# PALBOBIN Clinical Study Protocol

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

## NCT: NCT04494958

## Version 3.0 – 16 June 2021

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

**COORDINATING INVESTIGATOR:** Dr Miguel Quintela Fandino
CNIO - Breast Cancer Unit

**PROTOCOL CODE**: PALBOBIN

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- Version 1.0, 14/Jul/2020

- Version 2.0, 07/Sep/2020

**Current version (number and date):**

- Version 3.0, 16/Jun/2021

# 1. PROTOCOL SUMMARY

## 1.1. Sponsor

Fundación OncoSur

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## 1.2. Study Title

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

## 1.3. Protocol code

PALBOBIN

### 1.4. Ethics Committee

CEIm Hospital 12 de Octubre

### 1.5. Company responsible of the monitoring

APICES

CCI [redacted]

### 1.6. Investigational product

Palbociclib and binimetinib

### 1.7. Phase

Phase IB

### 1.8. Trial 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.

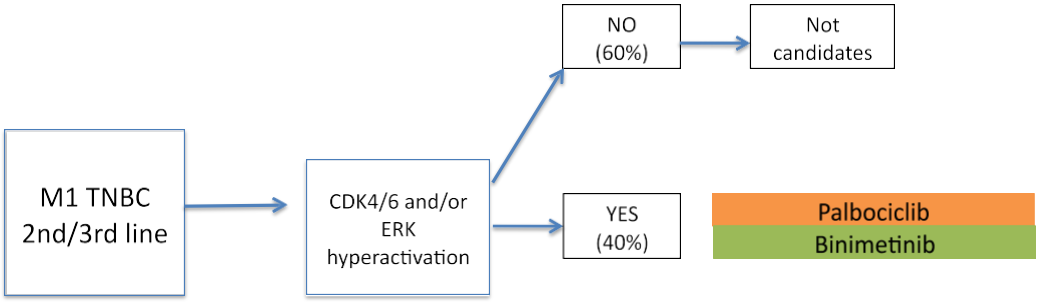
Exploratory objective:

- CCI [redacted]

## 1.9. Study 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. A fresh tumor sample will be obtained in order to determine the phosphoproteomic profile of the tumor, preferably obtained after last treatment or the most recent sample as possible (from metastasis or first diagnosis according to sample availability) prior to study inclusion. If the patient has not a tumor sample available prior to study inclusion, the patient will not be allowed to participate in the study. Activation of the two kinases of interest will be determined centrally at CNIO. Only patients with scores above the upper quartile of at least one of them will be candidates. It is expected that approximately 40% of patients are positive for CDK4/6 and/or ERK.

Patients will then start treatment with continuous oral binimetinib and palbociclib 21 days on / 7days off, until disease progression. Tumor evaluation will be performed every 8 weeks. Study treatment will continue until disease progression, unacceptable toxicity, intercurrent serious disease, consent withdrawal or investigator´s decision.

The study will be conducted at 8 Spanish sites and will enroll 25 patients.

## 1.10. Disease

Advanced triple negative breast cancer.

## 1.11. Study outcome measures

Primary outcome measure:

- Three-months PFS.

Secondary outcome measures:

- Overall response rate.
- CCI [redacted]
- Number of patients experiencing each AE will be summarized by CTCAE grade to evaluate safety profile, according to NCI-CTC v 5 criteria.

Exploratory outcome measures:

- CCI [redacted]

## 1.12. Study population and number of patients

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.

## 1.13. Selection criteria

### 1.13.1. 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 [1].
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) $\geq 1.500/mm^3$ (without granulocyte colony-stimulating factor support within 2 weeks before the first study drug administration)
    b. Hemoglobin $\geq 9$ g/dL (without transfusion or erythropoietin within 4 weeks before the first study drug administration)
    c. Platelet count $\geq 100.000/mm^3$ (without transfusion within 2 weeks before the first study drug administration)
    d. Total bilirubin $\leq 2 \times$ 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 $m^2$ 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.

### 1.13.2. 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.

## 1.14. Study calendar

First patient inclusion: 4Q 2020

Last patient inclusion: 4Q2021

Subject participation duration: 6 months + 6 months follow up Study duration: 32 months

# 2. TABLE OF CONTENTS

# 3. ABBREVIATIONS

| Abbreviation | Full terminology |
|---|---|
| AE | Adverse Event |
| AEMPS | Spanish Agency of Medicines and Medical Devices |
| AESI | Adverse Event of Special Interest |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| ANC | Absolut Neutrophil Count |
| aPTT | Activate Partial Thromboplastin Time |
| AST | Aspartate Aminotransferase |
| ATP | Adenosine triphosphate |
| BC | Breast cancer |
| BCRP | Breast cancer resistance protein |
| BID | Twice In Day |
| BUN | Blood Urea Nitrogen |
| CA | Competent Authority |
| CBR | Clinical Benefit Rate |
| CDK | Cyclin Dependent Kinase |
| CEIm | Medicinal Research Ethics Committee |
| CI | Confidence Interval |
| CK | Creatine kinase |
| CNIO | Centro Nacional de Investigaciones Oncológicas |
| CPK | Creatine phospokinase |

| Abbreviation | Full terminology |
|---|---|
| CR | Complete Response |
| CRA | Clinical Research Assistant |
| CRC | Colorectal cancer |
| CRF | Case Report Form |
| CRO | Clinical Research Organization |
| CSR | Central serous retinopathy |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | Cytochrome P |
| DLT | Dose-Limiting Toxicity |
| DNA | Deoxyribonucleic Acid |
| DUSP6 | Dual specificity phosphatase 6 |
| ECG | Electrocardiogram |
| ECHO | Echocardiogram |
| eCRF | Electronic Case Report Form |
| ECOG-PS | Eastern Cooperative Oncology Group-Performance Status |
| EDC | Electronic Data Capture |
| EGFR | Epidermal growth factor receptor |
| ER | Oestrogen Receptor |
| ERK | Extracellular Receptor Kinase |
| FFPE | Formalin fixed paraffin embedded |

| Abbreviation | Full terminology |
|---|---|
| GCP | Good Clinical Practice |
| GFR | Glomerular filtration rate |
| GGT | Gamma Glutamyl Transpeptidase |
| GTP | Guanosine triphosphatase |
| H&E | Haemotoxylin and eosin |
| HBcAb | Hepatitis B core antibody |
| HBsAg | Hepatitis B surface antigen |
| HBV | Hepatitis B Virus |
| HCV | Hepatitis C Virus |
| HER2 | Human Epithelial grow factor Receptor 2 |
| HIV | Human Immunodeficiency Virus |
| HR | Hormone receptor |
| IB | Investigator Brochure |
| ICF | informed consent form |
| ICH | International Conference on Harmonization |
| ICMJE | International Committee of Medical Journal Editors |
| ID | Identity |
| IEC | Independent Ethics Committee |
| IM | Intramuscular |
| IMP | Investigational Medicinal Product |
| INR | International Normalized Ratio |

| Abbreviation | Full terminology |
|---|---|
| LDH | Lactate Dehydrogenase |
| LHRH | Luteinizing hormone-release hormone |
| LLN | Lower Limit of Normality |
| LVEF | Left Ventricular Ejection Function |
| MAP | Mitogen-activated protein |
| MAPK | Mitogen-activated protein kinase |
| MDRD | Modification of Diet in Renal Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic Resonance Imaging |
| mRNA | Messenger Ribonucleic Acid |
| MTD | Maximum Tolerated Dose |
| MUGA | Multigated acquisition scan |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NGS | Next-generation sequencing |
| NSCLC | Non-small cell lung cancer |
| NYHA | New York Heart Association |
| OR | Objective Response |
| OS | Overall Survival |
| PARPi | Poly (adenosine diphosphate-ribose) polymerase inhibitors |
| PD | Progressive disease/Pharmacodynamics |
| PDXs | Patient derived xenografts |

| Abbreviation | Full terminology |
|---|---|
| PET-CT | Positron Emission Tomography-Computed Tomography |
| PFS | Progression-free survival |
| PI3K | Phosphatidylinositide 3-kinase |
| PIL | Patient Information Leaflets |
| PIS | Patient Information Sheet |
| PK | Pharmacokinetic(s) |
| PKC | Protein kinase C |
| PO | Oral |
| PR | Partial Response/Progesterone Receptor |
| PTMs | Post-translational modifications |
| PTT | Partial Thromboplastin Time |
| PVC | Polyvinyl Chloride |
| QC | Quality Control |
| QTc | Corrected QT interval |
| Rb | Retinoblastoma |
| RBC | Reed Blood Count |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| REPD | Retinal pigment epithelial detachment |
| RNA | Ribonucleic acid |
| RP2D | Recommend Phase 2 Dose |
| RPED | Retinal Pigment Epithelial Detachment |

| Abbreviation | Full terminology |
|---|---|
| RVO | Retinal vein occlusion |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SD | Stable disease |
| SOP | Standard operating procedure |
| SPC | Summary of Product Characteristics |
| TMF | Trial Master File |
| TNBC | Triple negative breast cancer |
| TSH | Thyroid stimulating hormone |
| TTD | Time To Deterioration |
| ULN | Upper Limit of Normal |
| WDC | White Blood Count |

# 4. CLINICAL TRIAL CHARACTERISTICS

## 4.1. Clinical trial identification

### Code:

PALBOBIN

### Title:

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

## 4.2. Phase

Pase IB

### 4.3. Investigational product

Palbociclib plus binimetinib

### 4.4. Sponsor

Fundación OncoSur

Address: Gran Via Marques del Turia nº 65, 3º-11. 46005 Valencia Office:

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### 4.5. Ethics Committee

CEIm Hospital de 12 de Octubre

### 4.6. Company Responsible of the Monitoring

APICES

CCI [redacted]

### 4.7. Study calendar

First patient inclusion: 4Q 2020

Last patient inclusion: 4Q2021

Subject participation duration: 6 months + 6 months follow up Study

duration: 32 months

# 5. STUDY RATIONALE AND OBJECTIVES

## 5.1. Background information

### 5.1.1. Triple negative breast cancer

Breast cancer is the most common invasive cancer in women worldwide, with more than one million cases diagnosed in 2012 and it is also the most common cancer in women in Europe and Spain, with more than 494.000 and 27.700 new cases diagnosed in 2012 respectively [2,3]. It is estimated than 1 in 8 women in the European Union will develop breast cancer before the age of 85 [4].

Triple-negative breast cancer (TNBC) is a notoriously aggressive disease, as indicated by poor survival rates relative to other forms of BC [5,6], defined as lacking expression of oestrogen receptor (ER) and/or progesterone receptor (PR) as well as amplification of human epidermal growth factor receptor 2 (HER2), respectively [7]. Although TNBC only constitutes approximately 15–20% of breast cancer cases, it is disproportionately responsible for breast cancer-associated deaths and carries a dismal prognosis, compared with hormone receptor-positive (HR+) breast cancers [8-10]. More than one-third of patients with TNBC will present distant metastases, either recurrent or de novo metastatic disease [5].

Adjuvant chemotherapy is the current standard treatment for TNBC, but modest response rates underscores a need for more effective treatments. For patients with HR+ breast cancer, endocrine therapy targeting ER is available in the form of aromatase inhibitors and selective oestrogen receptor modulators (e.g. tamoxifen)

and other antagonists [7], but no effective targeted therapy which exploits the molecular properties of tumour cells exists for TNBC patients.

Aggressive chemotherapy, radiotherapy and surgery remain the mainstay treatments [11]. Furthermore, patients who develop resistance to treatment, or who do not respond to treatment whatsoever, follow an aggressive clinical course characterised by metastasis and a higher 5-year mortality [12].

TNBC is a molecularly heterogeneous disease characterized by genomic instability along with high expression of cell-cycle genes [13] and clearly necessitates a more tailored approach to treatment. For chemotherapy-resistant TNBC patients, the development of targeted therapies which synergise with current treatment options to overcome resistance is therefore paramount. The complex biology of TNBC suggests that combination treatments will be required to achieve effective and durable disease control.

### 5.1.2. *Palbociclib*

Palbociclib is an orally active pyridopyrimidine, highly selective, reversible inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of multiple signaling pathways which lead to cellular proliferation.

Through inhibition of CDK4/6, palbociclib reduced cellular proliferation by blocking progression of the cell from G1 into S phase of the cell cycle. Palbociclib preclinical data indicate that it may be expected to have direct effect on growth arrest as well as potential secondary cytoreductive activity. Treatment of cultured tumor cells with palbociclib causes growth arrest that is accompanied by the inhibition of specific retinoblastoma (Rb) phosphorylation by CDK4 or CDK6 on residues serine -780 and
-795 of Rb. Consequently the phosphorylation status of these sites serves as specific biomarkers of CDK4/6 inhibition by palbociclib.

Testing of palbociclib in a panel of molecularly profiled breast cancer cell lines revealed high activity against luminal breast cancers, particularly ER-positive breast cancers.

Palbociclib is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer:

- in combination with an aromatase inhibitor;
- in combination with fulvestrant in women who have received prior endocrine therapy.

#### *5.1.2.1. Safety profile of palbociclib*

The overall safety profile of palbociclib is based on pooled data from 872 patients who received palbociclib in combination with endocrine therapy (N=527 in combination with letrozole and N=345 in combination with fulvestrant) in randomised clinical studies in HR-positive, HER2-negative advanced or metastatic breast cancer.

The most common (≥20%) adverse reactions of any grade reported in patients receiving palbociclib in randomised clinical studies were neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anaemia, diarrhoea, alopecia and thrombocytopenia. The most common (≥2%) Grade ≥3 adverse reactions of palbociclib were neutropenia, leukopenia, infections, anaemia, aspartate aminotransferase (AST) increased, fatigue, and alanine aminotransferase (ALT) increased.

#### *5.1.2.2. Clinical efficacy of palbociclib*

The efficacy of palbociclib in combination with fulvestrant versus fulvestrant plus placebo was evaluated in an international, randomised, double-blind, parallel-group, multicentre study conducted in women with HR-positive, HER2-negative locally advanced breast cancer not amenable to resection or radiation therapy with curative intent or metastatic breast cancer, regardless of their menopausal status, whose disease progressed after prior endocrine therapy in the (neo)adjuvant or metastatic setting.

A total of 521 pre/peri- and postmenopausal women who had progressed on or within 12 months from completion of adjuvant endocrine therapy or on or within 1 month from prior endocrine therapy for advanced disease, were randomised 2:1 to palbociclib plus fulvestrant or placebo plus fulvestrant and stratified by documented sensitivity to prior hormonal therapy, menopausal status at study entry (pre/peri- versus postmenopausal), and presence of visceral metastases. Pre/perimenopausal women received the LHRH agonist goserelin. Patients with advanced/metastatic, symptomatic, visceral spread, that were at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement), were not eligible for enrolment into the study.

Patients continued to receive assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first.

Patients were well matched for baseline demographics and prognostic characteristics between the palbociclib plus fulvestrant arm and the placebo plus fulvestrant arm. All patients had received prior systemic therapy and most patients

in each treatment arm had received a previous chemotherapy regimen for their primary diagnosis. More than half (62%) had an ECOG PS of 0, 60% had visceral metastases, and 60% had received more than 1 prior hormonal regimen for their primary diagnosis.

The primary endpoint of the study was investigator-assessed PFS evaluated according to RECIST 1.1. Supportive PFS analyses were based on an Independent Central Radiology Review. Secondary endpoints included OR, CBR, OS, safety, and time-to-deterioration (TTD) in pain endpoint.

The study met its primary endpoint of prolonging investigator-assessed PFS [11.2 (9.5, 12.9) vs 4.6 (3.5, 5.6) months; Hazard ratio of 0.497 (95% CI: 0.398, 0.620), $p<0.000001$], demonstrating a statistically significant prolongation in PFS and a clinically meaningful treatment effect.

A reduction in the risk of disease progression or death in the palbociclib plus fulvestrant arm was observed in all individual patient subgroups defined by stratification factors and baseline characteristics. This was evident for pre/perimenopausal women (HR of 0.46 [95% CI: 0.28, 0.75]) and postmenopausal women (HR of 0.52 [95% CI: 0.40, 0.66]) and patients with visceral site of metastatic disease (HR of 0.50 [95% CI: 0.38, 0.65]) and non-visceral site of metastatic disease (HR of 0.48 [95% CI: 0.33, 0.71]). Benefit was also observed regardless of lines of prior therapy in the metastatic setting, whether 0 (HR of 0.59 [95% CI: 0.37, 0.93]),
1 (HR of 0.46 [95% CI: 0.32, 0.64]), 2 (HR of 0.48 [95% CI: 0.30, 0.76]), or ≥3 lines
(HR of 0.59 [95% CI: 0.28, 1.22]).

### 5.1.3. *Binimetinib*

Binimetinib (also known as MEK162, ARRY-438162 or ONO-7703) is an orally bioavailable, selective and potent mitogen-activated protein (MAP) kinase, kinase (MEK)1 and MEK2 inhibitor.

As a MEK inhibitor, this compound has the potential to benefit patients with advanced cancers by inhibiting the RAS/RAF/MEK/ERK mitogen-activated protein kinase (MAPK) pathway.

Binimetinib is currently being investigated as a single agent and in combination with a variety of additional compounds, including inhibitors of serine/threonine-protein kinase B-Raf (BRAF), phosphatidylinositide 3-kinase (PI3K), epidermal growth factor receptor (EGFR), cyclin-dependent kinase 4/6 (CDK4/6), chemotherapy and immune checkpoint inhibitors.

Binimetinib in combination with encorafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

#### *5.1.3.1. Target Inhibition*

Binimetinib is an adenosine triphosphate (ATP)-uncompetitive inhibitor of MEK1 and MEK2. In cell-free systems, binimetinib inhibits MEK1 and MEK2. In vitro, binimetinib potently inhibits MEK-dependent phosphorylation of extracellular regulated signal kinase (ERK) in human BRAF-mutant melanoma cell lines, as well as NRAS-mutant melanoma lines.

In vivo, binimetinib has been evaluated for its ability to inhibit tumor growth and phosphorylation of ERK, the primary biomarker of MEK inhibitory activity, in xenograft models in nude mice. In vivo, binimetinib treatment results in dose- and time-dependent inhibition of phosphorylation of ERK in the HT-29 human colorectal cancer (CRC) xenograft. Similarly, levels of both phosphorylated ERK (pERK) and dual specificity phosphatase 6 (DUSP6) messenger ribonucleic acid (mRNA) (a target gene of pERK) are reduced in the A375 BRAF-mutant melanoma xenograft model. Lastly, in ex vivo experiments, binimetinib reduces pERK levels in ex vivo stimulated human whole blood cells.

#### *5.1.3.2. Tumor Growth Inhibition*

In vitro, binimetinib potently inhibits the proliferation of human cancer cell lines. Binimetinib is particularly active in cells harboring activating mutations in the BRAF, NRAS and KRAS genes, although activity is also observed in cell lines that lack such mutations. Synergistic interactions with the BRAF inhibitor encorafenib and PI3K inhibitors buparlisib and alpelisib have been observed in subsets of melanoma, CRC, pancreatic and lung-derived cancer cell lines. Lastly, binimetinib displays synergistic effects when combined with the protein kinase C (PKC) inhibitor sotrastaurin in cell line models of uveal melanoma.

In vivo, single-agent binimetinib inhibits the growth of tumors in numerous xenograft models, including those derived from NSCLC and CRC, pancreatic and melanoma cancers. Binimetinib is also active in primary human explant models derived from several cancer types (CRC, ampullary, pancreatic and cholangiocarcinoma). Combining binimetinib with a variety of standard chemotherapy agents such as cisplatin, gemcitabine, taxanes or 5-fluorouracil/oxaliplatin resulted in enhanced antitumor activity in numerous in vivo tumor models. Similarly, combinations of binimetinib with a variety of targeted agents have shown activity in vivo in multiple tumor models. In cutaneous melanoma, binimetinib combination effects are observed with the BRAF inhibitor encorafenib and the CDK4/6 inhibitor ribociclib. Similarly, in models of uveal melanoma, binimetinib combined effectively with the PKC inhibitor sotrastaurin. In subsets of xenograft models of CRC, NSCLC and pancreatic cancer, antitumor effects have been observed when binimetinib was combined with a variety of PI3K inhibitors (buparlisib, alpelisib). Moreover, in BRAF- mutant CRC, binimetinib combined effectively with encorafenib, and the EGFR

inhibitor cetuximab. Lastly, binimetinib also demonstrated anti-angiogenic activity in Matrigel plug assays in mice.

#### *5.1.3.3. Cancer and the MAP Kinase Pathway*

Growth factor-mediated proliferative signals are transmitted from the extracellular environment to the nucleus through several pathways, including the RAS/RAF/MEK/ERK mitogen-activated protein kinase (MAPK) pathway [14]. This pathway comprises an evolutionarily conserved signaling cascade initiated by the RAS family of small guanosine triphosphatases (GTPases), which activate the RAF kinases. Activated RAF kinases phosphorylate and thereby activate MEK1 and MEK2, which in turn phosphorylate and activate the extracellular regulated signal kinase (ERK)1 and ERK2 kinases. Subsequent phosphorylation of a variety of downstream effector proteins, including transcription factors, by activated ERK serve to regulate key cellular activities including proliferation, differentiation, migration, survival and angiogenesis. Aberrant signaling through this pathway has been shown to lead to unconstrained cell growth and cell transformation [15,16] and is a characteristic feature of many cancers.

Inappropriate activation of the RAS/RAF/MEK/ERK pathway can occur through a variety of mechanisms, including activating mutations in RAS and B-Raf proto- oncogene, serine/threonine-protein kinase (BRAF) [17,18], activated growth factor signaling [19,20] and stress response signals [21,22]. Preclinical studies indicate that the presence of mutations that activate RAS/RAF/MEK/ERK pathway signaling, are predictive for response to MEK inhibitors [23]. Collectively, these data suggest that targeting MEK may inhibit cancer signaling mediated by a wide variety of signals, making MEK an attractive target for the treatment of cancer and its associated symptoms.

#### *5.1.3.4. Rationale for the use of binimetinib*

Use of binimetinib in the clinic is based on:

- (a) potent target inhibition in human cancer cell lines and xenograft models;
- (b) inhibition of tumor growth in human cancer cell lines and xenograft models, both as a single agent and in combination with targeted and standard chemotherapy agents; and
- (c) hypersensitivity of BRAF-mutant, NRAS-mutant and KRAS-mutant human cancer cell lines to binimetinib.

Binimetinib has demonstrated potent activity against MEK1/2 both in vitro and in vivo. In cellular assays, binimetinib has been shown to markedly inhibit the phosphorylation of ERK in human cancer cell lines and in human whole blood. In the BRAF-mutant HT-29 human colon carcinoma tumor and BRAF-mutant A375

human melanoma xenograft models, binimetinib significantly inhibited the phosphorylation of ERK following oral (PO) doses.

Binimetinib has displayed antiproliferative activity in cell line models of cancer in vitro and in vivo. For instance, binimetinib inhibited the proliferation of both Malme- 3M melanoma and HT-29 colorectal cancer (CRC) cells in vitro. Further studies in large sets of human cancer cell lines have confirmed the antiproliferative activity of binimetinib, particularly in models harboring activated alleles of the BRAF, NRAS, and to a lesser extent, KRAS genes. In vivo, binimetinib has demonstrated significant dose-dependent inhibition of tumor growth in a wide array of xenograft models in mice. In addition, robust combination activity between binimetinib and both standard chemotherapy agents (cisplatin, gemcitabine, 5-fluorouracil [5- FU]/oxaliplatin, taxanes) and targeted agents, such as RAF inhibitors (encorafenib), phosphatidylinositide 3-kinase (PI3K) inhibitors (alpelisib, buparlisib, BEZ2335), cyclin-dependent kinase 4/6 (CDK4/6) inhibitors (ribociclib), protein kinase C (PKC) inhibitors (sotrastaurin) and epidermal growth factor receptor (EGFR) inhibitors (erlotinib, cetuximab), has been observed. Also, combining binimetinib with an immunomodulating anti-programmed death-1 (PD1) antibody (RPM1-14) in the syngeneic CT26 CRC allograft tumor model, resulted in enhanced tumor growth inhibition relative to treatment with either drug as a single agent.

#### *5.1.3.5. Safety profile of binimetinib*

As of 20 January 2018, a total of 2816 healthy subjects and patients have received at least 1 dose of binimetinib, either as a single agent or in combination with other targeted agents, standard chemotherapy agents or immunomodulating agents. These patients constitute the binimetinib safety population, which includes 229 healthy subjects, 17 subjects with hepatic dysfunction, 6 subjects with renal dysfunction, 164 patients with rheumatoid arthritis and 2400 patients with advanced cancer.

##### *5.1.3.5.1. Binimetinib as a Single Agent*

Binimetinib has been administered as a single agent to 943 patients with cancer across 7 studies.

1. Clinical Study ARRAY-162-111 (N = 93; completed): Phase 1, dose- escalation study in patients with advanced solid tumors followed by expansion cohorts in patients with advanced or metastatic biliary cancer or KRAS- or BRAF-mutant metastatic CRC.
2. Clinical Study CMEK162X1101 (N = 21; ongoing): Phase 1, dose-escalation study in Japanese patients with advanced solid tumors with an expansion phase in patients with RAS or BRAF mutation.

3. Clinical Study CMEK162X2201 (N = 183; ongoing): Phase 2 study in patients with locally advanced and unresectable or metastatic malignant cutaneous melanoma, with BRAF V600 or NRAS mutations.
4. Clinical Study CMEK162AUS11 (N = 110; completed): Phase 2 study in patients with select solid tumors or hematological malignancies that have been pre-identified to have activation of the RAS/RAF/MEK/ERK pathway.
5. Clinical Study CINC280X2205 (N = 22; ongoing): Phase 2 study in Chinese patients with advanced KRAS/BRAF/NRAS-mutant NSCLC.
6. Clinical Study CMEK162A2301 (N = 269; ongoing): Phase 3, 2-arm, randomized study in patients with advanced unresectable or metastatic NRAS Q61 mutation-positive melanoma.
7. Clinical Study ARRAY-162-311 (N = 245; ongoing): Phase 3, 2-arm, randomized study in patients with recurrent or persistent low-grade serous carcinomas of the ovary, fallopian tube or primary peritoneum.

The most frequently reported adverse events (AEs) with single-agent binimetinib 45 mg BID treatment (all grades) have been blood creatine kinase (CK) increased, diarrhea, dermatitis acneiform, edema peripheral, rash, nausea and fatigue. The majority of these AEs have been Grade 1/2, with the exception of blood CK increased, which was reported as Grade 3/4 for 21% of patients with metastatic melanoma in the "binimetinib 45 mg population" (N = 427) which includes pooled data from 2 clinical studies (CMEK162A2301 [Phase 3], CMEK162X2201 [Phase 2]), and for 29% of patients with low-grade serous carcinomas of the ovary, fallopian tube or primary peritoneum in the binimetinib arm of the randomized period of Clinical Study ARRAY-162-311 (Phase 3; N = 227).

#### *5.1.3.5.1.1. Clinical Study ARRAY-162-111*

Clinical Study ARRAY-162-111 is a completed Phase 1, open-label, dose-escalation study of oral binimetinib in patients with advanced solid tumors followed by expansion cohorts in patients with advanced or metastatic biliary cancer or KRAS- or BRAF-mutant metastatic CRC.

A total of 93 patients were enrolled and received at least 1 dose of binimetinib (4 patients at 30 mg BID, 44 patients at 45 mg BID, 41 patients at 60 mg BID and 4 patients at 80 mg BID), including 19 patients in the dose-escalation phase and 74 patients in the dose-expansion phase.

Four dose levels were evaluated (30 mg BID, 45 mg BID, 60 mg BID and 80 mg BID) following a 3+3 dose-escalation design. Enrollment of cohorts containing 4 patients each, 3 of whom in each cohort were evaluable for dose-escalation decisions, proceeded at doses of 30 mg BID and 45 mg BID without observation of DLTs. Seven patients were enrolled at 60 mg BID, 6 of whom were evaluable, and

no DLTs were observed. Enrollment proceeded to 80 mg BID; 4 patients were enrolled, 3 of whom were evaluable. Two patients receiving 80 mg BID experienced DLTs, thus the 80 mg BID dose was declared nontolerable and 60 mg BID was declared the MTD. Additional DLTs observed in the expansion cohorts included Grade 3 pneumonia and Grade 3 blood CK increased (one patient each at the 45 mg BID dose level) and Grade 3 mucosal inflammation and Grade 3 generalized edema (one patient each at the 60 mg BID dose level).

Following determination of the MTD in the dose-escalation phase, 74 patients were enrolled in the expansion phase, including 28 patients in the biliary cancer cohort, 31 patients in KRAS-mutant CRC cohort and 15 patients in the BRAF-mutant CRC cohort. After initiation of the expansion phase, a higher-than-expected frequency of ocular AEs affected the ability to treat patients continuously at the MTD, thus a reduced dose of 45 mg BID was implemented for the remainder of newly enrolled patients in the expansion phase cohorts.

All 93 patients reported at least 1 AE, the most common (≥ 20% of patients) of which were rash (59%), nausea (56%), vomiting (52%), diarrhea (51%), edema peripheral (46%), fatigue (43%), anemia (26%) and abdominal pain (22%).

Fifty-two patients (56%) experienced at least 1 Grade 3/4 AE. Grade 3 AEs reported for > 1 patient were anemia (10 patients [11%]); abdominal pain and dehydration (4 patients [4%] each); AST increased, blood alkaline phosphatase increased, blood CK increased, dyspnea, ECG QT prolonged, fatigue, hypokalemia, hyponatremia, small intestinal obstruction and syncope (3 patients [3%] each); and constipation, dermatitis acneiform, GI hemorrhage, hyperbilirubinemia, hypertension, international normalized ratio (INR) increased, lymphopenia, melena, pain in extremity, pneumonia, rash, and renal failure acute (2 patients [2%] each). The Grade 4 AE reported for > 1 patient was anemia (3 patients [3%]).

Twenty-eight patients (30%) reported at least 1 SAE on study or within 30 days of the last dose of binimetinib. Serious AEs reported in > 1 patient were anemia (4 patients [4%]); and bacteremia, dehydration, GI hemorrhage, small intestinal obstruction, pneumonia and ulcer hemorrhage (2 patients [2%] each). All other SAEs occurred in 1 patient (1%) each.

#### *5.1.3.5.1.2. Clinical Study CMEK162X1101*

Clinical Study CMEK162X1101 is an ongoing Phase 1, open-label, dose-escalation study of binimetinib as a single agent in Japanese patients with advanced solid tumors with an expansion cohort in patients with RAS or BRAF mutation.

Enrollment is complete, with 21 patients enrolled and treated with at least 1 dose of binimetinib (6 patients at 30 mg BID and 15 patients at 45 mg BID), including 14 patients in the dose-escalation phase and 7 patients in the dose-expansion phase.

Fourteen patients with advanced solid tumors received binimetinib in the dose- escalation phase and 11 were eligible for the dose-determining set. Two dose levels were evaluated (30 mg BID and 45 mg BID) and dose escalation was guided by an adaptive Bayesian Logistic Regression Model and implemented with the Escalation with Overdose Control principle. 45 mg BID was declared the MTD.

Following determination of the MTD in the dose-escalation phase, 7 patients were enrolled in the expansion phase and received binimetinib at the MTD (45 mg BID). No DLTs were reported in the expansion portion of the study.

All 21 patients (100%) reported at least 1 AE, the most common (≥ 20.0% of patients) of which were blood CK increased (81.0%); AST increased (71.4%); retinal detachment (61.9%); diarrhea and lipase increased (57.1% each); ALT increased (52.4%); pyrexia, blood ALP increased, hypoalbuminemia, and dermatitis acneiform (47.6% each); amylase increased and dry skin (42.9% each); stomatitis, paronychia and rash (38.1% each); fatigue, edema peripheral and decreased appetite (33.3% each); cheilitis, GGT increased and hemoglobin decreased (28.6% each); and lymphopenia, constipation, blood creatinine increased, epistaxis and pruritus (23.8% each).

Seventeen patients (81.0%) experienced at least 1 Grade 3/4 AE; those reported for > 1 patient were blood CK increased (7 patients [33.3%]); lipase increased and lymphopenia (4 patients [19.0%] each); and ALT increased, AST increased, cancer pain, fatigue, GGT increased and pneumonia (2 patients [9.5%] each). All other Grade 3/4 AEs occurred in 1 patient (4.8%) each.

Ten patients (47.6%) reported at least 1 SAE on study or within 28 days of the last dose of binimetinib. Serious AEs reported in > 1 patient was pneumonia (2 patients [9.5%]). All other SAEs occurred in 1 patient (4.8%) each.

#### *5.1.3.5.1.3. Clinical Study CMEK162X2201*

Clinical Study CMEK162X2201 is an ongoing Phase 2, open-label study of single- agent binimetinib in adult patients with locally advanced and unresectable or metastatic malignant cutaneous melanoma with BRAF V600 or NRAS mutation.

Enrollment is complete, with 183 patients enrolled and treated with at least 1 dose of binimetinib (158 patients at 45 mg BID [41 BRAF mutant and 117 NRAS mutant] and 25 patients at 60 mg BID [all BRAF mutant]). This section describes the data for the 25 patients treated with binimetinib 60 mg BID [all BRAF mutant]) as of the data cutoff date for the primary analysis (07 January 2014).

As of the data cutoff date for the primary analysis (07 January 2014) 25 patients were treated with binimetinib 60 mg BID. All 25 patients (100%) reported at least 1 AE, the most common (≥ 20.0% of patients) of which were blood CK increased and edema peripheral (56.0% each); diarrhea (52.0%); fatigue and nausea (48.0%

each); retinopathy (40.0%); vomiting (36.0%); dermatitis acneiform (32.0%); arthralgia (24.0%); and dry skin, hypertension and rash (20.0% each).

Eighteen patients (72.0%) in the 60 mg BID cohort experienced at least 1 Grade 3/4 AE; those reported for > 1 patient were blood CK increased (6 patients [24.0%]); nausea and vomiting (3 patients [12.0%] each); and AST increased, blood ALP increased, blood lactate dehydrogenase increased, gastritis and syncope (2 patients [8.0%] each). All other Grade 3/4 AEs occurred in 1 patient (4.0%) each.

Nine patients (36.0%) in the 60 mg BID cohort reported at least 1 SAE on study or within 30 days of the last dose of binimetinib. Serious AEs reported in > 1 patient was gastritis (2 patients [8.0%]). All other SAEs occurred in 1 patient (4.0%) each.

#### *5.1.3.5.1.4. Clinical Study CMEK162AUS11*

Clinical Study CMEK162AUS11 is a completed Phase 2, open-label study to determine the efficacy and safety of treatment with single-agent binimetinib in patients with select solid tumors or hematological malignancies that have been pre- identified (prior to study consent) to have activation of the RAS/RAF/MEK/ERK pathway and whose disease has progressed on or after standard treatment.

A total of 110 patients were enrolled and treated with at least 1 dose of binimetinib (45 mg BID). As of the data cutoff date for the final analysis (08 October 2015), all patients (100%) reported at least 1 AE, the most common (≥ 20.0% of patients) of which were fatigue (50.0%), diarrhea (47.3%), nausea (44.5%), rash (43.6%), edema peripheral (40.9%), vomiting (38.2%), blood CK increased (34.5%), dyspnea (30.9%), anemia (26.4%), constipation and decreased appetite (22.7% each) and AST increased (20.0%).

Eighty-one patients (73.6%) experienced at least 1 Grade 3/4 AE; those reported for ≥ 5.0% of patients were blood CK increased (17 patients [15.5%]), dyspnea (15 patients [13.6%]), anemia (11 patients [10.0%]), fatigue (10 patients [9.1%]) and abdominal pain and lipase increased (6 patients [5.5%] each).

Fifty patients (45.5%) experienced at least 1 SAE on study or within 30 days of the last dose of binimetinib. Serious AEs reported in > 1 patient were dyspnea (12 patients [10.9%]); abdominal pain, dehydration and small intestinal obstruction (4 patients [3.6%] each); hypoxia, pneumonia and urinary tract infection (3 patients [2.7%] each); and cellulitis, edema peripheral, hemoptysis, pleural effusion, pulmonary embolism, pyrexia, sepsis and vomiting (2 patients [1.8%] each). All other SAEs occurred in 1 patient (0.9%) each.

#### *5.1.3.5.1.5. Clinical Study CINC280X2205*

Clinical Study CINC280X2205 is an ongoing Phase 2, open-label, multiple-arm study of binimetinib, AUY922, alpelisib (BYL719), INC280 or LDK378 as single

agents in Chinese patients with advanced (stage IIIB or stage IV) non-small cell lung cancer (NSCLC) who have received ≤ 2 prior lines of antineoplastic therapy. Each treatment arm is independent from one another. Approximately 20 to 25 patients are planned to be enrolled to each treatment arm according to their molecular alterations, with KRAS-, NRAS- or BRAF-mutant patients enrolled to receive binimetinib.

As of the data cutoff date (18 January 2018), a total of 22 patients have been enrolled and treated with binimetinib 45 mg BID. All 22 patients (100%) reported at least 1 AE, the most common (≥ 30.0% of patients) of which were anemia, blood CK increased and rash (72.7% each), AST increased (68.2%), diarrhea (63.6%), hypoalbuminaemia (59.1%), edema peripheral and pyrexia (50.0% each), vomiting (40.9%), hyponatremia and mouth ulceration (36.4% each) and asthenia, dyspnea and hypocalcemia (31.8% each).

Twenty patients (90.9%) experienced at least 1 Grade 3/4 AE; those reported for > 1 patient were blood CK increased (8 patients [36.4%]), anemia (5 patients [22.7%]), hypokalemia dyspnea, pleural effusion (3 patients [13.6%]), and ECG QT prolonged, hypoalbuminemia, hypertension and pneumonia (2 patients [9.1%] each).

Eighteen patients (81.8%) experienced at least 1 SAE on study or within 30 days of the last dose of binimetinib. Serious AEs reported in > 1 patient were blood CK increased and dyspnea (4 patients [18.2%] each), pleural effusion and pyrexia (3 patients [13.6%] each) and lung infection and pneumonia (2 patients [9.1%] each).

#### *5.1.3.5.1.6. Clinical Study ARRAY-162-311*

Clinical Study ARRAY-162-311 (MILO study) is an ongoing Phase 3, 2-arm, multinational, randomized, open-label study to evaluate binimetinib (45 mg BID) vs. physician's choice of selected chemotherapies (liposomal doxorubicin, paclitaxel or topotecan) in patients with low-grade serous carcinomas of the ovary, fallopian tube or primary peritoneum who had recurrent or persistent disease after at least 1 prior platinum-based chemotherapy treatment and no more than 3 prior lines of chemotherapy. A total of 360 patients, were to be randomized 2:1 to receive binimetinib or physician's choice chemotherapy. The primary objective was to determine whether treatment with binimetinib prolongs PFS as compared to physician's choice chemotherapy. The study enrollment was discontinued after the planned interim analysis showed that the hazard ratio for PFS crossed the predefined futility boundary.

Enrollment is complete, with a total of 341 patients (228 binimetinib and 113 physician's choice) randomized to treatment and a total of 333 patients (227 patients binimetinib arm and 106 patients physician's choice arm) who received at least 1 dose of binimetinib or physician's choice in the randomized period.

All 227 binimetinib-treated patients (100%) reported at least 1 AE, the most common (≥ 30% of patients) of which were diarrhea (71%), nausea (59%), vomiting (56%), blood CK increased (53%), fatigue and edema peripheral (52% each), dermatitis acneiform (49%), abdominal pain (35%) and dry skin (33%). In the crossover period, all 18 binimetinib-treated patients (100%) reported at least 1 AE, and the most frequently reported AEs were similar to those reported in the randomized period.

Two hundred patients (88%) in the binimetinib arm experienced at least 1 ≥ Grade 3 AE in the randomized period. Of these AEs ≥ Grade 3, the events reported for ≥ 10% of patients in the binimetinib arm were blood CK increased (66 patients [29%]), hypertension (27 patients [12%]), vomiting (24 patients [11%]), anemia (23 patients [10%]) and diarrhea (22 patients [10%]). In the crossover period, 14 binimetinib- treated patients (78%) experienced at least 1 ≥ Grade 3 AE.

One hundred twenty-one patients (53%) in the binimetinib arm reported at least 1 SAE on study or within 30 days of the last dose of binimetinib in the randomized period. Serious AEs reported in ≥ 2% of patients in the binimetinib arm were vomiting (16 patients [7%]); intestinal obstruction (14 patients [6%]); small intestinal obstruction (11 patients [5%]); diarrhea (10 patients [4%]); anemia (9 patients [4%]); sepsis and urinary tract infection (8 patients [4%] each); abdominal pain, ascites, nausea and subileus (7 patients [3%] each); pulmonary embolism (6 patients [3%]); and pleural effusion and renal failure acute (5 patients [2%] each). In the crossover period, 15 binimetinib-treated patients (83%) reported at least 1 SAE on study or within 30 days of the last dose of binimetinib.

#### *5.1.3.5.2. Binimetinib in combination*

Binimetinib has been administered in combination with other targeted agents, standard chemotherapy agents or immunomodulating agents to 1457 patients across 16 clinical studies.

The most frequently reported AEs with the combination of binimetinib 45 mg BID + encorafenib 450 mg once daily (QD) treatment (all grades) in patients with *BRAF* V600- mutant metastatic melanoma who were previously naïve to BRAF/MEK inhibitors have been nausea, diarrhea, fatigue, vomiting, arthralgia, blood CK increased, constipation and headache. The majority of these AEs have been Grade 1/2. This data is derived from pooled data from 3 clinical studies of the combination of binimetinib + encorafenib.

See the updated version of binimetinib investigator brochure for more information.

### *5.1.3.6. Guidance for Investigators*

Binimetinib is an investigational drug for which limited safety data are available. It should be used with appropriate caution typical for an investigational drug.

Binimetinib has demonstrated an acceptable and manageable safety profile in nonclinical toxicology studies and clinical studies. As with any investigational drug, unexpected AEs may occur.

Available clinical data for binimetinib indicate a predictable safety profile consistent with those reported for other allosteric MEK1/2 inhibitors including the characteristic class effects of ocular toxicities, elevations of CK that are mostly asymptomatic, liver function test abnormalities (elevation of aspartate aminotransferase [AST], alanine aminotransferase [ALT] and total bilirubin), left ventricular dysfunction, skin toxicities including rash and acneiform dermatitis, hypertension, thromboembolic events, diarrhea, edema and hemorrhage. The majority of these toxicities are generally reversible and manageable by appropriate supportive medical care and/or dose modifications or discontinuation. Supportive therapy for the management of binimetinib-associated toxicities should be based on Investigator experience.

Binimetinib may cause fetal harm (teratogenicity) when administered to a pregnant woman. Binimetinib must not be used in pregnant women or nursing women, and the use of highly-effective contraception is recommended for male and female subjects participating in clinical studies. Additionally, women of childbearing potential must be advised to use highly effective contraception.

Ocular toxicities can occur with binimetinib administration. Patients should be assessed for symptoms of new or worsening visual impairment. Patients with a history or current evidence of retinal vein occlusion (RVO) or risk factors for RVO (e.g., uncontrolled glaucoma or history of hyperviscosity or hypercoagulability syndrome) should be excluded from studies with binimetinib.

New onset hypertension, or worsening of pre-existing hypertension, can occur with the use of binimetinib. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy.

Left ventricular dysfunction, defined as symptomatic or asymptomatic decreases in ejection fraction, can occur with binimetinib. Before binimetinib administration, patients should have a baseline left ventricular ejection fraction (LVEF) evaluation and periodically on study as per protocol.

Venous thromboembolism can occur with the use of binimetinib. Binimetinib should be used with caution in patients who are at risk for, or who have a history of venous thromboembolism.

Rash events are among the most frequently observed AEs reported with MEK inhibitors when used as a single agent. Patients receiving binimetinib should be monitored for skin toxicities and for secondary infections.

Overall, the risk for binimetinib to be a cause of or be affected by significant drug- drug interactions is predicted to be low. However, given the predominant role of

UGT1A1 in the metabolism of binimetinib, special consideration should be taken for co-administration of drugs that are UGT1A1 inhibitors or inducers, and administration of binimetinib to patients with low UGT1A1 activity. In addition, binimetinib has been shown to be a substrate for P-gp and BCRP in vitro. The impact of P-gp/BCRP inhibitors on the PK of binimetinib in vivo is unknown; therefore, it is recommended that P-gp and BCRP inhibitors are dosed with caution.

## 5.2. Study rationale

### Triple negative breast cancer phosphoproteomic taxonomy

Triple-negative breast cancer (TNBC) is an immunohistochemically-defined breast cancer subtype negative for ER, PR and HER-2 expression, with a dismal prognosis [24]. Approximately 80% overlap with the basal-like expression cluster [25-27]. Although several gene-centric approaches have been explored to classify TNBC [25,26, 28-33], no clear signatures have yet been reported that can be used for precision medicine treatment of individual patients. The extreme heterogeneity of this disease is illustrated by the fact of subgrouping the disease by paring the classifiers down to 29 of the most frequently mutated genes resulted in sets of mutations that are unique to individual patients [32]. Patient classification tools should not only accurately predict a patient's clinical course but also provide therapeutic solutions. These results are difficult to achieve because of the nature of high-throughput studies. For instance, the fine-tuning of gene-expression patterns is technically and conceptually challenging. NGS studies have defined cancer subtypes by point mutations, which are actionable targets in several malignancies, but not in breast cancer [34]. Highly penetrant oncogenes are rarely found in breast cancers, except for HER-2 amplification, which suggests that the "TNBC phenotype" is the result of coexisting, moderately penetrant, genetic changes.

TNBC can be simplistically reduced to 2 clinical subtypes: tumours of those patients who relapse within 3 years after treatment for locoregional disease, and tumours of the patients who, with few exceptions, rarely relapse [24]. To understand further the TNBCs classified by the 2 patterns of relapse, we chose a less commonly used investigative approach (in-depth high-throughput phosphoproteomics), based on the following reasons:

- 1) proteins are the "effector" molecules of tumour cells [35-38]; and
- 2) the functional status of proteins is modulated through post-translational modifications (PTMs), of which phosphorylation is the most ubiquitous in cellular signaling events [35-38].

The investigation of tumour behaviour assessing gene-centric layers ignores he "upper-level" (proteome) regulatory events [39,40]; thus, interrogating the proteome,

and, in particular its PTMs, might provide a more accurate and functional assessment of tumour behaviour. We hypothesized that all the existing (genomic, transcriptomic, etc.) aberrations across different patients might coalesce into a discrete number of phosphorylation-driven patterns of activation of the proteome that would account for the 2 main clinical subtypes of TNBC. These patterns would be driven by some of the ~500 kinases encoded by the human genome, and the kinases might be targetable by any of the available >200 clinical-grade inhibitors.

In this study, we aimed for 4 objectives:

- 1) to define the phosphoprofiles that could differentiate the relapsed cases from the other cases,
- 2) to identify the hyperactive kinases driving these profiles,
- 3) to translate this information into an application that could be usable in a routine clinical environment, and
- 4) to investigate the usefulness of driver kinases as therapeutic targets.

## Summary of our results

We profiled a training set of 34 TNBC cases [half of them with early relapse and half of them long-term (>12 years) relapse free; all of them paired by classic prognostic factors] and 10 TNBC cell lines. The cell lines were also classified by their ability to kill or not by distant metastatic spread nude mice (3 of them were classified as aggressive - MDA-MB-231, HS578T and MDA-MB-157 - whereas the other 7 were unable to kill the animals). We identified 15160 non-redundant phosphorylation sites. Of those, 702 showed significant regulation between the patients with and without relapse (159 were up-regulated in the patients with early relapse). Roughly 40% of these peptides were previously unknown, but the most important application is that we piggybacked this cluster of up-regulated phosphopeptides to their driving kinases. By using an in-house built bioinformatic algorithm (herein, KSEAS), we were able to pinpoint which kinases showed hyperactivation, and this activation was what caused the specific phosphoprofile of the aggressive cases. Twelve kinases were enriched in the phosphoprofile of the aggressive cases, and several of them overlapped with the kinases driving the profiles of the aggressive cell lines.


**Figure 1: workflow summary.** *Tumor samples and cell lines lysates were analyzed by mass spectrometry after phospho-enrichment. A matrix of 1.5 million spectra was analyzed and ~700 phosphosites were significantly regulated and splitting the relapsed cases versus the others. Driving kinases of this profile were predicted by an in house developed in silico algorithm. The hyperactivity of kinases accounting for the aggressive profiles was finally assayed in TMAs of an independent validation set by using conventional immunohistochemistry, turning these data into an easy application.*

We then performed a "mass-spectrometry-to-immunohistochemistry translation" step, in order to apply this information into the daily routine clinical practice. Six of the 12 kinases preserved independent prognostic factor (adjusted by conventional prognostic factors) in an independent validation set of N=173 early TNBC cases treated with surgery followed by adjuvant chemotherapy and >11 years follow-up. Finally, we used the six kinases to perform a "phosphosignature" and a taxonomy that could easily classify TNBC cases. The taxonomy showed two main patterns, one of them with 0/6 kinases activated that was associated to >93% long-term relapse-free. The second main pattern (1 or more out of six kinases with hyper- activity) gathered virtually all the relapsing cases. This second pattern could be further split into several sub-patterns characterized by activation of various kinases. Having 1 or more of the six kinases hyperactivated increased the risk of relapse by greater than 9-fold, adjusted by conventional prognostic factors. Such high risk justifies pharmacological interventions in this group beyond standard chemotherapy, whereas the remaining cases can be considered virtually cured. These six kinases were: KIT, PRKCE, P70S6K, PNKP, CDK6 and ERK.

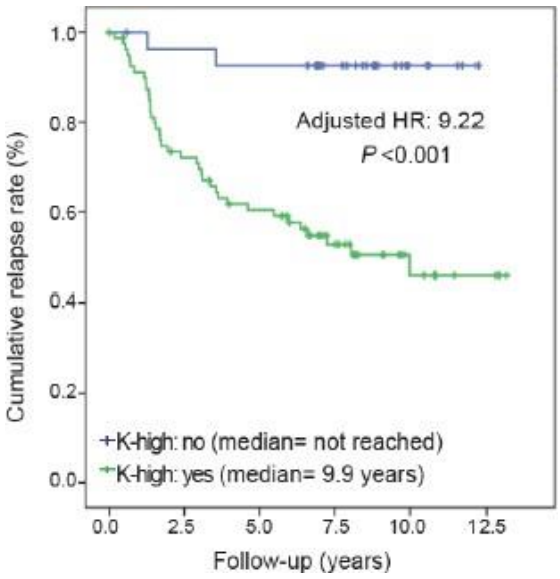



**Figure 2: Kaplan-Meier curve from patients having one of more hyperactivated kinases.** *By applying our phosphosignature, we were able to detect a group of patients (0/6 kinases of the phosphosignature hyperactivated) that was virtually long-term cured. The patients with one or more hyperactive kinases had a greater than 900% higher risk of relapse. Of note, as it can be observed in the curve, most of the relapses occurred during the 5 years after loco-regional treatment. This independent validation set was constituted by N=173 patients.*

Another question of key importance is whether a kinase-based classification is more parsimonious than a genomic classification (based on the status of mutated or wild- type genes). Considering that our taxonomy considers 6 kinasees, and only 2 status per kinase are possible, a maximum of different patterns would be found among a random patient series. However, we found that our 173 patients fitted to just 31 unique different patterns; 4-6 patients were found per pattern, and several patterns
(33) were not found in any patient. The most frequent patterns involved CDK6 and/or ERK (co)activation. Interestingly, when the mutational status of the top 20-mutated genes across the series was overlaid to the kinase classification, we found that diverse mutational patterns "collapsed" into single kinase patterns; in other words, kinase-activation patterns are a more over-arching classification of TNBC, functionally speaking, than any classification type that can be achieving by combining sets of mutated genes.

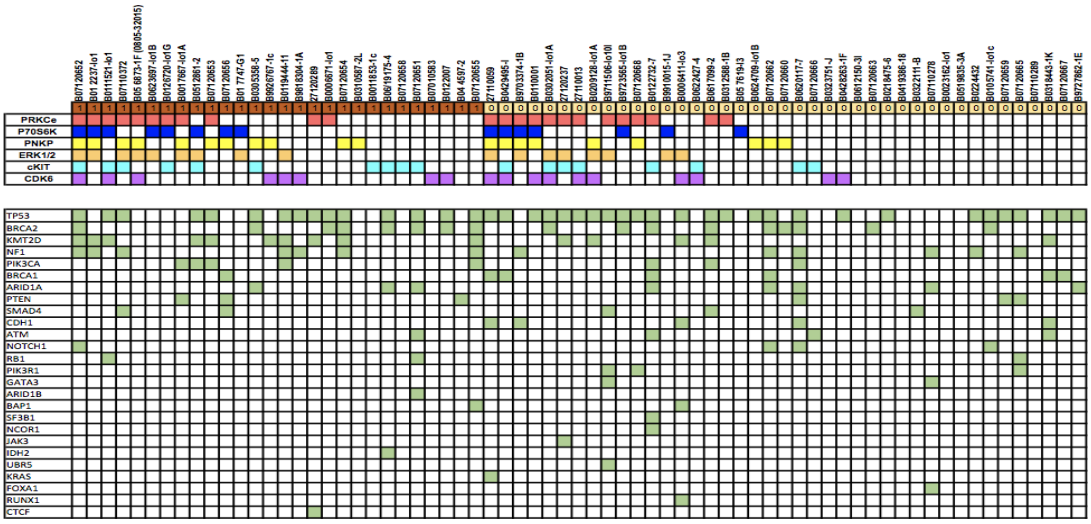
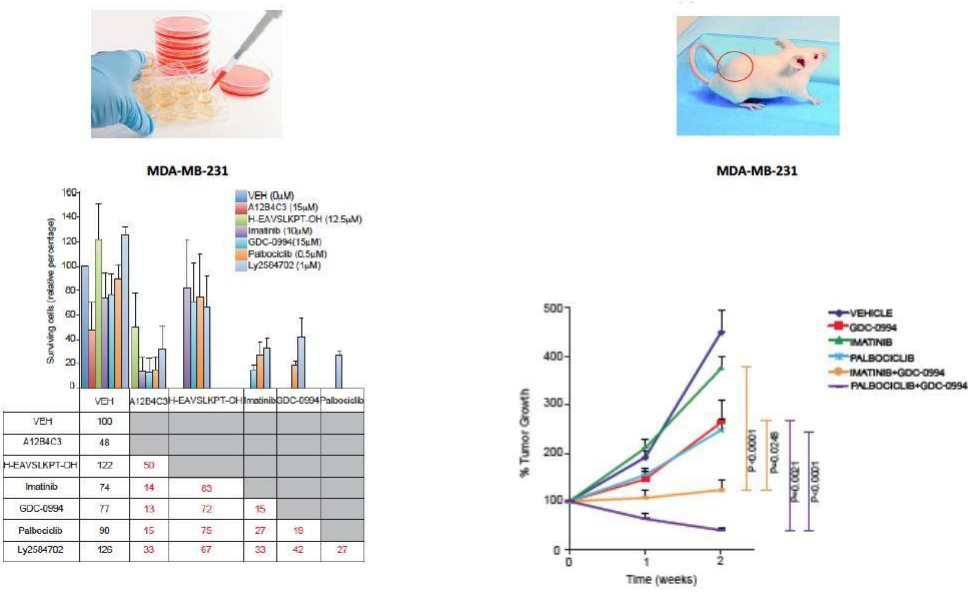



**Figure 3: convergence of diverse mutational patterns into discrete kinase patterns.** *This figure shows the status of the 6 kinases of the signature (colored if hyperactivated, empty if not) and the top 20-mutated genes (colored if mutated, empty if wild-type) among 65 patients of the validation set (red-colored squares: relapsed patients; yellow-colored squares: non-relapsed in >12 years). It can be observed how each pattern defined by a unique combination of hyperactivated kinases agglutinates several different mutational patterns.*

Regarding the therapeutic potential, we tested all the two-by-two combinations of agents targeting the six mentioned kinases in the TNBC cell lines (15 different regimens). Across the 10 cell lines, the combinations were synergistic in 99.4% of the cases. The findings were validated *in vivo*.




| | VEH | A12B4C3 | H-EAVSLKPT-OH | Imatinib | GDC-0994 | Palbociclib |
|---|---|---|---|---|---|---|
| VEH | 100 | | | | | |
| A12B4C3 | 48 | | | | | |
| H-EAVSLKPT-OH | 122 | 50 | | | | |
| Imatinib | 74 | 14 | 63 | | | |
| GDC-0994 | 77 | 13 | 72 | 15 | | |
| Palbociclib | 90 | 15 | 75 | 27 | 19 | |
| Ly2584702 | 126 | 33 | 67 | 33 | 42 | 27 |

**Figure 4: Therapeutic role of the 6 kinases in the signature**. *We gathered compounds with activity against each of the six kinases and tested in vitro their synergism against the 10 TNBC cell lines in the panel. The left panel shows the results in MDA-MB-231, where all the combinations yielded synergy. There are clinical-grade available drugs against some of these targets, specifically CDK6, KIT and ERK. The right chart shows the tumor growth inhibition from MDA-MB231 tumor xenografts allowed to grow to 500mm$^3$ and then exposed to different agents alone or in combination. As it can be observed, ERK inhibition plus CDK6 inhibition induces tumor regression, something that is not commonly observed in TNBC in absence of chemotherapy.*

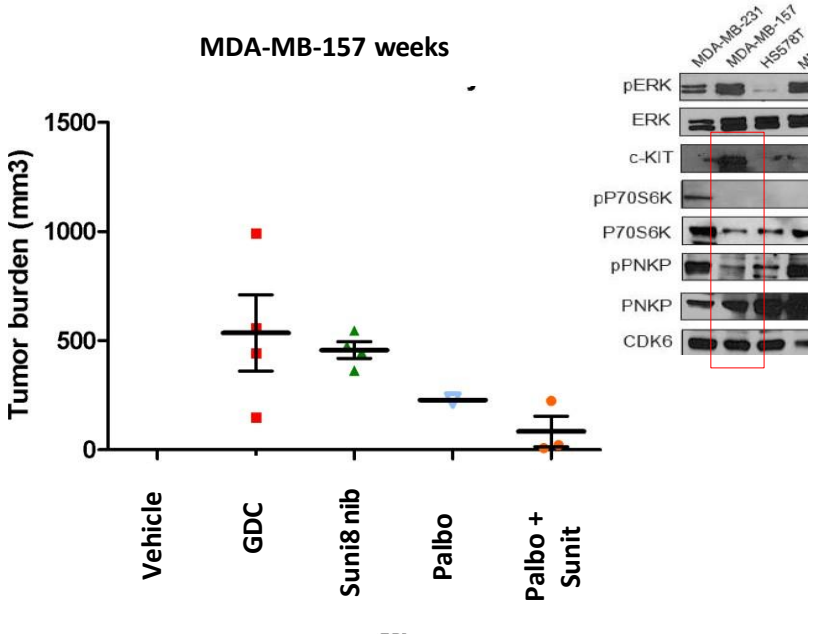



**Figure 5: Therapeutic combination selection based on hyperactive kinases:** *a different model (MDA-MB-157, aggressive TNBC) was xenografted and different doublets were administered to the animals. As it can be observed, in this model with hyperactivation of KIT and CDK6, the combination of palbociclib and sunitinib was the most effective. Doublets where one of the agents targets one non-activated kinase are usually non-effective.*

Up to 6 different xenografts from TNBC cell lines and 4 patient derived xenografts (PDXs) were studied. The activity of the doublets directed towards the most active kinases always exerted great therapeutic efficacy. Doublets targeting non-active kinases lacked efficacy. Of note, palbociclib alone was not effective in any case in monotherapy, despite observing CDK6 activation. The implications of these observations are mainly two:

- 1) we have uncovered the top-codependent signaling axes for tumor survival with CDK6 in TNBC;
- 2) contrary to what was previously thought, there is a clinical niche for palbociclib in TNBC, but always following rationale combinatorial strategies as the one laid out here.

## Summary and considerations

Our data constitute the first phosphoproteomic taxonomy of TNBC and constitutes a seminal manuscript in the field recently published in Nature Communications [1].

This tool allows not only to find novel phosphosites and kinases that account for the biology of this disease but also to use this knowledge to accurately classify this disease for the first time. We were also able to build a signature that is sufficiently parsimonious and easy to measure in daily clinical routine samples embedded in paraffin. More importantly, this taxonomy is not only able to provide prognosis information: it also reveals the targets that a patient should have modulated with targeted inhibitors in case her taxonomy results classified her in the adverse prognosis subgroup. Thus, our taxonomy also provides therapeutic solutions.

Next step is to validate the therapeutic results in humans. To this end, it is necessary to assess each of the possible 2-by-2 combinations individually, in advanced TNBC in order to detect which of them yield signals of activity. Although for some of these targets (i.e., PNKP, p70S6K) there are not clinical-grade available compounds, Pfizer has developed agents that effectively inhibit several of the kinases in the list, such as cKIT (sunitinib) or CDK6 (palbociclib, which according to our preclinical data seems the cornerstone agent for the doublets). In addition, a recent partnership with Array Biopharma will allow Pfizer developing the MEK inhibitor binimetinib (effective against models with high ERK signaling output).

Some previous studies have assessed the role of inhibitors against some of the former kinases but that have always been performed in monotherapy, without taking into account that the maintenance of aggressive TNBC biology, according to our results, requires the activity of several of these axes. Thus, it is unlikely to achieve a durable and/or meaningful benefit by using single-agent approaches. These agents have to be evaluated at least in 2-by-2 combinations.

Among all the combinations tested, CDK+MEK/ERK inhibition was the most powerful [1]. In order to set a proof of concept, and prior to launch a multi-arm trial with treatment allocation based on the status of each of the six kinases, we propose to launch a single-arm pilot trial testing palbociblib + binimetinib (CDK4/6 plus MEK inhibition) in advanced TNBC. Only patients within the highest quartiles of activation of CDK4/6 and/or ERK will be candidates for the trial. If no signal of activity is detected in this pilot trial, it is unlikely that the other combinations will be active.

In addition, it would make unlikely as well to observe activity outside the subsets of patients with CDK4/6/ERK within the highest levels of activation. Although this requires real-time determination by a centralized pathology lab during the screening procedures, such biomarker enrichment will allow maximizing the chances of success. Real-time patient selection assumes a positivity of activated ERK, CDK4/6 or both in 42% of incident TNBC patients [1]. Patients candidates for this trial will have sent to CNIO their tumor sample. Two duplicates for each staining will be processed and acquired by an automated Ariol Scanning Machine after pathologic

evaluation. We will set-up a circuit that supports sample shipment/processing twice per week coupled with a response time (with final pathologic evaluation and H-score report communicated to the CRO) of less than 7 days, in order to avoid delays in the screening processes. Should this pilot trial be successful, other doublets may be tested and also different cut-off values might be used for trial selection in the future.

Recent preclinical studies suggest that alternating schedules (continuous palbociclib administration plus 3 weeks on/1 off MEK inhibitor, or continuous MEK inhibitor plus 3 weeks on/1 off palbociclib) are more effective and better tolerated in animals than continuous dosing of both agents alone [41]. We propose to use as starting dose that one found as RP2D in a similar study ongoing in lung cancer that has already completed the safety lead-in part (NCT03170206, data on file). In this study binimetinib 45 mg BID was the recommended phase II dose [42]. Another study with binimetinib and palbociclib in colorectal cancer (NCT03981614) uses the same starting doses of both drugs without a preceding dose-escalation phase. A subsequent study in a larger number of patients in advanced melanoma showed that a significant number (61%) of patients had to undergo dose reduction to 30 mg/BID because of the former side effects and others such as hypertension, decreased LVEF or elevated CPK [43]. Some of these toxicities partially overlap with those already registered for palbociblib, such as diarrhea and decreased blood counts. So we propose to start on 45 mg/BID (binimetinib, continuous dosage) plus 100 mg daily (palbociclib, days 1-21/28). If tolerance is good (no side effects or at most tolerable grade 1 side effects) after a full cycle (28 days) patients will be allowed to escalate palbociclib to 125, according to the study investigators' decision. Alternatively, patients with non-tolerable grade 2 events will resume at 30 mg/BID of binimetinib upon recovery, maintaining palbociclib at 100 mg 21-on/7-off. Depending on the side-effects, in case of clear relationship with palbociclib is established, palbociclib - instead of binimetinib – will be reduced to 75 mg daily.

We propose a single-arm pilot trial testing palbociblib + binimetinib (CDK4/6 plus MEK inhibition) in advanced TNBC to evaluate preliminary activity of this combination by measuring 3-months PFS.

## 5.3. Study 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.

Exploratory objective:

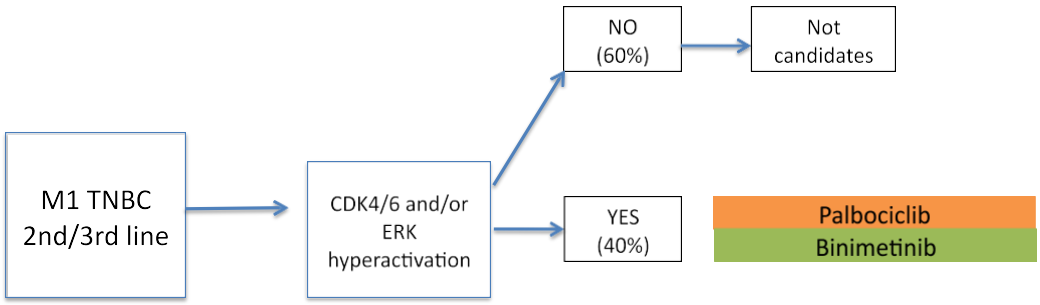
- CCI [redacted]

# 6. STUDY DESIGN

## 6.1. Overall 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 at least one treatment regimen for advanced disease will be candidates for the trial. A fresh tumor sample will be obtained in order to determine the phosphoproteomic profile of the tumor preferably obtained after last treatment or the most recent sample as possible (from metastatic site or first diagnosis according to sample availability) prior to study inclusion. If the patient has not a tumor sample available prior to study inclusion, the patient will not be allowed to participate in the study. Activation of the two kinases of interest will be determined centrally at CNIO. Only patients with scores above the upper quartile of at least one of them will be candidates (according to our series, approximately 40% of the patients are positive for CDK4/6 and/or ERK).

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. Tumor evaluation will be performed every 8 weeks. Study treatment will continue until disease progression, unacceptable toxicity, intercurrent serious disease, consent withdrawal or investigator´s decision.

If treatment tolerance is good (no side effects or at most tolerable grade 1 side effects) after a full cycle (28 days) patients will be allowed to escalate palbociclib to 125, according to the study investigators' decision. Alternatively, patients with non- tolerable grade 2 events will resume at 30 mg/BID of binimetinib upon recovery, maintaining palbociclib at 100 mg 21-on/7-off. Depending on the side-effects, in case of clear relationship with palbociclib is established, palbociclib -instead of binimetinib – will be reduced to 75 mg daily.

The study will be conducted at 8 Spanish sites and will enroll 25 patients.

### Study of immune resistance to study drugs

In addition to evaluate the efficacy of study treatment, it is highly probable that in the long term the tumor will grow again, even if promising data on activity are found. It is necessary to investigate the reasons that lead to this event, in order to be able to design new therapies or therapeutic combinations that delay or prevent the development of resistance.

To do this, we are working with murine models of breast cancer that mimic the therapeutic scenario of advanced breast cancer, but it is necessary to study and validate the possible findings in the clinical setting.

Currently, we are trying to understand how different targeted therapies impact the immune system's ability to control tumor growth. CCI [redacted]

### 6.2. Primary endpoint

- Three-months PFS.

### 6.3. Secondary endpoints

- Overall response rate.
- CCI [redacted]
- Number of patients experiencing each AE will be summarized by CTCAE grade to evaluate safety profile, according to NCI-CTC v 5 criteria.

### 6.4. Exploratory endpoints:

- CCI [redacted]

## 7. PATIENT SELECTION

### 7.1. Inclusion criteria

Patients must meet the following criteria for study entry:

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 [1].
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) $\geq 1.500/mm^3$ (without granulocyte colony-stimulating factor support within 2 weeks before the first study drug administration)
    b. Hemoglobin $\geq 9$ g/dL (without transfusion or erythropoietin within 4 weeks before the first study drug administration)
    c. Platelet count $\geq 100.000/mm^3$ (without transfusion within 2 weeks before the first study drug administration)
    d. Total bilirubin $\leq 2 \times$ the upper limit of normal (ULN).
    e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2.5 \times$ ULN ($\leq 5$ times ULN for patients with liver metastases)
    f. Glomerular filtration rate (GFR) > 50 mL/min/1.73 $m^2$ 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.

### 7.2. Exclusion criteria

Patients who meet any of the following criteria will be excluded from study entry:

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.

### 7.3. Randomization procedures

Not applicable. Single arm, open-label study.

### 7.4. Blinding procedures

Not applicable. Open-label study.

## 8. WITHDRAWAL CRITERIA

### 8.1. Reasons for Withdrawal

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

Reasons for withdrawal from the study may include but are not limited to the following:

- Unacceptable toxicity.
- If, in the investigator's opinion, continuation of study would be harmful to the patient's well-being.
- Any toxicity requiring dose reduction below 30 mg/BID of binimetinib or 75 mg daily of palbociclib.
- Any toxicity requiring dose interruption longer than 28 days to resolve to Grade 1 or better.
- Any other potential adverse reaction deemed sufficiently serious to warrant discontinuation of treatment by the investigator or his designated associate(s).
- Any decrease in visual acuity, or symptomatic or asymptomatic retinal disorders including retinal detachment / retinal pigment epithelial detachment / serous retinopathy / **retinal vein occlusion** classified analog to CTCAE v.5 as Grade 2 or higher. Based on the individual benefit risk assessment and after discussion with the sponsor, patient may interrupt treatment until recovery to at least Grade 1 and then treatment may be resumed at one dose level below.
- Grade 4 non-hematological toxicity (laboratory abnormalities of any grade will not be considered toxicity unless deemed clinically significant by the investigator).
- Any AE that meets criteria for discontinuation.

- Subject noncompliance that warrants withdrawal in the opinion of the investigator or sponsor.
- Initiation of alternative anticancer therapy including another investigational agent.
- Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with study treatment.

If the administration of any of the study drugs has to be stopped, the site principal investigator will consult with the sponsor to withdraw the patient from the study (depending on the duration of treatment, if she has benefit, if the benefit is attributed to the suspended drug, etc.).

### 8.2. Handling of Withdrawals

The investigator will be requested to collect all patient data until she leave the study treatment. If a subject will be withdrawn by the Investigator or withdraws from the study, the Investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal including the date of last treatment and the reason for withdrawal.

If the subject is withdrawn due to an adverse event, the Investigator will follow the subject until the adverse event has resolved or stabilized.

All patients who are withdrawn from the study should complete protocol specified withdrawal procedures.

### 8.3. Reserve and Replacement Subjects

Patients who withdraw or are withdrawn from the study prior to completing the first cycle for reasons other than toxicity will be replaced.

## 9. INVESTIGATIONAL PRODUCT

### 9.1. Investigational product description

#### 9.1.1. Binimetinib

##### 9.1.1.1.Description

Binimetinib is supplied as film-coated tablets in a dosage strength of 15 mg.

#### 9.1.1.2. Packaging

Binimetinib 15 mg are packaged in blister packs containing 12 tablets. Each pack contains 168 tablets.

#### 9.1.1.3. Shipping, Storage and Disposal

Binimetinib film-coated tablets should not be stored above 25°C and should be protected from light.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

#### 9.1.1.4. Dosage and administration

Patients will receive continuous binimetinib at 45 mg/BID. Binimetinib dose may be reduced to 30 mg/BID according to tolerance and investigator's criteria. Dose re- escalation is allowed in case toxicities are recovered and no new events are present in at least 28 days.

Patients should be encouraged to take their dose at approximately the same time each day. If the patient vomits or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.

Binimetinib tablets are intended for oral administration with water; tablets should be swallowed whole and should not be chewed. Binimetinib may be taken without regard to food.

### 9.1.2. Palbociclib

#### 9.1.2.1.Description

Palbociclib are opaque, hard capsules with 75, 100 and 125 mg of palbociclib.

#### 9.1.2.2. Packaging

Palbociclib 75 mg, 100 mg and 125 mg are packaged in blister packs of 21 hard capsules. PVC/PCTFE/PVC/Al blister strip containing 7 hard capsules (one capsule per cell). Each carton contains 21 hard capsules (3 blister strips per pack).

#### 9.1.2.3. Shipping, Storage and Disposal

Palbociclib does not require any special storage conditions.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

#### 9.1.2.4. Dosage and administration

Patients will receive palbociclib on day 1 at 100 mg per day until day 21 followed by a 7-day rest. Palbociclib may be escalated to 125 mg per day according to tolerance and investigator's criteria, starting in cycle 2.

Patients should be encouraged to take their dose at approximately the same time each day. If the patient vomits or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.

Palbociclib should be taken with food, preferably a meal and should not be opened. Capsules are intended for oral administration with a glass of water; capsules should be swallowed whole and should not be chewed or crashed.

## 9.2. Treatment duration

Treatment will continue until disease progression, unacceptable toxicity, significant intercurrent disease, consent withdrawal or investigator´s decision.

In case of discontinuation/interruption for toxicity of one of the 2 drugs of the combination therapy during treatment, the continuation of patient in the study with the other drug will be agreed with study sponsor (depending on the duration of treatment, if she has benefit, if the benefit is attributed to the suspended drug, etc.).

## 9.3. Criteria for dose adjustments

### 9.3.1. Palbociclib

Dose modification of palbociclib is recommended based on individual safety and tolerability. Management of some adverse reactions may require temporary dose interruptions/delays, and/or dose reductions, or permanent discontinuation as per dose reduction schedules provided in Tables 1, 2, and 3.

**Palbociclib recommended dose modifications for adverse reactions**

| Dose level | Dose |
|---|---|
| Recommended dose | 125 mg/day |
| First dose reduction | 100 mg/day |
| Second dose reduction | 75 mg/day* |

*If further dose reduction below 75 mg/day is required, discontinue the treatment.

Complete blood count should be monitored prior to the start of palbociclib therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated.

For patients who experience a maximum of Grade 1 or 2 neutropenia in the first 6 cycles, complete blood counts for subsequent cycles should be monitored every 3 months, prior to the beginning of a cycle and as clinically indicated.

Absolute neutrophil counts (ANC) of $\geq 1.000/mm^3$ and platelet counts of $\geq 50.000/mm^3$ are recommended to receive palbociclib.

### Palbociclib dose modification and management – Haematological toxicities

| CTCAE Grade | Dose modifications |
|---|---|
| Grade 1 or 2 | No dose adjustment is required. |
| Grade 3[a] | Day 1 of cycle:<br>Withhold palbociclib, until recovery to Grade ≤2, and repeat complete blood count monitoring within 1 week. When recovered to Grade ≤2, start the next cycle at the ***same dose***.<br><br>Day 15 of first 2 cycles:<br>If Grade 3 on Day 15, continue palbociclib at the ***current dose*** to complete cycle and repeat complete blood count on Day 22.<br>If Grade 4 on Day 22, see Grade 4 dose modification guidelines below.<br><br>Consider dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia on Day 1 of subsequent cycles. |
| Grade 3 ANC[b] (<1000 to $500/mm^3$) + Fever ≥38.5 ºC and/or infection | At any time:<br>Withhold palbociclib until recovery to Grade ≤2<br><br>Resume at next lower dose. |
| Grade 4[a] | At any time:<br>Withhold palbociclib until recovery to Grade ≤2.<br><br>Resume at next lower dose. |
| Grading according to CTCAE 4.0.<br>ANC=absolute neutrophil counts; CTCAE=Common Terminology Criteria for Adverse Events; LLN=lower limit of normal.<br>[a] Table applies to all haematological adverse reactions except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).<br>[b] ANC: Grade 1: ANC < LLN - $1500/mm^3$; Grade 2: ANC 1000 - <$1500/mm^3$;<br>Grade 3: ANC 500 - <$1000/mm^3$; Grade 4: ANC <$500/mm^3$. | |

### Table 3. Palbociclib dose modification and management – Non-haematological toxicities

| CTCAE Grade | Dose modifications |
|---|---|

| | |
|---|---|
| Grade 1 or 2 | No dose adjustment is required. |
| Grade ≥3 non-haematological toxicity (if persisting despite medical treatment) | Withhold until symptoms resolve to:<br>- Grade ≤1;<br>- Grade ≤2 (if not considered a safety risk for the patient)<br>Resume at the next lower dose. |
| Grading according to CTCAE 4.0.<br>CTCAE=Common Terminology Criteria for Adverse Events. | |

**Interstitial Lung Disease/Pneumonitis**

Severe, life-threatening, or fatal ILD and/or pneumonitis can occur in patients treated with cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors, including palbociclib when taken in combination with endocrine therapy.

Across clinical trials, 1.4% of palbociclib -treated patients had ILD/pneumonitis of any grade, 0.1% had Grade 3, and no Grade 4 or fatal cases were reported. Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported. Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (eg, hypoxia, cough, dyspnea). In patients who have new or worsening respiratory symptoms and are suspected to have developed ILD/pneumonitis, interrupt palbociclib immediately and evaluate the patient. Permanently discontinue palbociclib in patients with severe ILD or pneumonitis. **Permanently discontinue palbociclib in patients with severe interstitial lung disease (ILD)/pneumonitis.**

### 9.3.2. Binimetinib

For patients receiving 45 mg binimetinib twice daily, the recommended reduced dose of binimetinib is 30 mg twice daily. Dose reduction below 30 mg twice daily is not recommended. Therapy should be discontinued if the patient is not able to tolerate 30 mg orally twice daily.

If the adverse reaction that resulted in a dose reduction is under effective management, dose re-escalation to 45 mg twice daily may be considered. Dose re- escalation to 45 mg twice daily is not recommended if the dose reduction is due to left ventricular dysfunction or any Grade 4 toxicity.

**Recommended dose modifications for binimetinib for selected adverse reaction.**

| Severity of adverse reaction[a] | Binimetinib |
|---|---|
| *Cutaneous reactions* | |
| • Grade2 | Binimetinib should be maintained.<br>If rash worsens or does not improve within 2 weeks with treatment, binimetinib should be withheld until improved to Grade 0 or 1 and then resumed at the same dose if first occurrence or resumed at a reduced dose if recurrent Grade2. |
| • Grade 3 | Binimetinib should be withheld until improved to Grade 0 or 1 and resumed at the same dose if first occurrence or resumed at a reduced dose if recurrent Grade 3. |
| • Grade 4 | Binimetinib should be permanently discontinued. |
| *Ocular events* | |
| • Symptomatic retinal pigment epithelial detachments (RPED) (Grade 2 or 3) | Binimetinib should be withheld for up to 2 weeks and ophthalmic monitoring should be repeated including visual acuity assessment.<br>• If improved to Grade 0 or 1, binimetinib should be resumed at same dose.<br>• If improved to Grade 2, binimetinib should be resumed at a lower dose.<br>• If not improved to Grade 2, binimetinib should be permanently discontinued. |
| • Symptomatic RPED (Grade 4) associated with reduced visual acuity (Grade 4) | Binimetinib should be permanently discontinued. |
| • Retinal vein occlusion (RVO) | Binimetinib should be permanently discontinued. |

| Severity of adverse reaction[a] | Binimetinib |
|---|---|
| *Cardiac events* | |
| • Grade 2 Left ventricular ejection fraction (LVEF) decrease or asymptomatic, absolute decrease in LVEF of greater than 10 % from baseline that is below lower limit of normal (LLN) | LVEF should be evaluated every 2 weeks.<br>• If asymptomatic:<br>Binimetinib should be withheld for up to 4 weeks.<br>Binimetinib should be resumed at a reduced dose if all of the following are present within 4 weeks:<br>o LVEF is at or above the LLN<br>o Absolute decrease from baseline is 10 % or less.<br>• If the LVEF does not recover within 4 weeks, binimetinib should be permanently discontinued. |
| • Grade 3 or 4 LVEF decrease or symptomatic left ventricular dysfunction (LVD) | Binimetinib should be permanently discontinued.<br>LVEF should be evaluated every 2 weeks until recovery. |
| *Rhabdomyolysis/Creatine phosphokinase (CK) elevation* | |
| • Grade 3 (CK > 5 – 10x upper limit of normal (ULN)) asymptomatic | Binimetinib dose should be maintained and it should be ensured that patient is adequately hydrated. |
| • Grade 4 (CK > 10x ULN) asymptomatic | Binimetinib should be withheld until improved to Grade 0 or 1. It should be ensured that patient has adequate hydration. |
| • Grade 3 or grade 4 (CK > 5x ULN) with muscle symptoms or renal impairment | Binimetinib should be withheld until improved to Grade 0 or 1.<br>• If resolved within 4 weeks, binimetinib should be resumed at a reduced dose, or<br>• Binimetinib should be permanently discontinued. |
| *Venous thromboembolism (VTE)* | |
| • Uncomplicated deep vein thrombosis (DVT) or pulmonary embolism (PE) ≤ Grade 3 | Binimetinib should be withheld.<br>• If improved to Grade 0 or 1, binimetinib should be resumed at a reduced dose, or<br>• If not improved, binimetinib should be permanently discontinued. |
| • Grade 4 PE | Binimetinib should be permanently discontinued. |

| Severity of adverse reaction[a] | Binimetinib |
|---|---|
| *Liver laboratory abnormalities* | |
| • Grade 2 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3x – ≤ 5x upper limit of normal (ULN) | Binimetinib dose should be maintained.<br>If no improvement within 2 weeks, binimetinib should be withheld until improved to Grade 0 or 1 or to baseline levels, and then resumed at the same dose. |
| • First occurrence of Grade 3 (AST or ALT > 5x ULN and blood bilirubin > 2x ULN) | Binimetinib should be withheld for up to 4 weeks.<br>• If improved to Grade 0 or 1 or baseline level, binimetinib should be resumed at reduced dose, or<br>• If not improved, binimetinib should be permanently discontinued. |
| • First occurrence of Grade 4 (AST or ALT > 20 ULN) | Binimetinib should be withheld for up to 4 weeks.<br>• If improved to Grade 0 or 1 or baseline levels, binimetinib should be resumed at a reduced dose level, or<br>• If not improved, binimetinib should be permanently discontinued.<br><br>Or, binimetinib should be permanently discontinued. |
| • Recurrent Grade 3 (AST or ALT > 5x ULN and blood bilirubin > 2x ULN) | It should be considered to permanently discontinue binimetinib. |
| • Recurrent Grade 4 (AST or ALT > 20 ULN) | Binimetinib should be permanently discontinued. |
| *Interstitial lung disease (ILD)/pneumonitis* | |
| • Grade 2 | Binimetinib should be withheld for up to 4 weeks.<br>• If improved to Grade 0 or 1, binimetinib should be resumed at reduced dose, or<br>• If not resolved within 4 weeks, binimetinib should be permanently discontinued. |
| • Grade 3 or Grade 4 | Binimetinib should be permanently discontinued. |

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03

**Recommended dose modifications for binimetinib for other adverse reactions.**

| Severity of adverse reaction | Binimetinib |
|---|---|
| • Recurrent or intolerable Grade 2 adverse reactions<br>• First occurrence of Grade 3 adverse reactions | Binimetinib should be withheld for up to 4 weeks.<br>• If improved to Grade 0 or 1 or baseline level, binimetinib should be resumed at reduced dose, or<br>• If not improved, binimetinib should be permanently discontinued. |
| • First occurrence of Grade 4 adverse reactions | Binimetinib should be withheld for up to 4 weeks.<br>• If improved to Grade 0 or 1 or baseline levels, binimetinib should be resumed at a reduced dose level, or<br>• If not improved, binimetinib should be permanently discontinued.<br><br>Or, binimetinib should be permanently discontinued binimetinib. |
| • Recurrent Grade 3 adverse reactions | It should be considered to permanently discontinue binimetinib. |
| • Recurrent Grade 4 adverse reactions | Binimetinib should be permanently discontinued. |

## 9.4. Accountability

The trial medication will be sent directly from the sponsor to the investigator's site preceded by the Regulatory Green Light. The medication is to be used exclusively in the clinical trial according to the instructions of this trial protocol.

When a drug shipment is received, the Investigator or designee will check the amount and condition of the delivery, drug expiration date, and sign the Receipt of Shipment Form provided. The Receipt of Shipment Form should be faxed or emailed to the sponsor and also to CRO. The original form will preliminarily be retained at the site and will be collected at the next monitoring visit by the monitor and stored in the Centre File of the TMF at CRO. A copy remains in the Investigator File at the site. In case of shipment problems the Investigator or designee shall contact the CRA as soon as possible.

A Drug Accountability Record will be provided for the trial medication. The record must be continuously updated and contain the dates, quantities and compounds of drugs received, medication identification number(s), the patient identification number to whom the trial medication was dispensed, date and quantity of medication dispense and date and number of returned tablets/blisters/boxes, as well as the initials of the dispenser.

Trial medication will be monitored by the CRA at the respective hospital pharmacy prior to destruction after having completed a final inventory. Local or institutional regulations may require immediate destruction of the study drug used for safety reasons, e.g., cytotoxicity or to maintain the storage capacity and functionality of the storage at the site. In these cases, it may be acceptable to destroy it by the research staff, including partially used and empty vials, dispensed before a monitoring inspection, if the verification of original documents of empty boxes that indicate the information of batch number and dispensing date to the patient on the label. This documentation will be verified against the quantity shipped, dispensed, returned and destroyed.

Prior to the destruction a final trial medication reconciliation statement must be completed. Drug supplies will be destroyed according to the legal requirements in Spain.

All trial medication inventory forms must be made available for inspection by a Sponsor-authorized representative or designee and regulatory agency inspectors. The Investigator is responsible for the accountability of all used and unused study supplies at the site.

### 9.5. Auxiliary Medicinal Products

Not applicable

### 9.6. Concomitant medication

Overall, the risk for binimetinib to be a cause of or be affected by significant drug- drug interactions is predicted to be low. However, given the predominant role of UGT1A1 in the metabolism of binimetinib, special consideration should be taken for co-administration of drugs that are UGT1A1 inhibitors or inducers, and administration of binimetinib to patients with low UGT1A1 activity.

Binimetinib has been shown to be a substrate for P-gp and BCRP in vitro. The impact of P-gp/BCRP inhibitors on the PK of binimetinib in vivo is unknown; therefore, it is recommended that P-gp and BCRP inhibitors are dosed with caution.

The following concomitant treatments are allowed:

1. Zoledronic acid or denosumab for bone metastases, started at least 28 days prior to enrollment.

2. Low dose corticosteroids (with or without anti-seizure drugs) - equivalent to 10mg prednisone per day, although this situation can be addressed in a case- by-case basis through discussion with the trial coordinators, that has been stable for more than 28 days for brain metastases currently non-uncontrolled.

3. Supportive measures such as pain drugs, eritropoetin, antiemetics, antidiarrhea, etc - according to current standards of care.

4. Appropriate treatments for intercurrent conditions as long as not deemed severe enough by the investigator to justify coming off trial (i.e., antibiotics for an intercurrent infection, etc).

### 9.7. Prohibited drugs

Concomitant therapy with the following medication is prohibited:

- Concomitant use of strong inhibitors of CYP3A4 and strong inducers of CYP3A4 are not permitted for 2 weeks prior to start of study treatment or during the study.
- Concomitant use of moderate and weak CYP3A4 inducers should be avoided.
- Concomitant use of herbal preparations containing CYP3A4 inducers (e.g. St John's Wort) are not permitted during the study.
- Grapefruit and grapefruit juice (CYP3A4 inhibitor) consumption is not permitted during the study.
- Patients may not receive other investigational treatment or other approved anti-tumor therapy while on this protocol.

# 10. STUDY SCHEDULE

| Procedure | Screening (-28 to -1) | Cycle 1 and 2 (± 2 days) | | | | Cycle 3+ (± 2 days) | | EOT / Early withdrawal | Safety FU visit |
|---|---|---|---|---|---|---|---|---|---|
| | | D1 | D8 | D15 | D22 | D1 | D15 | | |
| **Informed consent** | X | | | | | | | | |
| **Demographic data** | X | | | | | | | | |
| **Selection criteria** | X | | | | | | | | |
| **Medical history[1]** | X | | | | | | | | |
| **Physical exam[2]** | X | X | X | X | X | X | X | X | X |
| **Ophthalmological examination** | X | X | X[3] | X | X[3] | X | | X | X |
| **Weight** | X | X | X | X | X | X | X | X | X |
| **Height** | X | | | | | | | | |
| **ECOG PS** | X | X | | | | X | | X | X |
| **Vital signs[4]** | X | X | X | X | X | X | X | X | X |
| **12-Lead ECG (qTC)** | X | If clinically indicated | | | | | | | |
| **LVEF (ECHO/MUGA)[5]** | X | X | | | | X[5] | | X | X |
| **Hematology[6]** | X | X | X | X | X | X | X | X | X |
| **Biochemistry[7]** | X | X | X | X | X | X | X | X | X |
| **TSH, fT3 y fT4[8]** | X | X | | | | X | | X | X |
| **Urinalysis[9]** | X | X | | | | X | | X | X |
| **Coagulation[10]** | X | X | | | | X | | X | X |
| **Serology[11]** | X | If clinically indicated | | | | | | | |
| **Serum pregnancy test [12]** | X | X | | | | X | | X | X |
| **Archival and fresh tumor biopsy[13]** | X | | | | | | | | |
| **Blood sample (correlative studies) [18]** | | X | | | | | | X | |
| **Tumor sample (correlative studies) [19]** | | | | | | | | X | |
| **Tumor evaluation (PET-CT/CT/MRI)** | X | X[14] | | | | X[14] | | X | |
| **Binimetinib administration** | | X | X | X | X | X | X | | |
| **Palbociclib administration[13]** | | X | X | X | X | X | X | | |
| **Adverse events[16]** | | X | | | | | | | |
| **Concomitant medications** | X[17] | X | X | X | X | X | X | X | X |

1. Medical history, including prior treatments for BC.

| |
|---|
| 2. A complete physical exam will be carried out during the screening visit and thereafter targeting symptoms in subsequent study visits. |
| 3. Only cycle 1. |
| 4. Vital Signs: pulse, blood pressure and temperature. |
| 5. ECHO/MUGA will be performed before start binimetinib treatment, 1 month after the start of treatment and every 3 months thereafter. |
| 6. Hematology include absolute red blood cell count (RBC), hemoglobin, hematocrit, platelet count, white blood cell count (WBC), with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils). Hematology will be performed in the 14 days previous to start study treatment. |
| 7. Alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), total bilirubin; blood urea/blood urea nitrogen (BUN), creatinine: creatinine clearance; glucose, albumin, cholesterol, triglyceride, phosphorus, lactate dehydrogenase (LDH), total protein, uric acid, creatinine phosphokinase (CPK); Sodium, potassium, calcium, magnesium, chloride, bicarbonate (HCO3). Biochemistry will be performed in the 14 days previous to start study treatment. |
| 8. Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system. In the 14 days previous to start study treatment. |
| 9. Urinalysis: bilirubin, blood, glucose, ketones, PH, protein specific gravity, colour and appearance. Dipstick test every cycle. Additional analyses will be done at investigator criteria in case of abnormal results. Urinalysis will be performed in the 14 days previous to start study treatment. |
| 10. Coagulation tests: prothrombin time, APTT and INR. In the 14 days previous to start study treatment. |
| 11. Serology: hepatitis B surface antigen, hepatitis C antibody, HIV antibody. In the 14 days previous to start study treatment and if clinically indicated thereafter. |
| 12. Serum pregnancy test only pre-menopausal female subjects of childbearing potential. At study entry, every 4 weeks during the study treatment and at the end of study treatment. |
| 13. All formalin-fixed, paraffin-embedded (FFPE) tissue samples block and one hematoxylin and eosin (H&E) stained tumor slide, both obtained in the 15 days before patient inclusion in the study, will be sent to CNIO in order to determine positivity of ERK and/or CDK4/6, preferably obtained after last treatment or the most recent sample as possible (from metastatic site or first diagnosis according to sample availability). |
| 14. Tumor evaluation will be performed every 8 weeks until confirmed PD. |
| 15. 21 days-on/7 days-off. |
| 16. This applies to all non-serious AEs and SAEs that occur at any time during the administration of the study drug and up to 30 days after end of treatment. |
| 17. Concurrent medications administered within the 28 days preceding day 1. |
| 18. Blood sample: two CPT tubes of 7 ml will be obtained at baseline visit before treatment administration, at C2D1 and at disease progression (a 2 weeks window is allowed from confirmation of disease progression). |
| 19. An image-guided biopsy will be done upon progression. The biopsy is allowed within 4 weeks after the confirmation of disease progression and in any case before starting the next line of treatment. |

### 10.1. Pre-study visit (screening)

For patient registration, site staff should complete the registration form at the eCRF. The CRO will send confirmation e-mail of registration of the patient's number assigned within 24 hours from receipt of the information.

The following procedures will be performed within 28 days prior to registration:

- Informed consent for in order to determine positivity of ERK and/or CDK4/6 for study treatment eligibility will be obtained prior to any study procedures being performed. Each participant will be given a copy of the signed informed consent forms (ICF). The ICF must be approved by an Independent Ethics Committee (IEC). Only patients ERK and/or CDK4/6 positive will be invited to participate in the study and sign the ICF for study treatment eligibility
- Tumor sample (FFPE block and H&E slide) for ERK and CDK4/6 analysis. ERK and CDK4/6 analysis will be performed at CNIO. Preferably obtained after last treatment or the most recent sample as possible (from metastasis or first diagnosis according to sample availability) prior to study inclusion. If the patient has not a tumor sample available prior to study inclusion, the patient will not be allowed to participate in the study
- Review selection criteria
- Demographics
- Tumor evaluation: PET-CT, CT and/or MRI
- Complete medical history (including prior treatments for breast cancer)
- Physical examination will be conducted on each patient for a review of systems and determination of any concurrent symptoms or conditions prior to the first dose of study drug
- Ophthalmological examination
- Vital Signs: pulse, blood pressure and temperature
- Height, weight
- ECOG performance status
- 12-lead ECG, including qTC
- ECHO / MUGA
- Concurrent medications: Record all concurrent medications administered within the 28 days preceding Day 1

The following procedures should be performed within 14 days prior to registration:

- Hematology: hemoglobin, hematocrit, platelet count, red blood cell (RBC) count, white blood cell (WBC) count, and percent and absolute differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils).
- Biochemistry: (glucose, urea/BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, total protein, uric acid, albumin, cholesterol, triglyceride, serum total bilirubin, alkaline phosphatase, LDH, CPK, AST, ALT and GGT).
- Coagulation: basic coagulation study following each center standards, including prothrombin time, aPTT and INR.
- TSH, fT3 y fT4. Free T3 and free T4 will only be measured if TSH is abnormal.
- Urinalysis: bilirubin, blood, glucose, ketones, PH, protein specific gravity, colour and appearance.
- Serologies: hepatitis B surface antigen, hepatitis C antibody, HIV antibody.

The following procedure should be performed within 7 days prior to Day 1:

- Pregnancy Testing. Pre-menopausal women of childbearing potential only are required to have a negative serum pregnancy test.

### 10.2. Study treatment visits

Study patients will be evaluated weekly during the first 2 months and every 2 weeks thereafter.
The following procedures will be performed during study treatment:

- Tumor evaluation: PET-CT, CT and/or MRI (every 8 weeks)
- Physical examination: will be performed at screening and thereafter targeting symptoms in subsequent study visits
- Ophthalmological examination: Ask patient for changes in vision at every visit. If change in vision is reported, an ophthalmological examination must be performed preferably within 3 days. Ophthalmologic examination will be performed weekly during first cycle, biweekly during second cycle and every 4 weeks thereafter. Particularly for patients who experience any decrease in visual acuity, or symptomatic or asymptomatic retinal disorders including retinal detachment / RPED / serous retinopathy / retinal vein occlusion (Grade 1 analog to CTCAE v.5) have to undergo ophthalmologic examinations on day 1 of every cycle.
- Weight: in all study visits

- Vital Signs: pulse, blood pressure and temperature; every week during first two cycles, and days 1 and 15 of each cycle thereafter
- ECOG performance status (day 1 of every cycle)
- 12-lead ECG: if clinically indicated
- ECHO/MUGA: before start binimetinib treatment, 4 weeks after the start of treatment and every 12 weeks thereafter.
- Hematology: every week during first two cycles, and days 1 and 15 of each cycle thereafter
- Biochemistry: every week during first two cycles, and days 1 and 15 of each cycle thereafter. Safety laboratory tests can be collected up to 2 days prior to drug administration.
- TSH, fT3 y fT4: day 1 of every cycle. Free T3 and free T4 will only be measured if TSH is abnormal.
- Coagulation: day 1 of every cycle
- Urinalysis: day 1 of every cycle
- Serologies: if clinically indicated
- Pregnancy Testing: every 4 weeks (day 1 of each cycle). Pre-menopausal women of childbearing potential only
- Adverse events: in all study visits
- Concomitant medications: in all study visits
- Blood sample: two CPT tubes of 7 ml will be obtained before treatment administration at D1C1 and D1C2.

### 10.3. End of treatment / early withdrawal

The following procedures will be performed at end of treatment / early withdrawal visit:

- Tumor evaluation: PET-CT, CT and/or MRI, if patient stops study treatment for any reason other than disease progression
- Physical examination
- Ophthalmological examination
- Weight
- Vital Signs
- ECOG performance status
- 12-lead ECG: if clinically indicated
- ECHO/MUGA

- Hematology
- Biochemistry
- Serology
- TSH, fT3 y fT4
- Coagulation
- Urinalysis
- Pregnancy test
- Adverse events
- Concomitant medications
- Blood sample: two CPT tubes of 7 ml will be obtained at disease progression (a 2 weeks window is allowed from confirmation of disease progression).
- An image-guided biopsy will be done upon progression. The biopsy is allowed within 4 weeks after the confirmation of disease progression and in any case before starting the next line of treatment.

### 10.4. Safety follow-up visit

The following procedures will be performed at Safety follow-up visit at day 30 and 6 months after last study dosage:

- Physical examination
- Ophthalmological examination
- Weight
- Vital Signs
- ECOG performance status
- 12-lead ECG: if clinically indicated
- ECHO/MUGA
- Hematology
- Biochemistry
- TSH, fT3 y fT4
- Coagulation
- Urinalysis
- Pregnancy test
- Adverse events
- Concomitant medications

# 11. ASSESSMENT OF SAFETY / ADVERSE EVENTS

Safety information should be collected in clinical studies in an efficient and consistent way. Adverse events must be identified and notified rapidly to identify possible risks to patients and satisfy regulatory requirements for notification of adverse events.

## 11.1. Definitions

### 11.1.1. Adverse event (AE)

An AE is any undesired experience that occurs in a patient participating in clinical research that is associated in time with the use of a medicinal product, whether or not it is considered to be related to the investigational products. Therefore, an adverse event can be any unintentional unfavorable sign (including an anomalous laboratory result), symptom or disease that is associated in time with the use of a medicinal product, whether or not it is considered to be related to the product. Pre-existing diseases that worsen during the study shall be notified as Adverse Events.

AEs include pre- or post-treatment events that occur as a result of study procedures (e.g. invasive procedures or modification of the patient's previous medication).

### 11.1.2. Serious adverse event (SAE)

A SAE is an undesired medical experience that, at any dose:

- Results in death.
- Is life-threatening: (NOTE: The term "life-threatening" refers to the fact that, according investigator criteria, the patient is at risk of death as a result of this event. Nevertheless, this definition does not consider the situation in if the AE had been more severe, patients had been in an immediate risk of death).
- Results in the patient's hospitalization or prolongs a previous hospitalization (NOTE: In general, hospitalization means that the patient has remained [at least 24 hours] in the hospital or emergency room. Complications that occur during a hospitalization are AEs. If a complication prolongs hospitalization or satisfies any of the other criteria for seriousness, then the event will be considered SAE. When any doubt exists as to whether a "hospitalization" has taken place or was necessary, the AE will be considered serious. The hospitalization to implement scheduled treatment of a disease present before the subject entered the study and that has not worsened with respect to baseline is not considered an AE) Hospitalizations for social reason are not consider an AE.
- It produces disability or incapacity (NOTE: Disability refers to an important alteration in a person's capacity to carry out his or her own daily living tasks, not minor clinical ailments such as headaches, nausea, vomiting, diarrhea, flu or accidental injuries (such as a sprained ankle), that can interfere with the functions of daily life, but do not alter them in an important way).
- It originates a congenital anomaly or birth defect.
- It is medically important, meaning medically important adverse event that the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the patient or required intervention to prevent one of the outcomes listed above.

### 11.1.3. Additional considerations

Alterations in laboratory parameters (hematology, biochemistry or urine analysis), as well as anomalous results of other studies (such as ECGs, radiology, measurements of vital constants), including those that deteriorate in relation to baseline, should be recorded as AEs or SAEs if, in the medical and scientific opinion of the investigator, they are clinically relevant.

On the contrary, clinically significant alterations in safety parameters that are associated with the study disease are not characterized as AEs or SAEs unless the investigator thinks that they are more serious than would be expected considering the state of the patient.

Lack of efficacy (i.e., disease progression) is a disease-related event and should not be classified as a SAE. Death as a result of disease progression is also excluded from the definition of SAEs.

### 11.1.4. Adverse reaction

Any harmful and non-intended response to a drug including adverse reactions derivative from any use apart from terms of commercialization authorization, abuse, and medication error. It exists a confirmed causality relationship with the administered medication.

## 11.2. Characteristics of an adverse event

### 11.2.1. Seriousness

See Serious Adverse Event definition (11.1.2 Serious Adverse Event (SAE)).

### 11.2.2. Causality assessment

The investigator has the obligation to establish the relation of causality between the investigational product administration and the adverse event(serious or not). "A reasonable possibility" is proposed to define cases in which there are facts/proof or arguments suggesting a causal relation, more than a relation that cannot be excluded. The investigator will use his or her clinical judgment to determine the relation. Alternative causes, such as the natural history of underlying diseases, concomitant treatment, other risk factors and the temporal relation between the event and the investigational drug will be considered and investigated. The investigator will also consult the investigator's brochure/summary of product characteristics in making the evaluation.

There may be situations in which a SAE occurs and the investigator has only minimal information to include in the initial report to the Sponsor. Nevertheless, it is very important that the investigator evaluate the causality of each event before the initial transmission of data to the Sponsor. The investigator can change his or her opinion about causality based on the information that appears during follow-up, which is why the SAE report may have to be modified. The evaluation of causality is one of the criteria that determine whether a case is compliant or not with the criteria of notification of the Health Authorities.

### 11.2.3. Expectedness

An unexpected adverse reaction is any untoward and unintended response that is related to study drug at any dose that is not described in the applicable product information (eg, investigators brochure for an unauthorized investigational medicinal product or summary of product characteristics for an authorized product).

APICES/Sponsor will classify a Serious Adverse Reaction as expected or unexpected according to the Reference Safety Information collected in investigator brochure or summary of product characteristics of investigational product, as appropriate.

### 11.2.4. Severity

The severity of any AEs will be graded using the CTCAE vs 5.0 (see Annex 4). If the CTCAE has no code that matches, the following guide should be used:

| Grade | Description |
|---|---|
| 0 | No adverse event |
| 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only |
| 2 | Moderate; minimal, local or noninvasive intervention indicated |
| 3 | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated |
| 4 | Life-threatening consequences; urgent intervention indicated |
| 5 | Death related to adverse event |

Grading of AEs is based on specific clinical criteria that will require evaluation by the study site Investigator. Should an AE stop and then restart, it will be considered two separate events and the severity assessed as described above.

## 11.3. Reporting procedures

### 11.3.1. Reporting of adverse events (AEs)

The investigator will try to obtain information about any adverse events that have occurred in all visits by examining or directly interrogating the patient. All information referring to adverse events must be recorded in the respective section of the CRF. AEs should be recorded according CTCAE v5.0. All adverse events that occur during the period comprehended from the start of study treatment to 30 days after last dose of the investigational products will be recorded. When one or more signs or symptoms correspond to a disease, the main diagnosis or syndrome will be notified. All adverse events will be followed until resolution or stabilization, or until it is determined that the study treatment or the patient's participation in the study has not been the cause. All adverse events still present at the end of the study period will be monitored until their final outcome is determined.

### 11.3.2. Reporting of serious adverse events (SAEs)

The investigator will notify CRO of all serious adverse events that occur during the period comprehended from the start of study treatment to 30 days after last dose within 24 h of receiving knowledge of the same or, at the latest, on the next working day.

**ATT. SAFETY DEPARTMENT**
**e-mail:** CCI [redacted]

The investigator will collect information about the SAE on the respective form. At least these **four elements are mandatory** always to report any adverse event must include the following:

- Name or any identifier of a **reporter**
- **Subject** ID number
- At least one **suspect drug**: current dose, route, dates
- **Adverse Event** information:
  - ***Adverse Event Term Seriousness Criteria***
  - ***Causality assessment***

### 11.3.3. Reporting of serious adverse events (SAEs) to Health Authorities

The sponsor is responsible for notifying to the Regulatory Health Authorities according to applicable regulations of all suspected unexpected serious adverse reactions and which occurred in the clinical trial. This communication shall be made within the time limits established by legislation.

### 11.3.4. Follow-up of AEs and SAEs

After the initial notification of an AE or SAE, the investigator is required to follow up each case and obtain more data on the patient's state. All the AEs and SAEs documented in previous visits must be reviewed in subsequent visits. All AEs and SAEs must be monitored until their resolution. This is applicable to all the patients, including those who withdraw early.

### 11.3.5. AEs or SAEs that occur after the study ends

Post-study AEs or SAEs are defined as any event that occurs outside the Follow-up period of detection defined in the protocol. The investigator is not required to actively seek out AEs or SAEs in patients who have participated in the clinical trial in the past. Nevertheless, if the investigator comes to know of the existence of any AE or SAE, including the death of the patient at any time after a patient has left the study, and this AE or SAE is considered related to the study drug, the investigator must notify the sponsor promptly.

### 11.3.6. Events of special interest

Binimetinib is an investigational drug and current knowledge of the AEs associated with this compound is limited. As with any new chemical entity, there is always potential for unexpected AEs, including hypersensitivity reactions.

The most frequently reported AESI for binimetinib groupings (≥ 20.0% of patients in either population) were retinopathy excluding RVO, muscle enzyme/protein changes, liver function test abnormalities and rash. Grade 3/4 AESIs reported for ≥ 5.0% of patients in either population were in the groupings of liver function test abnormalities, muscle enzyme/protein changes and hypertension.

#### Ocular AESIs

Retinopathy excluding RVO events were the most common AESI grouping reported. Retinopathy excluding RVO events reported in > 5.0% of patients were vision blurred, retinopathy, subretinal fluid, retinal detachment, visual field defect and macular edema. Events in the RVO grouping were uncommon.

#### Muscle Enzyme/Protein Changes and Myopathy/Rhabdomyolysis-Related AESIs

Muscle enzyme/protein changes were frequently observed, although Grade 3/4 events were less common in patients. All patients with an event in the muscle enzyme/protein changes grouping had at least 1 event reported under the PT of blood CK increased. No other muscle enzyme/protein changes by PT were reported in > 5.0% of patients in either population.

Events in the myopathy grouping were reported; few patients had a Grade 3/4 event. The myopathy event reported in > 5.0% of patients in either population by PT was myalgia.

Events in the rhabdomyolysis grouping were uncommon.

Symptomatic muscle-related AEs reported in the myopathy and rhabdomyolysis groupings that occurred within 15 days before to 30 days after the worst laboratory CK elevation were analyzed. Around 6% of patients with a worst post-baseline laboratory CK value ≥ Grade 1 had at least one symptomatic muscle-related AE reported.

#### Liver-related AESIs

Events in the liver function test abnormalities grouping were reported (between 20-26%) and about half of the patients with an event in the liver function test abnormalities grouping experienced at least 1 Grade 3/4 event. The events in the liver function test abnormalities grouping reported in > 5.0% of patients were GGT increased, ALT increased and AST increased.

Events in the hepatic failure grouping were uncommon.

#### Dermatologic-related AESIs

Rash events are frequently reported with single-agent binimetinib treatment.

Events in the skin infections grouping were reported; few patients had a Grade 3/4 event. The skin infection events reported in >2.0% of patients in either population by PT were folliculitis and cellulitis.

Nail disorder events were infrequently reported; no patients had a Grade 3/4 event in this grouping.

Severe cutaneous adverse reactions were rarely observed. No severe cutaneous reaction events were Grade 3/4 in severity. These events were reported under the PTs of dermatitis exfoliative, erythema multiforme, toxic skin eruption, dermatitis bullous and erythema multiforme.

### Hemorrhage AESIs

Hemorrhage events were reported; Grade 3/4 events were less common. The hemorrhage events reported in >2.0% of patients in either population were hematuria, rectal hemorrhage and hematochezia.

### Peripheral Edema AESIs

Peripheral edema events were reported in 11-16% of patients; few patients had a Grade 3/4 event. The peripheral edema event reported in >2.0% of patients was edema peripheral.

### Hypertension AESIs

Hypertension events were reported in 9-12% of patients and about half of the patients with an event in the hypertension grouping experienced at least 1 Grade 3/4 event. The PT of hypertension was the most frequently reported event (> 2.0% of patients) in the grouping.

### Cardiac-related AESIs

Left ventricular dysfunction events were reported in 6-8% of patients, with few patients experiencing a Grade 3/4 event. The most frequently reported event was ejection fraction decreased.

Bradycardia events were infrequently reported (around 1%); none were reported as Grade 3/4. The most frequently reported event was sinus bradycardia.

### Venous thromboembolism AESIs

Venous thromboembolism events were reported in 2-4% of patients, with few patients (around 1%) experiencing a Grade 3/4 event. The most frequently reported event was pulmonary embolism.

### Pneumonitis AESIs

Events in the pneumonitis grouping were uncommon and were reported in 2 patients (interstitial lung disease and pneumonitis).

### 11.3.7. Pregnancy

The investigator must report all pregnancies during the study, including follow up outcomes, within 24 hours of awareness.

Each pregnancy must be reported on a Pregnancy Report Form within 24 hours of becoming aware of the pregnancy. Pregnancy is not an AE, and therefore does not need to be reported as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.

Any SAE that occurs during pregnancy must be recorded on the Pregnancy Report Form, reported as an SAE on the SAE Report Form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported to the Sponsor within 24 hours. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

Any exposure during breast feeding must also be reported.

### 11.3.8. Special Situations: Abuse, Misuse, Medication Errors, Overdose, and Accidental or Occupational Exposure

- Abuse: is the persistent or sporadic, intentional excessive use of the study treatment which is accompanied by harmful physical or psychological effects.
- Misuse: medicinal product is intentionally and inappropriately used not in accordance with the authorized/approved product information.
- Medication error: is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.
- Overdose: is a deliberate or accidental administration of study treatment to a study patient, at a dose greater than that which was assigned to that patient per the study protocol and under the direction of the Investigator. Study investigator should notified overdose immediately, and the patient should be observed closely for AEs. Associated AEs should be treated and monitored by the Investigator.
- Accidental /Occupational exposure: is the unintentional exposure to a study treatment as a result of one's professional or non-professional occupation, or accidental exposure to a non-professional to whom exposure was not intended (i.e., study product given to wrong patient).

Reporting Special Situations: All occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure of study treatment must be reported on a Serious Adverse Event Report Form to the Sponsor within 24 hours of awareness regardless of whether or not an AE or SAE has occurred. If the abuse, misuse, medication error, overdose, or accidental / occupational exposure is associated with an AE, an SAE Report Form must also be submitted to the Sponsor within 24 hours of awareness.

# 12. STATISTICAL CONSIDERATIONS

## 12.1. General considerations

A comprehensive statistical analysis plan (SAP) will be prepared before database closure.

Continuous variables will be described by the mean, median, standard deviation, minimum and maximum. Categorical variables will be shown as absolute and relative distribution of frequencies and percentage. Also a 95% CI will be presented if this information is considered relevant to describe a singular variable.

## 12.2. Sample size

Patients with advanced TNBC that have received and experienced disease progression to the first/second line treatment are candidates to this trial. Patients that have received three or more treatment lines would be excluded.

Sample size has been calculated based on the primary objective of this clinical trial, to determine 3-months PFS of the palbociclib plus binimetinib in advanced TNBC, in patients with activation of ERK and/or CDK4/6.

Previous studies shown that the 3-months PFS in patients receiving chemotherapy in advanced TNBC was about 25% [44]. To accept the treatment efficacy we will assume that the 3-months PFS in patients treated with palbociclib plus binimetinib will be at least 50%. An overall sample size of 25 patients achieves 80% power at a 0.05 significance level (alpha) to accept the efficacy of palbociclib plus binimetinib in advanced TNBC. An accrual time of 12 months and follow-up time of 12 months (treatment and follow-up time) and 2 sided test have been considered in the sample size calculation.

Sample size has been calculated with one-sample survival method [45].

## 12.3. *Analytical Populations*

Safety population consists of all patients included in this study who received at least one dose of study treatment.

The efficacy population will be the basis for the primary endpoint analysis in this study; it 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. This will also be the patient population used for the analysis of the secondary endpoints.

## 12.4. Analysis of Primary Objective

Progression free survival (PFS) is defined as the time from the date of start treatment until objective tumor progression or death from any reason. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. PFS will be analysed according to the Kaplan-Meier method. Kaplan-Meier survival curves and median will be reported, along with associated 95% CI.

Three months PFS and the corresponding 95% CI will be provided.

### 12.5. Analysis of Secondary Objectives

#### 12.5.1. Secondary Efficacy evaluations

Objective response rate of the combination TNBC patients with metastatic disease that have received and experienced disease progression to the first/second line treatment will be measured according RECIST 1.1 criteria. Objective response rate (complete response + partial response) will be described using frequencies and percentages with its corresponding 95% CI.

CCI [redacted]

CCI [redacted]

#### 12.5.2. Secondary Safety evaluations

AEs and toxicity will be evaluated according NCI CTCAE vs 5.0 criteria. AEs and toxicities will be presented by frequency distribution and percentage according to CTCAE grade.

## 13. DATA HANDLING AND QUALITY ASSURANCE

### 13.1. Monitoring of the trial

The clinical monitors are employees of CRO, and representatives of the sponsor. As such, they have the obligation to follow the trial closely so that all aspects of the trial are carefully monitored for compliance with applicable government regulations and with ICH E6(R2) guidelines.

The clinical monitors will visit the study sites and Investigators at intervals as defined in the monitoring plan, in addition to maintaining necessary contact through telephone, e- mail, and letter. The clinical monitors will maintain current personal knowledge of the trial through observation, review of trial records and source documentation, and discussion of the conduct of the trial with the study site Investigators and staff.

### 13.2. Audits

The sponsor may choose to schedule and conduct periodic audits of ongoing clinical studies. Audits are independent of, and separate from, routine monitoring or quality control functions and are conducted to assure accuracy and compliance with the protocol, governing regulatory authorities and/or ICH E6(R2) guidelines.

### 13.3. Reporting of serious breaches

Serious breaches of the authorized protocol or of the Royal Decree 1090/2015 occurring in Spain must be reported by the sponsor without undue delay and no later than seven

calendar days from becoming aware of the breach to the Spanish Agency of Medicines and Medical Devices (AEMPS) and the CEIm.

To this end, a serious breach shall be defined as a breach that may significantly affect the safety and rights of the trial subjects or the reliability and robustness of the data generated in the clinical trial.

Only serious breaches should be notified to the AEMPS and the CEIm, and the breaches that do not constitute a serious breach should not be notified.

Each study site Investigator must document and explain in the subject's source documentation any breaches from the approved protocol and / or the Royal Decree 1090/2015. Investigators may implement a breach to eliminate an immediate hazard to trial subjects without prior IEC informed consent approval, but the breach must be reported to the monitor/CRA within 1 working day. Such incidents will be evaluated for potential safety hazards of the ongoing study, and if deemed appropriate, a protocol amendment will be issued.

The monitor/CRA will document breaches throughout the course of monitoring visits. The monitor will notify the Investigator during a visit and a "Breach Form" will be completed and signed by the investigator and by the monitor.

### 13.4. Data Management

CRO will be responsible for processing and quality control of the data. Data will be handled in accordance with the Data Management Plan, Standard Operating Procedures and applicable regulatory guidelines.

Data management based on GCP refers to activities defined to achieve safe routines for efficient entry of subject information into a database, avoiding errors. The routines include procedures for handling of eCRFs, database set-up and management, data entry and verification, data validation, quality control (QC) of database, and documentation of the performed activities, including information of discrepancies in the process. The database, the data entry screens and the program, will be designed in accordance with the clinical study protocol by CRO.

### 13.5. Electronic Case Report Forms (eCRFs)

Data collection for this study will consist of electronic data capture for all eCRF information. CRO will supply the eCRF.

All study site Investigators agree to maintain accurate eCRFs and source documentation as part of the case histories.

All information is to be filled in the subject's eCRF. If an enroled subject is not randomized into the study (ie, fails screening), only minimum data (such as demographics and consent date) and the reason for failing screening should be reported on the eCRF. In general, no queries for missing data on these subjects will be issued for procedures indicated as 'Not done'.

For randomized subjects, information captured on the source documents will be entered into the subject's eCRF by study site personnel and monitored at the study site. If an item is not available or is not applicable, this fact should be indicated by a missing reason. Blank spaces should not be present unless otherwise directed. Any corrections should be made using the procedure outlined in the Case Report Form Completion Guide of the study manual and will be recorded in the eCRF.

Each completed eCRF must be reviewed, signed, and dated by the study site Investigator in a timely manner. The completed eCRF will be reviewed by the study Monitor as soon as practical after completion. A copy of the final, approved and signed eCRF will be provided to the site and should be stored in the appropriate files.

### 13.6. Web-based eCRF

Clinical data (including AEs and concomitant medications) will be entered into an Electronic Data Capture (EDC) application. The data system is password protected and includes internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete or inaccurate. Clinical data will be entered directly from the source documents. Roles and rights of the study site personnel responsible for entering the study data into the eCRF will be determined in advance. Only authorized study site personnel designated by each study site Investigator will complete data collection. Appropriate training and security measures will be completed with the Investigator and all authorized study site personnel, prior to the study initiation, and before any study data is entered into the system.

### 13.7. Entering of Data into the eCRF

The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs should be completed as soon as possible during or after the subject's visit. Each study site Investigator must verify that all data entries in the eCRFs are accurate and correct.

If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator or authorized designee should indicate this in the eCRF. The investigator will approve the data using an electronic signature, and this approval is used to confirm the accuracy of the data recorded.

### 13.8. The Query Process

Each monitor will review the eCRFs and evaluate them for completeness and consistency. Each eCRF will be compared with the respective source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the Investigator or his/her authorized designee. The monitor cannot enter data in the eCRFs.

Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed (ie, the reason for any change, the name of the person who performed the change, and time and date will be logged). If additional corrections are needed, the responsible monitor or Data Manager will raise a query in the EDC

application. The appropriate investigational staff will answer queries generated in the application. This process is audit trailed meaning that the name of investigational staff, time, and date is logged.

### 13.9. Source Documents

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the study. They include enrolment and randomization log, investigational product accountability log, laboratory notes, memoranda, material dispensing records, subject files, etc.

Each Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. All supportive documentation submitted with the eCRF, such as laboratory data should be clearly identified with the study, visit and subject number. Any personal information (e.g., subject name, initials) should be removed or rendered illegible to preserve individual confidentiality.

### 13.10. User ID

eCRF records will be automatically appended with the identification of the creator, by means of their unique User ID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature. If an entry in an eCRF requires change, the correction should be made in accordance with the relevant software procedures.

### 13.11. Audit Trail

To meet regulatory requirements, the eCRF data will be electronically stored at sites. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required. Once all data have been entered, verified, and validated, the database will be locked to prevent any further changes in the clinical study data.

### 13.12. Inspection of Records

The Investigators and institutions involved in the trial will permit trial-related monitoring, audits, IEC review, and regulatory inspection(s) by providing direct access to all trial records. In the event of an audit, the Investigator agrees to allow the sponsor, representatives of the sponsor, and the governing regulatory agency access to all trial records.

The Investigator should promptly notify the sponsor of any inspections scheduled by any regulatory authorities and promptly forward copies of any inspection reports received to the sponsor.

### 13.13. Trial Record Retention

Essential documents and eCRF data should be retained during 25 years.

## 14. ADMINISTRATIVE CONSIDERATIONS

The following administrative items are meant to guide each study site Investigator in the conduct of the study but may be subject to change based on industry and government SOPs or working practice documents or guidelines.

### 14.1. Legal Considerations

The current clinical trial will be conducted in accordance with the protocol, the principles established in the current revised version of the Declaration of Helsinki (Annex 1) and the applicable regulatory requirements, particularly the ICH Tripartite Harmonized Guidelines for good clinical practice (1996), the Regulation (EU) 536/2014 relative to clinical trials on medicinal products for human use and the locally applicable regulations (e.g., In Spain, the Royal Decree on Clinical Trials 1090/2015).

### 14.2. Ethics committee review

ICH guidelines require that approval be obtained from Health Authorities and an Ethics Committee before human subjects can participate in research studies. Prior to the trial onset, the protocol, informed consent, advertisements to be used for subject recruitment (if applicable), and any other written information regarding this trial to be provided to the subject will be approved by the Ethics Committee. The clinical study will only be started when both the Health Authorities and an Ethics Committee have considered that the expected benefits for the trial subject and society justify the risks; in addition, the trial will only be continued if compliance with this criterion is constantly supervised.

CRO will obtain Ethics Committee approvals on behalf of the sponsor and investigators. All regulatory approvals should be signed by the Ethics Committee Chairman or designee and must identify the Ethics Committee name and address, the clinical protocol by title and/or protocol number and the date approval and/or favorable opinion was granted. Documentation of all Health Authorities and Ethics Committee approvals and of the Ethics Committee compliance with ICH E6(2) will be maintained by the site and will be available for review.

### 14.3. Modifications of the protocol

Any change in the approved protocol will require a Protocol amendment. The Investigator must not make any change in the study without favourable opinion from the Ethics Committee and authorization from the Health Authorities, except as necessary to eliminate an impending and obvious risk for the subjects except when necessary to remove an apparent, immediate hazard to subjects. Protocol changes introduced to eliminate an impending and obvious risk may be implemented immediately, but must subsequently be documented in an amendment, reported to the Ethics Committee and be submitted to the relevant Health Authorities within the required timeframe.

Any substantial amendments to the protocol must be submitted in writing to the Ethics Committee and the Health Authorities for approval before the changes proposed in the amendment are implemented. Depending on the magnitude of the change, the recruitment may be temporally halted.

The sponsor does not have to notify non-substantial amendments to the Health Authorities or the Ethics Committee. However, any non-substantial amendments will be recorded and contained in the documentation when it is subsequently submitted, for example in the subsequent notification of a substantial amendment. Documentation of any non-substantial amendments will be available on request for inspection at the trial site or the sponsor premises as appropriate.

### 14.4. Informed consent

A written informed consent in compliance with ICH E6 guidelines shall be obtained from each subject before being included in the study or performing any study specific procedures.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the Ethics Committee prior to being provided to potential subjects.

The written Informed Consent Form (ICF) should be prepared in the local language(s) of the potential subject population.

An approved informed consent form will be provided by the sponsor to investigative site.

Before a subject's participation in the study, it is the Principal Investigator's (or their designee) responsibility to obtain freely given consent in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential risks of the study and before any protocol-specific screening procedures or any study drugs are administered. Subjects must have the opportunity to ask questions and receive answers and will have adequate time to decide whether or not to participate in the study. Once the Investigator is assured that the subject understands the implications of participating in the trial, the subject will be asked to give consent to participate in the trial by signing the informed consent.

The ICF should be signed and personally dated by the subject and by the physician who conducted the informed consent discussion (Principal Investigator or designee). The subject's written informed consent should also be documented in the subject's medical records.

The Investigator shall provide a copy of the signed informed consent to the subject. A second original form shall be maintained in the Investigator study file at the site.

If the informed consent is revised during the course of the trial, all active participating subjects must sign the revised form approved by the Ethics Committee.

The subject participating in a clinical trial, or his/her legal representative, may withdraw consent at any time without giving any reason and without this involving any penalty or prejudice for the participating subject.

## 14.5. Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. Each Investigator will ensure that all site personnel involved will respect the confidentiality of any information about trial subjects. Management of personal data from subjects participating in the trial, particularly as regards consent, will comply with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and local laws.

At each site, all records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject. Subject identity is confidential and may only be known by the Investigator, trial personnel, appointed auditors and monitors, and Health Authorities.

Each Investigator and all employees and coworkers involved with this trial may not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the sponsor or its designee must be collected for the disclosure of any said confidential information to other parties.

## 14.6. Insurance

The sponsor has contracted an insurance policy to cover the responsibilities of the investigator and other parties participating in the study, according to the applicable legislation.

- Insurance company: QBE Europe SA/NV
- Policy Number: 063 0000488

## 14.7. Publications

The sponsor commits to responsible publication of both the positive and negative results from its clinical trials as required by all governing regulatory and health authorities.

Investigators will not publish the global study results (all sites) unless the sponsor has not done so in a suitable time period after the clinical study report (CSR) has been available. Should the Investigator(s) independently seek to publish results of this study which occur at their study site(s), they must inform the study sponsor of any/all drafts (including, but not limited to papers, manuscripts or abstracts) at least 60 days before submission to the congress, meeting or journal. The sponsor and Investigator(s) will

agree with all aspects related to any proposed publications with regards to the following:
1) any proposed publications will be drafted in agreement with international recommendations, such as those from the International Committee of Medical Journal Editors (ICMJE) and all elements of the Consort Statement, to maintain integrity of the trial results in all communications; 2) any proposed publications will state the Clinical Research Ethics Committees which approved the trial and the funding sources of the trial; 3) any proposed publications will occur before disclosure of results to lay people; 4) any proposed publications will not report premature or partial data prior to completion of the analysis of the overall results of the trial.

# 15. SPONSOR'S SIGNATURE PAGE

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

**Study code:** PALBOBIN

**Version number and date:** 3.0, 16th June 2021

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable regulations and ICH guidelines.

| Position (pre-printed name) | Signature | Signature date (DD-Mmm-YYYY) |
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| Position (pre-printed name) | Signature | Signature date (DD-Mmm-YYYY) |
| Position (pre-printed name) | Signature | Signature date (DD-Mmm-YYYY) |
| Position (pre-printed name) | Signature | Signature date (DD-Mmm-YYYY) |

# 16. INVESTIGATOR'S SIGNATURE PAGE

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

**Study code:** PALBOBIN

**Version number and date:** 3.0, 16th June 2020

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable regulations and ICH guidelines.

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| Principal Investigator's signature | Signature date (DD-Mmm-YYYY) |
| Investigator's name (capital letters) | |
| Investigator's signature | Signature date (DD-Mmm-YYYY) |
| Investigator's name (capital letters) | |
| Investigator's signature | Signature date (DD-Mmm-YYYY) |
| Investigator's name (capital letters) | |

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# Annex 1. Declaration of Helsinki

# WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

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

amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975 35th

WMA General Assembly, Venice, Italy, October 1983 41st WMA

General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 52nd WMA

General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added) 55th

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

59th WMA General Assembly, Seoul, Republic of Korea, October 2008 64th

WMA General Assembly, Fortaleza, Brazil, October 2013

## Preamble

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

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

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

## General Principles

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

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

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

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

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

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

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or

other health care professionals and never with the research subjects, even though they have given consent.

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

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

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

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

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

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

**Risks, Burdens and Benefits**

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

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

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

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

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

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

**Vulnerable Groups and Individuals**

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

All vulnerable groups and individuals should receive specifically considered protection.

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

**Scientific Requirements and Research Protocols**

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

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

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and

information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

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

## Research Ethics Committees

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

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

## Privacy and Confidentiality

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

## Informed Consent

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

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

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

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

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

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

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

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent

have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

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

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

## Use of Placebo

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

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

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

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

## Post-Trial Provisions

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

## Research Registration and Publication and Dissemination of Results

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

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

## Unproven Interventions in Clinical Practice

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

# Annex 2. List of Sites / Principal Investigators

Separate attachment.

# Annex 3. Informed Consent Form

Separate attachment.

# Annex 4. NCI-CTC AE Criteria

Common terminology criteria for classification of adverse events version 5.0 (NCI CTC AEv5) are available at the following Internet address:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf