Clinical Trial Protocol

MULTICENTER, RANDOMIZED, PHASE Ib/IIb STUDY TO EVALUATE THE EFFICACY AND TOLERABILITY OF GEFITINIB IN COMBINATION WITH OLAPARIB (AZD2281) VERSUS GEFITINIB ALONE, IN PATIENTS WITH EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATION POSITIVE ADVANCED NON-SMALL-CELL LUNG CANCER

Sponsor: Grupo Español de Cáncer de Pulmón (GECP) / Spanish Lung Cancer Group (SLCG)
C/ Villarroel 251, pral 2ª
08036 Barcelona
Spain

Acronym: GOAL (Gefitinib and Olaparib in Advanced Lung cancer)

Sponsor Code: GECP 10/03

EudraCT: 2010-024178-21

Study drugs: gefitinib and olaparib

Version: 1.0

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SIGNATURE PAGE

MULTICENTER, RANDOMIZED, PHASE Ib/IIb STUDY TO EVALUATE THE EFFICACY AND TOLERABILITY OF GEFITINIB IN COMBINATION WITH OLAPARIB (AZD2281) VERSUS GEFITINIB ALONE, IN PATIENTS WITH EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATION POSITIVE ADVANCED NON-SMALL-CELL LUNG CANCER.

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SPONSOR

Grupo Español de Cáncer de Pulmón (GECP) / Spanish Lung Cancer Group (SLCG)
C/ Villarroel 251, pral 2ª
08036 Barcelona
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PRINCIPAL INVESTIGATOR

Dr. Rafael Rosell _____ _____
Signature Date

COORDINATOR

Dr. Rosario García _____ _____
Signature Date

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LIST OF ABBREVIATIONS

AE	Adverse event
AEMPS	*Agencia Española del Medicamento y Productos Sanitarios* / Spanish Agency of Medicinal and Health Products
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
APTT	Activated partial thromboplastin time
BP	Blood pressure
CT	Computed tomography
CREC	Clinical Research Ethics Committee
CRF	Case report form
GGT	Gamma glutamyltransferase
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
ILD	Interstitial lung disease
INR	International normalised ratio
IPS	Investigational product supplies
LDH	Lactic dehydrogenase
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PET	Positron emission tomography
PFS	Progression-free survival
PG	Pharmacogenomics
PK	Pharmacokinetics
PR	Pulse rate
PT	Prothrombin time
RBC	Red blood cell count
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SPC	Summary of product characteristics
SUV	Standard uptake value

SUSAR	Suspected Unexpected Serious Adverse Reaction

SYNOPSIS

TITLE OF CLINICAL TRIAL

Multicenter, randomized, Phase Ib/IIb study to evaluate the efficacy and tolerability of gefitinib in combination with olaparib (AZD2281) versus gefitinib alone, in patients with Epidermal Growth Factor Receptor (EGFR) mutation positive advanced non-small-cell lung cancer

PROTOCOL CODE

GECP 10/03

VERSION DATE

22-Nov-2010.

VERSION NUMBER

V 1.0.

SPONSOR

Grupo Español de Cáncer de Pulmón (GECP) / Spanish Lung Cancer Group (SLCG)
C/ Villarroel 251, pral 2ª
08036 Barcelona
Spain

STUDY COORDINATOR

Dr. Rosario García Campelo
Oncology Department
Complejo Hospitalario Universitario de La Coruña
Xubias de Arriba, 84
La Coruña 15006, Spain

MONITOR

- CRO PIVOTAL will be responsible for monitoring the Phase I part of the clinical trial.
- SLCG will be responsible for monitoring the Phase II part of the clinical trial.

CLINICAL TRIAL PHASE

Phase Ib/IIb.

CLINICAL TRIAL SITES

A list of participating sites will be provided in a document apart of this protocol.

LABORATORY FOR PHARMACOGENOMIC ANALYSIS

Pangaea Biotech S.A.

CEIC OF REFERENCE

Hospital Germans Trias i Pujol.

INDICATION

Advanced non-small-cell lung cancer (NSCLC) with mutations of EGFR (exon 19 deletion or L858R, with or without T790M).

EXPERIMENTAL AND CONTROL PRODUCTS

Gefitinib and olaparib.

DESIGN

The study will be split into 2 parts: an open label Phase I dose escalation part and a randomized controlled, open label Phase II part.

OBJECTIVES

Phase Ib

Primary: to evaluate the safety [dose limiting toxicity (DLT) and maximum tolerated dose (MTD)] of orally administered olaparib in combination with gefitinib, in patients with advanced non-small-cell lung cancer with mutations of EGFR (exon 19 deletion or L858R with or without T790M).

Secondary:

- To explore the pharmacokinetics of olaparib when dosed with gefitinib
- To evaluate the preliminary antitumor activity (overall response rate) of the combination in the exposed population.

Phase IIb

Primary: to assess the efficacy in terms of progression-free survival (PFS) of gefitinib in combination with olaparib, compared with gefitinib alone, in 1st line patients with EGFR mutations advanced NSCLC.

Secondary:

- To identify the influence of BRCA1 mRNA expression, EGFR mutations (exon 19 deletion and L858R) and T790M on progression-free survival
- To monitor EGFR mutations (including T790M) in serum
- Overall survival (OS)
- Tumor response rate using RECIST criteria
- Toxicity profile of patients enrolled in the study

- To investigate exploratory biomarkers (i.e. HERC2, EZH2, 53BP1, BRCA2, OTUB1 y NPM1) in the tumour sample and serum, to ascertain if there are any ways in which to differentiate treatment effects, and to investigate their correlation with disease progression/response to therapy or an improved understanding of disease.

PRIMARY ENDPOINTS

- Phase Ib: safety (DLT and MTD)
- Phase IIb: progression-free survival (PFS).

SECONDARY ENDPOINTS

- Overall survival (OS)
- Overall response rate (ORR)
- Safety profile
- Additional translational research.

INCLUSION CRITERIA

1. Patients age 18 years or more.
2. Histologically confirmed diagnosis of non-small-cell lung carcinoma.
3. Stage IV disease, following the Seventh Edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual.
4. Tumor tissue available (according to the criterion of the specimen-processing laboratory) for EGFR mutation assessment: to be included in the study patients should present at least one EGFR mutation (exon 19 deletion or L858R with or without T790M).
5. Evidence of measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1.
6. ECOG score ≤ 2.
7. Life expectancy of ≥ 3 months.
8. For the Phase II part of the study, patients should not have received previous treatment with chemotherapy or other agents for advanced disease: chemotherapy is allowed if the initial diagnosis of the patient is limited disease and the patient has received adjuvant or neoadjuvant treatment, as long as a minimum of 6 months has passed since the end of the adjuvant and/or neo-adjuvant chemotherapy. **This criterion is not mandatory to patients to be included in the Phase I part of the study (these patients are allowed to have received a prior line of treatment for advanced disease).**
9. Patients with the following hematologic values:
    - Absolute Neutrophil Count (ANC) ≥1.5 x 10^9/L

- Hemoglobine (Hb) ≥ 10 g/dl
- Platelets ≥ 100 x 10^9/L

10. Patients with the following biochemical values:
    - Bilirubin ≤ 1.5 mg/dL
    - Aspartate aminotransferase (AST) and Alanine transaminase (ALT) < 1.5 upper limit of normality
    - Creatinine clearance ≥ 60 ml/min.
11. Patients of childbearing age of either sex must use effective contraceptive methods (barrier methods plus other birth control methods) before entering the study and while participating in the study.
12. Patients should sign an informed consent form before inclusion in the study that specifies that the clinical trial treatment entails consent for the analysis of biological samples of tumor and blood.
13. Patients must be available for clinical follow-up.

EXCLUSION CRITERIA

1. Patients diagnosed of another neoplasm, with the exception of cervical carcinoma in situ, treated squamous cell carcinoma or superficial bladder tumor (Ta and TIS), or other malignant tumors that have received curative treatment within the last 5 years before inclusion in the study.
2. Simultaneous participation in any other study involving an investigational medicinal product, or having participated in a study less than 28 days prior to the start of study treatment.
3. Patients with HIV infection, HCV infection, coronary disease or uncontrolled arrhythmia, uncontrolled cerebrovascular disease and other clinical conditions that, in the judgment of the investigator, contraindicate the patient's participation in the study.
4. Past medical history of interstitial lung disease (ILD), drug-induced interstitial disease, radiation pneumonitis which required steroid treatment or any evidence of clinically active interstitial lung disease.
5. Pre-exisiting idiopathic pulmonary fibrosis evidenced by CT scan at baseline.
6. Uncontrolled seizures.
7. Patients considered requiring radiotherapy to the lung at the time of study entry or in the near future.
8. Known or suspected brain metastases or spinal cord compression, unless treated with surgery and/or radiation and stable without steroid treatment for at least 4 weeks prior to the first dose of study medication.
9. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.

10. Patients who are pregnant or breastfeeding. Women of childbearing potential must have a negative pregnancy test performed within 7 days before the onset of treatment (Appendix 8).
11. Patients receiving the following classes of inhibitors of CYP3A4 (see Appendix 5 for guidelines and wash out periods):
    a. Azole antifungals
    b. Macrolide antibiotics
    c. Protease inhibitors
12. Concomitant use of known CYP3A4 inducers such as phenytoin, carbamazepine, rifampicin, barbiturates, or St John's Wort.
13. Major surgery within 2 weeks of starting study treatment; patients must have recovered from any effects of any major surgery.
14. Significant weight loss (= 10% of body weight) in the 6 weeks before inclusion in the study.
15. Any condition that is unstable or could endanger the patient's safety and/or the patient's compliance with the study.
16. Substance abuse or clinical, psychological or social conditions that can undermine the validity of the informed consent or protocol compliance.
17. Patients who present any contraindication or suspected allergy to the products under investigation in the study. Tablets of gefitinib contain lactose: patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption, will not be included in this trial.
18. Contraindication for steroid use.
19. Impossibility to comply with treatment due to cultural or geographic circumstances.

DISCONTINUATION CRITERIA

- Voluntary discontinuation by the patient, who is at any time free to discontinue his/her participation in the study without prejudice to further treatment
- Safety reasons as judged by the investigator and/or the Sponsor
- Severe non-compliance to protocol as judged by the investigator and/or the Sponsor
- Incorrect enrolment, i.e. the patient does not to meet the required inclusion/exclusion criteria for the study
- Patient lost to follow-up
- Adverse event.

PLANNED NUMBER OF SUBJECTS

Phase Ib

Around 20 patients are expected to participate in the Phase Ib part of the study. However, the number of patients may vary depending upon the tolerability of the combination and the number of dose levels required to identify the MTD.

Phase IIb

A total accrual of 248 subjects would be required. Given that approximately 17% of patients with NSCLC are expected to carry EGFR mutations, around 1,500 patients should be screened.

RANDOMIZATION

For the Phase IIb part, randomization will be centralized and conducted by the data center of the study after receiving from the laboratory the confirmation that an EGFR mutation (exon 19 deletion or L858R, with or without T790M) is present.

The data center will communicate to the investigator by fax the randomization number and treatment group to which each patient has been assigned.

Allocation will be done centrally and automatically by generation of randomized permuted blocks, with allocation of 1 (A, gefitinib monotherapy) and 1 (B, gefitinib in combination with olaparib) groups.

DURATION OF THE TRIAL

- Start date: Q1 2011
- Phase Ib duration: 6-9 months
- Planned enrolment period of Phase IIb: by assuming an accrual rate of 140 patients/year, a total accrual period of 24 months and a follow-up period of 12 months will be necessary
- Planned end of study date: 1 year after last patient has been enrolled.

1 GENERAL INFORMATION

1.1 Title, code and date.

Multicenter, randomized, Phase Ib/IIb study to evaluate the efficacy and tolerability of gefitinib in combination with olaparib (AZD2281) versus gefitinib alone, in patients with Epidermal Growth Factor Receptor (EGFR) mutation positive advanced non-small-cell lung cancer

Code: GECP 10/03

EudraCT: 2010-024178-21

Version: 1.0 (22-Nov-2010)

1.2 Name and addresses of the Sponsor and monitor.

Sponsor

Grupo Español de Cáncer de Pulmón (GECP) / Spanish Lung Cancer Group (SLCG)
C/ Villarroel 251, pral 2ª
08036 Barcelona
Spain
Phone: +34 93 430 20 06
Fax: +34 93 419 17 68

Monitor

- CRO PIVOTAL will be responsible for monitoring the Phase I part of the clinical trial.
- SLCG will be responsible for monitoring the Phase II part of the clinical trial.

1.3 Identification data of the authorized people for sign the protocol and amendments in name of the Sponsor.

PIVOTAL S.L.
C/ Gobelas 19
28023 Madrid, Spain
Tel: 91 708 12 50
Fax: 91 708 13 08

1.4 Identification data of the Sponsor medical experts.

- Dr. Rafael Rosell
  Oncology Department
  Hospital Universitari Germans Trias i Pujol
  Dirección Carretera del Canyet s/n
  08916 Badalona, Barcelona, Spain

- Dr. Rosario García Campelo
  Oncology Department
  Complejo Hospitalario Universitario de La Coruña
  Xubias de Arriba, 84
  La Coruña 15006, Spain

1.5 Identification data of the clinical trial investigators and sites.

A list of participating sites will be provided in a document apart of this protocol.

1.6 Identification data of the laboratory for pharmacogenomic analysis.

Laboratorio Oncología-Pangaea Biotech
Planta -1, lab -1.7
C/ Sabino Arana 5-9,
08028 Barcelona
Spain
Tfno: 93 546 01 22 / 648 2018 68

2 JUSTIFICATION

2.1 Name and description of the investigational products.

Gefitinib

Detailed information of the product is contained in the "Summary of product characteristics" (SPC) attached as an Appendix to this protocol (Appendix 2). Gefitinib (Iressa®) is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK.

Olaparib

Detailed information of the product is contained in the "Investigator's Brochure" (IB), edition 6 (4 January 2010) attached as an Appendix to this protocol (Appendix 1).

2.2 Summary of the studies of interest to the present trial.

Landmark outcomes of a 70.6% response rate, 14-month progression-free survival (PFS) and 27-month median survival have been attained in Caucasian erlotinib-treated non-small-cell lung cancer patients harboring activating mutations in the epidermal growth factor receptor (EGFR) kinase domain (1). The L858R mutation had a detrimental effect on survival in comparison with the deletion in exon 19 (del 19) (1). There were no differences in survival between patients receiving erlotinib as first- or second-line therapy (1), in contrast to findings in the erlotinib-sensitive PC9 cell line, containing the del 19, where prior exposure to platinum agents reduced erlotinib sensitivity fivefold (2). In a study of Asian patients (79% females and 93.6% never-smokers), a subgroup with EGFR mutations attained a response rate of 71.2% with gefitinib, compared to 47.3% with carboplatin-paclitaxel; PFS was longer in the gefitinib arm, while overall survival was around 23 months in both arms (3). Pooled data on Japanese EGFR-mutated patients also showed strikingly better response and PFS in patients receiving first-line gefitinib than in those receiving first-line chemotherapy, although overall survival was similar (27.7 vs 25.7 months) (4).

In three phase III trials of Asian patients with EGFR mutations, median PFS was significantly longer in patients receiving gefitinib (9.2-10.8 months) than in those receiving chemotherapy (5.4-6.3 months), with a significant improvement in the hazard ratios (HR) for progression (0.30-0.48; P<0.001) (3;5;6).

We examined the presence of the T790M mutation in pretreatment tumor samples of non-small-cell lung cancer patients who were prospectively treated with erlotinib as part of a Spanish Lung Cancer Group (SLCG) program (1) and correlated the presence of the T790M mutation with clinical outcomes. We also analyzed the potential influence of BRCA1, IGF-1R and RAP80 mRNA levels on outcome in an attempt to identify subclasses of EGFR-mutant patients for further refining treatment strategies, including the potential benefit of chemotherapy.

We have found the T790M mutation in 35% of 129 patients at baseline, which is similar to the frequency previously reported in 26 patients (7). The lower frequency (2.7%) found in Asian patients, using the ARMS technique, could be due to multiple factors, including the use of different assays. ARMS may be less sensitive at detecting point mutations present at low concentrations in the presence of a large amount of background wild-type sequences. EGFR mutations can be very heterogeneous in a single tumor sample, and some mutations are only present in less than 10% of total sequences (8). Our detection method does not involve any DNA purification and is based on microdissection of cancer cells followed by allele discrimination (TaqMan assay) in the presence of a peptide-nucleic acid clamp (9).

The T790M mutation was associated with a shorter PFS to erlotinib (hazard ratio, 3.96; P=0.001). Surprisingly, high levels of BRCA1 mRNA expression also predicted shorter PFS

(hazard ratios: intermediate tercile, 4.36, P=0.08; highest tercile, 5.81, P=0.001). Our findings show that BRCA1 expression levels by terciles are evenly distributed in tumors with double EGFR mutations (T790M) and in those with single mutations (L858R or del 19). For patients without T790M and low levels of BRCA1 expression, PFS to first-line erlotinib was 27 months, compared to 18 months for those with intermediate or high levels of BRCA1. Intriguingly, PFS was also 27 months for patients with the T790M mutation and low levels of BRCA1, while it plummeted to 3 months for those with intermediate or high levels. However, median survival was not reached in the group with intermediate levels of BRCA1 and was 21 months in those with high levels, suggesting that second-line chemotherapy was responsible for this better prognosis, in spite of failure to initial erlotinib treatment.

In a multivariate analysis (including T790M, sex, performance status, smoking history, del 19 vs L858R, first- vs second-line therapy, the presence of absence of brain or bone metastases, and BRCA1, IGF-1R and RAP80 mRNA levels), there was an association between poor PFS and the presence of the T790M mutation (hazard ratio, 3.96; 95% CI, 1.77 to 8.89; P=0.001), male sex (hazard ratio, 3.18; 95% CI, 1.31 to 7.69; P=0.01), the presence of brain metastases (hazard ratio, 4.55; 95% CI, 1.55 to 13.62; P=0.006), intermediate BRCA1 levels (hazard ratio, 4.36; 95% CI, 1.46 to 13.10; P=0.008), and high BRCA1 levels (hazard ratio, 5.81; 95% CI, 1.96 to 17.19; P=0.001) (Table 1).

Table 1: Multivariate analysis for progression-free survival

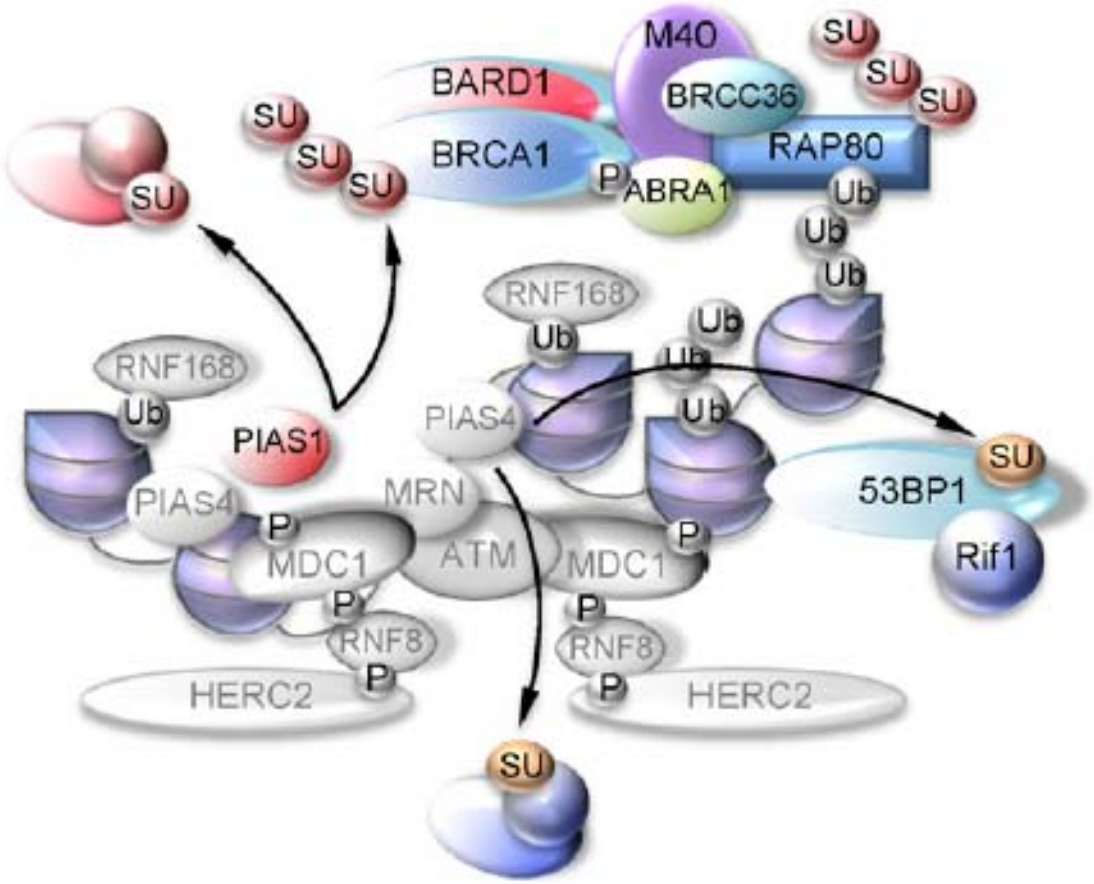
	Hazard Ratio	95% CI	P Value
T790M			
Negative	1.00		
Positive	3.96	1.77-8.89	0.001
Sex			
Female	1.00		
Male	3.18	1.31-7.69	0.01
ECOG PS			
0	1.00		
1	1.13	0.49-2.59	0.77
≥2	0.88	0.29-2.67	0.83
Smoking history			
Former smoker	0.53	0.17-1.62	0.27
Current smoker	2.63	0.77-8.89	0.12
Never smoked	1.00		
EGFR mutation			
del 19	1.00		
L858R	0.96	0.35-2.63	0.94
Erlotinib therapy			
First-line	1.00		
Second-line	0.46	0.17-1.21	0.11
Bone metastases			
No	1.00		
Yes	1.06	0.39-2.87	0.90
Brain metastases			
No	1.00		
Yes	4.55	1.55-13.62	0.006
BRCA1 mRNA levels			

≤4.92	1.00		
4.92-10.7	4.36	1.46-13.10	0.008
>10.7	5.81	1.96-17.19	0.001
IGF-1R mRNA levels			
≤2.36	1.00		
2.36-4.06	0.53	0.13-2.08	0.36
>4.06	0.43	0.43-1.58	0.20
RAP80 mRNA levels			
≤1.62	1.00		
1.62-3.68	0.67	0.22-2.04	0.48
>3.68	0.85	0.24-2.96	0.80

Continuous oral administration of olaparib at 400mg twice daily has demonstrated significant response rate in pre-treated breast and ovarian cancer patients with BRCA1 and BRCA2 mutations (10;11). Our hypothesis is that olaparib can attenuate and/or prevent BRCA1 mRNA elevated levels and therefore increase the sensitivity to gefitinib in patients with EGFR mutations.

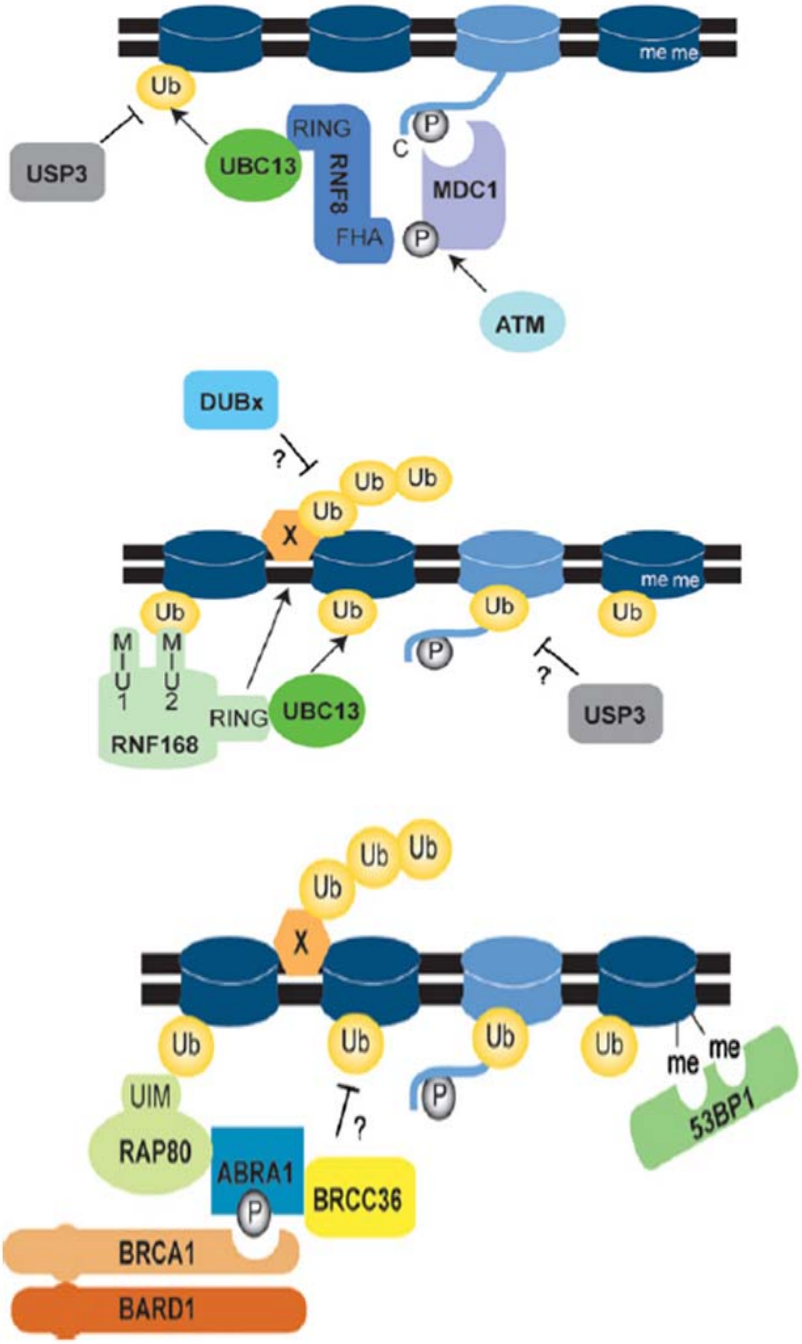
In order to further understand the role of BRCA1 mRNA levels, it may be relevant to understand why BRCA1 levels are low. It has recently been explained that HERC2 expression was inversely related to that of BRCA1 in some breast cancers, suggesting a mechanism that may lead to the emergence of BRCA1 negative breast cancers (12). This is a paradoxical finding since HERC2 facilitates assembly of the RNF8/Ubc13 and maintains the level of another E3 ligase RNF168, and is required for ubiquitin dependent retention of repair factors including 53BP1, RAP80 and BRCA1 (Figure 1). Another mechanism of downregulation of BRCA1 is due to overexpression of EZH2 which has been found in expression receptor-negative breast cancers (13). Increased expression of EZH2 is observed in the most common cancers, including lung cancer (14). It is important to identify the mechanism of downregulation of BRCA1 since the overexpression of EZH2 methylates and neutralizes DAB2IP, releasing NFkB (15). The activation of NFkB in tumors with EGFR mutations can hamper the activity of gefitinib.

Figure 1: Relation between HERC2 and BRCA1 expressions



In our previous work we examined multiple genes involved in DNA repair but only BRCA1 was significantly relevant. Our model shows that BRCA1 can independently repair the damage caused by EGFR TKI inhibitors in tumors with EGFR mutations (Figure 2). It could be cardinal for the interpretation of the olaparib activity to examine 53BP1 in conjunction with BRCA1. In wild-type cells BRCA1 displays 53BP1 from double strand breaks, enabling resection at the break site by factors such as CtIP, which promotes RPA loading onto single stranded regions of DNA. In contrast, in BRCA1 depleted cells, 53BP1 is not displaced and inhibits resection. In the absence of resection the break persists and these breaks are not repaired. However, in cells depleted by both BRCA1 and 53BP1, this causes 53BP1 not to be present at the double strand break site, enabling resection even in BRCA1 deficient cells (16). It could be crucial to interpret the outcomes of gefitinib plus olaparib, according to the levels of BRCA1 and 53BP1. In addition, BRCA2 also has an important role in the initial resection and RPA binding (17).

Figure 2: Repairing by BRCA1 of damage caused by EGFR TKI inhibitors in tumors with EGFR mutations



Other genes that can influence DNA repair include a novel deubiquitinating enzyme, OTUB1. OTUB1 is an inhibitor of DNA damage response which suppresses RNF168 and UBC13 dependent ubiquitination of chromatin (18).
Nucleophosmin (NPM1) is overexpressed in many tumors and also enhances DNA repair, especially when BRCA1 or RAP80 are depleted (19). In summary, BRCA1 mRNA levels and EGFR the T790M mutation are important discriminating factors in predicting outcome to erlotinib (inferring the same for gefitinib). In the study of gefitinib plus olaparib in patients with EGFR mutations, the PFS and other outcomes should be analyzed by BRCA1 mRNA levels and T790M. In addition, HERC2 and EZH2 are potential causes of downregulated BRCA1 with different clinical implications (EZH2 can activate NFkB and cause resistance to gefitinib). 53BP1 should also be examined in conjunction with BRCA1 to understand the potential effect of olaparib. Finally, BRCA2, OTUB1 and NPM1 mRNa levels should be examined.
In a meaningful number of patients, EGFR mutations can be detected in the circulating DNA, including the T790M (20). The clearance of EGFR mutations in blood could be a molecular of response and the reappearance of mutations can herald clinical progression. In the study EGFR mutations in serum or plasma will be determined at baseline and at the time of progression.

Justification of present clinical trial

Hypoxia suppresses homologous recombination repair in human cells via transcriptional downregulation of BRCA1 and RAD51. The downregulation is caused by stimulating E2F4/p130 occupancy of the BRCA1 and RAD51 promoters (21-23). Intriguingly, PARP inhibitors cause BRCA1 and RAD51 downregulation via induction of E2F4/p130 binding to the BRCA1 and RAD 51 promoters (24).

Our findings prompt us to propose a model of treatment whereby patients with EGFR mutations (single or with T790M) can attain a benefit with longer overall PFS when treated with gefitinib plus olaparib. We also postulate that both patients with double mutations and those with single mutations will have better prognosis in the presence of low BRCA1 levels.

2.3 Risks and benefits of the investigational products.

Risks and benefits of the drugs used in this study are detailed in the SPC of gefitinib and the IB of olaparib attached as Appendices to this protocol (Appendix 1 and Appendix 2).

2.4 Description and justification of method of administration and posology.

See SPC of gefitinib and IB of olaparib attached as Appendices to this protocol (Appendix 1 and Appendix 2).

The recommended dose of olaparib in combination with gefitinib will be defined in the first part of this study (Phase Ib).

2.5 Ethics and loyal aspects.

This trial will be carry out following the content of the present protocol, according to Good Practice Guidelines and all required laws (see details in Section 12).

2.6 Description of the study population.

Patients with advanced non-small-cell lung cancer who have not received treatment for the disease at this stage, measurable disease, and EGFR mutations (exon 19 deletion or L858R, with or without T790M).

2.7 References.

See “References” section at the end of the protocol.

3 STUDY OBJECTIVES

Primary objectives

Phase Ib

Primary: to evaluate the safety [dose limiting toxicity (DLT) and maximum tolerated dose (MTD)] of orally administered olaparib in combination with gefitinib, in patients with advanced non-small-cell lung cancer (NSCLC) with mutations of EGFR (exon 19 deletion or L858R, with or without T790M).

Phase IIb

To assess the efficacy in terms of progression-free survival (PFS) of gefitinib in combination with olaparib, compared with gefitinib alone, in 1st line patients with EGFR mutations advanced NSCLC.

Secondary objectives

Phase Ib

- To explore the pharmacokinetics of olaparib when dosed with gefitinib

- To evaluate the preliminary antitumor activity (overall response rate) of the combination in the exposed population.

Phase IIb

- To identify the influence of BRCA1 mRNA expression, EGFR mutations (exon 19 deletion and L858R) and T790M on progression-free survival
- To monitor EGFR mutations (including T790M) in serum
- Overall survival (OS)
- Tumor response rate using RECIST criteria
- Toxicity profile of patients enrolled in the study
- To investigate exploratory biomarkers (i.e. HERC2, EZH2, 53BP1, BRCA2, OTUB1 y NPM1) in the tumour sample and serum, to ascertain if there are any ways in which to differentiate treatment effects, and to investigate their correlation with disease progression/response to therapy or an improved understanding of disease.

4 STUDY DESIGN

4.1 Study endpoints.

Primary endpoints

- Phase Ib: safety (DLT and MTD)
- Phase IIB: progression-free survival (PFS).

Secondary endpoints

- Overall survival (OS)
- Overall response rate (ORR)
- Safety profile
- Additional translational research.

4.2 Design.

The study will be split into 2 parts: an open label Phase I dose escalation part and a randomized controlled, open label Phase II part.

4.2.1 Phase Ib development.

Gefitinib will be administered once daily, continuously, in 28-day cycles, as a fixed dose of 250 mg/day.

Olaparib will be administered at a starting dose of 100 mg in the morning and evening (the lowest PARP inhibitory dose with clinical activity) (25;26), with a dosing interval of about 12 h.

Cohorts of three patients will be treated at each dose level according to the following dose-escalation guidelines:

- The first two patients of the cohort can be included consecutively, whereas the third patient of each cohort must not be treated until the first patient has completed one treatment cycle (i.e., four weeks) without DLTs. Otherwise, the third patient can not start therapy until the second patient has finished the 4-week cycle period without DLTs.
- All patients within a dose level will be followed for at least one cycle before any dose escalation is defined for the next dose level.
- Decisions to escalate to the next level will be made jointly by the Sponsor and the investigators based on review of all the available data.
- No intra-patient dose escalation will be allowed.

Doses will be escalated according to the following scheme (Table 2):

Table 2: Proposed dose escalation schedule

Dose level	Gefitinib (mg), daily dose	Olaparib (mg), twice a day
1	250	100
2	250	200*

* If the dose of 200 mg twice-daily of olaparib is well tolerated, a further dose- escalation may be considered and the decision will be made jointly by the Sponsor and the investigators based upon review of all the data.

If one of the three patients shows a DLT during the first cycle, a maximum of six patients will be treated at that dose level. These patients will start treatment only after the prior patient has completed the first cycle and no DLTs have been observed.

- If no additional DLTs occur in these six patients, dose escalation will be resumed and new patients will be treated at the next highest dose level.
- If a second patient shows DLT during the first cycle, no more patients will be treated at this dose level. Dose escalation will cease, and the dose of the prior level will be defined as the MTD. Therefore, the MTD is defined as the highest dose at which $\leq$ 1 of 6 patients experience DLT during the first 28-day treatment period, with the next higher dose having at least 2 of the up to 6 patients experiencing a DLT during cycle 1.

Patients withdrawing from the study before completing the first cycle for reasons other than DLTs will be replaced.

As the study is planned to be conducted at 3-5 study sites, assignment of patient study numbers and verification of dose selection will be coordinated by the Sponsor. A teleconference attended by the participating investigators, and the Sponsor will be held weekly or as needed to assess cumulative safety data and jointly confirm a decision to expand a cohort or dose escalate.
Decisions concerning delayed-onset DLTs (i.e., those occurring after the first cycle) will be discussed individually between the investigators and the Sponsor, and might affect the definition of the proposed dose for the Phase II part of the study.

Dose limiting toxicity

Dose limiting toxicity (DLT) will be defined according to the following criteria:

- Hematological treatment-related AEs:
    - Any grade 4 neutropenia (ANC < 0.5 x10^9/L) lasting more than 5 days.
    - Any grade 4 neutropenia with concomitant fever (i.e., body temperature ≥ 38.5°C). Fever should not be disease-related.
    - Any grade 4 neutropenia and sepsis or other severe infection.
    - Any grade 3 or 4 thrombocytopenia associated with bleeding.
- Any other grade 3-4 non-hematological AEs related to the study treatment, except for the following:
    - Grade 3 fatigue, nausea and vomiting, diarrhoea, unless appropriate prophylactic or therapeutic measures have been administered.
    - Grade 3 rash.
    - Grade 3 elevation of hepatic transaminases lasting less than 7 days.
    - Non-clinically relevant biochemical abnormalities [i.e., isolated increase of gamma-glutamyltransferase (GGT)].
    - Hypersensitivity reactions.
- Grade 2 cardiac or neurological toxicity.
- Inability to tolerate the cycle of therapy due to toxicity.
- Any toxicity, which in the judgement of the Sponsor and investigator is viewed as DLT.
- If any haematological or non-haematological toxicity have not resolved (≤ Grade 1 CTCAE or baseline levels) within 2 weeks, the patient will be considered to have a DLT and must be discontinued from the trial.

In order to define DLT, patients should not be prophylactically prescribed growth factor support, antiemetics, anti-diarrhoeals or antipyretics during cycle 1 of therapy. If a patient experiences grade 3 or greater nausea and/or vomiting, diarrhoea, medical intervention should occur, including prophylactic administration of these agents for subsequent doses as indicated.

Pharmacokinetic measurements (Phase I only)

During the Phase I part, pharmacokinetics (PK) of olaparib when dosed with gefitinib will be evaluated in plasma.

During the first cycle of the Phase I part, up to one week before the start of combination treatment patients will receive olaparib alone. On the last day of that week (day 7) a full 12-hour plasma PK profile will be taken to get monotherapy PK information. Then (day 8) patients will start taking gefitinib too and, after a further week (day 14), a second olaparib PK profile will be obtained to enable a comparison of the plasma exposure to olaparib alone and in the presence of gefitinib. Sampling times on each sampling day would be immediately prior to the morning olaparib dose then at 30 mins, 1, 2, 4, 6 and 12 hours post dose.

Blood samples (4 mL) for determination of olaparib in plasma will be taken at the times presented in the study plan (Table 4). Blood samples will be collected, labelled and shipped as detailed in Appendix 6. The date and time of collection will be recorded on the appropriate case report form (CRF).

Samples should be stored at -20°C and analysed within the timeframe after collection for which the stability in the samples has been validated and found acceptable. Results from analyses stored longer than the period stated will not be reported.

Samples will be disposed of after the clinical study report has been finalised.

4.3 Screening and randomization.

After receiving authorization, patients will be screened for EGFR mutations and other biomarkers related with the disease, its prognosis, or sensitivity to treatment. Extraction, shipment, and specimen analysis will be conducted following the protocol in Appendix 9.

Only patients with specimens sufficient in amount and quality will be candidates for inclusion in this clinical trial (and randomization), as long as they satisfy inclusion and exclusion criteria and give informed consent to participate in the study.

For the Phase IIb part, randomization will be centralized and conducted by the data center of the study after receiving from the laboratory the confirmation that an EGFR mutation (exon 19 deletion or L858R with or without T790M) is present.

The data center will communicate to the investigator by fax the randomization number and

treatment group to which each patient has been assigned.
Allocation will be done centrally and automatically by generation of randomized permuted blocks, with allocation of 1 (A, gefitinib monotherapy) and 1 (B, gefitinib in combination with olaparib) groups.

4.4 Study treatments. Doses and schedules.

Treatments are described in detail in Section 6.1.

4.5 Duration of the study. Recruitment, treatment and follow-up periods.

- Start date: Q1 2011
- Start date: Q1 2011
- Phase Ib duration: 6-9 months
- Planned enrolment period of Phase IIb: by assuming an accrual rate of 140 patients/year, a total accrual period of 24 months and a follow-up period of 12 months will be necessary
- Planned end of study date: 1 year after last patient has been enrolled.

4.6 Criteria for discontinuation from study.

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient from this study are:

- Voluntary discontinuation by the patient, who is at any time free to discontinue his/her participation in the study without prejudice to further treatment
- Safety reasons as judged by the investigator and/or the Sponsor
- Severe non-compliance to protocol as judged by the investigator and/or the Sponsor
- Incorrect enrolment, i.e. the patient does not to meet the required inclusion/exclusion criteria for the study
- Patient lost to follow-up
- Adverse event (AE).

4.7 Contabilization and control of the study products.

Olaparib (AZD2281) will be supplied after randomization. Investigational Product Supplies (IPS), AstraZeneca, will provide bulk unlabelled bottles (of 32 tablets containing 100 mg of drug substance) to the hospitals after randomization. The Sponsor will provide labelled drug. Each container of olaparib will have an investigational-use label permanently affixed to the outside and will be labelled in accordance with local regulations, stating that the drug is for clinical trial use only and should be kept out of reach of children. Instructions stating that the

olaparib tablets should be taken twice-daily will be included on the label, and the days and the number of tablets required to make up the dose should be completed by the investigator/site staff. Labels will include blank lines for the patient enrolment code, visit and date dispensed. Each label will also include a tear-off portion that should be applied to individual patient CRF/drug accountability forms, upon dispensing.

The medication provided for this study is for use only as directed in the protocol. It is the investigator/institution's responsibility to establish a system for handling investigational medicinal products, so as to ensure that:

- Deliveries of such products from AstraZeneca are correctly received by a responsible person
- Such deliveries are recorded
- Study treatments are handled and stored safely and properly
- Study treatments are only dispensed to study patients in accordance with the protocol.

Centres will use their commercial supply of gefitinib (Iressa®) for this trial. Gefitinib should be managed according to the manufacturers' recommendation and the routine practice of the center, as it would be used in whichever patient not participating in the trial.

Patients will be given sufficient supplies of gefitinib (group A) or gefitinib and olaparib (group B) for a dispensing visit: the patient should record the daily intake of each drug. Each investigator/site staff will record precisely the date and the amount of each drug that is given to each patient.

4.8 Maintenance and opening of the randomization codes.

Not applicable: this is an open labelled study design.

4.9 Source data.

It is a prerequisite of this study that the study monitor has direct access to source data for data verification. This will be done by comparing data from the CRFs with those in the subject's medical notes.

4.10 Trial end.

The end of the study is defined as being the data cut-off, which will be one year after the last patient has started study treatment. Immediately following the data cut-off, all patients remaining in the study should be contacted so that survival status can be confirmed and recorded in the CRF.

5 SELECTION CRITERIA

All patients must fulfill ALL inclusion criteria and NONE exclusion criteria. To avoid the inclusion of ineligible patients, any doubts should be discussed with the Sponsor. If a patient does not fulfill eligibility criteria and is included inadvertently in the study, the Sponsor should be advised. The Sponsor will decide whether the patient should continue in the study by evaluating the risks and benefits for the patient and guaranteeing the patient's maximum safety.

5.1 Inclusion criteria.

1. Patients age 18 years or more.
2. Histologically confirmed diagnosis of non-small-cell lung carcinoma.
3. Stage IV disease, following the Seventh Edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (27).
4. Tumor tissue available (according to the criterion of the specimen-processing laboratory) for EGFR mutation assessment: to be included in the study patients should present at least one EGFR mutation (exon 19 deletion or L858R with or without T790M).
5. Evidence of measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1.
6. ECOG score ≤ 2.
7. Life expectancy of ≥ 3 months.
8. For the Phase II part of the study, patients should not have received previous treatment with chemotherapy or other agents for advanced disease: chemotherapy is allowed if the initial diagnosis of the patient is limited disease and the patient has received adjuvant or neoadjuvant treatment, as long as a minimum of 6 months has passed since the end of the adjuvant and/or neo-adjuvant chemotherapy. **This criterion is not mandatory to patients to be included in the Phase I part of the study (these patients are allowed to have received a prior line of treatment for advanced disease).**
9. Patients with the following hematologic values:
    - Absolute Neutrophil Count (ANC) ≥1.5 x 10^9/L
    - Hemoglobine (Hb) ≥ 10 g/dl
    - Platelets ≥ 100 x 10^9/L
10. Patients with the following biochemical values:
    - Bilirubin ≤ 1.5 mg/dL
    - Aspartate aminotransferase (AST) and Alanine transaminase (ALT) < 1.5 upper limit of normality

- Creatinine clearance ≥ 60 ml/min.

11. Patients of childbearing age of either sex must use effective contraceptive methods (barrier methods plus other birth control methods) before entering the study and while participating in the study.
12. Patients should sign an informed consent form before inclusion in the study that specifies that the clinical trial treatment entails consent for the analysis of biological samples of tumor and blood.
13. Patients must be available for clinical follow-up.

5.2 Exclusion criteria.

1. Patients diagnosed of another neoplasm, with the exception of cervical carcinoma in situ, treated squamous cell carcinoma or superficial bladder tumor (Ta and TIS), or other malignant tumors that have received curative treatment within the last 5 years before inclusion in the study.
2. Simultaneous participation in any other study involving an investigational medicinal product, or having participated in a study less than 28 days prior to the start of study treatment.
3. Patients with HIV infection, HCV infection, coronary disease or uncontrolled arrhythmia, uncontrolled cerebrovascular disease and other clinical conditions that, in the judgment of the investigator, contraindicate the patient's participation in the study.
4. Past medical history of interstitial lung disease (ILD), drug-induced interstitial disease, radiation pneumonitis which required steroid treatment or any evidence of clinically active interstitial lung disease.
5. Pre-exisiting idiopathic pulmonary fibrosis evidenced by CT scan at baseline.
6. Uncontrolled seizures.
7. Patients considered requiring radiotherapy to the lung at the time of study entry or in the near future.
8. Known or suspected brain metastases or spinal cord compression, unless treated with surgery and/or radiation and stable without steroid treatment for at least 4 weeks prior to the first dose of study medication.
9. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.
10. Patients who are pregnant or breastfeeding. Women of childbearing potential must have a negative pregnancy test performed within 7 days before the onset of treatment (Appendix 8).
11. Patients receiving the following classes of inhibitors of CYP3A4 (see Appendix 5 for guidelines and wash out periods):

a. Azole antifungals
b. Macrolide antibiotics
c. Protease inhibitors

12. Concomitant use of known CYP3A4 inducers such as phenytoin, carbamazepine, rifampicin, barbiturates, or St John's Wort.
13. Major surgery within 2 weeks of starting study treatment; patients must have recovered from any effects of any major surgery.
14. Significant weight loss (= 10% of body weight) in the 6 weeks before inclusion in the study.
15. Any condition that is unstable or could endanger the patient's safety and/or the patient's compliance with the study.
16. Substance abuse or clinical, psychological or social conditions that can undermine the validity of the informed consent or protocol compliance.
17. Patients who present any contraindication or suspected allergy to the products under investigation in the study. Tablets of gefitinib contain lactose: patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption, will not be included in this trial.
18. Contraindication for steroid use.
19. Impossibility to comply with treatment due to cultural or geographic circumstances.

5.3 Withdrawal procedures.

Patients may be withdrawn from the study treatment under any of the circumstances specified in Section 4.6.

Patients who discontinue should always be asked about the reasons for their discontinuation and the presence of any AE. The date and reasons for any premature interruption will be recorded in the CRF and will be taken into account in the final evaluation.

If possible, they should be seen and assessed by an investigator. After discontinuation from treatment, patients must be followed up for all existing and new AEs for 30 calendar days and followed until resolution unless, in the opinion of the investigator, the condition is unlikely to resolve due to the patient's underlying disease. All investigational products should be returned by the patient.

If treatment is terminated, follow-up of the patient will continue according to the protocol.

6 TREATMENT DESCRIPTION

6.1 Study treatment.

<u>Phase I part</u>

Except for the first cycle, patients will receive gefitinib 250 mg once a day, in combination with olaparib twice a day, continuously, in 28-day cycles.
During the first cycle of the Phase I part, up to one week before the start of combination treatment patients will receive olaparib (twice a day) alone: PK samples over 12 hours will be obtained to get monotherapy PK information. Olaparib will then be taken in combination with gefitinib from day 8 onwards.

Phase II part

Patients will be randomized into 2 treatment groups:

- Group A: gefitinib 250 mg once a day, continuously, in 28-day cycles.
- Group B: gefitinib 250 mg once a day, in combination with olaparib (at the recommended dose in the previous Phase Ib study) twice a day, continuously, in 28-day cycles.

Study treatment will be given until objective disease progression is documented or other criterion for discontinuation (eg, toxicity, withdrawal of consent) is met.

6.1.1 Gefitinib.

Gefitinib will be administered orally as one 250 mg tablet once a day. If a dose of gefitinib is missed, it should be taken as soon as the patient remembers. If it is less than 12 hours to the next dose, the patient should not take the missed dose. Patients should not take a double dose (two doses at the same time) to make up for a forgotten dose.
The tablet may be taken with or without food, at about the same time each day. The tablet can be swallowed whole with some water or if dosing of whole tablets is not possible, tablets may be administered as dispersion in water (non-carbonated). No other liquids should be used. Without crushing it, the tablet should be dropped in half a glass of drinking water. The glass should be swirled occasionally, until the tablet is dispersed (this may take up to 20 minutes). The dispersion should be drunk immediately after dispersion is complete (i.e. within 60 minutes). The glass should be rinsed with half a glass of water, which should also be drunk.

6.1.2 Olaparib.

Patients should swallow the medication whole with a glass of water in the morning and in the evening at the same time each day. This is to ensure approximately a 12-hour interval between doses. The dose of olaparib should be taken no sooner than 1 hour after food and patient should refrain from eating for 2 hours after dosing. If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets

can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next schedule time.

6.2 Dose modifications.

In principle, each patient will receive all treatment cycles at the dose established at the beginning of the study, except in the case of dose modifications foreseen for reasons of toxicity.

The guidelines to follow in case of toxicity are described below. All toxic effects will be graded using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

Gefitinib

Gefitinib will be managed as specified in the SPC attached as an Appendix to this protocol (Appendix 2).

Dose interruptions should be used as the first approach to managing toxicity. Repeat dose interruptions are allowed as required, for a maximum of 14 days on each occasion. Dose reductions are not permitted in this study.

Management of skin toxicity

Patients with poorly tolerated skin toxicity may be managed by providing a brief (maximum of 14 days) interruption of gefitinib; the daily dose of gefitinib should then be reinstated. However, the rash may improve without the need for interrupting gefitinib therapy.

Management of gastrointestinal toxicity

If gastrointestinal toxicity is not appropriately managed this may be associated with the development of dehydration. Patients should be advised to seek medical advice promptly in the event of developing severe or persistent diarrhoea, nausea, vomiting or anorexia.

Nausea and/or vomiting

In patients who have vomiting and are unable to retain gefitinib, every attempt should be made to control the nausea and vomiting. The dose of gefitinib may be repeated if vomiting occurs within 30 minutes of taking the tablet.

Diarrhoea

Diarrhoea has been successfully managed with anti-diarrhoeal agents such as loperamide.

- CTCAE grade 1-2 diarrhoea. No specific supportive care is usually needed or indicated. Oral fluid intake should be encouraged
- CTCAE grade 3 or 4 diarrhoea. If this occurs immediate supportive care measures should be initiated, gefitinib should be interrupted for up to a maximum of 14 days until resolution, or the diarrhoea has decreased in severity to CTCAE grade 1. If CTCAE grade 3 or 4 diarrhoea recurs, and in the investigator's opinion cannot be controlled by further drug interruptions and optimal symptomatic management, then gefitinib should be discontinued
- If a CTCAE grade 4 diarrhoea is associated with hemodynamic collapse, gefitinib should be discontinued.

Hepatotoxicity and liver impairment

Although liver function test abnormalities (including increases in ALT, AST, bilirubin) were common in patients treated with gefitinib, they were rarely observed as hepatitis. Therefore, periodic liver function testing is recommended. Gefitinib should be used cautiously in the presence of mild to moderate changes in liver function. Discontinuation should be considered if changes are severe.

Ophthalmology

Patients should be advised to seek medical advice promptly in the event of developing any eye symptoms.

Interstitial lung disease

Interstitial lung disease (ILD), which may be acute in onset, has been observed uncommonly in patients treated with gefitinib, and some cases have been fatal. If patients present with an acute worsening or new onset of respiratory symptoms such as dyspnoea, cough and fever, gefitinib should be interrupted and the patient promptly investigated for ILD. If ILD is confirmed, gefitinib should be discontinued and the patient treated appropriately.

Other toxicity

For any other CTCAE grade 3 or 4 toxicity or any clinically significant lower grade toxicity, treatment with gefitinib should be interrupted for a maximum of 14 days until the patient recovers completely or the toxicity reverts to CTCAE grade 1 or to the baseline grade.

Olaparib

Management of hematological toxicity

The following hematologic criteria must be met on day 1 of each cycle to administer dosing of olaparib:

- ANC ≥1.5 x 10^9/L
- Platelet count ≥100 x 10^9/L

If both of these criteria are no met, olaparib should be held for up to a total of 14 days until neutrophils and platelets have recovered to meet the above criteria. If olaparib must be held for greater than 14 days and the above hematologic criteria are not met, the drug should be definitely interrupted.

Management of neutropenic events

Olaparib may not be dosed until ANC ≥1.5 x 10^9/L.

Each of the following neutropenic events will be managed in a sequential fashion as described in Table 3:

1. ANC <1.5 x 10^9/L on day 1 of a cycle
2. Febrile neutropenia (ANC <1.0 x 10^9/L with fever ≥38.5ºC) at any time
3. NCI-CTCAE grade 4 neutropenia (ANC <0.5 x 10^9/L) lasting longer than 5 days in the middle of a cycle.

Management of thrombocytopenic events

Olaparib may not be dosed until platelet count ≥100 x 10^9/L.

Each of the following thrombocytopenic events will be managed in a sequential fashion as described in Table 3:

1. NCI-CTCAE grade ≥3 thrombocytopenia (platelets <50 x 10^9/L) at any point in the middle of a cycle
2. Platelet count <100 x 10^9/L on day 1 of any cycle.

Table 3: Management of grade 3 and 4 olaparib related adverse events

Initial dose level	**1st event occurrence Recommended dose reduction**	**2nd event occurrence Recommended dose reduction**
100 mg bd	Not reduction allowed - discontinuation of the drug	Not reduction allowed - discontinuation of the drug
200 mg bd	100 mg bd	Not reduction allowed - discontinuation of the drug
300 mg bd*	200 mg bd	100 mg bd

* In case the dose of 300 mg of olaparib is tested.

Management of non-hematological toxicity attributable to olaparib

Grade 3-4 non-hematological toxicities observed during the course of the study and attributable to olaparib will be first managed by interruption of the dose. Repeat dose interruptions are to be allowed as required. The maximum duration of any dose interruption is 14 days. If an interruption of longer than 14 days is required, olaparib should be discontinued. When olaparib is interrupted, the patient must either recover completely or the toxicity must revert to grade ≤ 1 or to the baseline situation, if the baseline situation was more than grade 1, before restarting treatment.

Where toxicity recurs following re-challenge with olaparib, and where further dose interruptions are considered inadequate for management of toxicity, the patient is to be considered for dose reduction or discontinuation of olaparib.

Management of non-hematologic grade 3-4 olaparib treatment related AEs

Treatment with olaparib must be interrupted for any non-hematologic grade 3 or 4 AE which the investigator considers to be related to administration of olaparib.

Repeated dose interruptions of up to a maximum of 14 days are allowed. Patients whose grade 3 or 4 event does not resolve to ≤ 1 or to the baseline grade after a 14 days dose interruption should discontinue olaparib.

Upon appropriate resolution of the toxicity (i.e., to grade ≤ 1 or to the baseline situation, if the baseline situation was more than grade 1), the patient should restart treatment with olaparib but with a dose reduction as indicated in Table 3. The dose of olaparib should not be reduced to less than 100 mg bd daily.

If the event recurs with the same severity, treatment should be interrupted again and, on resolution, a further dose reduction made where allowed.

Once an olaparib dose is reduced due to toxicity, dose re-escalation is not permitted.

Management of non-hematologic grade ≤ 2 olaparib treatment related AEs

For non-hematologic toxicities of grade ≤ 2 that the investigator feels are related to the administration of olaparib, the investigators should use their discretion in deciding whether dose interruptions are necessary and should also treat the events as medically appropriate based on signs and symptoms.

Except as noted above, the dose of olaparib must not be modified under any other circumstances unless prior agreement is given by the Sponsor.

Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormality occurs, an interruption in olaparib dosing is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if

no evidence of abnormality is observed on CT imaging and symptoms resolve, the olaparib treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Sponsor.

All dose reductions and/or interruptions (including any missed doses), and the reasons for them are to be recorded in the CRF.

6.3 Concomitant medication permitted and prohibited.

Any medications, with the exceptions noted below ("prohibited treatments"), which are considered necessary for the patient's welfare, and which it is believed will not interfere with the study medication, may be given at the discretion of the investigator.
All relevant concomitant medications should be recorded in the CRF, according to the following rules:

- Information relative to the medication that the patient is taking previously will be recorded only in the baseline visit.
- During the treatment period **only** the following information should be recorded:
    - Antiemetic medication
    - Hematopoietic supportive treatment (erythropoietin, colony-stimulating factors if required)
    - Medication required for the treatment of adverse effects (serious or not serious)
    - Transfusions, if needed
    - All treatment that begins to be taken regularly during the treatment period
- **It is not necessary** to record information on sporadic treatment that the patient receives during the treatment period (e.g., sporadic analgesic or anti-inflammatory agents, occasional antacids).

In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period should be recorded in the CRF, including the date, indication, description of the procedure(s) and any clinical finding.

Between study visits, in order to verify dosing compliance and times of administration of gefitinib (groups A and B) and olaparib (group B), patients will be asked to complete details of any self-medication in a diary card, and during the study visits special attention will be paid to questioning patients in relation to any self-medication.

Prohibited treatments

- No other chemotherapy, immunotherapy, hormonal therapy or other novel agent is to be permitted during the course of the study for any patient. Moreover, patients must not receive any concurrent anti-cancer therapy while on study treatment. Patients may continue the use of biphosphonates for bone disease and corticosteroids provide the dose is stable before and during the study; also, palliative radiotherapy may be used for treatment of pain in the site of bony metastases that were present at baseline providing the investigator does not feel that these are indicative of clinical disease progression during the study period.
- The use of any herbal/natural products or other “folk remedies” should be discouraged.
- CYP3A4 inducers may increase metabolism of gefitinib and decrease gefitinib plasma concentrations. Therefore, concomitant administration of CYP3A4 inducers (e.g. phenytoin, carbamazepine, rifampicin, barbiturates or herbal preparations containing St John’s Wort/Hypericum perforatum) may reduce efficacy of the treatment and is not allowed during study treatment.
- Concomitant use of CYP3A4 inhibitors (e.g. ketoconazole, posaconazole, voriconazole, protease inhibitors, clarithromycin, telithromycin), resulted in an 80% increase in the mean AUC of gefitinib in healthy volunteers. This increase in exposure may be clinically relevant since adverse experiences are related to dose and exposure. Co-administration of potent CYP3A4 inhibitors is not precluded in this trial since doses higher than gefitinib 250 mg have been investigated and considered tolerable, however, patients should be closely monitored for adverse reactions.
- International normalised ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin together with gefitinib. Patients taking warfarin and gefitinib concomitantly should be monitored regularly for changes in prothrombin time (PT) or INR.
- Medicinal products that cause significant sustained elevation in gastric pH, such as proton-pump inhibitors and H2-antagonists may reduce bioavailability and plasma concentrations of gefitinib and, therefore, may reduce efficacy. Antacids if taken regularly close in time to administration of gefitinib may have a similar effect.

6.4 Treatment compliance.

Patients will self-administer both study drugs. A member of the investigative site`s study team will query the patient for treatment compliance at each visit. All patients must return their bottles of drugs at each scheduled visit, when new bottles will be dispensed. An assessment of compliance (tablet count) of any remaining tablets in the bottles will be performed in order to determine if the patient is following their treatment dose schedule.

Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the CRF. Patients judged to be non-compliant (defined as taking less than 80% or more than 120% of the prescribed dose of investigational product) may continue in the study, but should be counselled on the importance of taking their study medication as prescribed.

After the tablet count of olaparib has been performed, the remaining tablets will not be returned to the patient but will be retained by the investigative site until the study monitor completes reconciliation.

Any unused supply of olaparib will be returned to the Sponsor or its representative upon completion of the trial or destroyed at site following written approval from the Sponsor.

7 EFFICACY EVALUATIONS

7.1 Description of efficacy parameters.

- Progression free survival (PFS): time from randomization until objective tumor progression or death from any cause. Patients who remain alive, without progressing or dying during the study, will be tabulated on their last date of evaluation. Patients who withdraw from the study before reaching progression, will be tabulated on their last date of evaluation or the date of randomization, whichever is later. Patients who withdraw from the study before reaching progression and without completing the withdrawal consent will be followed up to determine their disease status whenever possible. Patients who do not have an evaluation of response after baseline will be tabulated on day 1.

- Overall survival (OS): time from randomization until death from any cause. Patients who have not died during the study will be tabulated on their last date of evaluation. Patients who withdraw from the study will be tabulated to the date of withdrawal. Patients who withdraw from the study without having completed the withdrawal consent will be followed up to determine their status whenever possible.
- Tumor response will be assessed according to RECIST criteria.

7.2 Clinical trial calendar and procedures.

Baseline

Unless specified elsewhere assessments will be performed in both parts of the study.

The following assessments and procedures should be performed within 28 days prior to first dose of study treatment. A cycle of treatment is scheduled to last 4 weeks (28 days). For details of the schedule and nature of the assessments, see below.

- Signed informed consent
- Date of birth and race
- Menopausal status; serum or urine pregnancy test for women of childbearing potential (preferably within 7 days prior to treatment start)
- Clinical history
- Current and concomitant medications including previous cancer therapies (if applicable)
- Physical examination, ECOG performance status, vital signs (blood pressure and pulse rate, body temperature), 12-lead ECG
- Laboratory assessments:
    - Haematology: haemoglobin, red blood cell count (RBC), platelet count, white blood cells, differential white cell count, absolute neutrophil count, activated partial thromboplastin time (APTT), international normalised ratio (INR)
    - Clinical chemistry: Calcium, sodium, potassium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase (GGT), alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), urea or BUN, phosphorus, total protein, albumin, lactic dehydrogenase (LDH), amylase and lipase
    - Urinalysis: blood, protein and glucose
- Tumour assessment: all measurable lesions in the two treatment groups will be assessed by imaging studies. The baseline evaluation and response evaluation in the following cycles will be made by computed tomography (CT) scan or PET-CT (positron emission tomography) scan according to each center's routine practice. The same imaging technique will always be used for the assessment. If follow-up is carried out by PET, specific information will be recorded in the CRF on each lesion evaluated during follow-up, e.g., the SUV (standard uptake value) of each lesion.

  The PET-CT scan evaluation should meet the following criteria:
    - The same machine will be used to evaluate the baseline lesion and during follow-up
    - The result will be recorded as the size of the unidimensional lesion and used according to the indications of the RECIST criteria
    - If PET is used, the SUV of each measurable lesion will be recorded
    - Follow-up by CT or PET-CT will be recorded in the CRF. In the case of PET-CT, the SUV of each measurable lesion will be recorded in a field
    - When follow-up is by PET-CT, both size and SUV will be considered in the evaluation of response according to RECIST criteria and SUV

On trial assessments

Unless specified otherwise assessments will be done in both parts of the study.

Patients will self administer the study drugs at home except in the Phase I part of the study on the days when PK profiles will be taken (Appendix 6).

Patients will attend the clinic on a weekly basis during the Phase I part of the study, and every four weeks (1 cycle) during the Phase II part of the study. The following assessments will be performed at time points specified in the study plan (Table 4).

- Physical examination including ECOG performance status and vital signs at the start of every cycle
- Haematology, clinical chemistry and urinalysis
- PK samples **(Phase I only)**
- AE & concomitant medications (every visit)
- Tumour assessment: the baseline assessment method will be repeated every other cycle until disease progression.

Follow-up visits

Where possible, a follow up medical examination should be performed 30 days after the last dose of gefitinib (as summarised in Table 4). This will consist of a 12-lead ECG, a physical examination, haematology, clinical chemistry, urinalysis assessments and a review of AEs and concomitant medication. Any new findings or any deterioration in existing abnormalities should be recorded as adverse events.

Any serious and/or non-serious AEs ongoing at the time of the withdrawal visit or which have occurred during the defined 30-day follow-up period must be followed-up. Appropriate safety evaluations should be repeated and/or additional tests performed at any time when clinically indicated, or at the discretion of the investigator, until resolution, unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. If the patient is lost to follow-up, then this should be noted in the CRF.

The follow-up of the patients of both groups who finalize treatment before progression, will include CT or PET-CT, as well as other imaging tests in the case of previous lesions or suspected new lesions not evaluable by CT. CT or PET-CT will be performed every **6 weeks** until progression of the disease.

After disease progression, the record of second-line and successive treatments will be completed for both groups, together with the date of death for overall survival.

Table 4: Calendar and procedures

Parameter	Pre-treatment (4 weeks earlier)	During Treatment (at the start of every cycle)	End of treatment	Follow-up
Informed consent	X			

Confirm eligibility	X[a]			
Clinical history	X	X	X	X
Physical examination	X[a]	X	X	X
Vital signs[b]	X[a]	X	X	X
Performance status (ECOG)	X[a]	X	X	X
ECG[c]	X[a]			
Pregnancy test[d]	X[a]			
Haematology	X[a]	X[e]	X	X
Clinical chemistry	X[a]	X[e]	X	X
Urinalysis	X[a]	X[e]	X	X
PK blood sampling[f]				
PG blood sample[g]	X		X	
PG tumor tissue specimen	X			
Safety assessment[h]	X	X	X	X
Tumor assessment:				
Thoraco-abdominal CT or PET-CT	X	X[i]	X	X
Other assessment tests	X	X[i]	X	X

PK: pharmacokinetics; PG: pharmacogenomics; CT: computed tomography; PET: positron emission tomography.
[a] To be performed within 7 days before study day -1. Eligibility to be confirmed before commencing treatment on study day 1.
[b] Vital signs to include blood pressure (BP), pulse rate (PR) and body temperature. BP and PR should be taken after the patient has been sitting at rest for 5 minutes and before blood sampling.
[c] ECG to be performed at baseline, and if clinically indicated at any other time.
[d] Pre-menopausal women of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to day 1. In the event of suspected pregnancy during the study, the test should be repeated and if it is positive, the patient withdrawn immediately.
[e] Haematology, clinical chemistry and urinalysis to be performed weekly during the Phase I part of the study. Samples only need to be collected predose on day 1 if the screening assessments were performed more than 3 days before.
[f] During the first cycle of the Phase I part, up to one week before the start of combination treatment patients will receive olaparib alone. On the last day of that week (day 7) a full 12-hour plasma PK profile will be taken. Then (day 8) patients will start taking gefitinib too and, after a further week (day 14), a second olaparib PK profile will be obtained. Blood samples for olaparib PK will be taken relative to the morning dose of olaparib: predose, 30 mins, 1, 2, 4, 6 and 12 hrs postdose (Appendix 6).
[g] Biomarkers for the PG study will be analyzed in blood samples at baseline and at the time of progression (Appendix 9).
[h] Safety evaluations will be conducted at baseline, and then at the start of every cycle. During the Phase Ib, additional safety evaluations will be conducted on days 2, 8, 15, 22, 27, and 28 of cycle 1, and weekly subsequently.
[i] The baseline assessment method will be repeated every other cycle until disease progression. The follow-up of the patients of both groups who finalize treatment before progression, will include CT or PET-CT, as well as other imaging tests in the case of previous lesions or suspected new lesions not evaluable by CT. CT or PET-CT will be performed every **6 weeks** until progression of the disease.

8 SAFETY EVALUATION

8.1 Description of safety parameters.

The number and percentage of adverse effects observed and their severity will be reported. Each patient will be monitored regularly to detect possible adverse effects before beginning each cycle. The NCI-CTCAE v 4.0 criteria will be followed for assessment. AEs that cannot be classified using this system will be classified according to the **MedDRA** method:

- Mild (asymptomatic).
- Moderate (symptomatic but does not interfere significantly with function).

- Severe (interferes significantly with function).
- Life-threatening.

8.2 Documentation, notification and follow-up of adverse event

An AE is any unfavorable medical occurrence in a patient or human subject participating in clinical research in which a medicinal product has been administered. The AE does not necessarily have a causal relation with the treatment. Therefore, an AE can be any disease, symptom or untoward or unfavorable sign (including an abnormal laboratory finding) associated in time to the use of a medicinal product in investigation, whether or not it is considered related to the medicinal product.

AEs associated to the use of a medicinal product in human beings, whether or not related to the product, include:

- An AE appears during the use of medicinal product in professional practice
- An AE derived from an overdose, whether accidental or deliberate
- An AE derived from abuse of a drug
- An AE derived from withdrawal of a drug
- When a reasonable possibility exists that the AE occurred merely because of the participation of the patient in the study (e.g., AE caused by discontinuing antihypertensives during the washout phase), it will also be reported as an AE, even if it does not have any relation to the product under investigation.

The clinical manifestation of the failure of the expected pharmacologic action (progression) will not be recorded as an AE if it has already been recorded among the data in the CRF. However, if the episode meets any criteria of a serious adverse event (SAE), it must be recorded and reported as such.

Serious adverse event

A SAE is any unfavorable medical occurrence that, at any dose:

- Results in death
- Is life threatening
- Requires hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect, or
- Any other AE that may jeopardize the subject's health.

Life threatening: The term "life-threatening" used in the definition of "serious" refers to an AE that resulted in the subject running a risk of dying when it occurred. It does not refer to an AE that hypothetically could have caused death if it had been more intense.

Hospitalization: Any AE that results in or prolongs hospitalization will be considered serious, EXCEPT for the following exceptions:

- Admission involves a hospital stay of less than 24 hours.

or

- The admission was planned previously (e.g., surgery scheduled before initiation of the study).

or

- The admission is not related to an AE (e.g., a social hospitalization to allow the caretaker to rest).

Nevertheless, it should be noted that invasive treatment applied during any hospitalization can meet the criteria of "medically important" and, as such, must be reported as a SAE depending on clinical discretion. In addition, when local health authorities specifically require a stricter definition, local law will have preference.

Disability means substantial alteration of a person's capacity to perform normal vital functions.

Important medical event: An AE can be considered serious if it puts the subject in danger and requires intervention to avoid another serious disorder. The WHO publication "WHO Adverse Reaction Terminology – Critical Terms List" serves as guide to assess important medical occurrences. The terms listed refer to or may indicate a serious morbid condition.

These episodes require special attention because they may be associated to a serious disease and give rise to more forceful measures than the notifications made using other terms.

Reporting of serious adverse events

All the serious adverse events that occur during the period of study treatment or in the 30 days after the last infusion of chemotherapy must be communicated following the procedure described below. For any late SAE (which is manifested after this 30-day period) that is possibly or probably related with the study chemotherapy, the same notification procedure should be followed.

Progression of an underlying disease of the patient that gives rise to one of the events described previously should be reported as a serious adverse experience (but expected) that (a) is not related with the study medication or (b) is produced by failure of the anticipated therapeutic effect of the study drug.

The investigator will notify the Sponsor by telephone or fax, all serious adverse events that occur during the study within 24 h of having knowledge of the adverse event or on the next work day. In the case of SAEs that are life-threatening or result in death, the investigator must notify the Monitor immediately:

PIVOTAL, SL
Gobelas, 19, La Florida
28023 Madrid, Spain
Tel: + 34 91 708 1250
Fax: +34 91 708 1301

All reports of SAE by telephone must be followed by the respective notification report in writing in the following 48 hours. For notifications by fax the investigator will collect the information on the SAE on the corresponding form.

The minimum initial information for the notification of an adverse event must include the following:

- Description of the adverse event and date of onset of the same.
- Sex and age (or date of birth) of patient.
- Information on the treatment received.
- Name and address of the notifying physician.
- Whether or not a relation of causality with the study drugs exists.

When the SAE is notified by telephone or fax with the minimum initial information, the complete SAE notification form with all the information will be sent in the next 2 work days.

The investigator and people in charge of the patient's care should initiate any complementary investigation of the serious adverse events based on their clinical opinion of the possible causal factors. This procedure may include the need to seek the opinion of a specialist in the field of the adverse event.

If the death of a participating subject has been communicated, the investigator will provide the Sponsor and Clinical Research Ethics Committees (CRECs) involved all the complementary information that they request.

In accordance with the dispositions of this protocol, the investigator has to assume these responsibilities.

Pregnancy

While pregnancy is not considered to be a SAE, pregnancies that occur during a clinical trial must be notified in the same time periods as a SAE. The pregnancies of patients enrolled in the clinical trial or their partners will be notified. The outcome of the pregnancy will be monitored closely and any abnormality experienced by the mother or child will be reported.

The same is applicable to pregnancies resulting from the sexual relations of fathers who have received the product under investigation.

Unexpected adverse event

An unexpected AE is any adverse reaction to the medicinal product whose nature or severity is not consistent those indicated in the IB/SPC in effect. Reports that add significant information about the specificity or intensity of a known and documented AE constitute unexpected AEs. For example, a more specific or more intense AE than is described in the investigator's brochure must be considered "unexpected." Specific examples are:

- Acute renal insufficiency notified as an AE followed by another notification later of interstitial nephritis and
- Hepatitis with a first notification of fulminant hepatitis.

The Sponsor is responsible for notifying all suspected unexpected serious adverse reaction (SUSAR) in the time periods established by Spanish regulations in effect to:

- Spanish Agency of Medicinal and Health Products (AEMPS, *Agencia Española del Medicamento y Productos Sanitarios*)
- The CREC involved in the clinical trial for SUSARs that occur in participating subjects belonging to centers in their area of influence.
- The competent bodies of the autonomous communities, when the SUSAR has occurred in health centers of the respective Community
- The principal investigators.

Appendix D, supplied by the AEMPS at *Aclaraciones* is used to notify SUSARs to CRECs and Health Authorities, in application of clinical trial regulations effective as of 1 May 2004 (version no. 4, of 30 November 2006).

Relation between the AE and the product in investigation

The assessment of the relation between an AE and the administration of the study drug is a clinical decision based on all the information available when the case report form is completed.

A "negative" assessment implies:

- The existence of a clear alternative explanation, for example, mechanical bleeding in the surgical area.

or

- Lack of probability; for example, if the subject is run over and there are no indications that the drug caused disorientation that might have lead to the accident or if a cancer appears days after the first administration of the drug.

A "positive" assessment indicates that reasonable suspicions exist that the AE is associated with the use of the drug in investigation.

The factors that must be taken into account when the relation between the AE and the study drug is assessed are:

- Temporal sequence with respect to administration of the study drug: the episode must occur after the drug is used. The time from exposure to the drug to occurrence of the episode will be evaluated within the clinical context.
- Recovery occurs with interruption (withdrawal of exposure) and recurs with resumption (renewed exposure): the subject's response to interruption of the drug (withdrawal of exposure) or resumption of the drug (renewed exposure) will be assessed in light of the usual clinical course of the episode in question.
- Underlying, concomitant, and intercurrent diseases: any notification will be evaluated considering the natural history and evolution of the disease treated and any other disease that the subject may have.
- Concomitant medicinal products or treatment: the other drugs that the subject is taking or treatment that the subject is receiving must be examined to ascertain whether one of them could have caused the episode in question.
- Pharmacology and pharmacokinetics of the study drug: the pharmacokinetics properties (absorption, distribution, metabolism and excretion) of study drugs will be evaluate, in addition to the subject's pharmacodynamics.

Intensity of the adverse event

The intensity of AEs will be classified according to the toxicity criteria of the NCI-CTCAE version 4.0:

- Grade 1: Mild AE
- Grade 2: Moderate AE
- Grade 3: SAE
- Grade 4: Life-threatening or potentially disabling AE.
- Grade 5: Death related to the AE.

Documentation of adverse events

All AEs that occur during the study and all SAEs that appear after the subject has signed the informed consent form, whether or not causally related with the study drug, must be recorded in detail in the subject's CRF.

The documentation must be supported by an annotation in the subject's file. Any clinically relevant abnormality in an analysis, such as abnormalities that force the subject to withdraw from the study, require treatment, cause evident clinical manifestations, or are considered relevant by the investigator, must be notified as an AE. Each event will be describe in detail, including the date of onset and conclusion, the intensity, relation with the product under investigation, measures taken, and outcome.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment in the study should be followed up by the investigator for as long as medically indicated, but without further recording in the CRF. The Sponsor will retain the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

9 STATISTICAL PROCEDURES

9.1 Sample size. Justification

Phase Ib

Around 20 patients are expected to participate in the Phase Ib part of the study. However, the number of patients may vary depending upon the tolerability of the combination and the number of dose levels required to identify the MTD.

Phase IIb

A total of 116 events are required to demonstrate an increase in progression free survival of 6 months, 10 months in gefitinib arm relative to 16 months in the gefitinig/olaparib arm (equivalent to HR=1.6) by using a one-sided log rank test with an overall 80% power at a 0,05 significance level. From our previous experience on other studies, by assuming an accrual rate of 140 patients/year, a total accrual period of 24 months and a follow-up period of 12 months with a 5% of losses on each arm, then a total accrual of 248 subjects would be required.

On the basis of our preliminary study (1), we expected approximately 17% of patients to carry EGFR mutations. Therefore, to get the required number of subjects around 1.500 patients should be screened.

9.2 Statistical analysis

The following analyses will be performed for the primary objective of PFS:

- A one-sided log-rank test will provide a basic comparison of the two treatment groups on PFS without adjustment for further potential prognostic factors.
- Median and the 95% confidence limits will be estimated using Kaplan-Meier survival methodology. Time units will be months.
- Plots of the Kaplan-Meier estimates for each treatment group will be generated.
- Estimates of the treatment effect will be expressed as HR (gefitinib compared to gefitinib plus olaparib) with their corresponding 95% confidence intervals.

In order to measure the robustness of the estimation of differences between treatments, and to account for the known influence of the two main markers on treatment effect, which are BRCA1 and T790M, a stratified analysis, using both markers will be carried out. Cox-regression analyses, both unadjusted and adjusted for these stratification factors, will be performed, including HRs for gefitinib compared to gefitinib plus olaparib and their 95% confidence intervals and p-values from the Wald test.

Additionally, Cox-regression analysis will be also used in pre-specified subgroup analyses for PFS as follows:

- A test of interaction, involving Cox regression model, will be carried out in order to detect the heterogeneity of treatment effect according to tertiles of BRCA1 mRNA expression levels as well as to T790M status. A forest plot will be used to present this information together with the estimate of the effect and its confidence interval for each test of interaction being performed.

Secondary analysis will be tested at a two-sided level of significance of 0.05.

For OS analysis, we will use the same statistical plan than for PFS except that analysis will be regarded as exploratory analysis instead of pre-specified subgroup analyses.

The response rate in each treatment arm will be summarized by presenting the rate and 95% confidence limits according to Binomial distribution.
Difference of response will be tested with a two-sided chi-squared test at 5% significance level. In addition, 95% confidence limits for the difference will be calculated.

10 DIRECT ACCESS TO DATA/SOURCE DOCUMENTS

The CRFs and all source data must be easily available for review during scheduled visits by the monitor.

11 CONTROL AND QUALITY ASSURANCE

In order to verify compliance with the protocol, the representatives designated by the Sponsor will be allowed to visit all the study centers periodically to check data integrity and to validate the quality and veracity of the study. The study documents will be reviewed in the center, compared with the source documents (e.g., clinical histories), and discussed with the investigator. The suitability of the facilities will be evaluated continuously.

The study may be evaluated by the Sponsor's internal auditors or authorized representatives and the inspectors designated by health authorities. They will be allowed access to the CRFs, source documents, and other study files. The audit reports will be kept confidential.

The investigator must notify the Sponsor immediately of any inspection by the Health Authorities and provide a copy of the resulting reports.

12 ETHICS

The study will be conducted according to the guidelines specified in the Declaration of Helsinki, Good Clinical Practice, ICH (International Conference on Harmonisation) directives, and the legislation in effect.

The study will be conducted according to protocol requirements. Before beginning the study, the protocol and any relevant amendment, as well as the patient information sheet and informed consent form must receive the approval/favorable opinion of the CREC and the AEMPS. Minor amendments will be approved according to the procedures indicated in the legislation in effect.

The informed consent form of each subject must be freely granted and obtained in writing before the subject may participate in the clinical trial.

The rights, safety, and well-being of the clinical trial subjects have prevalence over the interests of science and society.

The study personnel involved in conducting this clinical trial will be qualified to carry out the assigned tasks. Personnel who have been sanctioned and/or suspended for scientific fraud or clinical malpractice may not participate.

Patient information sheet and informed consent

Informed consent will be obtained in accordance with the legislation in effect and the Declaration of Helsinki and its modifications.

The patient must be properly informed by the investigator before he or she may be included in the clinical trial. The patient will give his or her consent after having received all the pertinent information adapted to his or her level of understanding. This will documented in the patient information sheet and informed consent form. Consent should reflect the subject's presumptive wishes and may be withdrawn at any time without prejudice to the patient.

The Investigator must give the subject the time to ask about the details of the study. When ready, the subject will sign and date the informed consent personally. The Investigator will provide the subject with a copy of the consent form and patient information sheet.
The informed consent and any other information given to the subjects must be revised whenever relevant new information becomes available that may affect the subject's voluntary participation. These documents will have to receive the approval/favorable opinion of the CREC before they may be used. The Investigator, or a person designated by the Investigator, will have to inform the subject fully about all relevant aspects of the study and about any new information that may affect the subject's willingness to continue participating in the study. This communication must be documented.
The subject participating in the clinical trial may withdraw consent at any time, without having to give any explanation and without this resulting in any responsibility or prejudice.

Clinical Research Ethics Committee

The protocol and informed consent form will be reviewed by a duly constituted CREC. The decision of the CREC regarding the development of the study will be delivered to the investigator in writing; a copy of this decision will be sent to the sponsor.
Any modification to the protocol must be documented in writing as an amendment.
Amendments will be properly identified by a number corresponding to their chronological order and will be dated and signed by the Sponsor and Investigator.
All protocol amendments will be reported to the CRECs involved in the clinical trial, the AEMPS, and the respective Autonomous Communities (if applicable) before they are applied. Authorization by the CRECs involved and the AEMPS is necessary for relevant modifications.
The Sponsor will submit the required progress reports on the study to the CREC. Suspected unexpected serious adverse reactions (SUSARs) will also be reported to the CREC. The sponsor will inform the CREC of the termination of the study.

Subject data protection

The informed consent form will incorporate wording that complies with relevant data protection and privacy legislation.

13 DATA MANAGEMENT AND ARCHIVING DATA

The Sponsor will provide CRFs, which will consist of a white-colored original and several colored copies. Case report forms will be completed in **LEGIBLE CAPITAL LETTERS** using a ball-point pen with black ink. The clinical trial monitor will verify the CRFs by comparing them with the source data recorded (and work logs, if necessary) before they are collected.

The last copy will be conserved in the Investigator's files and the other copies will be returned to the Sponsor. No CRF will be sent by mail to the Sponsor without specific authorization.

Archives and reports

The Investigator will prepare and maintain clinical histories, recording all relevant examinations and data for the study of each subject treated with the medicinal product in investigation. The data recorded in the CRF from the source documents must coincide with these original documents; any discrepancies must be explained.

The confidentiality of any documents that can identify the subjects must be protected to respect their privacy and the rules of confidentiality in accordance with the applicable regulatory requirements.

The investigator will maintain a Signature Page to document everyone authorized to make entries and/or corrections in the CRFs. Corrections should be made by crossing out the incorrect entry and writing the correct information in the adjacent space. The correction should be initialed by the person who makes the correction, who will date the correction and add an explanation (if applicable). The original entry should remain legible.

The completed CRF will be reviewed, signed and dated immediately by a qualified physician who is either an investigator or collaborator. The Investigator will conserve a copy of the CRFs with the changes and corrections.

Conservation of archives

The Sponsor is responsible for the archive of clinical trial documentation. The investigator will conserve the authentication codes of the patients for at least 15 years the conclusion or termination of the clinical trial. The patients' clinical histories and other original data will be conserved for the maximum time period allowed by the hospital, institution, or clinic where the clinical trial is conducted.

The Investigator must contact the Sponsor before destroying any records associated with the study. The Sponsor will notify the Investigator when it no longer is necessary to conserve of the clinical trial archives.

If the investigator leaves the study, the records will be transferred to another person designated by mutual agreement. The Sponsor will communicate this transfer to the CREC and AEMPS.

14 INSURANCE POLICY

An insurance policy for the clinical trial has been contracted with the insurance company HDI Hannover Internacional (España) Seguros y Reaseguros, S.A. (C/ Luchana 23, Madrid, Spain): Policy number 130/001/007116.

15 PUBLICATION CONDITIONS

The Sponsor will review all requests for publication of the results of the present study. The Sponsor recognizes the importance of disseminating the results and agrees to allow the principal investigators to publish part or all of these results, as long as the manuscript has been previously approved by the Sponsor. The Sponsor may require changes considered necessary to ensure quality and protect intellectual property rights. The principal investigator understands and accepts that under certain conditions the publication of results may be delayed to guarantee the scientific quality and integrity of the data, for instance, until the results from a representative number of study centers are available. The principal investigator understands and accepts the Sponsor's authority to choose the proper moment for disseminating the data. By signing the present protocol, the principal investigator accepts the terms of the Sponsor's publication policy and agrees to abide by them.

16 REFERENCES

1. Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med. 2009;361:958-967.

2. Chin TM, Quinlan MP, Singh A, et al. Reduced Erlotinib sensitivity of epidermal growth factor receptor-mutant non-small cell lung cancer following cisplatin exposure: a cell culture model of second-line erlotinib treatment. Clin Cancer Res. 2008;14:6867-6876.

3. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361:947-957.

4. Morita S, Okamoto I, Kobayashi K, et al. Combined survival analysis of prospective clinical trials of gefitinib for non-small cell lung cancer with EGFR mutations. Clin Cancer Res. 2009;15:4493-4498.

5. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. 2010;362:2380-2388.

6. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol. 2010;11:121-128.

7. Maheswaran S, Sequist LV, Nagrath S, et al. Detection of mutations in EGFR in circulating lung-cancer cells. N Engl J Med. 2008;359:366-377.

8. Yung TK, Chan KC, Mok TS, et al. Single-molecule detection of epidermal growth factor receptor mutations in plasma by microfluidics digital PCR in non-small cell lung cancer patients. Clin Cancer Res. 2009;15:2076-2084.

9. Nagai Y, Miyazawa H, Huqun, et al. Genetic heterogeneity of the epidermal growth factor receptor in non-small cell lung cancer cell lines revealed by a rapid and sensitive detection system, the peptide nucleic acid-locked nucleic acid PCR clamp. Cancer Res. 2005;65:7276-7282.

10. Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet. 2010;376:245-251.

11. Tutt A, Robson M, Garber JE, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet. 2010;376:235-244.

12. Wu W, Sato K, Koike A, et al. HERC2 is an E3 ligase that targets BRCA1 for degradation. Cancer Res. 2010;70:6384-6392.

13. Gonzalez ME, Li X, Toy K, et al. Downregulation of EZH2 decreases growth of estrogen receptor-negative invasive breast carcinoma and requires BRCA1. Oncogene. 2009;28:843-853.

14. Friedman JM, Liang G, Liu CC, et al. The putative tumor suppressor microRNA-101 modulates the cancer epigenome by repressing the polycomb group protein EZH2. Cancer Res. 2009;69:2623-2629.

15. Min J, Zaslavsky A, Fedele G, et al. An oncogene-tumor suppressor cascade drives metastatic prostate cancer by coordinately activating Ras and nuclear factor-kappaB. Nat Med. 2010;16:286-294.

16. Bunting SF, Callen E, Wong N, et al. 53BP1 inhibits homologous recombination in Brca1-deficient cells by blocking resection of DNA breaks. Cell. 2010;141:243-254.

17. Jensen RB, Carreira A, Kowalczykowski SC. Purified human BRCA2 stimulates RAD51-mediated recombination. Nature. 2010.

18. Nakada S, Tai I, Panier S, et al. Non-canonical inhibition of DNA damage-dependent ubiquitination by OTUB1. Nature. 2010;466:941-946.

19. Koike A, Nishikawa H, Wu W, et al. Recruitment of phosphorylated NPM1 to sites of DNA damage through RNF8-dependent ubiquitin conjugates. Cancer Res. 2010;70:6746-6756.

20. Kuang Y, Rogers A, Yeap BY, et al. Noninvasive detection of EGFR T790M in gefitinib or erlotinib resistant non-small cell lung cancer. Clin Cancer Res. 2009;15:2630-2636.

21. Bindra RS, Gibson SL, Meng A, et al. Hypoxia-induced down-regulation of BRCA1 expression by E2Fs. Cancer Res. 2005;65:11597-11604.

22. Chan N, Koritzinsky M, Zhao H, et al. Chronic hypoxia decreases synthesis of homologous recombination proteins to offset chemoresistance and radioresistance. Cancer Res. 2008;68:605-614.

23. Bindra RS, Glazer PM. Repression of RAD51 gene expression by E2F4/p130 complexes in hypoxia. Oncogene. 2007;26:2048-2057.

24. Hegan DC, Lu Y, Stachelek GC, et al. Inhibition of poly(ADP-ribose) polymerase down-regulates BRCA1 and RAD51 in a pathway mediated by E2F4 and p130. Proceedings of the National Academy of Sciences. 2010;107:2201-2206.

25. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med. 2009;361:123-134.

26. Fong PC, Yap TA, Boss DS, et al. Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. J Clin Oncol. 2010;28:2512-2519.

27. *AJCC cancer staging manual, Seventh Edition*. New York: Springer-Verlag; 2010.

28. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-247.

APPENDICES

Appendix 1. Investigator's brochure of olaparib

See attached document.

Appendix 2. Summary of product characteristics: Iressa® (gefitinib)

See attached document.

Appendix 3. National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0

See attached document (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

Appendix 4. Performance status

Description	ECOG Grade	Karnofsky Equivalent	
Fully active, able to carry on all pre-disease performance without restriction	0	100	Normal, no complaints; no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature ie, light housework, office work	1	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self but unable to carry on normal activity or to do work.
Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2	60	Requires occasional assistance but is able to care for most of personal needs.
		50	Requires considerable assistance and frequent medical care.
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3	40	Disabled; requires special care and assistance.
		30	Severely disabled; hospitalisation is indicated although death not imminent.
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4	20	Very ill; hospitalisation and active supportive care necessary.
		10	Moribund.

Appendix 5. Cytochrome P450 isoenzymes: inducers and inhibitors

Olaparib is an investigational drug, for which no data on in vivo interactions are currently available. Based on in vitro data and clinical exposure data olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. In vitro data have, however, also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, although the contribution of metabolic clearance to total drug clearance in man is currently unknown, to ensure patient safety the following potent inhibitors of CYP3A4 must not be used during this study for any patient receiving olaparib.

Whilst this is not an exhaustive list, it covers the known potent inhibitors which have most often previously been reported to be associated with clinically significant drug interactions:

- Ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin (wash-out period 1 week).

In addition, to avoid potential reductions in exposure due to drug interactions, the following CYP3A4 inducers are excluded:

- Phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbitone and St John's Wort (wash-out period for phenobarbitone 5 weeks and for any of the others 3 weeks).

If use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient's safety and welfare, the investigator must contact the Sponsor, and a decision to allow the patient to remain on study will be made on a case-by-case basis.

Appendix 6. Handling and shipment of pharmacokinetics samples: Phase I only

OLAPARIB PK SAMPLE PREPARATION

A full 12 PK profile for the determination of olaparib plasma concentration will be collected at the following time points

Study day	Time point*
7	Predose, 30 mins, 1, 2, 4, 6 and 12 hrs post olaparib dose
14	Predose, 30 mins, 1, 2, 4, 6 and 12 hrs post olaparib and gefitinib dose

* Blood samples for olaparib PK will be taken relative to the morning dose of olaparib

The following method will be used for preparation of blood samples for olaparib:

1. At each time point, collect 4 mL whole blood into a pre-labelled Lithium Heparin tube and mix well. Avoid unnecessary exposure to light.
2. Centrifuge at 2000 g for 10 minutes at a nominal 10°C (room temperature is acceptable).
3. Transfer the plasma into eppendorf tubes and store samples at -20°C in the boxes provided, until shipment.

Olaparib PK sample handling, storage and shipment

Plasma samples should be stored at -20°C until the monitor advises on shipment (approximately once each cohort of 3 patients has been completed).

Samples will only be shipped once there are complete profiles for patients.

Samples will be labelled with the centre number, patient number, protocol number, sample number, date and time.

Olaparib plasma samples should be sent on dry ice by overnight courier to:

QBR
Newmarket Road
Fordham
Cambridgeshire
England
CB7 5WW
Tel: +44 (0) 1638 720500

Appendix 7: Definitions of measurable, target and non target lesions and objective: RECIST criteria v 1.1

See attached document (*Eisenhauer et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur.J Cancer 2009; 45(2): 228-247*) (28)

Appendix 8: Acceptable birth control methods

Olaparib is regarded as a compound with medium/high foetal risk.

Patients of childbearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception throughout their participation in the study and for 3 months after last dose of study drug(s).

Acceptable non-hormonal birth control methods include:

- Total sexual abstinence. Abstinence must be for the total duration of the trial and the drug washout period
- Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia
- Tubal occlusion plus male condom with spermicide
- IUD plus male condom + spermicide. Provided coils are copper-banded.

Acceptable hormonal methods:

- Etonogestrel implants (e.g. Implanon, Norplan) + male condom with spermicide
- Normal and low dose combined oral pills + male condom with spermicide
- Norelgestromin/EE transdermal system + male condom with spermicide
- Intravaginal device + male condom with spermicide (e.g., EE and etonogestrel)
- Cerazette (desogestrel) + male condom with spermicide. Cerazette is currently the only high efficacious progesterone based pill.

Appendix 9: Patient registration procedure and specimen extraction, shipment, and analysis for the pharmacogenomics study

See attached document.

Appendix 10: Investigator's agreement. Protocol signature page by principal investigator

I have read the preceding protocol:

"**Multicenter, randomized, Phase Ib/IIb study to evaluate the efficacy and tolerability of gefitinib in combination with olaparib (AZD2281) versus gefitinib alone, in patients with Epidermal Growth Factor Receptor (EGFR) mutation positive advanced non-small-cell lung cancer**"

and agree that it contains all necessary details for conducting this study.

I will conduct the study as outlined therein and will attempt to complete the planned enrolment of patients within 24 months of the receipt of clinical supplies. I will provide copies of the protocol and all drug information relating to the preclinical and prior clinical experience, furnished to me by the Sponsor, to all relevant staff/members. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study. I agree to keep accurate records on all patient information (Case Report Forms and patient informed consent statement), drug transportation and return forms, and all other information collected during the study for a minimum period of 15 years.

I agree not to publish all or any part of the results of the study carried out under this protocol, without the prior written consent of the Sponsor.

All parties agree to ensure direct access to examine, analyze, verify and reproduce source data/documents, and reports from all trial related sites for the purpose of monitoring and auditing by the Sponsor, and inspection by domestic and foreign Regulatory Authorities.

Investigator Name:

Printed	Signature	Date (dd/mmm/yy)

Sponsor

Name and Title	Signature	Date (dd/mm/yy)