[redacted]

6.2.2. Stratification Factors

Not applicable.

7. HANDLING OF MISSING VALUES

7.1. Missing Dates

In compliance with Pfizer standards, if the day of the month is missing for any date used in a calculation, the 1st of the month will be used to replace the missing date unless the calculation results in a negative time duration (e.g., date of onset cannot be prior to day one date). In this case, the date resulting in 1 day duration will be used. If the day of the month and the month is missing for any date used in a calculation, January 1 will be used to replace the missing date.

Missing dates for adverse events will be imputed based on the similar principle.

- For the start date, if the day of the month is missing, the 1st day of the month will be used to replace the missing date. If both day and month are missing, January 1 of the non-missing year will be used to replace the missing date. If the first dose date is later than this imputed date, then impute the start date again to the first dose date.
- For the stop date, if the day of the month is missing, the last day of the month will be used to replace the missing date. If both day and month are missing, December 31 of the non-missing year will be used to replace the missing date.

If the start date is missing for an AE, the AE is considered to be treatment emergent unless the collection date is prior to the treatment start date.

7.2. Missing Tumor Assessments

If baseline tumor assessment is inadequate the patient cannot be assessed for response.

Inadequate baseline assessment may include

- Not all required baseline assessments were done
- Assessments were done outside the required window
- Measurements were not provided for one or more target lesions
- One or more lesions designated as target were not measurable.

If measurements for one or more target lesions are missing for an evaluation and disease does not qualify as progression (or symptomatic deterioration if applicable), the objective status for that evaluation is Indeterminate.

If non-target disease was not assessed, then objective status cannot be a CR even if all target disease has disappeared. Otherwise, missing non-target disease assessments do not necessarily affect response determination. Such cases will be reviewed carefully.

If a lesion measurement is missing because it is documented as too small to measure, the value 5 mm will be assigned and objective status calculated accordingly.

In the assessment of OR, patients who do not have on study radiographic tumor re-evaluations will be counted as non-responders.

7.3. Missing Data in PFS Derivation

PFS cannot be assessed in patients with inadequate baseline tumor assessment. PFS cannot be assessed in patients who have no on-study assessments unless death occurs prior to the first 2 planned assessment time.

If a substantial number of patients have questionable failure or censorship dates for either PFS definition (such as progression or death not documented until after multiple missing assessments) scenarios such as best case (failure at time of documentation) and worst case (progression at earliest possible planned assessment date) will be investigated.

For time to event endpoints, no values will be imputed for missing data and non-event observations will be censored as defined in Section 6. If conventions result in a negative duration, durations will be reset to 1 day.

7.4. Missing QTc Data

For QTc analysis, no values will be imputed for missing data except for averaging of triplicate measurements. If one or two of the triplicate measurements for an ECG parameter are missed, the average of the remaining two measurements or the single measurement can be used in the analyses. If all triplicate measurements are missing at a time point for an ECG parameter, no values will be imputed for this time point and no analyses related to this time point will be performed. If the triplicate is not good because of an artifact, then if the triplicate is repeated within about ± 15 minutes can be used at that nominal time. Patients who have data on other days or unscheduled ECGs but not at the times of the formal statistical analysis will be included in the categorical tables but not the statistical analyses.

CCI

[redacted]

7.6. Missing PK Samples

Concentrations below the limit of quantification

For all calculations, figures and estimation of individual pharmacokinetic parameters, all concentrations assayed as below the level of quantification (BLQ) will be set to zero. In log-linear plots these values would not be represented. The BLQ values will be excluded from calculations of geometric means and their confidence intervals. A statement similar to "All

values reported as BLQ have been replaced with zero" should be included as a footnote to the appropriate tables and figures.

Deviations, missing concentrations and anomalous values

In summary tables and plots of median profiles, statistics will be calculated. Concentrations will be set to missing if one of the following cases is true:

- A concentration has been reported as ND (i.e., not done) or NS (i.e., no sample),
- A deviation in sampling time is of sufficient concern or a concentration has been flagged as anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing. For analysis of pharmacokinetic concentrations, no values will be imputed for missing data.

Pharmacokinetic parameters

Actual PK sampling times will be used in the derivation of PK parameters (and where possible the actual dosing information). If a PK parameter cannot be derived from a patient's concentration data, the parameter will be coded as NC (i.e., not calculated). (Note that NC values will not be generated beyond the day that a patient discontinues).

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will not be presented for a particular treatment if more than 50% of the data are NC. For statistical analyses (i.e., analysis of variance), PK parameters coded as NC will also be set to missing.

If an individual patient has a known biased estimate of a PK parameter (due for example to an unexpected event such as vomiting before all the drug is absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

7.7. Missing/Duplicate Biomarker Data

No values will be imputed for missing data. If there is duplicate biomarker data for an assessment that is not expected (e.g., the same sample was sent twice to the assay laboratory, or the laboratory reported two assessments for the same sample), the following will occur. Numerical biomarker values will be averaged for reporting purposes and the average will be included in the listing of biomarker data along with the original data. Non-numerical data (e.g., mutations present) will be reviewed by the clinical subteam to determine which data will be included in the analyses, if any; that record will have a flag added to show it was used for analysis purposes.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

8.1.1. mTPI Method - Dose Escalation/De-Escalation

The rules for dose escalation/de-escalation will follow a modified toxicity probability interval (mTPI) method. 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 (i.e., all patients in that cohort are evaluable for DLT), a decision to escalate, de-escalate, or stay (i.e., 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 (Table 8.1). Thus, compared to other advanced model-based designs published in the literature, the mTPI design is logistically less complicated and easier to implement.

Table 8.1 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) have demonstrated that the decision based on UPM is optimal in that it minimizes a posterior expected loss (i.e. 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.

8.1.2. 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-paclitaxel 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-paclitaxel 125 mg/m^2 may have a higher proportion of observed toxicities than, say, palbociclib 125 mg, nab-paclitaxel 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. 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 MTD expansion cohort(s) in case no clear choice exists between more than 1 competing MTD combinations. 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.

8.1.3. Analyses for Time-to-Event Data

Time-to-event endpoints will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and 2-sided 95% confidence interval (CI) for the median based on Brookmeyer-Crowley method will be provided.

The X-year survival probability will be estimated using the Kaplan-Meier method and a 2-sided 95% CI for the log [-log(X-year survival probability)] will be calculated using a normal approximation and then back transformed to give a confidence interval for the X-year survival probability itself.

8.1.4. Analyses of Binary Data

Binary endpoints will be summarized by percentage rates along with the corresponding exact 2-sided 95% CIs using the exact method based on Clopper-Pearson method.

8.1.5. Analyses of Continuous Data

Continuous endpoints will be summarized by descriptive statistics, including the mean, standard deviation, median, minimum, and maximum values. Descriptive statistics for PK parameters and biomarkers will include %CV.

8.1.6. Analyses for Categorical Data

The number and percentage of patients in each category will be provided for categorical variables.

8.1.7. Analyses for QTc Data

8.1.7.1. Derived Analysis Variables

All ECGs will be recorded in triplicate i.e. three ECGs taken 2 minutes apart. ECG assessments reported by the site will include the following parameters:

ECG Parameter	Units	Abbreviation
QTc, Fridericia's correction	msec	QTcF
QTc, Bazett's correction	msec	QTcB
QT Interval	msec	QT
Heart Rate	bpm	HR
PR Interval	msec	PR
RR Interval	msec	RR
QRS Complex	msec	QRS

Averaging of triplicate measurements:

After the above variables have been derived within each patient and scheduled time-point, each ECG parameter (including QTcF, QTcB, QT, HR, PR, RR, QRS) should each be

averaged as follows: (1st measurement + 2nd measurement + 3rd measurement) / 3. All summary statistics, analyses and figures will be based on the triplicate averaged data.

8.1.7.2. Assessment of QT Correction Methods

This assessment will utilize only Screening and Day 0 triplicate averaged data ("Study drug-free" ECG data).

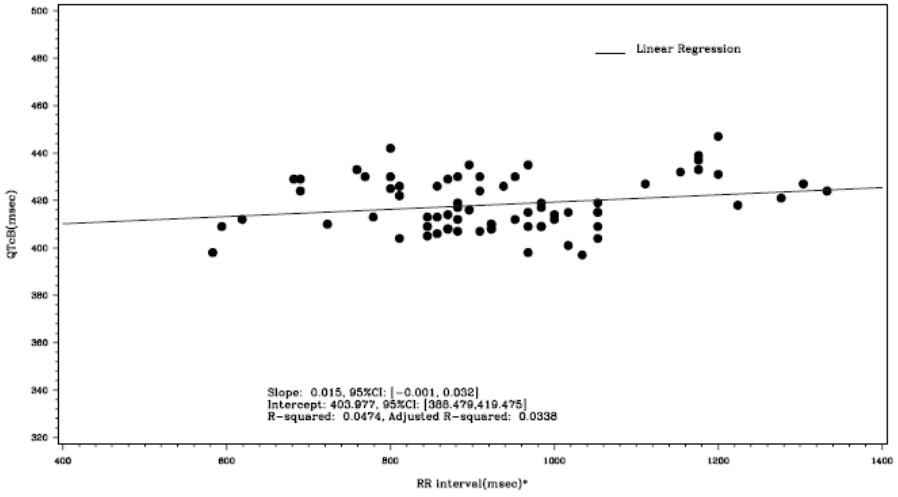
The relationship between QT/QTc and RR and the adequacy of each of the 3 QT correction methods will be assessed by the following scatterplots (see Figure 1):

- QT, QTcF, and QTcB vs. RR

Interpretation of the scatterplots should give the following information:

- Variability of the QT/QTc relative to changing RR
- Slope or lack of slope and pattern to assess adequacy of QT correction method
- Apparent patterns in the data

Figure 8.1. A Sample scatterplot of relationship between QT/QTc and RR



8.1.7.3. Change from Baseline Definition

The change from baseline calculations for ECG measurements (abbreviated as "change") is derived from the triplicate averaged measurements. The baseline ECG assessment is defined as the triplicate ECG assessment taken pre-dose on Cycle 1 Day 1, or the most recent triplicate ECG assessment reported prior to the first administration of study drug. Change from baseline is defined as a patient's parameter value at a particular time-point minus the appropriately matched baseline value (value - baseline value). Change from baseline calculations should only use post-dose ECG measurements.

8.1.7.4. Outlier Analysis

QT/QTc outlier values will be summarized and tabulated by the following CTCAE grade v.4.03.

Grade	1	2	3	4	5
Prolonged QTc interval	QTc 450 – 480 msec	QTc 481 – 500 msec	QTc ≥501 msec on at least two separate ECGs	QTc ≥501 or >60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Death

The change from baseline will summarize occurrences of shift by ≥ 1 grade by CTC. Individual QT and QTc values ≥501 msec from each ECG within a triplicate will be flagged in data listings.

In addition, the maximum QTc value for each patient can be categorized and summarized in the following cut-offs. All post dose QTc interval data should be used in determining the maximum for a patient, including all scheduled and unscheduled ECG's.

Absolute QTc interval prolongation
QTc < 450 msec
450 msec ≤ QTc ≤ 480 msec
481 msec ≤ QTc ≤ 500 msec
QTc ≥501 msec

The maximum increase from baseline QTc value for each patient by treatment will be categorized and summarized as well. For reporting the maximum increase QTc value the following categories: <30 msec, 30-59 msec and ≥60 msec will be used.

8.2. Statistical Analyses

All safety and efficacy analyses will be conducted on safety analysis set. Efficacy analyses will also be conducted on Per Protocol Analysis Set Evaluable for Anti-tumor Activities. All analyses will be performed by using SAS® Version 9.4 or higher.

The analyses of endpoints dependent on disease assessments (PFS, OR, and DR) will be based on investigator assessments of disease response and progression.

8.2.1. Analysis of Primary Endpoint (DLT)

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 protocol. Adverse Events constituting DLTs will be listed per dose level with the following information.

- Patient ID.
- Dose and Date at which DLT occurred.
- Time from treatment start to onset of DLT.
- Time to resolution of DLT to Grade 1 or baseline.
- Dose interruption (yes, no).
- Time to resumption of treatment.
- DLT term.
- Action(s) taken due to DLT (stopped temporarily, permanently discontinued, no action taken, etc).

8.2.2. Analysis of Secondary Safety Endpoints

8.2.2.1. Adverse Events

All patients treated with at least one dose of study treatment (i.e. palbociclib or nab-paclitaxel) will be included in all the safety analyses.

Adverse events will be classified using the medical dictionary for regulatory activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE v.4.03 whenever possible (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for selected events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation.

Adverse events will be summarized by treatment and by the frequency of patients experiencing treatment emergent adverse events corresponding to body systems and MedDRA preferred term. Adverse events will be graded by worst NCI CTCAE v.4.03 grade. Adverse events will be summarized by cycle and by relatedness to trial treatment. Detailed information collected for each AE will include a description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Emphasis in the analysis will be placed on AEs classified as treatment emergent, 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).

Adverse events leading to death or discontinuation of trial treatment, events classified as NCI CTCAE v.4.03 Grade 3 or higher, trial drug related events, and serious adverse events will be considered with special attention.

The percentage of patients with an event will be calculated using the number of patients in the safety analysis set as the denominator. The denominator for summary tables for each laboratory parameter will be all patients in the safety analysis set with at least one evaluable cycle for that parameter.

The following summaries of treatment emergent adverse events will also be provided:

- Discontinuations Due to Adverse Events including causality: all cause, treatment related, including relationship to specific study treatment of palbociclib and/or nab-paclitaxel.

- Temporary Discontinuations or Dose Reductions Due to Adverse Events including causality and relationship to specific study treatment of palbociclib and/or nab-paclitaxel.

- Treatment-Emergent Adverse Events (All Causality, and Treatment Related) including the number of patients evaluable for adverse events, total number of adverse events (counting each unique preferred term across all patients), number of patients with serious adverse events, number of patients with Grades 3 and 4 adverse events, number of patients with Grade 5 adverse events, and number with dose reductions or temporary discontinuations due to adverse events

- Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term and Maximum NCI CTCAE v.4.03 Grade (All Causality, and Treatment related)

- Treatment-Emergent Adverse Events by MedDRA Preferred Term sorted by Descending Order of AE Frequency (All Causality, and Treatment related)

- Treatment-Emergent Adverse Events by Preferred Term – Grade 3/4/5 events with number of patients experienced Grade 3-5 AEs and total number of Grade 3-5 AEs, sorted by Descending Order of AE Frequency (All Causality, and Treatment Related).).

A summary of Serious Adverse Events and listing of deaths reported as serious adverse events will be provided.

8.2.2.2. Laboratory abnormalities

Hematologic, chemistry and urinalysis laboratory data will be summarized by cycle. The hematologic and chemistry laboratory results will be graded according to the NCI CTCAE v.4.03 severity grade. 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.

For CA19-9, results will be summarized in patients count (n) and percentage under the un-mutually exclusive categories as Maximum %Reduction from baseline ≥20%, ≥50%, ≥70%, and ≥90%. Reduction from baseline at Week 8 ≥20%, >50%, and ≥70%‘ , respectively.

8.2.3. ECG Analyses

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 [i.e. 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, QTc (QTcF, QTcB), 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, 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.

For all patients in the safety analysis set, categorical analysis of the QTcF/QTcB data will be conducted and summarized as follows:

- QT/QTc outlier values will be summarized and tabulated by the following CTCAE grade v.4.03 according to Section 8.1.7.5.
- The change from baseline will summarize occurrences of shift by ≥ 1 grade by CTC.
- Individual QT and QTc values ≥501 msec from each ECG within a triplicate will be flagged in data listings.
- The number of and percentage patients with maximum post-dose QTcF/QTcB (<450, 450-480, 481-500, and ≥501 ms), including all scheduled and unscheduled ECG's.
- The number and percentage of patients with maximum increase from baseline in QTcF/QTcB (<30, 30- 60, and > 60 ms), including all scheduled and unscheduled ECG's.
- PR changes from baseline ≥ 50% if absolute baseline value was < 200 ms, and ≥ 25% if absolute baseline value was > 200 ms.
- QRS changes from baseline ≥ 50% if absolute baseline value was < 100 ms, and ≥ 25% if absolute baseline value was > 100 ms.
- The number and percentage of individuals with abnormal ECG findings.

8.2.4. Analyses of Efficacy Endpoints

The number and proportion of patients achieving objective response (CR or PR) will be summarized in the Per Protocol Analysis Set Evaluable for Anti-tumor Activities along with the corresponding exact 2-sided 95% CI.

PFS based on the assessment of investigator will be summarized in the safety analysis set using the Kaplan-Meier method and displayed graphically where appropriate. The median event time and corresponding 2-sided 95% CI for the median will be provided for PFS.

DR will be summarized using the Kaplan-Meier methods and displayed graphically where appropriate. DR will be calculated for the subgroup of patients with objective tumor response. The median event time and 2-sided 95% CI for the median will be provided.

Six-month progression-free survival (6m-PFS) rate 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% 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 6-month PFS rate itself. Analysis result will be included in the table for the PFS analysis.

Patients will be followed and have tumor assessments performed every 8/12 weeks until disease progression or death, patient refusal, start of another anti-cancer treatment, or until 1-year from C1D1 of last enrolled patient, whichever occurs first.

Tumor Response will be presented in the form of patient data listings that include, but are not limited to, received (maximum) dose, overall tumor response at each visit, and best overall response. In addition, progression date, death date, date of first response and last tumor assessment date, dates of first dose and last dose will be listed, together with DR and PFS.

OS will be summarized in the safety analysis set using the Kaplan-Meier methods and displayed graphically where appropriate. The median event time and 2-sided 95% CI for the median will be provided.

The 6-months, 1-year and 2-year survival probabilities will be provided with their 95% CIs.

The Clinical Benefit Response (CBR) rate is defined as the percentage of patients with CBR. The CBR rate will be summarized in the Per Protocol Analysis Set Evaluable for Anti-tumor Activities along with the corresponding exact 2-sided 95% CI.

8.2.5. Standard Analyses

Descriptive statistics will be used to summarize study conduct and patient disposition, baseline characteristics, and treatment administration/compliance.

- **Study Conduct and Patient Disposition** - an accounting of the study patients will be tabulated including treated, accrual by study center, assessed for AEs, laboratory data, biomarkers, PK, and QTc, etc. Patients not meeting the eligibility criteria will be identified. Patients not completing the study will be listed along with the reason for their premature discontinuation. Reasons for premature discontinuation will be summarized.

- **Baseline Characteristics** - patient characteristics such as patient age, height, weight, gender, race, ethnicity, Karnofsky performance status, Ca19Ca19-9, primary diagnosis, prior therapy (radiotherapy, surgery, systemic therapy), baseline disease site, prior medication, medical history, and signs and symptoms at study entry will be summarized in frequency tables, and descriptive statistics will be provided for quantitative variables.

- **Treatment Administration and Compliance**

  - **Extent of Treatment**

    The extent of treatment will be summarized as follows:
    - The number and % of patients on treatment and off for each reason
    - Treatment assigned vs. actual received
    - The number and percent of patients beginning 1, 2, 3, 4, 5+ cycles of either study drug
    - The number of cycles started (median, minimum, maximum) will be reported (overall and by study treatment).
    - Duration of treatment (weeks) (overall and by study treatment)
    - Cumulative dose and relative dose intensity (see Appendix 10.7 for details) (overall and by cycle; by study treatment).).

  - **Treatment Delays and Dose Modifications**

    Treatment delays and dose modifications of study treatments will be summarized as follows including number and percent (see Appendix 10.7 for details):

- The number of patients with at least one palbociclib or nab-paclitaxel dose reduction and the number of patients with at least one palbociclib or nab-paclitaxel dose omission at any time during drug administration will be reported.

- The number of patients with at least one palbociclib or nab-paclitaxel dose reduction due to an adverse event will be reported.
- The number of patients with at least one palbociclib or nab-paclitaxel dose delay (i.e. start of following cycle is delayed) and percentage due to each reason for the delay will be reported

- **Concomitant medications and Non-drug treatments**

  Concomitant and non-drug treatments refer to all drug and non-drug treatments taken while on active treatment (during the effective duration of study treatment), whether or not they are recorded at baseline (i.e. have stop day greater than or equal to day 1 relative to first dose of study drug). Concomitant medication will be summarized in frequency tables by treatment.

- **Follow-Up Therapy**

  Follow-up cancer therapy will be summarized by treatment as patients with number of regimens (0, 1, 2, ≥3), and patients with particular agents.

8.2.6. Analyses of Pharmacokinetic and Pharmacodynamic

8.2.6.1. Palbociclib

PK samples for palbociclib determination will be collected on Day 13 of Cycle 1 when palbociclib is given in combination with nab-paclitaxel 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 $AUC_{ss,\tau}$), and apparent clearance (CL/F) for palbociclib will be estimated using non-compartmental analysis. The effect of nab-paclitaxel 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.

8.2.6.2. Nab-Paclitaxel

PK samples for total paclitaxel determination will be collected on Days -2 to 1 when nab-paclitaxelis given alone and on Days 13-15 when nab-paclitaxel is given in combination with multiple doses of palbociclib. Plasma PK parameters including maximum plasma concentration (C_{max}), time for Cmax (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-paclitaxel in combination with palbociclib/nab-paclitaxel alone) and 90% CIs for the ratios (AUC_{inf} and C_{max}).

8.2.6.3. Analysis of Pharmacokinetic endpoints

For both palbociclib and nab-paclitaxel 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-paclitaxel given in combination with palbociclib vs. nab-paclitaxel given alone) will also be provided.

For patients who had dose reduction during the treatment and PK samples were collected after dose reduction, dose normalized concentrations and PK parameters for these patients may be generated and used for the analysis.

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.

8.2.6.4. 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.

The relationship between palbociclib exposure and PD endpoint(s), such as p-Rb1, and CC
activity will be explored if data permit.

8.2.7. Analyses 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 in tumor tissue at baseline, the relationship of the biomarkers (individually) with PFS and OS will be explored using graphical methods such as box plots, at baseline. A sensitivity analysis of p16 (absent vs. any staining intensity level) vs PFS will be performed both graphically (box plots) and summary statistics/analysis, such as p16 as a covariate in a Cox model. Receiver Operating Characteristic (ROC) curve analysis will be

performed using the baseline biomarkers as predictors of PFS and OS; the area under the curve (AUC) will be calculated. Curves will be produced for median PFS and OS times, along with 4 months before median, 2 months before median, 2 months after median and 4 months after median. If increasing values of the biomarker lead to better PFS/OS response, the actual value of the biomarker will be used in the ROC analysis. If increasing values of the biomarker lead to worse PFS/OS response, the ROC analysis will use the inverse of the biomarker value with 1/0 being set to 0. The biomarker value which produces the maximal sensitivity/1-specificity point will be identified for each curve.

CCI [redacted]

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 [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

8.2.8.4 Time-to-event endpoints

Time to deterioration (TTD) in Global QOL is defined as the time from randomization to the first time the patient's score shows a 10-point or higher decrease in the global QOL subscale score of the QLQ-C30. Patients who do not have a TTD event up to the time of progression will be censored on the date when they last completed the PRO assessment or at end of treatment, if that occurs prior to progression.

Kaplan-Meier estimates will be presented together with a summary of associated statistics including the median TTD time with 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley.

8.3. Summary of Key Clinical Efficacy Analyses

Type of Analysis	Endpoint	Analysis Set	Statistical Method
Secondary	ORR, CBR	Evaluable (All, MTD expansion, MTD arm + MTD expansion), Investigator assessments (See 8.2.4.)	Exact CI based on Clopper-Pearson method (95% CI)
Secondary	DR	Evaluable (All, MTD expansion, MTD arm + MTD expansion), patients with a CR or PR Investigator assessments (See 8.2.4.)	K-M method (median and 95% CI)
Secondary	PFS	Safety analysis set (All, MTD expansion, MTD arm + MTD expansion), Investigator assessment (See 8.2.4.)	K-M method (median and 95% CI)
Secondary	OS	Safety analysis set (All, MTD expansion, MTD arm + MTD expansion) (See 8.2.4.)	K-M method (median and 95% CI)

Abbreviations:
Evaluable: Per Protocol Analysis Set Evaluable for Anti-tumor Activities; MTD expansion cohort is a subset of Evaluable.
DR: duration of response; OR: objective response; OS: overall survival; PFS: progression-free survival.

9. REFERENCES

1. Brookmeyer R, Crowley JJ. A confidence interval for the median survival time. Biometrics 1982; 38:29-41.
2. Cox DR. Regression models and life-tables (with discussion). Journal of the Royal Statistical Society, Series B 1972; 34:187-220.
3. Eisenhauer E, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: Revised RECIST guideline version 1.1. Eur J Can 45: 228-47, 2009.
4. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457-481.
5. ICH Harmonised Tripartite Guideline. The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. E 14. May 12, 2005.
6. National Cancer Institute (NCI). Common Terminology Criteria For Adverse Events (CTCAE). http://evs.nci.nih.gov/ftp1/CTCAE/About.html
7. Sprangers MAG, Groenvold M, Arraras JL, et. Al. The European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality-of-Life Questionnaire Module: First Results From a Three-Country Field Study. J Clin Oncol 1996; 14(10): 2756-2768.
8. 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.
9. Dykstra R, Robertson T. An algorithm for isotonic regression for two or more independent variables. *Ann Stat.* 1982; 10:708-716.

10. APPENDICES

10.1. Criteria for Dose Escalation

Dose escalation will start from DL 1. The sequential dose escalation scheme and the rules for determining dose escalation, de-escalation, or 'stay' (i.e. 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 DL1:

- 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 DL 2B will be expanded to 9 patients, unless already done, in order to determine the MTD.
- If no dose escalation is determined at DL 2A and DL 2B, then no further dose escalation will be performed and DL 1 will be re-evaluated (expanded up 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 re-evaluated (expanded up 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 DL 3A or DL 3B will be expanded to 9 patients, unless already done, in order to determine the MTD.
- 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 re-evaluated (expanded up 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 re-evaluated (expanded up 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 re-evaluated (expanded up to 9 patients, unless already done, in order to enable a dose escalation or de-escalation decision).

If dose escalation to DL 4:

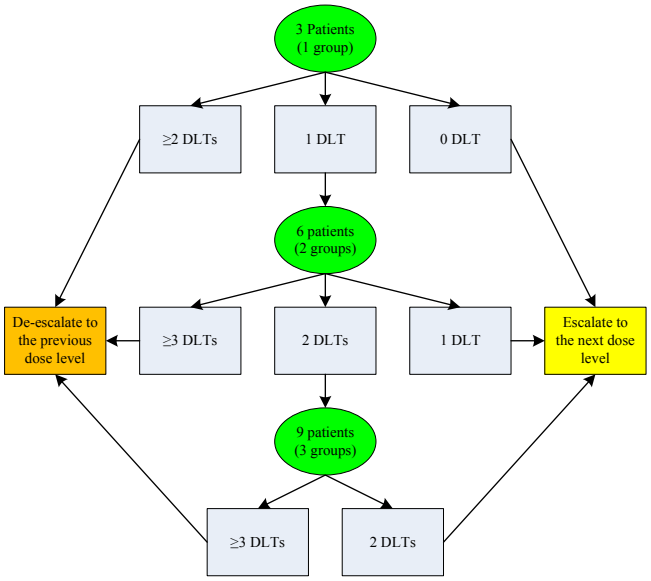
- Dose escalation will be stopped at this DL.
- If dose de-escalation is recommended after DL 4, then DL 3A and DL 3B will be re-evaluated (expanded up to 9 patients, unless already done, in order to enable a dose escalation or de-escalation decision; the order of the evaluation will be determined based 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 (expanded up to 9 patients, unless already done, in order to enable a dose escalation or de-escalation decision).
- 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 10.1 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 Figures 10.2 -10.5.

Figure 10.1 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 either escalate, de-escalate, or stay. Table 8.1 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 (i.e. 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 (i.e. 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 8.1);
- 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 MTD dose expansion cohort(s), taking into account the MTD(s) from the dose-escalation component, and other factors related to safety, efficacy, and PK/PD involving all available data from all tested DLs.

Figure 10.2 Dose de-escalation scheme to a previous dose level where 3 patients have been treated with 0 DLT

Figure 10.3 Dose de-escalation scheme to a previous dose level where 6 patients have been treated with ≤1 DLT

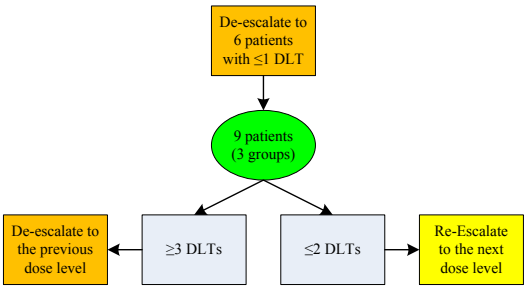
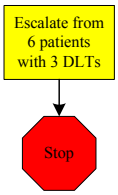


Figure 10.4 Dose re-escalation scheme from a previous dose level where 3 patients have been treated with 2 DLTs

Figure 10.5 Dose re-escalation scheme from a previous dose level where 6 patients have been treated with 3 DLTs



10.2. 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.

- 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)
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper
- 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, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical examination 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 (e.g. '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 (e.g., 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 10.4. 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 10.5. 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

BOR Based on Confirmed Responses

CR: Two objective statuses of CR a minimum of four weeks apart documented before progression and start of new anti-cancer therapy.

PR: Two objective statuses of PR or better (PR followed by PR or PR followed by CR) a minimum of four weeks apart documented before progression and start of new anti-cancer therapy, but not qualifying as CR. Sequences of PR- Stable- PR are considered PRs as long as the two PR responses are observed at a minimum of 4 weeks apart.

SD: At least one objective status of stable or better documented at least 6 weeks after start date and before progression and the start of new anti-cancer therapy but not qualifying as CR or PR.

PD: Progression documented within 18 weeks after start date and not qualifying as CR, PR or SD.

Not Evaluable (NE): All other cases. Note that reasons for NE should be summarized and the following reasons could be used:

- Early death (*Note: death < 6 weeks after start date)*
- No post-baseline assessments
- All post-baseline assessments have overall response NE
- New anti-cancer therapy started before first post-baseline assessment
- SD too early (<6 weeks after start date)
- PD too late (>18 weeks after start date)

Special and rare cases where BOR is NE due to both early SD and late PD will be classified as 'SD too early'.

An objective status of PR or SD cannot follow one of CR. SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds. If this occurs the sequence PR-SD-PR is considered a confirmed PR. A sequence of PR – SD – SD – PD would be a best response of SD if the window for SD definition has been met.

The **overall response rate** (ORR) is defined as the percentage of patients with a best overall response of CR or PR relative to the appropriate analysis set.

10.3. Rules for Determining PFS Status and Date

Situation	Date of Progression/Censoring[1]	Outcome
Inadequate baseline assessment	First dose date (Day 1)[2]	Censored
No on-study assessments	First dose date (Day 1) [2]	Censored
Alive and no Progression	Date of last objective tumor assessment documenting no progression	Censored
Progression Documented on or between scheduled tumor assessments	Date of first objective tumor assessment documenting objective progression	Progressed (Event)
Patients are removed from the study (withdrew the consent, lost to follow up, etc.) prior to progression or death	Date of last objective tumor assessment documenting no progression	Censored
New anticancer treatment prior to progression or death	Date of last objective tumor assessment documenting no progression prior to new anticancer treatment	Censored
Death prior to first planned tumor assessment	Date of death	Death (Event)
Death without objective progression prior to treatment discontinuation[2]	Date of death	Death (Event)
Death or progression after 2 or more missed tumor assessments	Date of last objective tumor assessment documenting no progression prior to the event	Censored

[1] For date of censorship, if a tumor assessment takes place over a number of days (e.g., superficial lesions one day, scans another), the first date is used as PD date and the last date is used as the other assessment date.
[1] First dose date is defined as the first Palbociclib dose date

10.4. Data Derivation Details

Enrollment	Date of assignment of the randomization number
Study Day 1	First dose day
Treatment-Palbociclib start	Day 1 of Cycle 1
Treatment-nab-P start	Day -2 of Cycle 1
Day 1 (cycle start date) of Cycle x	Day 1 of a cycle is every 28 days unless there is a dosing delay.
Cycle length (all but final cycle)	Cycle length is 28 days (previous cycle length may exceed planned length if there is a delay in study treatment administration).
Final cycle	For patients off treatment, from Day 1 of final cycle to 28 days after final dose or until start of new anticancer treatment (whichever comes first). For patients on treatment, from Day 1 of most recent cycle start to protocol specified cycle length.
Follow-up Period for AEs	From 28 days after final dose until start of new anticancer treatment (whichever comes first).
Baseline lab values	From date closest to, but prior to, start of study treatment.
Baseline triplicate ECGs	Cycle 1 Day -2 dose date or from date closest to, but prior to, start of any of study treatments if C1D-2 is not available.
Tumor assessment baseline values	From date closest but prior to first dose.
Adequate baseline tumor assessment	Within 35 (28 + 7) days prior to first dose. Maximum diameter reported for each target lesion listed. All required pre-treatment scans done.
Cycle k treatment delayed.	If study treatment administration is delayed for cycle k then cycle k-1 is extended.

10.5. Study Treatment Modification and Compliance

10.5.1. Dose Modification

In the event of significant treatment-related toxicity, palbociclib and/or nab-paclitaxel dosing may be interrupted or delayed and/or reduced as described below. 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 may occur in three ways:

- Within a cycle: **dosing interruption** until adequate recovery and **dose reduction**, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be **delayed** due to persisting toxicity when a new cycle is due to start;
- In the next cycle: **dose reduction** may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

10.5.2. Summarizing Relative Dose (RD) and Relative Dose Intensity (RDI)

The following types of summaries are proposed for administration of palbociclib and nab-paclitaxel.

When palbociclib is administered orally once a day for 21 days of every 28-day cycle followed by 7 days off treatment (cyclical dosing) in combination with nab-paclitaxel (IV, D1, D8, D15), the following summaries can be presented:

- RDI for palbociclib: by Cycle and Overall
- RDI for nab-paclitaxel: by Cycle and Overall

When palbociclib is administered orally daily in combination with nab-paclitaxel (IV, D1, D15) and uses 28 days as a cycle definition, the following summaries can be presented:

- RDI for palbociclib: by Cycle and Overall
- RDI for nab-paclitaxel: by Cycle and Overall

Note: the denominator for tables summarizing “nab-paclitaxel” will be all patients who received at least one dose of nab-paclitaxel and for tables summarizing “palbociclib” will be all patients who took at least one dose of palbociclib.

Examples for the summaries described in above are included in the tables below.

Conventions:

- The Intended Daily Dose is the same for all cycles: the daily dose is fixed at the start of treatment rather than start of a cycle and the intended treatment duration is the same for

the entire dosing period (e.g. for a 3/1 dosing schedule, all non-last cycles have an intended duration of 4 weeks. The intended treatment duration for the last cycle is from the 1st dose date of the last cycle to the EOT date or duration of 4 weeks which is shorter);

- Actual Dose Intensity is calculated based on actual cycle length

Table 10.6 Cyclical Palbociclib By Cycle

Treatment / Summary Type	Calculation of RDI
Cyclical palbociclib (3/1) or continued/ By Cycle	
	$RDI = \frac{ActualDailyDoseIntensity}{IntendedDailyDose} * 100\ \%$ % Where: ***Intended Daily Dose*** (mg/day in 21/7 schedule or continued schedule) = 75, 100, 125 ***Actual Daily Dose Intensity*** (mg/day in 21/7 schedule) = Actual Average Daily Dose (mg/day in x/y schedule) * (Actual Dose Days / Intended Dose Days) * (Intended Cycle Duration / Actual Cycle Duration) • Actual Average Daily Dose (mg/day in x/y schedule) = Actual Total Dose / Actual Dose Days • Intended Dose Days = ❖ For 3/1 schedule: For non-last cycle: 21 For last cycle: minimum (21, (Decision date of stopping trt from EOT page -1st dose date in last cycle +1)) ❖ For continued schedule: For non-last cycle: 28 For last cycle: minimum (28, (Decision date of stopping trt from EOT page -1st dose date in last cycle+1)) • Intended Cycle Duration = For non-last cycle: 28 For last cycle: minimum (28, (Decision date of stopping trt from EOT page -1st dose date in last cycle+1)) • Actual Cycle Duration for last cycle = o For non-last cycle: Next cycle's Day 1 date – Current cycle's Day 1 date o For last cycle: (Min [Decision date of stopping trt from EOT page, EOS date] - 1st dose date in last cycle +1)

Table 10.7 Cyclical Palbociclib Overall

Treatment / Summary Type	Calculation of RD/RDI
Cyclical palbociclib / Overall	$RDI = \frac{ActualDailyDoseIntensity}{IntendedDailyDose} * 100\,\%$ % Where: ***Intended Daily Dose*** (mg/day in 21/7 schedule or continued schedule) = 75, 100, 125 ***Actual Daily Dose Intensity*** (mg/day in 21/7 schedule or continued schedule) = Actual Average Daily Dose (mg/day in x/y schedule) * (Actual Dose Days / Intended Dose Days) * (Intended Cycle Duration / Actual Cycle Duration) • Actual Average Daily Dose (mg/day in x/y schedule) = Sum over all cycles of "Actual Total Dose" / Sum over all cycles of "Actual Dose Days" • Actual Dose Days = Sum over all cycles of "Actual Dose Days" • Intended Dose Days = Sum over all cycles of "Intended Dose Days" • Actual Cycle Duration = Sum over all cycles of "Actual Cycle Duration" • Intended Cycle Duration = Sum over all cycles of "Intended Cycle Duration"

Table 10.8 Nab-paclitaxel by Cycle and Overall

Treatment (Schedule) / Summary Type	Calculation of Relative Dose Intensity (RDI)
Nab-P (3/1 or Biweekly) / By Cycle	$RDI = \frac{ActualDoseIntensity}{IntendedAverageDose} * 100\%$ % Where: ***Intended Average Dose*** (mg/Q7d) = $\begin{cases} 100 & \text{for DL1, DL2A, DL3A, MDR2} \\ 125 & \text{for DL2B, DL3B, DL4, MDR1} \\ \textit{same as their original dose cohort} & \textit{on the MTD or MDR Expansion} \end{cases}$ ***Actual Dose Intensity*** (mg/Q7d in planned schedule) = Actual Average Dose each time (mg/Qxd) in the Cycle * (Actual Freq in the Cycle/ Intended Freq in the Cycle) * (Intended Cycle Duration/ Actual Cycle Duration) • *Factor in dose reductions or potential overdose:* Actual Average Dose each time (mg/Qxd) in the Cycle = Actual Total Dose in the Cycle / Actual Freq in the Cycle • *Factor in dose interruptions:* Actual freq on Drug / Intended Freq on Drug • *Factor in cycle delays:* Intended Cycle Duration / Actual Cycle Duration • Intended Freq on Drug in each Cycle $\begin{cases} 2 & \text{for non-last Cycle in MDR1, MDR2, MDR Expansion} \\ 3 & \text{for non-last cycle in DL1, DL2A, DL2B, DL3A, DL3B, DL4, MTD, MTD Expansion} \\ 1 & \text{for last Cycle and its actual cycle duration} \leq 14 \text{ in MDR1, MDR2, MDR Expansion} \\ 2 & \text{for last Cycle and its actual cycle duration} > 14 \text{ in MDR1, MDR2, MDR Expansion} \\ 1 & \text{for last cycle and actual cycle duration} \leq 5 \text{ in DL1, DL2A, DL2B, DL3A, DL3B, DL4, MTD, MTD Expansion} \\ 2 & \text{for last cycle and actual cycle duration} \leq 10 \text{ in DL1, DL2A, DL2B, DL3A, DL3B, DL4, MTD, MTD Expansion} \\ 3 & \text{for last cycle and actual cycle duration} \leq 17 \text{ in DL1, DL2A, DL2B, DL3A, DL3B, DL4, MTD, MTD Expansion} \end{cases}$ • Intended Cycle Duration = $\begin{cases} 28 & \text{for non-last cycle} \\ \min(28, \text{Actual last Cycle Duration}) & \text{for last cycle} \end{cases}$ • Actual Cycle Duration =

	$\begin{cases} \text{(Day 1 of next cycle - Day 1 of of current cycle)} & \text{for non-last cycle} \\ \text{max(nabP EOT date, NabP last dose date from dose page)} - \text{1st day of the last cycle} + 1 & \text{for last cycle} \end{cases}$

Nab-P (3/1 or Biweekly) / Overall	$RDI = \frac{ActualDoseIntensity}{IntendedAverageDose} * 100\%$ % Where: ***Intended Average Dose*** (mg/Q7d) = $\begin{cases} 100 & \text{for DL1, DL2A, DL3A, MDR2} \\ 125 & \text{for DL2B, DL3B, DL4, MDR1} \\ \textit{same as their original dose cohort} & \textit{on the MTD or MDR Expansion} \end{cases}$ ***Actual Dose Intensity*** (mg/Q7d in planned schedule) = Actual Average Dose each time (mg/Qxd) * (Actual Freq in the Cycle/ Overall Intended Freq) * (Intended Total Cycle Duration/ Overall Actual Cycle Duration) • *Factor in dose reductions or potential overdose:* Actual Average Dose each time (mg/Qxd) = Actual Total Dose / Actual Total Freq on Drug • *Factor in dose interruptions:* Actual Total Freq on Drug / Intended Total Freq on Drug • *Factor in cycle delays:* Intended Total Cycle Duration / Actual Total Cycle Duration • Intended Total Freq on Drug: **For MDR1, MDR2, MDR Expansion Expansion:** = 2*(total of non-last cycle) + (1 or 2 for last cycle based on following situation) 1 for last Cycle and its actual cycle duration ≤ 14 2 for last Cycle and its actual cycle duration > 14 **For DL1, DL2A, DL2B, DL3A, DL3B, DL4, MTD, MTD Expansion:** = 3*(total of non-last cycle) + (1 or 2 or 3 for last cycle based on following situation) 1 for last cycle and actual cycle duration ≤ 5 2 for last cycle and actual cycle duration ≤10 3 for last cycle and actual cycle duration ≤ 17 • Intended Total Cycle Duration = {28*(total of non-last cycle) + min(28, Actual last Cycle Duration) • Actual Total Cycle Duration: max(decision date on stopping NabP from EOT page, NabP last dose date+6) – Day 1 of Cycle 1 +1

10.6. 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

[redacted]

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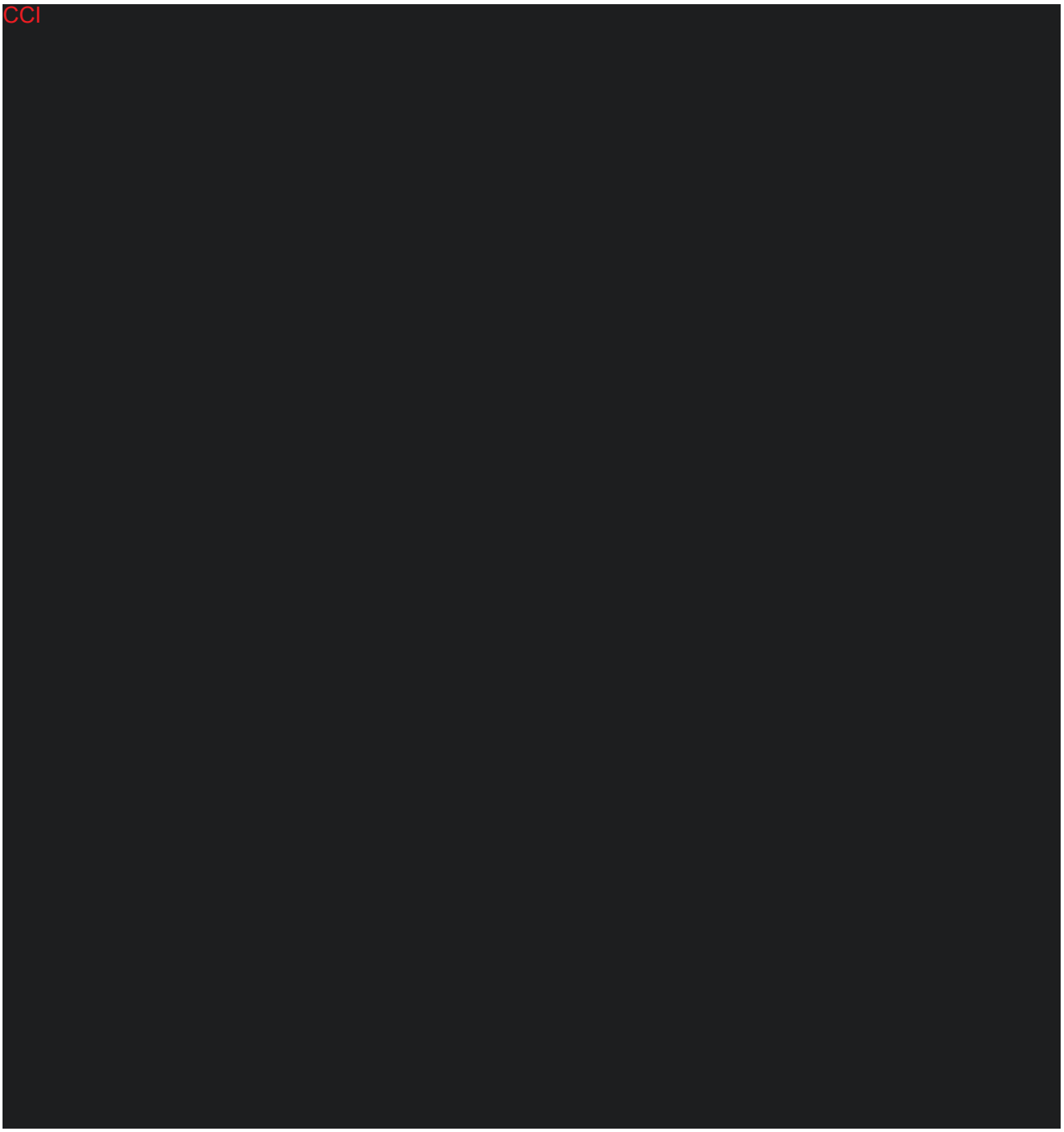

10.9. List of Abbreviation

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	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
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)

eg	for example
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
G-CSF	granulocyte-colony stimulation factor
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high-density polyethylene
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
MD	multiple dose
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

NGS	Next Generation Sequencing
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
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
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SIB	suicidal ideation and behavior
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
WBC	white blood cell