PALBOBIN Statistical Analysis Plan

Phase IB Clinical trial of palbociclib and binimetinib in advanced triple negative breast cancer with hyperactivation of ERK and/or CDK4/6.

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"Phase IB Clinical trial of palbociclib and binimetinib in advanced triple negative breast cancer with hyperactivation or ERK and/or CDK4/6"

PALBOBIN Study

APICES Project No. ONC227009

Statistical Analysis Plan

(Final analysis)

Version 1.0

January 8th, 2024

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1. HISTORY OF REVISION (Documentation of changes)

SECTIONS	VERSION	DATE REVISED	REVISED BY	DESCRIPTION OF CHANGES

INDEX

2. INTRODUCTION

This statistical analysis plan (SAP) describes the planned analysis for PALBOBIN study. In it is described all consideration over study data and are defined the tables, figures and listing (TLFs) that will be presented as result of the study.

Additionally includes definition of the different population and missing data consideration.

The statistical analysis plan will be signed and per protocol dataset will be defined before database lock.

Table of abbreviations

95% CI	95% confident interval
AEs	Adverse events
AESI	Adverse events of special interest
BID	"Bis in die" twice a day
CR	Complete response
CTC AE	Common terminology criteria for adverse events
HIV	Human immunodeficiency virus
MedDRA	Medical dictionary for regulatory activities
ORR	Overall response rate
PD	Progression disease
PFS	Progression-free survival
PR	Partial response
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
TNBC	Triple negative breast cancer

3. SYNOPSIS

3.1. Study title

"Phase IB Clinical trial of palbociclib and binimetinib in advanced triple negative breast cancer with hyperactivation or ERK and/or CDK4/6"

3.2. Study Code

PALBOBIN.

3.3. Protocol Version and Amendments

Previous protocol versions / amendments (number and date):

- Version 1.0, 14/Jul/2020
- Version 2.0, 07/Sep/2020

Current version (number and date):

- Version 3.0, 16/Jun/2021

3.4. Sponsor

Fundación OncoSur

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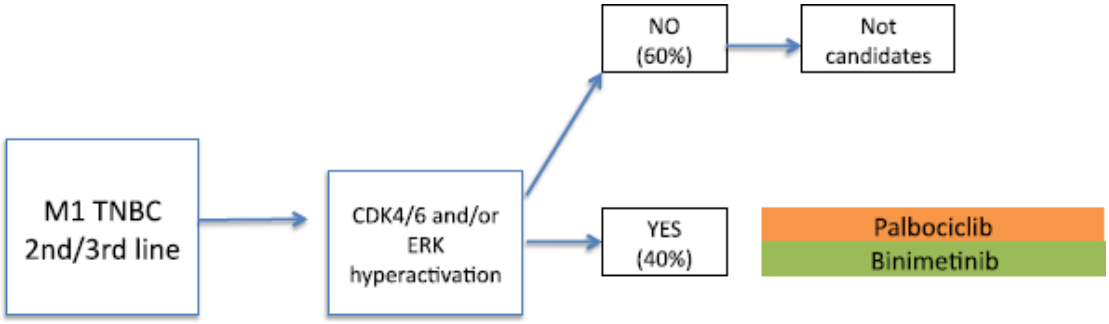
3.5. Design

This is an interventional, prospective, multicentric, single-arm, open label, phase IB clinical trial. The following scheme depicts the basic trial design.



Patients diagnosed of metastatic or locally advanced non-curable TNBC that have received one or two treatment regimens for advanced disease will be candidates for the trial.

3.6. Objectives

Primary objective:

Primary objective of this study is to determine the 3-months PFS of palbociclib plus binimetinib in advanced triple negative breast cancer (TNBC), in patients with activation of ERK and/or CDK4/6.

Secondary objectives:

- To determine response rate of the combination in advanced TNBC, in patients with activation of ERK and/or CDK4/6.
- CCI [redacted]
- To assess the safety of the combination in patients with advanced TNBC.

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3.7. Total number of subjects

It is expected to include 25 patients in this trial. Patients diagnosed of metastatic or locally advanced non-curable TNBC that have received one or two treatment regimens for advanced disease will be included in this study.

3.8. Inclusion Criteria

1. Women >18 years-old.
2. Diagnostic of metastatic or locally advanced non-resectable TNBC.
3. Patient must have received a minimum of one and a maximum of two treatment lines for metastatic TNBC. Previous treatments can be of any nature (chemotherapy, immunotherapy, antiangiogenics, experimental therapy, etc.).
   Women with known BRCA1/BRCA2 germline mutations must have received a platinum-based treatment or treatment with a PARP inhibitor.
4. Patient must have experienced disease progression to the previous treatment line according to the RECIST 1.1 or iRECIST criteria.
5. Availability of tumor tissue for ERK and CDK4/6 testing is mandatory prior to study inclusion, preferably obtained after last treatment or the most recent sample as possible (from metastatic site or first diagnosis according to sample availability). If the patient has not a tumor sample available prior to study inclusion, the patient will not be allowed to participate in the study.
6. Ability to understand and signing of the written patient information/informed consent form (PIS/ICF) for ERK and CDK4/6 testing. ERK and CDK4/6 testing will be performed centrally at CNIO.
7. Ability to understand and signing the written PIS/ICF for study treatment eligibility. Signed informed consent form must be available before any study-specific procedure for the respective study parts may begin.
8. Positivity for ERK and/or CDK4/6, defined as showing an H-score above the top-quartile according to published definitions.
9. ECOG performance status of 0-1.
10. Evaluable disease according to RECIST 1.1 criteria.
11. Life expectancy >24 weeks.
12. Adequate bone marrow, liver and renal function as assessed by laboratory requirements conducted within 7 days before first study drug administration:
    a. Absolute neutrophil count (ANC) ≥ 1.500/mm3 (without granulocyte colony-stimulating factor support within 2 weeks before the first study drug administration).
    b. Hemoglobin ≥ 9 g/dL (without transfusion or erythropoietin within 4 weeks before the first study drug administration).
    c. Platelet count ≥ 100.000/mm3 (without transfusion within 2 weeks before the first study drug administration).

d. Total bilirubin ≤ 2 × the upper limit of normal (ULN).
e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN (≤ 5 times ULN for patients with liver metastases).
f. Glomerular filtration rate (GFR) > 50 mL/min/1.73 m2 according to the modification of diet in renal disease (MDRD) abbreviated formula.

13. Patients must have recovered to ≤ Grade 1 in terms of toxicity from prior treatments (excluding neuropathy which can be ≤ Grade 2, and alopecia).
14. Patients must be able to take oral medications.
15. Patients must have adequate cardiac function, defined as:
    a. Left ventricular ejection fraction (LVEF) > 50% as determined by echocardiogram or multigated acquisition scan (MUGA).
    b. QTc < 480 msec.
16. Negative serum pregnancy test in women of childbearing potential (performed within 7 days before the first treatment). Negative results must be available before the first study drug administration.

    A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

    Pregnancy test will not be performed in postmenopausal women.
17. Women of reproductive potential must agree to use adequate contraception when sexually active. This applies for the time period since the signature of the informed consent form and until at least 1 month after the last study drug administration. The definition of adequate contraception will be based on the judgment of the investigator and on local requirements. Acceptable methods of contraception include, but are not limited to, (i) condoms (male or female) with or without a spermicidal agent; (ii) diaphragm or cervical cap with spermicide; (iii) intra-uterine device; (iv) hormone-based contraception.

    Zoledronic acid or denosumab started prior to trial registration is allowed, but in case they are required after initiation of trial procedures, adequate justification is required.

3.9. Exclusion Criteria

1. Participants who have had chemotherapy, radiotherapy, or major surgery within 2 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study.
2. Patients that received during the metastatic disease setting any of the study drugs, palbociclib or binimetinib.
3. Participants receiving any other study agents concurrently with the study drugs. Zoledronic acid or denosumab for bone metastases, started at least 15 days prior to enrollment are allowed.
4. Participants with symptomatic brain metastases that require chronic steroids. Patients with a history of brain metastases are permitted to enroll as long as they have been treated, are off of steroids, and have been stable for a minimum of one month on imaging.
5. Irradiation of single lesions in the last 28 days prior to trial recruitment, if it is the only location of the disease and it has not progressed. Patients with radiated single lesions that has progressed are allowed.
6. Concurrent use of strong CYP3A4 inhibitors/inducers is prohibited due to drug-drug interactions with palbociclib. Moderate CYP3A4 inhibitors/inducers should be used with caution.
7. Uncontrolled intercurrent illness including, but not limited to:
    a. ongoing or active infection requiring systemic treatment.
    b. symptomatic congestive heart failure.
    c. cardiac arrhythmia.
    d. psychiatric illness/social situations that would limit compliance with study requirements.
    e. hypertension, defined as systolic blood pressure > 160 mmHg despite medical management.
    f. myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting < 6 months prior to screening.
8. History of QT syndrome, Brugada syndrome, known history of QTc prolongation, or Torsades de Pointes.
9. History of Gilbert's syndrome.
10. History of neuromuscular disorders that are associated with elevated CK (e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).
11. Previous or concurrent cancer except:
    a. cervical carcinoma in situ.

b. treated basal-cell carcinoma or squamous cell skin cancer.
c. any other cancer curatively treated > 3 years before the first study drug administration.

12. Malabsorption syndrome or uncontrolled nausea, vomiting, or diarrhea that may interfere with the absorption of oral study medication in the opinion of the investigator.
13. Pregnant women or breast-feeding.
14. Known HIV-positive individuals on combination antiretroviral therapy.
15. Active hepatitis B virus (HBV; chronic or acute; defined as having a known positive hepatitis B surface antigen [HBsAg] test at the time of screening) or hepatitis C infection requiring treatment.
    a. Patients with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible if HBV DNA is negative.
    b. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
16. Any condition that in the opinion of the investigator would interfere with evaluation of study treatment or interpretation of patient safety or study results, or inability to comply with the study and follow-up procedures.
17. Participation in another clinical study with investigational medicinal products within 4 weeks before the first study drug administration.
18. Clinically active infections within 2 weeks before the first study drug administration.
19. Treatment with therapeutic oral or i.v. antibiotics within 2 weeks before the first study drug administration. Patients receiving prophylactic antibiotics (e.g. for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible.
20. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation.
21. Current diagnosis of any retinal disorders including retinal detachment, retinal pigment epithelial detachment (RPED), serous retinopathy or retinal vein occlusion or risk factors for RVO (e.g., uncontrolled glaucoma or history of hyperviscosity or hypercoagulability syndrome).
22. Peripheral sensory neuropathy of CTCAE v.5.0 Grade 2 or higher.
23. Major surgery, open biopsy or significant traumatic injury within 4 weeks before the first study drug administration (central line surgery is not considered major surgery).
24. Renal failure requiring peritoneal dialysis or hemodialysis.

25. Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results.

3.10. Study treatment

Patients will then start treatment with continuous oral binimetinib 45 mg/BID and palbociclib 100 mg daily, 21 days on / 7days off, until disease progression. Study treatment will continue until disease progression, unacceptable toxicity, intercurrent serious disease, consent withdrawal or investigator´s decision.

4. GENERAL CONSIDERATIONS

The statistical analysis will be performed using SPSS software vs 26.

Data will be generally provided with one decimal. In those cases that a greater accuracy is required, as much decimals as needed will be provided.

Adverse events will be codified using MedDRA dictionary (latest version available).

Continuous variables will be described by mean, median, standard deviation, minimum, maximum, Q1 and Q3. Categorical variables will be shown as distribution of frequencies and percentage

All available efficacy and safety data will be included in data listings and tabulations. No imputation of values for missing data will be performed unless otherwise stated. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

5. STUDY POPULATIONS

5.1. Definition of study populations to analyze

The following describes the different populations that will be used in the analyses process:

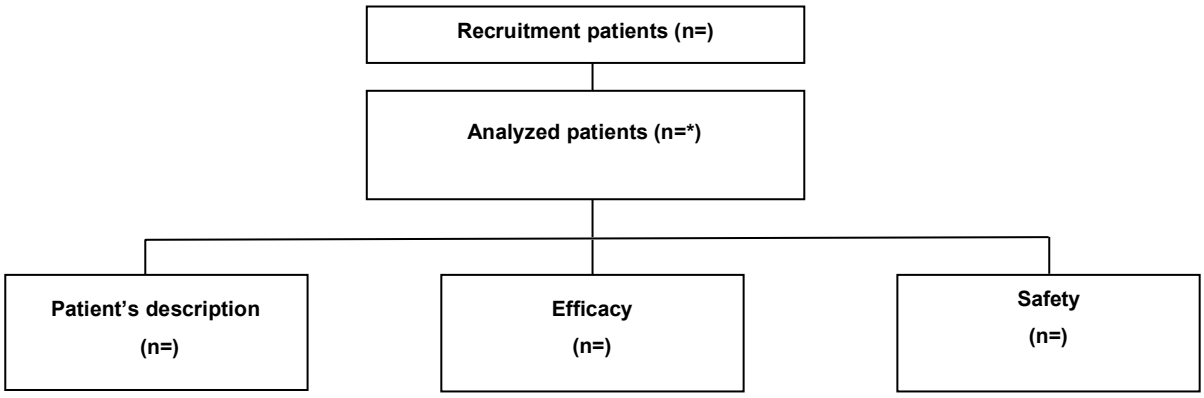
- **Efficacy population:** consists of all patients included in this study that received at least one dose of study treatment and have at least one evaluation visit after received the first dose of treatment. The efficacy population will be the basis for the primary endpoint analysis in this study. This will also be the patient population used for the analysis of the secondary endpoints.
- **Safety population**: consists of all patients who received at least one dose of the study treatment and had at least one valid post baseline safety assessment.

5.2. Study recruitment period

The date of informed consent form for the first subject and the last subject included in the study will be provided.

5.3. Disposition of subjects

Figure 1: Disposition of subjects



*Discrepancies between the number of analysed patients and number of recruitment patients into the database will be described.

The frequency distribution and percentage of patients analysed will be provided by site.

5.4. Study Discontinuations

Number and percentage of patients who discontinued the study and their reasons will be described. Those patients who leave the study for reasons related to study medication will be described in detail.

5.5. Deaths

Number and percentage of patients who died during the study and their reasons will be provided per treatment group. Patients who have died due to adverse events or adverse reactions will be described in detail.

6. SUBJECT DESCRIPTION

6.1. Demographic and baseline description. General considerations

All demographics and baseline characteristics will be described for efficacy population.

6.2. Subject Characteristics

a) Demographics

The following variables will be described:

- Age, years (continuous).
- Ethnicity (categorical).

b) Baseline characteristics

The following variables will be described:

- Vital signs:
  - Weight (Kg) (continuous).
  - Height (cm) (continuous).
  - Systolic blood pressure (mmHg) (SBP) (continuous).
  - Diastolic blood pressure (mmHg) (DBP) (continuous).
  - Pulse rate (b.p.m) (continuous).
  - Temperature (ºC) (continuous).
- 12-lead ECG (Done/not done) (categorical), if performed:
  - Result (Normal/ abnormal not clinically significant / abnormal clinically significant).
- ECO/MUGA (Done/not done) (categorical), if performed:
  - Result (Normal/ abnormal not clinically significant / abnormal clinically significant).

- Hepatitis B surface antigen (Positive / Negative / Not done) (categorical).
- Hepatitis C antibody (Positive / Negative / Not done) (categorical).
- HIV (Positive / Negative / Not done) (categorical).

c) Cancer history

The following variables will be described:

- Performance status at screening (ECOG-PS) (categorical).
- Time from initial diagnosis, defined as the elapsed time in months between the initial diagnose date to informed consent date (continuous).
- TNM & Stage at initial diagnosis (categorical).
- Current disease status (Advanced/Metastatic) (categorical).
- Time from advanced/metastatic disease, defined as the elapsed time, in months, between the advanced/metastatic disease date to informed consent date (continuous).
- Histology (categorical).
- Histologic grade (differentiation): GX: Grade cannot be assessed, G1: Well differentiated (Low grade), G2: Moderately differentiated (Intermediate grade), G3: Poorly differentiated (High grade), G4: Undifferentiated (High grade), Not Available (differentiation) (categorical).
- Actual TNM & Stage (categorical).
- Breast cancer previous treatments:
    - Previous surgeries (Yes/No) (categorical), if affirmative: surgery description by patient (categorical).
    - Previous chemotherapy-based treatment (Yes/No) (categorical), if affirmative:
        - Localized disease chemotherapy (Yes/No) (categorical), if affirmative: chemotherapy scheme by patient (categorical).
        - Metastatic disease chemotherapy (Yes/No) (categorical) , if affirmative: chemotherapy scheme by patient (categorical).
    - Previous radiotherapy (as primary therapy) (Yes/No).
    - Previous hormonal therapy (Yes/No) if affirmative: hormonal treatment by patient (categorical).
    - Previous immunotherapy (Yes/No) if affirmative: immunotherapy treatment by patient (categorical).
    - Other previous treatments (Yes/No) if affirmative: treatment by patient (categorical).

d) Baseline lesions:

The analysis of target and non-target baseline lesions will be performed together.

It will be considered affected location when the patient presents at least one lesion in one organ or system, regardless of the number of lesions in the organ or system is more than one. It will be provided:

- The number and percentage of patients with each affected location (categorical).
- The number and percentage of patients by number of affected locations (categorical).

7. TREATMENT ADMINISTRATION

7.1. Treatment description. General considerations

The information related to treatment descriptions, dose intensity and subsequent treatments will be presented for the efficacy population defined in section 5.1..

7.2. Treatment administration

It will be considered as cycle administered when the patient receives at least one treatment dose. Number of cycles administered will be described as continuous variable.

The following data will be described for each drug (palbociclib and binimetinib):

- Treatment interruption (Yes, No): If affirmative:
  - Number and percentage of patients by the no. interruptions (Categorical).
  - Reason for interruption (Categorical).
  - Total number of cycles interrupted and percentage regarding total cycles (Categorical).

- Dose reductions (Yes, No): If affirmative:
  - Number and percentage of patients by the no. dose reduction (Categorical).
  - Reason for reduction (Categorical).

The exposure treatment time will be defined as the elapsed time, in months, between the date of first administered dose of study treatment (binimetinib or palbociclib) and the end of treatment date. For patients with treatment ongoing or without end of treatment date, the last administration date of any drug will be considered.

7.3. Dose intensity

Dose intensity will be defined as the total of each study drug received by the patient with respect to the exposure treatment time. The dose intensity will be described as mg/week.

The relative dose intensity will be defined as the total dose of each drug received by the patient in relation to the theoretical total dose that patient should had received per protocol.

The dose intensity and relative dose intensity will be evaluated as continuous variables.

8. EFFICACY ASSESSMENT

8.1. Efficacy Assessment; general considerations

Efficacy assessment will be performed for efficacy population defined in section 5.1.
Time-to-event variables will be analyzed according to the Kaplan-Meier method. Kaplan-Meier survival curves, median, 95% CI, number of events and censored and number of patients at risk will be presented.
The follow-up time is defined as the elapsed time, in months, between the date of first administered dose of study treatment (binimetinib or palbociclib) and the end of study date. For patients without end of study, the last follow-up date will be taken into account.
The *swimmer pool plot* will be provided displaying the follow-up time, the treatment exposure time and the moment of progression disease.

8.2. Primary efficacy endpoint. PFS

Progression-free survival (PFS) is defined as the elapsed time, in months, between the start of treatment until the documentation of disease progression (radiological RECIST v1.1 or clinical) or death due to any cause, whichever occurs first. For subjects who are alive and not present disease progression at the time of data cut-off for analysis, PFS will be censored at the last tumor assessment date, if no one tumor assessment date is available PFS will be censored at start of treatment date.

PFS will be analyzed according to the Kaplan-Meier method. Kaplan-Meier survival curves and the median estimation will be reported, along with associated 95% CI. In order to response to primary end point, PFS rate at 3 month will be estimated and the 95% CI will be reported. In addition, PFS rate at 1 year with 95% CI will be calculated.

In addition, PFS will be evaluated by mutation ERK and CDK4/6.

8.3. Secondary efficacy endpoints

- **Overall response rate (ORR)** per RECIST v1.1 as assessed by investigator. ORR is defined as the proportion of patients with an overall response of complete or partial response, as per local investigator´s assessment and according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 criteria. The table below provides a summary of the overall response calculation.

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

Counts and percentages of ORR will be reported, along with associated 95% confidence interval (CI).

In addition, the response rate and ORR will be provided by mutation ERK and/or CDK4/6.

A *waterfall plot* will be provided with the percentual change of tumoral change between baseline evaluation and the patient's evaluation with the best response tumor assessment. Additionally, a spider plot with the percent change of tumoral size respect baseline evaluation in each patient's evaluation performed will be provided.

9. SAFETY ASSESSMENT

9.1. Safety Assessment; general considerations

The assessment will be performed for safety population defined in section 5.1. Adverse events will be evaluated according to NCI CTCAE vs 5 criteria. Adverse events will be coded by the latest available version of MedDRA dictionary. AEs will be evaluated with the MedDRA code by system organ class (SOC) and preferred term (PT).

The analysis will be performed with the information completed into the adverse event eCRF section.

The analysis of adverse events will be performed per patient, for that the maximum grade for each adverse event completed of each patient will be calculated.

9.2. Adverse Events

All adverse events evaluated will be described. The analysis of AEs will be described the following:

- The number and percentage of patients with at least one adverse event.
- The number and percentage of patients with each adverse event by grades (1-5).

9.3. Adverse reactions

All adverse event indicated as related with any study treatment drug in the eCRF adverse event section will be considered. The analysis of toxicities will be provided:

- The number and percentage of patients with at least one toxicity.
- The number and percentage of patients with each toxicity by grade (1-5).

9.4. Serious Adverse Events (SAEs)

Serious adverse events listing will be provided the following information:

- Site
- Subject ID
- AE description
- PT Term
- Grade (1-5) NCI CTC AE v5
- Start date
- End date

- AESI (Yes/No)
- Action taken (None / Delay / Dose reduction / Dose interruption / Withdrawn / Not applicable / Unknown / Other)
- Relationship (Palbociclib / Binimetinib / Concomitant medication or procedure / Other / Not related)
- Seriousness criteria (Death / Life-threatening / Hospitalization / Prolonged hospitalization / Persistent or significant disability/incapacity / Congenital anomaly or birth defect / Medically important)
- Outcome (Recovered / Recovered with sequelae / Not recovered/ongoing / Death / unknown)
- DLT (Yes/No)

Serious adverse events analysis includes the following:

- The number and percentage of patients with at least one serious adverse.
- The number and percentage of patients with each serious adverse event by grade (1-5).

9.5. Adverse Events of Special Interest (AESI)

Serious adverse events listing will be provided the following information:

- Site
- Subject ID
- AE description
- PT Term
- Grade (1-5) NCI CTC AE v5
- Start date
- End date
- Serious (Yes/No)
- Action taken (None / Delay / Dose reduction / Dose interruption / Withdrawn / Not applicable / Unknown / Other)
- Relationship (Palbociclib / Binimetinib / Concomitant medication or procedure / Other / Not related)
- Seriousness criteria (Death / Life-threatening / Hospitalization / Prolonged hospitalization / Persistent or significant disability/incapacity / Congenital anomaly or birth defect / Medically important)

- Outcome (Recovered / Recovered with sequelae / Not recovered/ongoing / Death / unknown)
- DLT (Yes/No)

Serious adverse events analysis includes the following:

- The number and percentage of patients with at least one serious adverse.
- The number and percentage of patients with each serious adverse event by grade (1-5).