CLINICAL TRIAL PROTOCOL

VICTORIA

(hormone receptor postiVe endometrIal Carcinoma treated by dual mTORC1/mTORC2 Inhibitor and Anastrozole)

A Multicentric, randomized, non comparative, open-label Phase I/II evaluating AZD2014 (dual mTORC1/mTORC2 inhibitor) in combination with anastrozole versus anastrozole alone in the treatment of metastatic hormone receptor-positive endometrial adenocarcinoma

Version 6.0 dated 4 april 2019

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PROTOCOL APPROVALS

French Competent Authority : ANSM	Approval Date	18 02 2016
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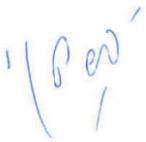
SIGNATURES

TITLE	**VICTORIA - A Multicentric, randomized, non comparative, open-label Phase I/II evaluating AZD2014 (dual mTORC1/mTORC2 inhibitor) in combination with anastrozole versus anastrozole alone in the treatment of metastatic hormone receptor-positive endometrial adenocarcinoma**
PROTOCOL VERSION	**Version 6.0 dated 4 april 2019**
COORDINATING INVESTIGATOR	**Dr Pierre Etienne HEUDEL, MD, PhD** **04/04/2019**  **Date / Signature**
SPONSOR REPRESENTATIVE	**Dr David PEROL, MD, Head of Clinical Researh Department** **04/04/2019**  **Date / Signature**

INVESTIGATORS AGREEMENT

I,……the Principal Investigator, understand that the clinical trial entitled " **VICTORIA -** *Multicentric randomized non comparative open-label phase I/II evaluating AZD2014 (dual mTORC1/mTORC2 inhibitor) in combination with anastrozole versus anastrozole alone in the treatment of metastatic hormone receptor-positive endometrial adenocarcinoma*".

will not start without the prior written approval of a properly constituted Ethics Committee and French competent authority (ANSM). No changes will be made to the study protocol without the prior written approval of the sponsor and, the Ethics Committee and the competent authority.

I have read, understood, and agreed to abide by all the conditions and instructions contained in this protocol. I agree to comply with the National regulations and ICH Harmonized Tripartite Guideline for Good Clinical Practice for conducting clinical trials and local regulations and will conduct the above study under these standards.

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ABREVIATIONS

AE	Adverse Event
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
CLB	Centre Léon Bérard
CR	Complete response
CPP	Comité de Protection des Personnes
CRF	Case Report Form
DMC	Data Monitoring committee
DRCI	Direction de la Recherche Clinique et de l'Innovation
EC	Ethic Committee
ECOG	Eastern Cooperative Oncology Group
EudraCT	European drug regulatory authorities clinical trials
ER	Estrogen receptor
IB	Investigator Brochure
OS	Overall survival
MTD	Maximum Tolerated Dose
PD	Progressive disease
PFS	Progression-free survival
PgR	Progesterone receptors
PR	Partial response
po	Per os
PS	Performance Status
PTEN	Phosphatase and tensin homolog
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SD	Stable disease
SUSAR	Suspected Unexpected Serious Adverse Reaction

SYNOPSIS

TITLE	A Multicentric randomized non comparative open-label phase I/II evaluating AZD2014 (dual mTORC1/mTORC2 inhibitor) in combination with anastrozole in the treatment of metastatic hormone receptor-positive endometrial adenocarcinoma
PHASE	I/II
SPONSOR	Centre Léon Bérard
COORDINATING INVESTIGATOR	Dr Pierre-Etienne HEUDEL, MD
NUMBER OF PATIENTS	72 patients
CONTEXT & RATIONALE	Endometrial cancer is the most common gynecologic malignancy and the fourth most common cancer in European and North American women, accounting for about 6% of new cancer cases and 3% of cancer-related deaths per year. Approximately 75% of endometrial cancer cases are diagnosed with the tumor confined to the uterine corpus, but after primary surgery, 20% of these tumors recur and have limited response to systemic therapy. Five-year survival rate for women with advanced FIGO stage III or IV disease is 57–66% and 20–26%, respectively. Endometrial cancers are commonly classified into 2 histologic subtypes: endometrioid (Type I), accounting for 60-70% of endometrial cancers and non-endometrioid (Type II; 30-40%) (1-3). Therapies for advanced and recurrent disease are rarely curative, median overall survival being approximately 12 months. Cytotoxic chemotherapy (anthracyclins, platinum compounds and taxanes) is indicated as frontline treatment for the majority of women with metastatic or recurrent disease. Hormone therapy is a particularly attractive option for the treatment of advanced endometrial cancer because it is well tolerated and lacks the usual toxicities associated with chemotherapy, especially for patients with Type I endometrioid disease, low tumor grade, and those who present an asymptomatic recurrence (2, 4-7). Data are less positive regarding the use of aromatase inhibitors for the treatment of recurrent or metastatic disease. A single-arm Phase II trial of anastrozole (1 mg/day, orally), a non-steroidal aromatase inhibitor, in patients with advanced or recurrent endometrial cancer observed only 2 partial responses in 23 patients (9%) and median progression-free survival (PFS) and overall survival (OS) of 1 and 6 months, respectively. Patients enrolled in this trial had mainly non-endometrioid tumors (ER and PgR positivity was reported in only 21.7% of the patients), that might explain the limited clinical benefit observed (7, 8). Type I endometrial cancers are estrogen-dependent with high expression of estrogen (ER) and progesterone (PgR) receptors, exhibit microsatellite instability and frequent loss-of-function mutations in the PTEN (phosphatase and tensin homolog) tumor suppressor gene (in up to 80% of endometrioid cancers) and mutational activation of the PI3K pathway (PIK3CA mutations: 36-52%; PIK3R1 mutations: 21-43%) (9, 10). In patients with recurrent and/or metastatic endometrial cancer, monotherapy with mTOR inhibitors everolimus, temsirolimus, and ridaforolimus has led to various clinical benefit rates (from 21% to 66%) (10, 11) with favorable toxicity profile of the mTOR inhibitors. In a randomized phase II trial, ridaforolimus was associated with a significantly longer progression-free survival (median PFS:3.6 months (95%

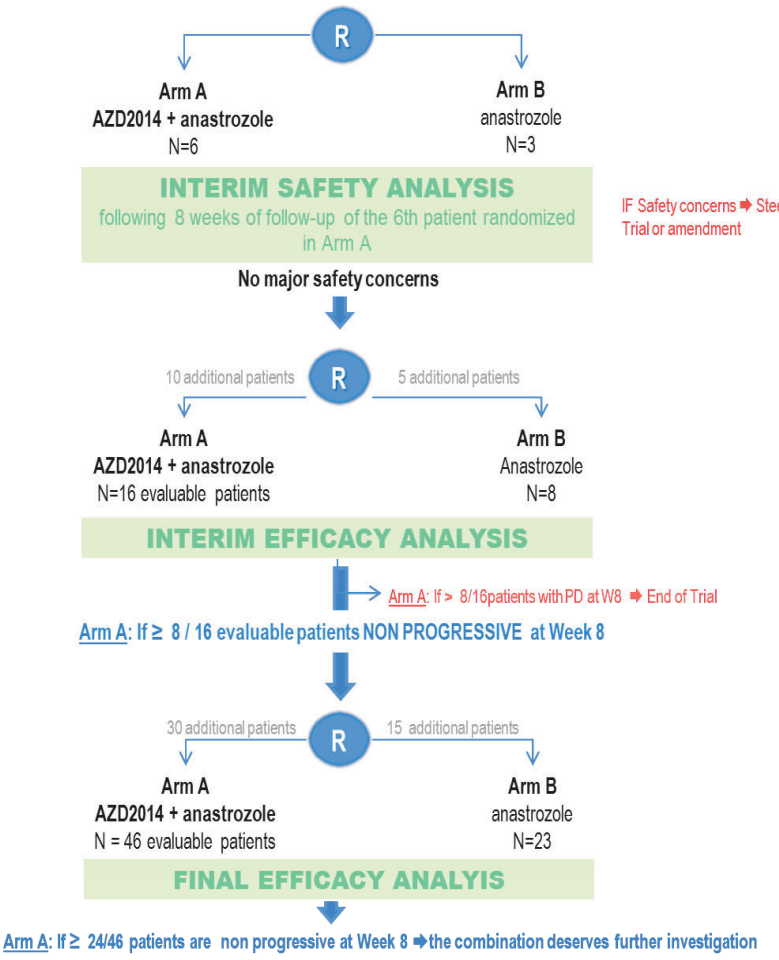
	CI, 2.7 to 7.3 months)) compared with progestin or investigator choice chemotherapy (comparator, median PFS:1.9 months (95% CI, 1.9 to 2.3 months) with hazard ratio, 0.53; 95% CI, 0.31 to 0.90; P =0.008) (11). Recently, a phase II study has evaluated the combination of everolimus (10 mg/day, orally) and letrozole (2.5 mg/day, orally) in endometrial cancer patients (n=35) previously treated with chemotherapy (12). Out of the 35 evaluable patients, the clinical benefit rate (OR + SD confirmed at 16 weeks) was 40% (14/35 patients) and the objective response rate (CR+PR) was 32% (11/35 patients) with 9 CR. Median OS time was 14 months (95% CI, 9.5 to 24.4 months) and the 12-month OS rate was 54.3% (95% CI, 40.1% to 73.6%). Median PFS time was 3.0 months (95% CI, 1.9 to 15.7 months) and the 12-month PFS rate was 37.1% (95% CI, 24.1% to 57.2%). Considering these data, the combination of an aromatase inhibitor with a mTOR inhibitor seems promising. AZD2014 is a highly potent and selective inhibitor of mTOR kinase. It inhibited downstream targets of both mTORC1 (pS6 and p4EBP1) and mTORC2 (pAKT s473) in several *in vitro* models. The safety and tolerability profile of AZD2014 was studied in a Phase 1 dose-escalation and expansion study in 50 patients with solid tumors. Two patients with endometroid cancer remained stable for 274 and 333 days, respectively (see current IB of AZD2014). The majority of adverse events observed at the maximum tolerated dose (MTD) for AZD2014 (50 mg bi-daily continuously) were CTCAE Grade 1 or 2. Reduced phosphorylation p70S6K and 4E-BP1 was seen in paired biopsies. Of note, a Phase I trial evaluating AZD2014 in combination with fulvestrant (anti-estrogen) in ER-positive breast cancer patients showed a manageable toxicity profile (see current IB of AZD2014). In this context, we propose to conduct a two-step, open-label randomized Phase I/II trial evaluating the combination of AZD2014 with anastrozole versus anastrozole alone in selected patients with hormone receptor-positive (HR^+) advanced endometrial adenocarcinoma.
OBJECTIVES	***Primary objectives*** *Safety run-in Part* To evaluate the safety of AZD2014 in combination with anastrozole in patients with hormone receptor-positive advanced endometrial adenocarcinoma. *Phase II* To evaluate the clinical benefit of AZD2014 + anastrozole in terms of 8-week non-progression rate in patients with hormone receptor-positive advanced endometrial adenocarcinoma. ***Secondary objectives*** ▪ To further assess the overall safety profile of the combination ▪ To further assess the anti-tumor activity of AZD2014 combined to anastrozole ***Exploratory objectives*** **:** See Translational research program section

EXPERIMENTAL PLAN

Design

This is a multicentric, randomized (2:1), non-comparative, open-label Phase II trial conducted in patients with advanced or recurrent hormone-receptor positive endometrial carcinoma.

Figure 1 - Study scheme



The study is a 2-step trials including

- A ***safety run-in phase*** aiming to evaluate the safety of the proposed combination AZD2014 + anastrozole versus anastrozole alone. No dose escalation is scheduled : the dose selection is based on the maximum tolerate dose defined in the Investigator Brochure for AZD2014 and the relatively low risk for drug-drug interaction according to the data found in the summary of product characteristics of anastrozole (Arimidex®). However, dose de-escalation for AZD2014 will be applied in case of severe toxicity.
- A ***two-stage randomized Phase II*** part aiming to evaluate the clinical benefit of the AZD2014 + anastrozole combination versus anastrozole. The first 9 patients enrolled in the safety run In phase will be part of the Phase II analysis.

Treatment Plan

Following randomisation patients will receive

- Arm A: AZD2014 plus anastrozole or
- Arm B: anastrozole alone

	AZD2014 will be administered with an intermittent schedule i.e. 125 mg Bid intermittent with 2 days on followed by 5 days off per week for a total weekly dose of 500 mg/week (250mg D1 and D2, 5 days off) ***Anastrozole*** will be administered at the standard dose defined in the SPC i.e. 1mg/d, per os, continuously. Both treatment will be administered until PD, unacceptable toxicity or willingness to stop.
POPULATION	***Inclusion criteria*** **I1.** Postmenopausal female patient at the time of consent **I2.** Histologically-confirmed diagnosis of advanced or recurrent endometrial carcinoma, not amenable to curative treatments. Carcinosarcoma are not eligible. **I3.** Documented ER and/or PgR positive endometrial cancer. Hormone receptor positivity is defined according to routine practice at each participating site. **I4.** Availability of a pre-treatment tumor sample (archival FFPE block or fresh biopsy if feasible) and presence of at least one biopsable tumor lesion for on-treatment biopsy **I5.** Documented disease progression after no more than one prior first-line chemotherapy regimen and/or more than 2 lines endocrine therapy in the metastatic setting **I6.** ECOG Performance Status (PS) 0 or 1 and minimum life expectancy of 8 weeks (Appendix 1 - ECOG Performance Status) **I7.** At least one measurable lesion according to RECIST 1.1 (Appendix 2 - RECIST 1.1) **I8.** Adequate bone marrow, renal and liver function as shown by: ▪ ANC > 1.5 x 10^9/L, Platelets > 100 x 10^9/L, Hb >9 g/dL ▪ Serum bilirubin ≤ 1.5 ULN, ALT and AST ≤ 2.5 ULN (≤ 5 ULN in patients with liver metastases) ▪ Creatinine clearance > 50 mL/min (using Cockcroft formula, or MDRD for patients over 65 years Appendix 3 - Creatinine Clearance) **I9.** Fasting serum cholesterol ≤ 300 mg/dL (7.75 mmol/L) AND fasting triglycerides ≤ 2.5ULN (lipid-lowering drugs allowed), **I10.** Fasting plasma glucose ≤ 7 mmol/L (126 mg/dL) **I11.** Recovered from prior significant treatment-related toxicity i.e. no persistent treatment-related toxicity > Grade 1 as per CTCAE v4.3 (Appendix 4), except grade 2 alopecia, grade 2 anemia but with Hb >9 g/dL. **I12.** Minimal wash-out period before the start of the study drugs for the following treatments: ▪ Any anti-cancer treatment approved or investigational medicinal product :> 21 days ▪ Any chemotherapy, radiation therapy, androgens : > 21 days (not including palliative radiotherapy at focal sites). ▪ Any monoclonal antibody therapy : > 4 weeks ▪ Major surgery: > 4 weeks ▪ Minor surgery (excluding tumour biopsies) >14 days. ▪ Any haemopoietic growth factors (e.g., filgrastim [granulocyte colony-stimulating factor; G-CSF], sargramostim [granulocyte-macrophage colony-stimulating factor; GM-CSF]): > 14 days ▪ Vaccinated with live, attenuated vaccines : > 4 weeks. ▪ Sensitive or narrow therapeutic range substrates of drug transporters OATP1B1, OATP1B3, MATE1 and MATE2K: see the appropriate

wash-out period (a minimum of 5 x reported elimination half-life) in Appendix 5 - Restricted CYP and transporter related co-medications)

- Potent or moderate inhibitors or inducers of CYP3A4/5, Pgp (MDR1) and BCRP : see the stated washout periods in Appendix 5 - Restricted CYP and transporter related co-medications

I13. Patient willing to follow sunlight-protection measures. Patients should be advised of the need for sunlight protection measures during administration of AZD2014, and should be advised to adopt such measures for a period of 3 months after receiving their final dose of AZD2014.

I14. Patient able and willing to provide informed consent with ability to understand and willingness for follow-up visits.

I15. Covered by a medical insurance

Non-inclusion criteria

E1. Patient pre-treated by a non-steroidal aromatase inhibitor

E2. Active uncontrolled or symptomatic central nervous system metastases or spinal cord compression

E3. Clinically relevant abnormal levels of potassium or sodium.

E4. Use of any forbidden concomitant treatment during the treatment period:

- Any anti-cancer treatment (approved or investigational) not mentioned in the protocol
- Chronic treatment with corticosteroids or other immunosuppressive agents. Stable low dose of corticosteroids are allowed (unless contra-indicated) provided that they were initiated before the last disease progression or were started at least 4 weeks prior to study treatment. Topical or inhaled corticosteroids are allowed.
- Potent or moderate inhibitors or inducers of CYP3A4/5, Pgp (MDR1) and BCRP (see Appendix 5 - Restricted CYP and transporter related co-medications)
- Sensitive or narrow therapeutic range substrates of the drug transporters OATP1B1, OATP1B3, MATE1 and MATE2K outside the wash out period and restrictions presented in Appendix 5 - Restricted CYP and transporter related co-medications)

E5. Patient with known hypersensitivity to anastrozole or to any of the excipients (Lactose monohydrate, Povidone, Sodium starch glycollate, Magnesium stearate, Hypromellose, Macrogol 300, Titanium dioxide)

E6. History of hypersensitivity to active or inactive excipients of AZD2014 or drugs with a similar chemical structure or class to AZD2014

E7. History of other malignancies except for basal cell or squamous cell skin cancer, in situ cervical cancer, unless they have been disease-free for at least five years

E8. Patient who has any severe and/or uncontrolled medical conditions such as:

- Recent history of specific cardiovascular events, or laboratory parameters that may affect cardiac parameters including : unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤6 months prior to start of study drug, serious uncontrolled cardiac arrhythmia, or any other clinically significant cardiac disease; Symptomatic congestive heart failure of New York heart Association Class III or IV.
- Haemorrhagic or thrombotic stroke, including transient ischemic attack (TIA) or any other CNS bleeding.

	▪ Mean resting corrected QT interval (QTc), calculated using Fridericia's formula, > 470 msec obtained from 3 electrocardiograms (ECGs), family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation or Torsade de Pointes within 12 months of the patient entering in the study ▪ Abnormal cardiac function at baseline :left ventricular ejection fraction [LVEF] <50% ▪ Any evidence of interstitial lung disease and uncompensated respiratory conditions. ▪ Active (acute or chronic) or uncontrolled severe infection, liver disease such as cirrhosis, decompensated liver disease, and active or chronic hepatitis (i.e. quantifiable HBV-DNA and/or positive HbsAg, quantifiable HCV-RNA), ▪ Active, bleeding diathesis ▪ Current refractory nausea and vomiting, chronic GI diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of AZD2014. ▪ Rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption ▪ Type 1 and uncontrolled Type 2 diabetes ▪ Pre-existing renal disease including glomerulonephritis, nephritic syndrome, Fanconi Syndrome or renal tubular acidosis.
STATISTICS	***Sample size*** **A total of 72 patients will be randomized in the study.** Safety run-in Phase on the first 9 patients randomized - As no dose escalation will be performed, the safety will be evaluated following the treatment and 8-week follow-up of the first 6 patients by the experimental association AZD2014+anastrozole (experimental arm). By similarity to a classic 3+3 design, based on binomial probabilities, there is a 90% probability of observing one or more patients with a toxicity event, if that event occurs in at least 32% of the target population. Assuming a 2:1 randomization ratio, a total of 9 patients (Arm A - Experimental: 6 patients, Arm B - Control: 3 patients) will be enrolled in this safety run-in phase and will be included in the evaluation of Phase II part. Phase II The sample size calculation was based on a Simon optimal two-stage design, with a minimum success (8-week non progression) rate considered of interest p_1=60% and an uninteresting rate p_0=40%. Assuming a type I error alpha of 0.05 and 80% power, 46 evaluable patients are needed in the experimental arm to reject the null hypothesis H0: p≤p0 versus the alternative hypothesis H1: p ≥ p1 in a unilateral situation (16 patients in Stage I and 30 additional patients in Stage II). With a 2:1 randomization and based on the assumption that 5% of the patients may be non-evaluable, a total of 72 patients will be included in the study : 48 patients in Arm A - experimental and 24 patients in Arm B - control). ***Primary endpoints :definitions and analysis*** *Safety Run In Phase* The primary endpoint is the number of severe toxicities (STs) occurring during the first 8 weeks of treatment. STs are defined as the occurrence of any of the

	following events evaluated as related to study drug and occurring during the first 8 weeks of treatment: ▪ Any grade ≥ 4 treatment related toxicity, ▪ Any grade≥ 3 treatment related toxicity lasting more than 7 days. Depending of the incidence of severe toxicities, enrolment could be suspended after 8 weeks of follow-up of the 9th patient randomized in order to allow toxicity assessment. Safety data will be reviewed by the Data Monitoring Committee (DMC): ▪ if >1/6 patients exposed to AZD2014 + anastrozole experienced severe toxicities (ST) related to the combination: the study will be amended and lower doses of AZD2014 will be evaluated in combination with anastrozole in an additional cohort of 6 patients. ▪ *a contrario*, if ≤ 1/6 patients experienced severe toxicities related to the combination: the safety data will be considered acceptable and the phase II part will be initiated and enrolment/randomization will continue. Of note, the DMC will be informed of all ST on real time in order to assess the safety of the combination regularly. *Phase II part* The 8-week non-progression rate is defined as the rate of patients without disease progression within the first 8 weeks after randomization. It will be summarized in both arms by a proportion together with its one sided 95% confidence interval. Initially, 16 evaluable patients of the experimental arm will be analysed at the end of the Stage I (i.e. 6 patients from the safety run in part and 10 from the Phase II –Stage I): ▪ If the number of successes in Arm A is < 8/16, the study will be definitively closed for inefficacity of the combined treatment. ▪ If the number of successes in Arm A is ≥8/16 successes (i.e. non-progression at 8 weeks), the stage II will be initiated for a total (Stage 1 + Stage 2) of 46 evaluable patients. At the end of Stage II, if the number of successes in Arm A is ≥24/46, the treatment will be considered of interest for further investigation in this indication. No formal comparison between the experimental arm (Arm A) and the control arm (Arm B) will be performed. In the proposed trial design, the control arm is used to prospectively and contemporaneously validate the hypothesis of the success rate of anastrozole alone i.e. to test consistency between the enrolled patients and historical controls, in order to validate the hypotheses set for the experimental arm. In addition, the randomization eliminating the selection bias, it ensures that the experimental results are not obtained in a selection-biased population. ***Secondary endpoints*** • Safety • Progression-free survival (PFS) • Overall Survival (OS) • Overall response rate (ORR) • Duration of response (DoR)
STUDY COMMITTEES	***Data monitoring committee (DMC)*** The DMC will be constituted by the sponsor and will be composed of statisticians and clinical experts. This committee will review each event that could modify the benefit risk ratio.

	Steering committee The Steering committee will be composed of the coordinating investigator and representatives of the coordinating center. The Steering Committee has primary responsibility for the general organization of the trial and makes any major decision recommended by the DMC. Meetings are scheduled every 3 months from the beginning of the trial. ***Imaging Review committee*** The central review committee, composed of radiologists from Centre Léon Bérard, will review each radiological tumor assessment from baseline to disease progression on a timely manner and reported tumor status as per RECIST 1.1
CORRELATED TRANSLATIONAL PROGRAMM RESEARCH	A large translational program is associated to this clinical phase I/II trial in order to: ▪ To evaluate the pharmacodynamics activity of AZD2014 and identify predictors of response/resistance to the AZD2014+anastrozole combination therapy ▪ To assess the activity and quality of ribosome biogenesis in endometrial carcinomas and evaluate the effect of the mTORC1/2 inhibitor AZD2014, associated or not with anastrozole, on ribosome biogenesis ▪ To follow the evolution of the mutations identified in circulating tumoral DNA (ctDNA) and to evaluate the correlation with efficacy endpoints. ▪ To compare the type of mutations identified before study drug initiation and at time of relapse using ctDNA. ▪ To evaluate the PK parameters of AZD2014 in combination with anastrozole ▪ To evaluate the impact of the treatment with AZD2014 on circulating NK cell phenotype and function. Blood and tumor samples will be collected before and during treatment period as summarized in Study Flow chart and as described in Section XIII.
PLANNED TIMETABLE	***Inclusion period:*** 42 months ***Treatment period and follow-up:*** 13 months (48 weeks of treatement)

I. BACKGROUND & RATIONALE

1.1 Overview of study disease and medical need

1.1.1 Current therapeutic options and Unmet medical need

Endometrial cancer is the most common gynecologic malignancy and the fourth most common cancer in European and North American women, accounting for about 6% of new cancer cases and 3% of cancer related deaths per year (13). About 81 500 women are affected every year in the European Union and the incidence is increasing. Approximately 75% of endometrial cancer cases are diagnosed with the tumor confined to the uterine corpus (Stage I according to the FIGO [International Federation of Gynecology and Obstetrics] staging system) with a favorable prognosis following surgery: the 5-year survival of Stage I disease is close to 90% (14). However, 20% of these tumors will recur and have limited response to systemic therapy (4). For women with advanced stage III or IV disease, the 5-year survival rate is 57-66% and 20–26%, respectively (2). Endometrial cancers are commonly classified into 2 histologic subtypes (1, 15, 16), Figure 1):

- Type I, accounting for 60-70% of endometrial cancers, is estrogen-related, low-grade, histologically endometrioid adenocarcinoma in most cases and shows minimal myometrial invasion and occurs at a younger age
- Type II (non-endometrioid), accounting for 30-40% of endometrial cancers, is commonly described as estrogen independent, high-grade, histologically serous or clear cell adenocarcinoma and shows deep myometrial invasion.

Figure 1 - Type I versus Type II endometrial cancers

	Type I	Type II (serous/ clear cell)
Oestrogen associated	Yes	No
Hormone receptors	ER/PR+	ER/PR-
Background endometrium	Hyperplasia	Atrophy
Tumour grade*	Low	High
Myometrial invasion	Superficial	Deep
Clinical behaviour	Indolent	Aggressive
Mean age/ diagnosis	61.9-63.7 yrs	66.8-69.3 yrs (serous) 64.1-66.4 yrs (clear cell)
Diagnosis	Early stage (FIGO I/II) 86%	Late stage (FIGO III/IV) 41% (serous) and 33% (clear cell)

Cytotoxic chemotherapy (anthracyclins, platinum compounds and taxanes) is indicated as frontline treatment for the majority of women with metastatic or recurrent disease. However, therapies for advanced and recurrent disease are rarely curative, median overall survival (OS) being approximately 12 months (5).

Hormone therapy is a particularly attractive option for the treatment of endometrial cancer because it is well tolerated and lacks the usual toxicities associated with chemotherapy, especially for patients with endometrioid estrogen receptor (ER)-positive and progesterone receptor (PgR)-positive Type I disease.
In chemotherapy-naïve advanced endometrial carcinoma patients, progestin have demonstrated response rates of 18–34 % with median OS of 6–14 months (See Table 1, (17)). Commonly used regimens include megestrol acetate (MA) 160 mg/d, or MA for 3 weeks alternating with tamoxifen (TAM) for 3 weeks. In general, the highest response rates are found in patients with well-differentiated hormone receptor positive tumors.

Table 1 - Hormone therapy in endometrial cancers

Treatment (References)	Objective Response Rate (%)	Median OS (months)
Medoxyprogesterone acetate (MA) 800mg/d (18)	24	7.6
MPA 200mg/d (19)	25	11.1
MPA 200 mg/day every other week and TAM 40 mg daily (20)	33	13
Tamoxifen, 40mg/d (21)	10	8.8

However, a recent Cochrane review found no evidence that hormonal treatment as single agent improves survival of patients with metastatic or recurrent disease (7).
In the metastatic setting, aromatase inhibitors including letrozole and anastrozole have shown response rates of less than 10 % :

- A small multicenter phase II study of the National Cancer Institute of Canada (NCIC) Clinical Trials Group testing the use of letrozole found a 9.4 % response rate and median OS of 6.7 months (22).
- A single arm Phase II trial of anastrozole (1 mg/day, orally), a non-steroidal aromatase inhibitor, in patients with advanced or recurrent endometrial cancer observed 2 partial responses (PR) in 23 patients (9%) and median progression-free survival (PFS) and OS of 1 and 6 months respectively (8). Of note, patients enrolled in this trial had mainly non-endometrioid tumors (ER and PgR positivity was reported in only 21.7% of the patients) and that might explain the limited clinical benefit observed.

Such low response rates of endocrine therapy in endometrial cancers, especially with aromatase inhibitors (in monotherapy), may reflect the need to identify the subset of women most likely to respond to such therapy, i.e. with hormone receptor positive tumors.

1.1.2 Molecular profile of endometrial cancer and targeted therapies

mTOR is a member of the PI3K–AKT family, which promotes cell proliferation, survival, and angiogenesis. mTOR forms 2 different protein complexes, mTORC1 and mTORC2, that mediate very different functions. Deregulation of mTOR signaling is observed in many tumor types, and mutations or loss of function of upstream regulators such as TSC1/2, LKB1, or components of the PI3K pathway such as PIK3CA, AKT or PTEN have been reported in most types of human tumors (23). Type I endometrial cancers exhibit microsatellite instability and frequent loss-of-function mutations in the PTEN tumor suppressor gene (in up to 80% of endometrioid cancers) and mutational activation of the PI3K pathway (PIK3CA mutations: 36-52%; PIK3R1 mutations: 21-43%) (3, 9).

In patients with recurrent and/or metastatic endometrial cancer, monotherapy with mTOR inhibitors everolimus, temsirolimus, and ridaforolimus has led to various clinical benefit rates (from 21% to 66%) (10, 11) with favorable toxicity profile. In a randomized phase II trial, ridaforolimus was associated with a significantly longer progression-free survival (median PFS:3.6 months (95% CI, 2.7 to 7.3 months)) compared with progestin or investigator choice chemotherapy (i.e. comparator, median PFS:1.9 months (95% CI, 1.9 to 2.3 months) with hazard ratio, 0.53; 95% CI, 0.31 to 0.90; p = 0.008) (11).

Rapalogs combined to hormonal treatment for gynecological malignancies have also been evaluated in clinical trials (10). Of note, the combination of everolimus with the aromatase inhibitor, exemestane, significantly improved PFS in patients with aromatase inhibitor–refractory breast cancer, thus demonstrating proof of concept that PI3K/AKT/mTOR pathway inhibitors may reverse resistance to endocrine therapy (24).

Recently, a Phase II study evaluated the combination of everolimus (10 mg/day, orally) and letrozole (2.5 mg/day, orally) in previously treated endometrial cancer patients (n=35) (12). Out of the 35 evaluable patients, the clinical benefit rate (OR + SD confirmed at 16 weeks) was 40% (14/35 patients) and the objective response rate (CR+PR) was 32% (11/35 patients) with 9 CR.

Median OS time was 14 months (95% CI, 9.5 to 24.4 months) and the 12-month OS rate was 54.3% (95% CI, 40.1% to 73.6%). Median PFS time was 3.0 months (95% CI, 1.9 to 15.7 months) and the 12-month PFS rate was 37.1% (95% CI, 24.1% to 57.2%). Considering these data, the combination of an aromatase inhibitor with an mTOR inhibitor seems promising.

1.2 Hypothesis and proposal

Hormonal therapies have only modest activity in the treatment of advanced endometrial cancer and current clinical programs in this target population focused on combination trials.

Considering:

1. The high frequency of alterations in components of the PI3K/AKT/mTOR pathway in endometrial carcinomas (3, 9), including inactivating mutations in PTEN, activating mutations in PIK3CA, and mutations in PIK3R1,
2. The clinical activity of mTOR inhibitors, including temsirolimus, everolimus, and ridaforolimus, against endometrial cancer,
3. The encouraging preliminary results of the Phase II trial combining letrozole and the mTOR inhibitor everolimus (12),

4. The potential role of the PI3K/AKT/mTOR pathway in resistance to hormonal therapy. Indeed, the combination of everolimus with the aromatase inhibitor, exemestane, significantly improved PFS in patients with aromatase inhibitor–refractory breast cancer , thus demonstrating proof of concept that PI3K/AKT/mTOR pathway inhibitors may reverse resistance to endocrine therapy (24).

We hypothesize that the dual inhibition of mTORC1/mTORC2 by AZD2014 combined with inhibition of aromatase enzyme by anastrozole will act synergistically and may be an interesting therapeutic option for endometrial cancer with a manageable toxicity profile.

Our proposal is to conduct a multicenter, 2-step, randomized, Phase I/II trial to evaluate the safety and efficacy of a combination treatment associating anastrozole to AZD2014 in advanced endometrial cancer patients.

1.3 Overview of Study Drugs

1.3.1 AZD2014

AZD2014 is a highly potent and selective inhibitor of mTOR kinase that inhibits downstream targets of both mTORC1 (pS6 and p4EBP1) and mTORC2 (pAKT s473) in several *in vitro* and *in vivo* models in a dose and time-dependent manner.

In safety pharmacology and toxicology studies, AZD2014 exerts effects on bone marrow and lymphoid tissues (with associated changes in hematology parameters), gastro-intestinal tract, testes and adrenal gland; effects on glucose homeostasis and on cardiovascular, respiratory and renal function. *In vitro* assays indicate a potential for phototoxicity. AZD2014 showed no evidence of genotoxic potential.

As of 05 October2018, a total of 390 patients have received at least 1 dose of AZD2014 in 9 AZ-sponsored studies (152 patients as monotherapy and 238 patients as combination therapy) and 760 in 22 externally-sponsored research (ESR) studies in several indications including breast cancer, solid tumours and squamous non-small cell lung cancer (sqNSCLC).

Multiple dose tablet PK data from the intermittent weekly BiD Days 1&2 dose schedules show that: i) high AZD2014 doses are more slowly absorbed than lower doses (median t_{max} 1.5–2.75 h at 100–225 mg BiD Days 1&2), ii) mean $t_{1/2}$ intermittent weekly BiD Days 1&2 schedules=5.1–10.7 h across the 100-225 mg dose range; iii) accumulation of drug is higher for the higher multiple tablet doses of drug in the intermittent weekly BiD Days 1&2 schedules than for the lower tablet doses given in the continuously dosed BiD and QD cohorts; iv) a lower overall weekly dose for the intermittent 125 mg BiD Days 1&2 dosing schedule (500 mg per week) achieves exposure and much higher peak plasma levels (approximately 3-fold C_{max}) than the 50 mg BiD continuous dosing schedule (700 mg per week) providing the exposure over only the first 3 days of the week. In a Phase I trial of AZD2014 in combination with Fulvestrant, the intermittent schedule achieved similar efficacy compared with the 50 mg continuous dose schedule and the cohort is still enrolling patients. The safety profile of the intermittent schedule was also favorable compared to continuous dosing with reduced frequencies of rash and mucositis. Therefore, the 125 mg BID 2 days on and 5 days off schedule is currently the recommended Phase II dose.

An intra-patient investigation of the effect of food on exposure to AZD2014 indicates that dosing with food will on average decrease exposure (AUC by 21% and C_{max} by 33%) following a single 50 mg dose. An inter-patient investigation of food effect indicates a reduction in exposure to AZD2014 when 125 and 175 mg single and multiple doses are administered with food.

CYP3A5 and CYP3A4 have been identified *in vitro* as the principal P450s responsible for human metabolism of AZD2014 (respectively 80% and 16%). AZD2014 has also been identified *in vitro* as a substrate for the drug transporters Pgp (MDR1) and BCRP. Therefore,

- Co-administration of CYP3A4, CYP3A5, Pgp (MDR1) or BCRP inhibitors may increase exposure to AZD2014 and increase the likelihood of toxicity.
- Co-administration of CYP3A4, CYP3A5, Pgp or BCRP inducers may decrease the exposure to AZD2014 and hence potentially affect its efficacy.

AZD2014 showed no time dependent inhibition of CYPs, and only weak reversible inhibition of CYPs 2C8, 2C9, 2C19 and 2D6 ($IC_{50} \approx 21$, 47, 37 and 55 μM, respectively).
AZD2014 inhibited human gastro-intesinal tract / hepatic MDR1 and BCRP efflux transporters (IC_{50} of 28.8 μM and 69.5 μM respectively).

AZD2014 is a weak inhibitor of multiple P450 enzymes in vitro, including CYPs 2D6, 2C8, 2C9 and 2C19 and MDR1 (PgP) and BCRP transporters, respectively. Clinical drug interaction studies with appropriate substrate probes have not been conducted. However, results of computer simulations using the validated proprietary software SIMCYP™ (Certara Inc., Ca), using the intermittent monotherapy MTD regimen, 125 mg BID, 2 days on 5 days off, demonstrates a clinically relevant PK drug interaction with sensitive substrates of these P450 enzymes and transporters is unlikely (validated probe drugs used: 2D6 –dextromethorphan, 2C8 – repaglinide, 2C9 – warfarin, 2C19 – omeprazole, MDR1 – digoxin,BCRP – pravastatin).

In drug transporter studies, AZD2014 inhibited the hepatic uptake transporters OATP1B1 and OATP1B3 and the IC_{50} values derived (5.10 μM and 11.7 μM, respectively) when compared with plasma concentrations indicated meaningful inhibition is possible after dosing at 50 mg BD or 125 mg BD 2/5. AZD2014 had no meaningful inhibitory effect when compared with plasma concentrations on renal transporters OAT1 and OCT2, and only a minor effect on OAT3 at the 125 mg BD 2/5dose schedule. However, AZD2014 inhibited the renal transporters MATE1 and MATE2K and the IC_{50} values derived (0.822 μM and 0.022 μM, respectively) when compared with plasma concentrations indicated meaningful inhibition is possible after dosing at 50 mg BD or 125 mg BD 2/5.

Bi-directional transport studies indicated that AZD2014 was a substrate for both human MDR1 and BCRP but was not a substrate for OATP1B1, OATP1B3 and OCT1.

Therefore, co-administration of AZD2014, particularly at high doses,

- with known or possible substrates of the drug transporters, OATP1B1, OATP1B3, MATE1, MATE2K may lead to their increased exposure and requires careful evaluation.

Co-medications which are moderate or potent inhibitors or inducers of CYP3A4/5, Pgp and BCRP or are sensitive or narrow therapeutic range substrates ofor the drug transporters Pgp, BCRP, OATP1B1, OATP1B3, MATE1 and MATE2K will be restricted and listings of such co-medications are given in Annex 5.

Overall AZD2014 is considered to be generally well tolerated. The main expected adverse events (AE, with incidence >5%) are listed below (MedRA SOC – Medical Term) with highlights on implication for clinical trial protocols:

- **General disorders – Fatigue, asthenia and mucositis (including stomatitis)**. This is consistent with literature reports having described an association with other mTOR inhibitors and lethargy or fatigue (23-24). Furthermore, fatigue is reported amongst most common side effects for several Dual-kinase PI3K-mTOR inhibitors (GDC-0980, NVP-BEZ235, XL765). These AE improved or resolved on dose reduction or on stopping treatment.
- **Nervous system disorders – Lethargy**
- **Skin and subcutaneous tissue disorders - Rash** (i.e. erythematous, macular popular and/or pruritic;
- **Metabolism and Nutrition - Hyperglycemia.**This is consistent with the role of the PI3K/Akt/mTOR pathway in regulating glucose metabolism particularly by affecting glucose transport into adipocytes and muscle tissues. Hyperglycemia is thus considered as an "on target" effect of AZD2014.
- **Metabolism and Nutrition - Decreased in appetite**
- **Metabolism and Nutrition - Hypokalaemia**
- **Metabolism and Nutrition - Hypophosphataemia**
- **GI disorders - Nausea, vomiting and diarrhea**
- **Respiratory, thoracic, and mediastinal disorders - Pneumonitis**

Additional potential risks associated to AZD2014 treatment (low incidence in previous human experience and/or only based on preclinical studies) include: hematological effects (i.e. anemia, neutropenia and thrombocytopenia, and lymphopenia), cardiovascular events (ECG repolarisation changes, hypertension, tachycardia, and bradycardia), respiratory effects (dyspnea, cough), liver tests functions abnormalities (transaminase elevations, bilirubin increase), infections and renal effects (i.e. reversible changes in several urinary parameters in rats (including increases in urine volume, glucose, electrolytes, decreases in pH and total protein but no clinically significant renal findings were reported at any dose of AZD2014) and constipation and abdominal pain.

In addition, there is a risk for :

- Reproductive toxicity
- Phototoxicity. AZD2014 had positive effects in the in vitro 3T3 neutral red uptake phototoxicity test. Sunlight protection measures should be adopted during treatment with AZD2014

1.3.2 Anastrozole

Anastrozole (Arimidex®) is a potent and highly selective non-steroidal aromatase inhibitor. In postmenopausal women, estradiol is produced primarily from the conversion of androstenedione to estrone through the aromatase enzyme complex in peripheral tissues. Estrone is subsequently converted to estradiol. Reducing circulating estradiol levels has been shown to produce a beneficial effect in women with breast cancer.

Up to date, anastrozole (1mg/d, per os) is approved by EMA and FDA for:

- the treatment of hormone receptor-positive advanced breast cancer in postmenopausal women.
- the adjuvant treatment of hormone receptor-positive early invasive breast cancer in postmenopausal women.
- the adjuvant treatment of hormone receptor-positive early invasive breast cancer in postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen.

The most recent efficacy and Safety data are summarized in the most recent edition of the SPC (Appendix 6 - SPC of Arimidex).

II. OBJECTIVES

2.1 Primary objectives

Safety run-in Phase I (on the first 9 patients randomized)

To evaluate the safety of AZD2014 in combination with anastrozole versus anastrozole in patients with hormone receptor-positive (HR+) advanced endometrial adenocarcinoma.

Phase II

To evaluate the clinical benefit of AZD2014 + anastrozole versus anastrozole in terms of 8-week progression-free rate (PFR_{8w}) in patients with HR+ advanced endometrial adenocarcinoma.

2.2 Secondary objectives

- To further assess the overall safety profile of the combination
- To further assess the anti-tumor activity of AZD2014 combined to anastrozole

2.3 Exploratory objectives

(See also Section XIII. Translational research program)

- To evaluate the pharmacodynamics activity of AZD2014 and identify predictors of response/resistance to the AZD2014+anastrozole combination therapy
- To assess the activity and quality of ribosome biogenesis in endometrial carcinomas and evaluate the effect of the mTORC1/2 inhibitor AZD2014, associated or not with anastrozole, on ribosome biogenesis
- To follow the evolution of the mutations identified in circulating tumoral DNA (ctDNA) and to evaluate the correltation with efficacy endpoints.
- To compare the type of mutations identified before study drug initiation and at time of relapse using ctDNA.
- To evaluate the PK parameters of AZD2014 in combination with anastrozole
- To evaluate the impact of the treatment with AZD2014, an inhibitor of both mTORC1 and mTORC2, on circulating NK cell phenotype and function.

III. STUDY POPULATION

The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient.

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or patient safety.

3.1 Inclusion criteria

I1. Postmenopausal* female patient at the time of consent

*: Post-menopausal women defined as either women aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments, or, women under 50 years old who have been amenorrhoeic for at least 12 months following the cessation of exogenous hormonal treatments, and have serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels in the postmenopausal range for the institution or surgical menopause

I2. Histologically-confirmed diagnosis of advanced or recurrent endometrial carcinoma, not amenable to curative treatments

I3. Documented ER and/or PgR positive endometrial cancer. Hormone receptor positivity is defined according to routine practice at each participating site. Carcinosarcoma are not eligible.

I4. Availability of a pre-treatment tumor sample (archival FFPE block or fresh biopsy if feasible) and presence of at least one biopsable tumor lesion for on-treatment biopsy

I5. Documented disease progression after no more than one prior first-line chemotherapy regimen and/or more than 2 lines endocrine therapy in the metastatic setting

I6. ECOG Performance Status (PS) 0 or 1 and minimum life expectancy of 8 weeks (Appendix 1 - ECOG Performance Status)

I7. At least one measurable lesion according to RECIST 1.1 (Appendix 2 - RECIST 1.1)

I8. Adequate bone marrow, renal and liver function as shown by:

- ANC > 1.5 x 10^9/L, Platelets > 100 x 10^9/L, Hb >9 g/dL
- Serum bilirubin ≤ 1.5 ULN, ALT and AST ≤ 2.5 ULN (≤ 5 ULN in patients with liver metastases)
- Creatinine clearance > 50 mL/min (using Cockcroft formula, or MDRD for patients over 65 years Appendix 3 - Creatinine Clearance)

I9. Fasting serum cholesterol ≤ 300 mg/dL (7.75 mmol/L) AND fasting triglycerides ≤ 2.5ULN (lipid-lowering drugs allowed),

I10. Fasting plasma glucose ≤7 mmol/L (126 mg/dL)

I11. Recovered from prior significant treatment-related toxicity i.e. no persistent treatment-related toxicity > Grade 1 as per CTCAE v4.3 (Appendix 4), except grade 2 alopecia, grade 2 anemia but with Hb >9 g/dL.

I12. Minimal wash-out period before the start of the study drugs for the following treatments:

- Any anti-cancer treatment approved or investigational medicinal product :> 21 days
- Any chemotherapy, radiation therapy, androgens : > 21 days (not including palliative radiotherapy at focal sites).
- Any monoclonal antibody therapy : > 4 weeks.
- Major surgery: > 4 weeks
- Minor surgery (excluding tumour biopsies) >14 days.

- Any haemopoietic growth factors (e.g., filgrastim [granulocyte colony-stimulating factor; G-CSF], sargramostim [granulocyte-macrophage colony-stimulating factor; GM-CSF]): > 14 days
- Vaccinated with live, attenuated vaccines : > 4 weeks.
- Potent or moderate inhibitors or inducers of CYP3A4/5, Pgp (MDR1) and BCRP : see the stated washout periods in Appendix 5 - Restricted CYP and transporter related co-medications
- Sensitive or narrow therapeutic range substrates of the drug transporters, OATP1B1, OATP1B3, MATE1 and MATE2K: see the appropriate wash-out period (a minimum of 5 x reported elimination half-life) in Appendix 5 - Restricted CYP and transporter related co-medications)

I13. Patient willing to follow sunlight-protection measures. Patients should be advised of the need for sunlight protection measures during administration of AZD2014, and should be advised to adopt such measures for a period of 3 months after receiving their final dose of AZD2014.

I14. Patient able and willing to provide informed consent with ability to understand and willingness for follow-up visits.

I15. Covered by a medical insurance

3.2 Non-inclusion criteria

Patients eligible for this study must not meet **ANY** of the following criteria:

E1. Patient pre-treated by a non-steroidal aromatase inhibitor

E2. Active uncontrolled or symptomatic central nervous system metastases or spinal cord compression

E3. Clinically relevant abnormal levels of potassium or sodium.

E4. Use of any forbidden concomitant treatment during the treatment period:

- Any anti-cancer treatment (approved or investigational) not mentioned in the protocol
- Chronic treatment with corticosteroids or other immunosuppressive agents. Stable low dose of corticosteroids are allowed (unless contra-indicated) provided that they were initiated before the last disease progression or were started at least 4 weeks prior to study treatment. Topical or inhaled corticosteroids are allowed
- Potent or moderate inhibitors or inducers of CYP3A4/5, Pgp (MDR1) and BCRP (see Appendix 5 - Restricted CYP and transporter related co-medications)
- Sensitive or narrow therapeutic range substrates of the drug transporters OATP1B1, OATP1B3, MATE1 and MATE2K outside the wash out period and restrictions presented in Appendix 5 - Restricted CYP and transporter related co-medications)

E5. Patient with known hypersensitivity to anastrozole or to any of the excipients (Lactose monohydrate, Povidone, Sodium starch glycollate, Magnesium stearate, Hypromellose, Macrogol 300, Titanium dioxide)

E6. History of hypersensitivity to active or inactive excipients of AZD2014 or drugs with a similar chemical structure or class to AZD2014

E7. History of other malignancies except for basal cell or squamous cell skin cancer, in situ cervical cancer, unless they have been disease-free for at least five years

E8. Patient who has any severe and/or uncontrolled medical conditions such as:

- Recent history of specific cardiovascular events, or laboratory parameters that may affect cardiac parameters including : unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤ 6 months prior to start of study drug, serious uncontrolled cardiac arrhythmia, or any other clinically significant cardiac disease; Symptomatic congestive heart failure of New York heart Association Class III or IV
- Haemorrhagic or thrombotic stroke, including transient ischemic attack (TIA) or any other CNS bleeding.
- Mean resting corrected QT interval (QTc), calculated using Fridericia's formula, > 470 msec obtained from 3 electrocardiograms (ECGs), family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation or Torsade de Pointes within 12 months of the patient entering in the study
- Abnormal cardiac function at baseline : left ventricular ejection fraction [LVEF] <50% Any evidence of interstitial lung disease and uncompensated respiratory conditions.
- Active (acute or chronic) or uncontrolled severe infection, liver disease such as cirrhosis, decompensated liver disease, and active or chronic hepatitis (i.e. quantifiable HBV-DNA and/or positive HbsAg, quantifiable HCV-RNA),
- Active, bleeding diathesis
- Current refractory nausea and vomiting, chronic GI diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of AZD2014.
- Rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
- Type 1 and uncontrolled Type 2 diabetes
- Pre-existing renal disease including glomerulonephritis, nephritic syndrome, Fanconi Syndrome or renal tubular acidosis.

IV. INVESTIGATIONAL PLAN

4.1 Overview of Study design

This is a multicentric, randomized (2:1), non-comparative, open-label Phase I/II trial conducted in patients with advanced or recurrent hormone-receptor positive endometrial carcinoma.

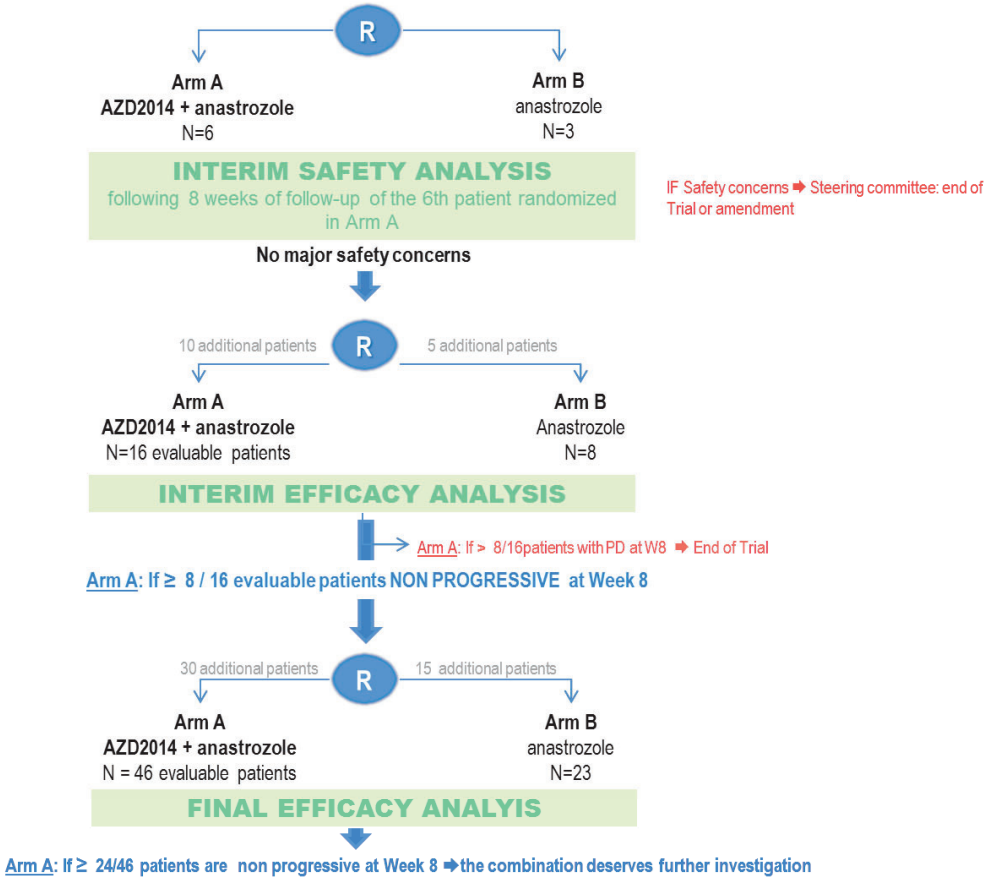
The study is divided in 2 steps (Figure 2):

- **A safety run-in phase** aiming to evaluate the safety of the proposed combination AZD2014 + anastrozole (Arm A) versus anastrozole alone (Arm B). No dose escalation is scheduled (doses are based on MTD defined for AZD2014 and the SPC of anastrozole). However, dose de-escalation for AZD2014 will be applied in case of toxicity.

- **A two-stage randomized Phase II** part aiming to evaluate the clinical benefit of the AZD2014 + anastrozole (Arm A) combination therapy versus anastrozole (Arm B).

Both study treatments will be administered until disease progression, unacceptable toxicity or willingness to stop.

Figure 2 - Study Scheme



Randomisation will be stratified according to the number of prior lines received before randomisation: None versus ≥1 prior chemotherapy line of treatment at baseline.

4.2 Rationale for dose selection

Anastrozole will be administered at the standard dose defined in the SPC i.e. 1 mg/d, per os, continuously.

AZD2014 will be administered with an intermittent schedule i.e. 125 mg Bis in Die (BiD) intermittent with 2 days on followed by 5 days off/ week for a total weekly dose of 500 mg/week. Both dosing schedules of 50 mg BiD continuous and 125 mg BiD intermittent (2 days on, 5 days off) have an acceptable safety profile for further investigation in clinical programs. However,

- Multiple dose tablet PK data from the intermittent weekly BiD Days 1&2 dose schedules show that: i) accumulation of drug is higher for the higher multiple tablet doses of drug in the intermittent weekly BiD Days 1&2 schedules than for the lower tablet doses given in the continuously dosed BiD and QD cohorts and ii) a lower overall weekly dose for the intermittent 125 mg BiD Days 1&2 dosing schedule (500mg per week) achieves higher exposure (AUC) and much higher peak plasma levels (approximately 3-fold C_{max}) than the 50 mg BiD continuous dosing schedule (700 mg per week) providing the exposure over only the first 3 days of the week

- The introduction of intermittent dosing of AZD2014 at a dose of 125 mg BiD was accompanied by a change in the safety profile of the drug particularly reducing the incidence of rash, hyperglycaemia and mucositis. This change led to a reduction in the number of patient permanently discontinuing treatment when compared with continuous dosing schedules.

For these reasons, the intermittent schedule was selected for this trial : 125 mg BiD Day1-Day2 followed by 5 days off for a total weekly dose of 500 mg.

V. BENEFIT AND RISK ASSESSMENT

Patients randomized in Arm B will received the standard treatment, anastrozole, previously approved for the treatment of advanced breast cancer with positive hormone receptors and currently used in daily medical practice as a reference treatment for endometrial cancer ER/PgR+. There is no specific risks associated to this study for patients randomized in Arm B.

The benefit / risk ratio of the Arm A is based on the followings:

- **The strong rationale and the previous human experience with combination trials associating study drugs of the same therapeutic class.** Indeed, several evidence suggest the clinical pertinence of such combination trial including i) the high frequency of alterations in components of the PI3K/AKT/mTOR pathway in endometrial carcinomas, ii) the encouraging results of the Phase II trial combining letrozole and the mTOR inhibitor everolimus and iii) the positive results of the combination trial associating everolimus plus exemestane interms of efficacy and tolerance, thus demonstrating the proof of concept of such combination trial associating a PI3K/AKT/mTOR pathway inhibitor with an endocrine therapy.

- **The low risk for drug-drug interaction.** CYP3A5, and CYP3A4 were identified *in vitro* as the principal P450s responsible for AZD2014 metabolism, indicating the possibility of drug-drug interactions with inhibitors and inducers of these enzymes. AZD2014 has also been identified *in vitro* as a substrate for the drug transporters Pgp (MDR1) and BCRP. *In vitro*, anastrozole inhibits CYPs 1A2, 2C8/9 and 3A4. However, clinical studies with antipyrine and warfarin showed that anastrozole at a 1 mg dose did not significantly inhibit the metabolism of antipyrine and R– and S-warfarin indicating that the co-administration of anastrozole with other medicinal products is unlikely to result in clinically significant medicinal product interactions mediated by CYP enzymes. In addition, AZD2014 showed no time dependent inhibition of CYPs, and only weak reversible inhibition of 2C8, 2C9, 2C19 and 2D6 (IC50 ≈ 21 , 47, 37 and 55 µM, respectively).

- **The specific eligibility criteria, the dose interruptions and standard dose modifications to the AZD2014 dose schedule planned for patients who develop significant reactions (See Section Treatment Plan)**. In particular:
  - ***Hyperglycemia*** is considered as an "on target" effect of AZD2014. Therefore, patients with evidence of abnormal glucose metabolism are not eligible and monitoring of glucose and insulin levels is planned, together with stopping criteria and guidance for management of hyperglycaemia.
  - Patients who develop ***mucuosal inflammation*** should be instructed to rinse their mouth frequently between 1 and 2 h after administration of AZD2014
  - If a patient develops GI disorders (***Nausea, vomiting and diarrhea)*** after starting AZD2014 for the first time, on subsequent dosing days, a treatment with serotonin antagonist should be initiated potentially with Olanzapine 5–10 mg by mouth prophylactically daily and Lorazepam 0.5–2 mg by mouth or sublingual every 4 to 6

h as needed on the AZD2014 dosing days. In case of stomach pain, a H2 blocker or proton pump inhibitor can be added but should be taken only on days when AZD2014 is not given (during drug holidays).

- ◊ Patients, who are developing any mild changes in their ***skin conditions*** should be treated with antihistaminergic drugs in order to prevent rash from appearing (non sedative antihistamines may be preferred due to side effects of fatigue, known for AZD2014). Patients who develop skin rash may require an interruption in treatment. Treatment with topical steroid cream/ointment and/or antihistamines/antibiotics should be considered early, if possible before the full clinical picture evolves. A detailed treatment guidance document is presented in Section 6.1.2
- ◊ ***Transient changes in respiratory parameters*** (increase in inspiratory flow, respiratory rate and minute volume with decreases in inspiration time and tidal volume) occurred in a respiratory safety pharmacology study in rats following single oral doses of AZD2014. Therefore, a high resolution thorax CT scan and a complete pulmonary function test will be performed at baseline and as clinically indicated. The test will include the highest of 3 forced expiratory volumes, forced vital capacity, and carbon monoxide diffusing capacity (DLCO% & DLCO). A recent haemoglobin measurement should also be available at the time of the DLCO evaluation.
- ◊ Considering the potential risks of ***cardiac events***; the study protocol includes a baseline assessment of troponin T or I, the requirement of followed up of all abnormal ECG findings, including T-wave changes, with assessment of cardiac markers (troponin T or I, lactate dehydrogenase and AST) after the ECG finding. Regular monitoring of vital signs and ECG parameters are also planned.
- ◊ Considering that occurrences of anemia, neutropenia and thrombocytopenia, lymphopenia, the clinical study protocol excludes patients with anaemia (Hb $\leq$9.0g/dL), neutropenia (absolute neutrophil count $\leq 1.5 \times 10^9$/L) and thrombocytopenia (platelets $\leq$100 g/L) and patients are monitored regularly (including differential blood counts).
- ◊ Considering the ***potential for phototoxicity,*** patients will be advised to use sunlight protection measures such as use of sunscreen during administration of AZD2014, and should be advised to adopt such measures for a period of 3 months after receiving their final dose of AZD2014.

Overall, the Sponsor considers that benefit-risk profile is favorable to proceed with the proposed clinical study.

VI. STUDY TREATMENTS

Following inclusion, patients will be randomized (2:1) to receive

- Arm A : AZD2014 + anastrozole
- Arm B : anastrozole alone

6.1 Investigational Medicinal Product 1 : AZD2014 (AstraZeneca)

6.1.1 Overview

Name or code	AZD2014 (Vistusertib)
Mode of Action	Selective and specific mTOR kinase inhibitor targeting both mTORC1 and mTORC2 complexes.
Formulation	Plain, round, biconvex, yellow, film-coated tablets comprising three strengths, containing 25 or 50 mg AZD2014.
Composition	AZD2014 tablets contain AZD2014, mannitol, microcrystalline cellulose, croscarmellose sodium, povidone and magnesium stearate. The tablet film coat comprises polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc and yellow iron oxide.
Packaging	The drug product is supplied in white, high-density polyethylene bottles with standard, lined, screw-neck closures. These bottles are child-resistant and tamper-evident. 40 tablets / bottles.
Storage	Room temperature (below 30°C).
Route of Administration	Oral
Dosage regimen	125mg BID with intermittent schedule (2 days of treatment followed by 5 days off (500mg/week)) For Dose adaptation procedures see below, Section 7.
Duration of treatment	Until the patient experiences unacceptable toxicity, disease progression and/or treatment is discontinued per patient or investigator request.
Missed doses	Should a patient miss a scheduled dose, the patient is allowed to take the dose up to 2 hours after the scheduled dose time. If >2 hours, the missed dose should be noted in the patient diary and dosing resumed with the next planned dose. The leftover drug should be returned to the study site upon patient follow up visit.
Overdose	No known antidote to AZD2014, and the treatment of overdose should be supportive for the underlying symptoms.

Drug-Drug interactions	CYP3A4, CYP3A5, Pgp (MDR1) or BCRP moderate or potent inhibitors or inducers. Known or possible substrates of the drug transporters OATP1B1, OATP1B3, MATE1 and MATE2K. Listings and recommendations of such co-medications are given in Annex 5.
Recommendations / Food restrictions	AZD2014 can be given with or without food at approximately the same time each morning and 30 min before taking anastrozole (in case of randomization Arm A). The second dose of the day should be taken approximately 12 hours after the morning dose. Sugary and fatty foods should be kept to a minimum in the meals prior to taking a dose. Large amounts of grapefruit and Seville oranges (and other products containing these fruits e.g. grapefruit juice or marmalade) should be avoided whilst taking AZD2014. No more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1 to 2 teaspoons (15g) of Seville orange marmalade daily is allowed. Patients who develop mucuosal inflammation should be instructed to rinse their mouth frequently between 1 and 2 h after administration of AZD2014. If vomiting occurs within 30 minutes after dosing or later if the tablets can be identified in the vomit content, the patient can retake new tablets. Use of sunlight protection measures such as use of sunscreen during administration of AZD2014 and for a period of 3 months after receiving their final dose of AZD2014

6.1.2 Dose levels, Dose adaptations and management of specific toxicities

Table 2 - Dose levels and dose reductions for AZD2014

Dose levels and dose reduction	
Starting dose level	500mg/week : 125mg BID on D1 and D2 then 5 days off
Dose level -1	400mg/week : 100mg BID on D1 and D2 then 5 days off
Dose level -2	300mg / week : 75mg BID on D1 and D2 then 5 days off

General guidelines for dose modifcations in case of AE are presented in SectionVII.
In case of treatment interruption, if the toxicity resolves or reverts to ≤ CTCAE grade 2 within 2 weeks and the patient is showing clinical benefit, treatment with AZD2014 may be restarted. If

the toxicity does not resolve to ≤ CTCAE grade 2 after 2 weeks then study drugs treatment should be permanently discontinued. No dose re-escalation is allowed.

6.2 Investigational Medicinal Product 2: anastrozole (AstraZeneca)

6.2.1 Overview

Name or code	**Anastrozole**
Other Names	Arimidex®
Therapeutic Class	Aromatase inhibitor
Mode of Action	Potent and highly selective non-steroidal aromatase inhibitor.
Formulation	1 mg film-coated tablets. Each film-coated tablet contains 93 mg of lactose monohydrate. White, round, biconvex tablet with logo on one side and strength on the other
Route of Administration	Oral
Premedication	None
Dosage regimen	1 mg tablet once a day
Duration of treatment	Patients may continue treatment with anastrozole until the patient experiences unacceptable toxicity, disease progression and/or treatment is discontinued per patient or investigator request.
Missed doses	In case of missed doses, the missed dose should be noted in the patient diary and dosing resumed with the next planned dose. The leftover drug should be returned to the study site upon patient follow up visit.
Packaging	PVC blister/aluminium foil packs of 30 tablets
Storage	Do not store above 30°C. See Section "6.3" and Pharmacy Manual.

6.2.2 Dose levels and dose adaptations

No dose adaptations. In case of study drug interruption > 28 days, the treatment should be permanently discontinued.

6.3 Study treatments management

6.3.1 Ordering and site supplies

AZD2014 and anastrozole will be provided by AstraZeneca and supplied to the participating centres by LC[2].
The first study drug supply will be organized by the sponsor following the study set-up meeting directly. The following drug requests should be addressed to the Sponsor by Fax: 04.69.85.61.82 using the *clinical supplies request form* (See Pharmacy Manual).

Study drugs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated staff have access in accordance with the applicable regulatory requirements. Upon receipt, Study drug should be stored according to the instructions specified on the drug labels and in the Pharmacy Manual.

6.3.2 Labelling and packaging

AZD2014 and anastrozole will be provided to the participating centers with specific and regulatory required labels according to GCP and GMP.

6.3.3 Treatment Compliance

Each patient should be instructed to return all study drug packaging and unused material to the study site at each visit.
Treatment with study medication will be assessed at each visit and reported on eCRF.

6.3.4 On site Accountability

Study drug shall be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate Drug accountability record form (DARF) of study drugs is maintained with information related to drug receipt, drug dispensing and destruction (See Pharmacy Manual for specific forms).
The study site personnel will keep a record of all drug dispensed to and returned by the patients throughout the study. Compliance will be assessed by counting returned tablets. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A copy of the DARF is available in the Pharmacy Manual. These records must be available for inspection by the Study Monitor.

Under no circumstances will the Investigator supply study drugs to a third party, allow the study drugs to be used other than as directed by this Clinical Trial Protocol, or dispose of study drugs in any other manner.

6.3.5 Recall

A potential defect in the quality of study drugs may be subject to initiation by the Sponsor of a recall procedure. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall study drugs and eliminate potential hazards.

6.3.6 Unused products

At the end of the study, the unused or partially used study drugs should be kept until destruction. A written authorization must be obtained from the sponsor before destruction. Following destruction, a written Report of destruction (see Pharmacy Manual) containing the following:

- Reason for destruction
- Batch numbers of study drugs destroyed
- Quantity of study drugs destroyed
- Date of destruction
- Name and signature of responsible person who discarded the study drugs in a hazardous container for destruction

must be faxed to the French Coordinating Center : 04 69 85 61 82.

VII. SAFETY PLAN

In case of toxicity during the study treatment period, the guidelines presented in the following tables should be followed.
For anastrozole: No dose adaptations are planned as per Arimidex SPC. In case of study drug interruption > 28 days, the treatment should be permanently discontinued.

Table 3 – General guidelines for dose modifications in case of non hematological AE

NCI CTCAE Toxicity	ACTION
Grade ≤ 2	None (See specific supportive care guidelines for expected AEs in section below) **Except for Grade 2 Stomatitis/Oral Mucositis/Mouth Ulcers (See Table 5 below)**
Grade ≥ 3 or clinically significant	Hold study drugs and initiate supportive care
▪ **If AE lasts ≤14 days and resolves to ≤ Grade 2**	Reduce AZD2014 by 1 DL and restart AZD2014 and anastrozole if applicable (Arm A)
▪ **If AE lasts > 14 days**	Discontinue both study drugs.
▪ **If recurrence of Grade ≥3**	Reduce AZD2014 by 1 DL if available as per Table 2. If not, discontinue AZD2014 and anastrozole
▪ **If recurrence of Grade 3[a] cardiac event**	Discontinue both study drugs
▪ **If recurrence of Grade 4**	Discontinue both study drugs

a: Includes significant change in CK/CK-mb ratio (relative index >5%), increases in heart rate of +25 bpm (up to 100-125 bpm for more than 24hrs or increase in heart rate >125 bpm for more than 12 hours), recurrent or persistent (>24 hours) or symptomatic increases in blood pressure (increases by >20 mmHg diastolic or >156/100 mmHg) despite standard antihypertensive treatment, QTc prolongation >500 ms.

Table 4 – General guidelines for dose modifications in case of hematological AE

NCI CTCAE Toxicity	ACTION
Grade ≤ 2	None
Febrile neutropenia Grade 3 or 4	Withhold **AZD2014** until infection is resolved, antibiotics no longer required and ANC Grade ≤2 or baseline. Then, **AZD2014** can be restarted with 1st dose reduction. **If 2nd episode,** Withhold **AZD2014** until infection is resolved, antibiotics no longer required and ANC Grade ≤2 or baseline, then **AZD2014** can be restarted with 2nd dose reduction. If 3rd episode: discontinue AZD2014 permanently
Non-febrile neutropenia Grade 4 lasting >7 days despite growth factor support during dose holydays	Withhold **AZD2014** until Grade ≤2 or baseline, then restart **AZD2014** with 1st dose reduction

	If 2nd episode, Withhold **AZD2014** until Grade ≤2 or baseline, then restart A**ZD2014** with 2nd dose reduction **If 3rd episode :** Discontinue **AZD2014**
Thrombocytopenia, Grade 4 without bleeding requiring red blood cell (RBC) transfusion	Withhold **AZD2014** until Grade ≤2 or baseline, then restart **AZD2014** with 1st dose reduction **If 2nd episode,** Withhold **AZD2014** until Grade ≤2 or baseline, then restart **AZD2014** with 2nd dose reduction **If 3rd episode :** Discontinue **AZD2014**
Thrombocytopenia, Grade 3 or 4 **with bleeding** requiring RBC transfusion	Withhold **AZD2014** until Grade ≤2 or baseline; then restart **AZD2014** with 1st dose reduction. If 2nd episode of **thrombocytopenia**, Grade 3 or 4 **with bleeding** requiring RBC transfusion : Withhold **AZD2014** until Grade ≤2 or baseline, then restart **AZD2014** with 2nd dose reduction If 3rd episode; Discontinue **AZD2014**

Table 5 – Management of specific AEs and Recommended dose modifications

Toxicity and Worst toxicity (CTCAE Grade)	Recommendations and/or Dose Modifications
Fatigue	
Grade ≥ 3	AZD2014 should be held for up to 14 days, before being restarted at a lower dose. In cases of severe fatigue, cardiovascular parameters, vital signs including supine and standing BP and HR, and ECGs should be re-assessed, together with lab parameters including venous lactate, to address underlying causes such as metabolic acidosis (electrolytes [Na, K, Cl] and HCO3), with calculation of anion gap using the following formula: =([NA+]+[K+] – ([Cl-]+[HCO3-]) If metabolic acidosis has been diagnosed, local standards for treatment should be applied as appropriate
Stomatitis/Oral Mucositis/Mouth Ulcers	
Grade 1	Use non-alcoholic mouth wash or salt water (0.9%) mouth wash several times immediately after drug administration (1-3h) and during the day as required until resolution. AZD2014 treatment can be continued without a dose reduction.
Grade ≥2	Use topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol), with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (e.g., Kenalog in Orabase®) or alcohol-free 0.5-2 mg/5ml dexamethasone oral solution (i.e.for example Dexsol® or PMS Dexamethason 0.5/5 ml Elixir) . The mouth rinse will be self administered at a daily dose of 10 ml 3 times per day Most importantly, patients must be instructed to swish and **expectorate** the mouth rinse to avoid systemic exposure to Dexamethasone.

Toxicity and Worst toxicity (CTCAE Grade)	Recommendations and/or Dose Modifications
	Agents containing hydrogen peroxide, iodine, and thyme derivatives may worsen mouth ulcers. It is preferable to avoid these agents. **AZD2014 should be stopped until stomatitis improves to ≤ Grade 1, and then resumed without a dose reduction.** **If Grade 2 to 3 stomatitis recurs, reduce the DL of AZD2014 if possible as per** Table 2 - Dose levels and dose reductions**.** ***If the toxicity resolves or reverts to ≤ CTCAE Grade 2 within 14 days of AE onset and the patient is showing clinical benefit***, treatment with AZD2014 may be restarted, at the same dose, at the discretion of the Investigator. ***If the toxicity does not resolve to ≤ CTCAE Grade 2 after 14 days***, then the patient should be withdrawn from the study and observed until resolution of the toxicity.
Electrolyte changes including hypokalemia and hypophosphataemia	
AZD2014, like other mTOR inhibitors inhibits pump mechanisms in renal tubules, leading to hypokalkaemia and hypophosphataemia in a small proportion of patients. The presence of biochemical abnormalities should be monitored as per the protocol and electrolyte abnormalities should be corrected using oral supplements. The Investigator should also consider whether other medication the patient may be receiving, such as diuretics may have contributed to these abnormalities.	
Hyperglycemia	
In the case of patients developing **≥ Grade 3 hyperglycaemia**, patients may require treatment in an intensive care unit. In this instance, an appropriate example of guidance for treatment is given in Turina *et al.* 2006 (25). Due to the predicted short half-life of AZD2014, only a short period of insulin resistance is expected. Therefore early treatment with high doses of insulin should be carefully evaluated and blood sugars and hypokalemia monitored as per standard clinical practice. **In case of Blood Glucose levels > 13.9mmol/L for longer than 1 week**: continuous oral anti-diabetic treatment should be started at the discretion of the investigator as per local standard. Treatment with Metformin should be carefully evaluated due to effects on the PI3Kinase pathway. In general management of hyperglycaemia should be performed according to local standards at the discretion of the investigator.	
Nausea and vomiting	
In order to decrease the incidence of nausea and vomiting, an anti-emetic regimen has been instituted for patients, who develop nausea after starting AZD2014. It should be noted that not all patients require antiemetics and therefore they should not be given prophylactically in every patient. However, ***in case a patient develops nausea after starting AZD2014 for the first time, antiemetics should be administered and continued daily during AZD2014 dosing,*** for the subsequent dosing days: Serotonin (5-HT3) antagonist (choose one from this list below): • Dolasetron 100 mg by mouth daily • Granisetron 2 mg by mouth daily or 1 mg by mouth twice a day • Ondansetron 16-24 mg by mouth daily ***If nausea/vomiting are not being managed*** with the regimen above, start either ▪ an atypical antipsychotic like Olanzapine 5-10 mg by mouth prophylactically daily **or** ▪ an antihistaminergic agent like Promethazine (Phenergan) on the AZD2014 dosing days prior to the AZD2014 dose.	

Toxicity and Worst toxicity (CTCAE Grade)	Recommendations and/or Dose Modifications
	If this is still not managing the nausea/vomiting sufficiently, add Lorazepam 0.5-2 mg by mouth or sublingual every 4 to 6 hours as needed, but only on the AZD2014 dosing days. **Should** upper abdominal pain **pain develops** a H2 blocker or proton pump inhibitor can be added but should be taken only on days when AZD2014 is not given (i.e. during drug holidays). • As AZD2014 is being administered in combination, the investigator must confirm, that treatment with H2 blocking agents or drugs known to increase gastric pH do not affect the pharmacokinetics of the combination agent : anastrozole.
Diarrhea	
	Patients should be made aware of the risk of diarrhea while receiving treatment with AZD2014. Patients should be advised to drink sufficient fluids and have a supply of loperamide available throughout treatment. However, loperamide should not be administered prophylactically. As soon as the first liquid stool occurs, patients should start treatment with loperamide immediately and also take electrolyte-containing fluids. The recommended antidiarrhoeal treatment is loperamide; to be administered as per package information and usual clinical practice .Loperamide should not be administered for more than 48 consecutive hours. Hospitalisation is recommended for management of diarrhoea under the following circumstances: • Diarrhoea associated with fever • Diarrhoea requiring intravenous hydration • Diarrhoea persisting beyond 48 hours following the initiation of high-dose loperamide therapy.
Decreased Appetite:	
	Decreased appetite should be treated according to local clinical practice. Dietary review is recommended.
Interstitial Lung disease any new respiratory symptoms including cough, dypsnea, lower respiratory tract infection not clearly explained by other factors such as disease progression or anaemia.	
	A baseline thorax CT scan must be available for all patients treated with AZD2014, for retrospective analysis and comparison with a high resolution CT scan, should it be required, when symptoms occur during trial conduct. Should a patient experience any new respiratory symptoms including cough, dypsnoea, lower respiratory tract infections not clearly explained by other factors such as disease progression or anaemia, a high resolution CT scan and pulmonary function tests should be performed, including 3 forced expiratory volumes, forced vital capacity, and carbon monoxide diffusing capacity (DLCO% & DLCO). A recent haemoglobin measurement should also be available at the time of the DLCO evaluation. For any new respiratory symptoms (cough, dyspnoea, lower respiratory infection) not clearly explained by other factors (eg, dyspnoea associated with substantial drop in haemoglobin), patients should have oxygen saturation measured. If <92%, the high resolution CT scan of the chest should be repeated and pulmonary function tests should be performed. If these investigations are suggestive of pneumonitis or interstitial lung disease and causality with the study drug cannot be excluded, treatment should be interrupted. In more severe cases treatment with corticosteroids should be considered as per reference (26, 27)

Toxicity and Worst toxicity (CTCAE Grade)	Recommendations and/or Dose Modifications
ECG changes	
Patients who develop persistent, confirmed T wave repolarisation abnormalities (inversion or flattening) on regularly scheduled ECGs should be referred for a cardiology opinion and undergo a follow up ejection fraction measurement using the same technology to that used at baseline. The followings should be evaluated in case of ECG changes : • Increase ECG frequency as medically appropriate • Troponin measurement should be performed within 24-hours if a new T-wave abnormality (such as T wave inversion or flattening or other repolarisation is recorded (and as clinically indicated) and during EOT visit (i.e. 30 days after the last study drugs administration) • LV function assessment: - approximately 2 weeks after a new T wave inversion or flattening is first recorded (and as clinically indicated) and during EOT visit (i.e. 30 days after the last study drugs administration)	
Liver Function tests abnormalities	
Evidence of abnormal liver function should be monitored as per the protocol guidelines. Increased levels of serum AST, ALT or serum bilirubin should trigger an investigation of the cause which may include viral infection or progression of liver metastases. If hepatic dysfunction is thought to be a consequence of treatment with AZD2014 treatment: interruption and/or reduction should be considered. The investigator should consider whether the abnormal liver function meets the criteria for expedited reporting (Appendix 7**: Actions required in case of increases in liver biochemistry and evaluation of Hy's Law)**	
Rash / skin Toxicity Use antihistaminergic drugs (Non sedative antihistamines may be prefered due to side effects of fatigue, known for AZD2014). Treatment with topical steroid cream/ointment and/or antihistamines/ **antibiotics** should be considered **early**	
Grade 1 **Dry skin/Xerosis**	**Face/Body:**Over the counter moisturizing cream or ointment Plus consider antihistamines **Body:** Ammonium lactate 12% cream bid or 6% salicylic acid cream bid plus consider antihistamines Treatment can be continued without a dose reduction.
Grade 1 **Pruritus**	Same as above, only **add topical steroids** (moderate strenght) or topical antipuritic bid Treatment can be continued without a dose reduction.
Grade 1 **Macules, papules and/or pustules** covering <10% BSA, with or without symptoms (pruritus, burning, tenderness)	Consider treatment with antihistamins – if no improvement add topical steroid cream/ointment ,and/or **topical antibiotic bid or oral antibiotic for 6 weeks.**

Grade 2 Macules, papules and/or pustules covering 10-30% BSA, with or without symptoms (pruritus, burning, tenderness, skin changes, oedema, papulation, excoriation etc); associated with psychosocial impact; limiting instrumental ADL	**Face/Body:**Over the counter moisturizing cream or ointment Plus consider topical steroids and antihistamins **Body:** Ammonium lactate 12% cream bid or 6% salicylic acid cream bid plus consider topical sterpoids antihistamines **If topical antibiotic has been used, switch to oral antibiotic for 6 weeks** AZD2014 Treatment can be continued without a dose reduction.
Grade ≥ 3 **For dry skin/Xerosis**	Face/Body:Over the counter moistyurizing cream or ointment Body: Ammonium lactate 12% cream bid or 6% salicylic acid cream bid Consider treatment with non sedating antihistamines Interrupt AZD2014 until rash improves to ≤ Grade 1 or baseline. If no improvement consider systemic steroids If rash improves to ≤ Grade 1 or baseline within 2 weeks – reduce AZD2014 one dose level. If rash lasts >2 weeks, discontinue AZD2014
Grade ≥ 3 **With/without eczematous areas**	Add topoical steroids for eczematous areas and Consider treatment with topical steroid cream/ointment and/or antihistamines. If Grade 3 AE last >10 days and/or if steroids have been used as part of anticancer treatments before starting the study, doses up to 100 mg/d may be possible to treat treatment related rash, especially in drug combination trials of AZD2014 Interrupt AZD2014 until rash improves to ≤ Grade 1 or baseline. If no improvement consider systemic steroids If rash improves to ≤ Grade 1 or baseline within 2 weeks – reduce AZD2014 one dose level. If rash lasts >2 weeks, discontinue AZD2014
Grade ≥ 3 **Macules, papules and/or pustules** covering >30% BSA, with or without symptoms (pruritus, burning, tenderness, skin changes, oedema, papulation, excoriation etc); associated with psychosocial impact; limiting self care ADL;	**Add oral antibiotics for 6 weeks** (switch to borad spectrum/garm negative cover if infection suspected (yellow crusts, purulent discharge, painful skin/nares) Consider swab for bacterial culture
Examples for topical steroids: Triamcinolone acetonide 0.025%: Desonide 0.05%; Fluticasone proprionate 0.05%, Aclometasone 0.05% **Example for topical antipruritics:** Pramoxine 1%; Doxepin 5% cream **Oral antihistamines:** Loratidine, cetirizine, Fexofenadine; Diphenhydramine 25-50 mg every 8h; Hydroxyzine 25 mg every 8h; **Topical antibiotics:** Clindamycin 1-2%; Erythromycin 1-2%; Metronidazole 1%; Silver sulphadiazine1% **Oral antibiotics:** Doxycycline 100 mg bid; Minocycline 100 mg bid; Oxytetracycline 500 mg bid	

VIII. ASSESSMENTS & SCHEDULE

8.1 Definition of study periods: Screening, Study treatment, Short-term safety follow-up, long-term follow-up and continued access period

A description of the periods of the study is provided below.

Screening period: begins on the day of ICF signature and ends on the day of study drugs treatment starts. In this trial, screening period lasts for 28 days.

Treatment period: begins on the day of study drugs treatment starts and ends when the decision to permanently discontinue study drugs is taken.
During the treatment period,

- All patients will continue to receive study drugs treatment until disease progression, unacceptable toxicity, willingness to stop or a discontinutation criterion is met (See Section IX).
- Patients will be followed-up per study flow-chart i.e. on Week 1, Week 2, Week 4, Week 6, Week 8 then every 8 weeks until Week 48.
- Patient still benefiting form the study treatments at W48, could entered in the *Continued access period*

Post-treatment discontinuation follow-ups:

- *Short-term (safety) follow-up* : for all patients, a short-term follow-up visit should be scheduled 30 days (±3 days) after the last study drugs intake.

- *Long term (progression/survival) follow-up* : begins the day after the short-term follow-up visit is completed and ends with the patient's death, loss to follow-up or end of trial, whichever is earlier. The long- term follow-up visits (not formal visits) will occur every 6 months to document tumor status and/or survival status.

The End of Trial is defined as last patient last visit defined as either the date of the last visit of the last patient to complete the study, or the date at which the last data point from the last patient, which is required for statistical analysis is received, whichever is the later date.

Continued Access period: For patient with clinical benefit following the 48 weeks of the treatment period, the study drugs can be continued until disease progression, unacceptable toxicity, willingness to stop or a discontinutation criteria is met. During this continued access period, the study drugs should be administered according to the current protocol version and patient followed-up as per usual institutional practice. For such patient, tumor and vital status as well as related SAEs should be collected and reported as described in Section 10.3.

8.2 Assessments to be performed at screening

The investigator will have to proceed to the following information/procedures during the screening visit:

- Fully inform the patient of the study treatments, the objectives and the design of the study, answer to any questions that the patient may have and ensure that the patient underdtands the potential risks and benefits of participating in the study before signing the informed consent form. None study-related procedure can be started before ICF is signed and dated by both the patient (and impartial witness, if applicable) and the investigator.
  - Check the eligibility criteria list and perform the following exams:

Table 6 - Screening/Baseline assessments

TYPE OF ASSESSMENT	TIMING
General demography and Relevant medical history • Demography (age, sex) • A complete history of endometrial carcinoma diagnosis and treatment (including staging, diagnosis information, previous anti-cancer treatments, and sites of disease). • Past relevant medical and surgical history	Within 28 days before study drugs start
Concomitant treatments and symptoms Assessment of baseline signs and symptoms (concomitant disease) and prior/concomitant therapies. All treatments received within 4 weeks prior to the first dose of study treatment should be documented	
Thorax CT Scan NB: a high resolution thorax CT scan must be performed at baseline and as clinically indicated considering the risk of pneumonitis (this scan can be part of the Tumor assessment exams).	
Tumor assessment CT-scan (chest/abdomen/pelvis). For each patient, the same method of assessment and the same technique must be used to evaluate measurable disease sites at baseline and throughout the entire study.	
Echocardiogram	Within 14 days before study drug start
ECG Patients should rest in the supine position for at least 10 minutes before each 12-lead ECG recording is started. The ECGs should be reviewed, signed, and dated by a qualified physician (or qualified physician's assistant or nurse practitioner) and any clinically important finding recorded on the appropriate eCRF screen. The investigator is responsible for providing the interpretation of all ECGs. ECGs recorded during the screening period will be obtained in triplicate (with 2-5 minute lag time between each)	

Complete physical examination • Vital signs (blood pressure, pulse) • Weight • Performance Status (PS) will be measured using the Eastern Cooperative Oncology Group (ECOG) Scale (Appendix 01).	Within 7 days before study drugs start
Laboratory tests • *Hematology*: white blood cells and differential WBC, hemoglobin, and platelet count • *Biochemistry*: serum creatinine, creatinine clearance (calculated according to Cockcroft –Gault or MDRD for > 65 years formula), sodium, potassium, calcium, albumin, glucose, Fasting Plasma Glucose (FPG), cholesterol and triglycerides, total bilirubin, alkaline phosphatase, AST, ALT; creatine kinase, CK-MB and troponin T or I. • Urinalysis (sodium, potassium, urea, creatinine)	
Biosamples for translational research program **Tumor samples** Archival tumor FFPE block (or fresh biopsy with patient consent)	To be sent to Sponsor before the end of the 2nd month of treatment or performed within 14 days before W1D1 for fresh biopsy

Following validation of eligibility criteria, patients will be randomly assigned to a treatment arm using IVRS platform.

8.3 Assessments to be performed during treatment period

As long as patients will be under study treatment, they should be followed-up according to the Table below.

Table 7 – On-treatment assessments

TYPE OF ASSESSMENT	TIMING
Study treatment intake and compliance reporting Week 1 Day 1 should be initiated within 7 days from randomisation at maximum. **AZD2014, per os, (Arm A only)**	Every week on Days 1 & 2 : 125mg bid, 12h apart. NB: The first dose of AZD2014 must be taken 30 min before anastrozole Days 3 to 7: off treatment
Anastrozole, per os (Both Arms)	1mg/d, daily and continuously.
Complete physical examination • Vital signs (blood pressure, pulse) • Weight • Performance Status (PS) will be measured using the Eastern Cooperative Oncology Group (ECOG) Scale (Appendix 01).	Week 1 Day 1 pre-dose (dispensable if done at screening within 7 days before W1 D1) Week 2, 4, 6, 8 : Day 1 pre-dose Thereafter, every 8 weeks

TYPE OF ASSESSMENT	TIMING
Concomitant treatments and symptoms Assessment of signs and symptoms (concomitant disease) and concomitant therapies.	Daily on patient diary with reporting during physical exam visit
Laboratory tests (a 24h-delay is allowed) • *Hematology*: white blood cells and differential WBC, hemoglobin, and platelet count • *Biochemistry*: serum creatinine, creatinine clearance (calculated according to Cockcroft –Gault or MDRD for > 65 years formula), sodium, potassium, calcium, albumin, glucose (FPG), total bilirubin, alkaline phosphatase, AST, ALT; creatinine kinase, CK-MB and troponin T or I. • *Urinalysis (sodium, potassium, urea, creatinine)*	Week 1 Day 1 pre-dose (dispensable if done at screening within 7 days before W1 D1) Week 2, 4, 6, 8 : Day 1 pre-dose Thereafter, every 8 weeks
ECG ECGs recorded during the treatment phase will be single tracing.	Week 2 Day 1 pre-dose Week 8 Day 1 pre-dose then every 8 weeks
Echocardiogram	Triggered by the presence of symptoms
Tumor assessment CT-scan (chest/abdomen/pelvis). For each patient, the same method of assessment and the same technique must be used to evaluate measurable disease sites at baseline and throughout the entire study.	Every 8 weeks
Biological samples collection for Translational program	
PK Blood sampling (Arm A only)	Week 1 Day 1: pre-dose, 2h and 6-8 hours later Week 2 Day 1: pre-dose, 2h and 6-8 hours later
PD Blood samples	Week 1 Day 1 pre-dose Week 8 Day 1 pre-dose At time of relapse
Blood samples for ctDNA – Mutations analysis	Week 1 Day 1 pre-dose Week 4 Day 1 pre-dose Week 8 Day 1 pre-dose At time of relapse
Blood Sample for the impact on circulating NK cell (Arm A only and patients of Centre Léon Bérard))	Week 1 Day 1: pre-dose Week 8 Day 1 pre-dose
Tumor biopsies	Week 8 Day 1 pre-dose At time of relapse

8.4 Assessments to be performed during the short-term (safety) follow-up visit

A short-term (safety) follow-up visit should be scheduled 30 (± 3 days) days after the last study drugs administration (both study drugs). The assessments to be performed are described in the study flow-chart and summarized below:

TYPE OF ASSESSMENT
Complete physical examination • Vital signs (blood pressure, pulse) • Weight • Performance Status (PS) using the ECOG Scale (Appendix 01).
Laboratory tests • *Hematology*: white blood cells and differential WBC, hemoglobin, and platelet count • *Biochemistry*: serum creatinine, creatinine clearance (calculated according to Cockcroft – Gault or MDRD for > 65 years formula), sodium, potassium, calcium, albumin, , cholesterol and triglycerides, glucose (FPG), total bilirubin, alkaline phosphatase, AST, ALT; creatinine kinase, CK-MB and troponin T or I. • Urinalysis (sodium, potassium, urea, creatinine)
ECG
Tumor assessment CT-scan, and/or any other clinically indicated exams. For each patient, the same method of assessment and the same technique must be used to evaluate measurable disease sites at baseline and throughout the entire study.

8.5 Data to be collected during the long-term follow-up visists

For patients with no progressive disease at time of the short-term safety visit, the following data should be collected every 6 months

DATA to be collected
• Date of last tumor assessment • Tumor status • Survival status or date of death • Date of initiation of a new treatment

8.6 Data to be collected during the continued access period

For patients still benefiting from study drugs treatment following 48 weeks of treatment, the following data should be collected every 6 months until a discontinuation criteria is met:

DATA to be collected
• Related SAEs • Tumor status including Date of last tumor assessment • Survival status or date of death • Date of initiation of a new treatment

8.7 Global study flow chart

	Screening Within 28 days before Day 1	Week 1	Weeks 2, 4, 6	W8, W16, W24, W32, W40, W48	Safety follow-up term	Long-term (progression /survival) follow-up
Days	**-28 to -1**	**1**	**1**	**1**	**30 days after the permament study drugs discontinuation (± 3 days)**	**Every 6 months until the patient's death, loss to follow-up or End of Trial**
Signature of informed consent form	X[a]					
Validation of eligibility criteria	X[a]					
Relevant medical history (past and current), symptoms/medical conditions at baseline	X[a]					
Cancer diagnosis and treatment history	X[a]					
Physical examination including weight and vital signs : blood pressure, pulse	X[b]	X[d]	X	X	X	
ECG	X[b]		X at W2 only	X	X	
Echocardiogram	X[b]					
Thorax CT Scan	X[a]	In case of symptoms, medically required, in addition with Complete pulmonary function test				
PS ECOG	X*	X[c]	X[d]	X[d]	X	
Hematology, clinical chemistry testing (a 24h-delay is allowed)	X*	X[c]	X[d]	X[d]	X	
Urinalysis (a 24h-delay is allowed)	X*	X[c]	X[d]	X[d]	X	
AE and significant concomitant medications	X	X[d]	X[d]	X[d]	X	
Tumor assessment	X[a]			X	X	
Tumor status and/or Survival status					X	X
Biosamples collection for translational program – See Section XIII for details						
Blood samples PD Biogenesis of ribosomes		X[d]		X[d] at W8 only	X at relapse	
ctDNA analysis of mutation		X[d]	X[d] at W4 only	X[d] at W8 only	X at relapse	
PK AZD2014 (Arm A only)		X[e]	X[e] at W2 only			
PD Impact on circulating NK cell**(Arm A only)		X[d]		X at W8 only		
Tumor samples	X			X at W8 only	X at relapse	

a: within 28 days before Day 1,
b: within 14 days before Day 1;
c: within 7 days before Day 1 ;
d: at pre-dose;
e: pre-dose then 2 and 6-8 hours post dose ;
*: to be checked for validation of eligibility criteria but not collected in the eCRF
A delay of 3 days is allowed for each scheduled visit.
**: only patients of Centre Léon Bérard

IX. DISCONTINUATION

9.1 Study treatment discontinuation

The treatment with the study drugs should be continued as per protocol and in accordance with the investigator's judgment and patient consent. Patients have the right to voluntary discontinue (i.e. permanently stop) study drugs or withdraw from the study at any time for any reason. In addition, the investigator has the right to discontinue a patient from study treatment or withdraw a patient from the study at any time.

Reasons for study drug treatment discontinuation include:

- Patient's willingness to stop the treatment*
- Withdrawal of consent*
- Disease progression
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator
- Unacceptable adverse events(s)
- Patient non-compliance, as defined as unable or unwilling to complete the required study dosing or assessments

*: In case withdrawal of consent: the effective date of patient withdrawal of consent should be noted on the source data and no data collection could be performed after that date.
It should be clearly documented if the patient is willing to discontinue from study treatment or is withdrawing her consent.

For all patients discontinuing the study drugs treatment, a 30-day safety follow-up should be scheduled 30 days after the last study drugs intake. During this visit, a complete final evaluation should be made with an explanation of why the study drugs is discontinued.
A patient who discontinues study participation prematurely for any reason is defined as a dropout if the patient has already been administered at least 1 dose of study drugs.
A patient who discontinues, for any reason, study participation before randomisation is considered as a screening failure.

9.2 Study discontinuation

The Sponsor may stop the study at any time. Reasons for stopping the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other study indicate a potential health hazard to patients treated with study drug
- Patients enrolment is unsatisfactory
- If any information leads to doubt as to the benefit/risk ratio of the clinical trial
- If the Investigator has received from the Sponsor all study drug, means and information necessary to perform the Clinical Trial and has not included any patient after a reasonable period of time mutually agreed upon
- In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the Clinical Trial Protocol, breach of the applicable laws and regulations or breach of the ICH guidelines for Good Clinical Practice

In any case, the sponsor will notify the Investigator of its decision by written notice.

The investigator has also the right to stop the study at any time. He/she must notify (30 days' prior notice) the sponsor of his/her decision and give the reason in writing.

In all cases (decided by the Sponsor or by the Investigator), the appropriate Ethics Committee(s) and Competent Authority should be informed according to applicable regulatory requirements.

9.3 Site discontinuation

The Sponsor has the possibility to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- No compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice

X. SAFETY

ICH GCP requires that both investigators and sponsor follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

10.1 Definitions

The following standard definitions for adverse events will be used:

Adverse event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment.

NB: Signs and symptoms that are present prior to the first study drug administration are to be recorded on the medical history pages included in the eCRF. They are to be recorded as AEs as soon as one of the following changes occurs: increased intensity, relationship, action taken regarding study drug.

Serious adverse event (SAE): any untoward medical occurrence or effect that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital abnormality or birth defect
- is a significant medical event (i.e. that may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above).

Suspected Unexpected Serious Adverse event (SUSAR): An adverse reaction, not mentioned in or differing in terms of nature, intensity or clinical course from that listed in the latest edition of AZD2014 Investigator's Brochure and anastrozole's SPC.

Severe toxicities (STs): the following AE occurring during the first 8 weeks of treatment and evaluated as related to study drug:

- any grade ≥4 treatment related toxicity,
- any grade≥ 3 treatment related toxicity lasting more than 7 days.

New safety issues: Any new safety data that could lead to revaluate the ratio between the benefits and the risks of the research, or that could be sufficiently important to consider modifications of the research documents, the research management or, if need be, the drug utilization.

10.2 Reporting of adverse events

General Guidelines for reporting of clinical AEs

All AE regardless of the seriousness or relationship to the study drug, panning from the signature of the ICF and the first intake of study drug until the end of the study for a patient are to be recorded on the corresponding eCRF screens. AE occurring before the first study drug dosing should not be reported as an AE unless the investigator feels the event may have been caused by a protocol procedure.

As far as possible, the AE should be described using medical terms: diagnosis or single syndrome should be reported instead of symptoms.

For all AE, the Investigator should specify:

1. ***whether the event is serious or not***. The severity is related to the intensity whereas a serious AE is defined by the criteria described in Section 10.1. A severe AE should not be always considered as serious, and a serious AE may not be of severe intensity.
2. ***the start and end dates*** . The Investigator should follow up the outcome of any AEs until the return to normal or consolidation of the patient's condition. All adverse events still evolving at the end of the study are to be followed up by the investigator until their resolution or stabilization.
3. ***the intensity*** (using NCI CTCAE v.4.03 [Appendix 4]),
4. ***action taken with respect to study drug*** (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this AE; hospitalization/prolonged hospitalization),
5. ***The relationship between the study drug and an AE*** : related or not related to study drugs (EVCTM criteria)

CASE OF ROUTINE LABORATORY MEASUREMENTS

A value outside the normal or reference range in a routine safety assessment, such as clinical laboratory may be considered as an AE. However, laboratory as well as vital signs abnormalities are to be recorded into the eCRF as AEs only if they are considered medically relevant by the investigator: i.e. symptomatic, requiring corrective treatment, leading to IMP discontinuation/dose modification (reduction and/or delay), and/or fulfilling a seriousness criterion.

NB: If the findings contribute to a clinical diagnosis (such as hepatitis in case of increased liver enzymes) this diagnosis should be recorded as an adverse event.

10.3 Reporting of serious adverse events

10.3.1 Responsabilities of the investigator

The investigator must report to the Sponsor (contact: Ms. Anne Millaret, PharmD) by Fax: 09 81 40 42 80 and to the coordinating center 04 69 85 61 82 SAEs occurring or observed during the course of the study and within 30 days after the last administration of the study drug, whatever their relationship to the study treatment. This has to be done within 24 hours after the investigator becomes aware of the event.

SAE occurring before the first study drug dosing should not be reported as an SAE unless the investigator feels the event may have been caused by a protocol procedure (for example tumor biopsy).
SAEs occurring more than 30 days after study treatment completion need to be reported only if a relationship to the investigational product (e.g. secondary malignancy) is suspected by the investigator.

In case of SAE, the investigator will have to:

1. Fill and sign the adequate report forms (SAE form – Appendix 08) with at least :
    a. An identified patient
    b. A notifier (investigator)
    c. An event/reaction
    d. A study drug
2. Collect any additional document necessary for SAE assessment (such as hospitalization report, blood tests results)
3. Assess the seriousness and causality of the event with the study treatments using the causality criteria: related versus not related
4. Send the SAE form within 24 hours and additional documents by fax to:

The Sponsor (Ms. Anne Millaret, PharmD): Fax: 09 81 40 42 80
AND to study monitor: Fax : 04 69 85 61 82

A complete description and medical diagnosis shall be provided. In case of incomplete information, the investigator will have to provide follow-up information (outcome, more precise medical details, results of investigations, copy of discharge summary, etc…) as soon as possible, again using the SAE Report Form (follow-up) to the Sponsor (Ms. Anne Millaret, pharmD) by Fax: 09 81 40 42 80 and to the study monitor **by Fax :**04 69 85 61 82**.** When this information is passed on, care must be taken to continue to respect patient anonymity. The study monitor or Ms A. Millarret may contact, or visit the investigator, in order to obtain details of the event.

All SAEs must be followed by the investigator until resolution or stabilization, and a final assessment sent to to the Sponsor (Ms. Anne Millaret, pharmD) by Fax: 09 81 40 42 80 and to the study monitor **by Fax :**04 69 85 61 82**.** as a SAE follow-up. Sometimes this may mean that follow-up will extend beyond the patient's withdrawal from the trial.

Nota bene: The following events **are not** to be considered as SAE:

- Any event requiring short consultation in an hospital
- An external treatment in a hospital emergency service, however, the reason of the treatment initiation has to be reported as SAE
- Any event clearly related to disease progression
- Hospitalisation (1 night or more) or hospitalisation prolongation for one of the following reasons:
    - Planned hospitalisation for routine intervention
    - Hospitalisation or intervention requested by the protocol
    - Hospitalisation for explorations not related to a modification of the patient health

- Hospitalisation for comfort or for social reasons (for example: hospitalisation of an elderly person due to dependence on his partner who was hospitalised)
- Hospitalisation not related to a patient health worsening and not related to the study objectives (for example: plastic surgery)

Nota-Bene: **Misuse or overdose of the study treatment will have to be considered as SAE, even if they don't meet the seriousness criteria.**

10.3.2 Responsabilities of the sponsor

The sponsor will have to report all SUSAR to the EMA (Eudravigilance database), the Competent Authorities, the Ethics Committees and the Principal Investigators within the requested period. The evaluation of expectedness is based on knowledge of the adverse reaction on the reference document: the current reference document is the latest version of the Investigator's Brochure of AZD2014 and/or SPC of Anastrozole.

The sponsor will also have to inform the Ethics review committee of any SAE with the potential to modify the benefit/risk ratio of the present study.
The sponsor will be responsible for reporting of New Safety Issues and Development Safety Update Reports (DSUR) to Competent Authorities, to Ethics Committees and to Principal Investigators.

10.4 Reporting of severe toxicities

The following AE occurring during the first 8 weeks of treatment and evaluated as related to study drug:

- any grade ≥4 treatment related toxicity,
- any grade≥ 3 treatment related toxicity lasting more than 7 days.

Should be reported as severe toxicities using the ST reporting Form by Fax to the Study monitor: 04 69 85 61 82within 24 hours after the investigator becomes aware of the event.

XI. STATISTICAL CONSIDERATIONS

11.1 General considerations

The two following populations will be defined for the statistical analysis:

- The intent-to-treat (ITT) population includes all randomized patients.
- The efficacy-evaluable (per protocol [PP] population) consists of all treated and evaluable patients. A patient will be considered evaluable and assessable if 1) all eligibility criteria are satisfied, 2) the patient has received at least one dose of the study drugs and 3) has at least one post-baseline tumor assessment.
- The safety population includes all patients who received at least one dose of study drugs.
- The pharmacokinetics analysis population consists of all patients who provide reportable plasma concentration and PK parameter data, and who have no significant protocol deviations or AEs that may impact on the PK.

Considering that the response to study drugs may be different in naïve versus pre-treated patients, the randomisation will be stratified according to the number of prior lines received before randomisation: None versus ≥1 prior line of treatment.

11.2 Sample size determination

Safety run-in Phase

As no dose escalation will be performed, the safety will be evaluated following the treatment of 6 patients by the experimental association AZD2014+anastrozole (Arm A : experimental arm). By similarity to a classic 3+3 design, based on binomial probabilities, there is a 90% probability of observing one or more patients with a toxicity event, if that event occurs in at least 32% of the target population. Assuming a 2:1 randomization ratio, 9 patients will be initially enrolled in this safety run-in phase (6 in experimental Arm and 3 in control arm) and will be included in the evaluation of Phase II part.

Of note, if >1/6 patients exposed to AZD2014 + anastrozole experienced severe toxicities related to the combination: the study protocol will be amended and a lower dose of AZD2014 could be evaluated in combination with anastrozole in additional cohort of 6 patients.

Phase II

The sample size determination was calculated considering an Optimal Simon's two-stage design. Assuming the following parameters, where π is the true probability of success (i.e. non progression after 8 weeks of treatment):

- Null hypothesis : $\pi 0 = 40\%$: the largest 8-week non progression rate below which the combination will be considered as ineffective
- Alternative hypothesis : $\pi 1 = 60\%$: the smallest 8-week non progression rate proportion above which the combination will be considered as effective,
- a type I error alpha of 0.05 and 80% power,

46 evaluable patients are needed in the experimental arm (Stage I: 16 patients and Stage II: 30 patients) to reject the null hypothesis H0: $\pi \leq \pi 0$ versus the alternative hypothesis H1: $\pi \geq \pi 1$ in a unilateral situation.

With a 2:1 randomization and based on the assumption that ≈5% of the patients may be non-evaluable, **72 patients will be included in the study :Experimental arm: 48 patients and control arm: 24 patients.**

11.3 Endpoint definition and analysis

11.3.1 Primary endpoint

Safety Run In Phase

The primary endpoint is the number of severe toxicities (STs) occurring during the first 8 weeks of treatment. STs are defined as the occurrence of any of the following events evaluated as related to study drug and occurring during the first 8 weeks of treatment:

- any haematological and non hematological Grade ≥ 4 treatment related toxicity,
- any Grade ≥ 3 treatment related toxicity lasting more than 7 days.

The safety profile owill be summarized with descriptive statistics (appropriate proportions with their 95% confidence interval).

During the Phase I, the analysis of the safety run In phase will be performed after 8 weeks of follow-up of the first 6th patients randomized in Arm A. Depending of the occurrence of ST, the enrolment could be suspended during the 8 weeks of follow-up of the 6th patient randomized in Arm A in order to allow for toxicity assessment.

These safety data will be reviewed by a Data Monitoring Committee (DMC):

- If >1/6 patients exposed to AZD2014 + anastrozole experienced severe toxicities related to the combination: the study protocol will be amended and lower dose of AZD2014 could be evaluated in combination with anastrozole in an additional cohort of 6 patients.
- *A contrario*, if ≤ 1/6 patients experienced severe toxicities related to the combination: the safety data will be considered acceptable and enrolment/randomization will continue.

In addition, the DMC will be informed of all ST on real time in order to assess the safety of the combination regularly.

Phase II part

The ***8-week non-progression rate*** is defined as the rate of patients without disease progression within the first 8 weeks after randomization. Disease progression will be reviewed by a centralized imaging review committee. It will be summarized in both arms by a proportion together with its one-sided 95% confidence interval.

One **interim efficacy analysis** will be performed following the 8-week follow-up of the first 16 evaluable patients in Arm A (at the end of the Stage I: Safety Run: 6 patients + Stage I: 10 patients^{NB}).

- If the number of successes in Arm A is < 8/16, the study will be definitively closed for inefficacity of the combined treatment.
- If the number of successes in Arm A is ≥ 8/16, the stage II will be initiated and 30 additional evaluable patients will be enrolled and analysed for a total of 46 evaluable patients in Arm A.

At the end of Phase II-Stage II, if at least 24 successes are observed over 46 evaluable patients in Arm A, the combination will be considered as sufficiently efficient to deserve further investigation.

Nota Bene: As 16 patients must be evaluable for primary endpoint analysis 8 weeks after the start of study treatments, the recruitment might need to be temporally stop following the inclusion of 17^{th} patient (it is estimated that ≈5% of enrolled patients could be non-evaluable).

Of note, no formal comparison will be made between the experimental arm and the control arm. In the proposed trial design, the control arm is used to prospectively and contemporaneously validate the hypothesis success rate of anastrozole alone (set from the literature to $\pi 0 = 40\%$) i.e. to test consistency between the enrolled patients and historical controls. In addition, the randomization, eliminating the selection bias, it ensures that the experimental results are not obtained in a selection-biased population.

11.3.2 Secondary endpoints

Progression-free survival (PFS) will be measured from the date of randomization to the date of event defined as the first documented disease progression or death from any cause. Patients with no event at the time of analysis will be censored at the date of last adequate tumor assessment.

Overall Survival will be calculated from the date of randomization until the date of death due to any cause and censored at the date of last contact for patients alive at last contact.
PFS and OS will be estimated using the Kaplan-Meier method and will be described in terms of medians and 2-sided 95% CIs per arm.

Median follow-up will be calculated using the reverse Kaplan-Meier method.

Additional secondary endpoints will include:

- Overall response rate, defined as the proportion of patients with complete response (CR) or partial response (PR) according to RECIST1.1. It will be described on the PP and ITT population, together with its two-sided 95% CI.
- Duration of response, calculated from the date of first documented objective response (ie, CR or PR) until date of first documented progression or death due to underlying cancer, and censored at the date of the last available tumor assessment.

Safety analysis will be performed in the ITT population. The assessment of safety will be based mainly on the frequency of adverse events based on the common toxicity criteria (CTCAE-V4) grade. Descriptive statistics will be provided for characterizing and assessing patient tolerance to treatment. Adverse events will be coded according to the MedDRA®. Patients with at least one serious adverse event, patients with at least one grade 3/4 adverse event, patients with at least one adverse event requiring the discontinuation of study treatment will be described by arm.

XIII. TRANSLATIONAL RESEARCH PROGRAM

13.1 Tracking ribosome biogenesis during cancer

13.1.1 Rationale

Translation is one of the last steps of gene expression during which ribosomes synthesize proteins. A growing body of evidences indicate that the translation process *per se* plays a key role in tumorigenesis (28). In particular, the abnormal elevation of ribosome biogenesis observed in most cancers is crucial to support cell growth and proliferation. High levels of ribosomes in cancer cells result from hyper-activation of the RNA polymerase I (RNA pol I) induced by the activation of oncogenic pathways (Ras/MAPK/Erk, PI3K/Akt/mTOR…) or inactivation of tumour suppressor pathways (PTEN, p53…). Ribosome biogenesis takes place in the nucleoli, where ribosomal RNA (rRNA) are produced, processed and assembled with ribosomal proteins, with help of more than 200 factors. Compared to normal tissues, ribosome biogenesis is elevated in endometrial carcinomas, as shown by AgNOR staining that directly reflect the nucleoli morphology and thus ribosome biogenesis (29, 30). In addition, high AgNOR scoring was significantly and positively correlated with the grade of endometrial cancer and with poor patient survival (30, 31).
In tumours, alterations of translational control of specific mRNAs encoding oncogenes or tumour suppressors have been extensively reported (28). Unexpectedly, it emerges that ribosome itself acts as a direct regulator of translation. JJ Diaz team recently showed that composition of ribosomes is altered during tumour progression and affects translational control of cancer promoting genes (32, 33). Indeed during tumour progression, rRNA methylation is altered and associated with an increased translation of mRNAs encoding oncoproteins (IGF-1R and C-Myc), known to favour tumorigenesis. Changes in ribosome composition are promoted by increased expression of Fibrillarin (FBL), a gene involved in regulating RNA pol I activity, ribosome biogenesis and rRNA methylation. We showed that FBL over-expression promotes chemotherapy resistance of breast cancer cell lines (34). Moreover, FBL is over-expressed in squamous cell cervical carcinoma (35) and in breast cancer (34). In addition, JJ Diaz team showed high FBL expression is associated with poor recurrence-free survival of breast cancer.

It has been reported that therapeutic effects of numerous clinically approved chemotherapeutic drugs are, at least in part, mediated by disruption of ribosome biogenesis (34, 35). A systematic analysis of 36 commonly used chemotherapeutic drugs on ribosome biogenesis indeed revealed that 20 of these drugs inhibit ribosome biogenesis at low IC50, however at different specific steps (transcription and early or late processing) (36). Since then, several agents have been developed to specifically target translational machinery for cancer therapy. The most advanced one corresponds to mTOR inhibitors, whose mechanisms of action mainly lay on inhibition of translation (37). In addition, two breakthrough studies recently demonstrated that inhibiting ribosome biogenesis by targeting RNA Pol I activity is an efficient and selective anti-cancer strategy (38, 39). A phase I clinical trial with CX-5461, an RNA polymerase I inhibitor, is currently ongoing in patients with advanced haematologic malignancies (http://www.australiancancertrials.gov.au/search-clinical trials/search-results/clinical-trials details.aspx?TrialID=364713&ds=1).

Since production of ribosomes is a high energy-consuming task, ribosome biogenesis is tightly regulated by nutrient-sensing and mitogenic pathways in order to adapt the pool of ribosomes to cell's needs. Most of these pathways are altered in cancer and contribute to the elevation of ribosome biogenesis in tumors. In particular, RAS/MAPK/Erk and PI3K/Akt/mTOR are key signalling pathways regulating ribosome biogenesis during rRNA synthesis, processing and modification.
PI3K/AKT/mTOR signalling pathway regulates the RNA Polymerases producing all 4 rRNA species (40-43). First, RNA Pol I activity is up-regulated by PI3K/AKT/mTOR pathway signalling through increase expression of UBF or phosphorylation of UBF leading to their active forms. Second, PI3K/AKT/mTOR promotes RNA PolIII activity by phosphorylating BrfI involved in TF-IIIB complex. Interestingly, Akt is a negative regulator of the tumour suppressor protein p53, a major regulator of ribosome biogenesis. In addition to control RNA Pol I activity, we have recently showed that p53 is a direct regulator of rRNA methylation through regulating FBL expression (34).

It is now recognized that cancer cells display a "ribosome addiction" similar to that of "oncogene addiction" (44) which results in part from the abnormal activation of mTOR pathway. We propose to complement the trial with a ribosome-focused ancillary study to evaluate the activity and quality of ribosome biogenesis in response to the mTORC1/2 inhibitor AZD2014 associated or not with anastrozole.

13.1.2 Biosample collection

Collection of biosamples during on-treatment period is critical for assessing drug effect and is **mandatory** for all study participants.

Type of Biological samples	Timing of collection	Details
Tumor samples	Pre-treatment: at Screening	Archival FFPE material will be collected ideally surgery specimen. If not available and if feasible and accessible, a screening biopsy may be collected with patient consent within 14 days before W1D1 dosing.
	On-treatment : • At Week 8 • At time of relapse	Such biopsy should be conducted when feasible and accessible and upon patient consent. Collection of tumor biopsies will be guided by ultrasound or CT scan (see Laboratory Manual for further details on tumor sample collection and storage).
Blood samples	***PD samples*** • Week 1 Day 1 pre-dose • Week 8 Day 1 pre-dose • At time or relapse	2*5mL (1 EDTA and 1 w/o EDTA) for plasma/serum isolation

13.1.3 Objective and Type of analysis

Objective 1 - To identify predictors of response/resistance and to evaluate the PD activity of the AZD2014+anastrozole combination therapy	
Tasks	**Required biospecimens** **Analytical methods,** *Platform involved*
Assessment of mutational status of frequently altered genes in endometrial cancers (PTEN, PI3KCA, PI3KR1, KRAS, P53, CTNNB1 (beta-catenin), AKT1, AKT2, TSC1, TSC2, pRB, EGFR, p14ARF (CDKN2A), FGFR2, ARID1A & POLE)	DNA extracted from archival FFPE pre-treatment tumor samples: DNA sequencing using NGS Ion Torrent, specific NGS bioassays, *Genomic platform, Centre Léon Bérard,(Qing Wang, PhD*)
Assessment of the expression /phosphorylation status of PI3K/Akt/mTOR pathway components [pS6 (S235/236), p4E-BP1 (T37/46)], mTORC2 inhibition [pAKT (S473 and T308)], PTEN, beta-catenin, phosphorylation state of FKHRL1, PRAS40, p70S6K)	Pre and on-treatment (W8) tumor sample (i.e. Archival FFPE pre-treatment tumor sample and fresh biopsy performed 8 weeks after treatment start) Immunohistochemistry, T*ranslational research platform, Centre Léon Bérard (Isabelle Treilleux*):

Objective 2 - To assess the activity and quality of ribosome biogenesis before and under treatment with AZD2014, +/- anastrozole	
Tasks	**Required biospecimens** **Analytical methods,** *Platform involved*
2.1 To evaluate the expression of key markers of ribosome biogenesis (fibrillarin, nucleolin, B23, UBF and phosphorylated UBF)	Tissu Macroarrays from pre (baseline) and on-treatment (W8)Tumor sample Immunohistochemistry, *JJ Diaz Lab / I Treilleux, Centre Léon Bérard*
2.2 To assess the accumulation of the 47S precursor rRNA, which reflects RNA PolI activity	Pre and on-treatment (W8) FFPE tumor samples Fluorescent in situ hybridization (FISH) *(JJ Diaz Lab, Centre Léon Bérard)*
2.3 To assess the expression of components of rRNA methylation complex	mRNA samples from FFPE pre and on-treatment (W8) tumor samples High-through put real time PCR and IHC for fibrillarin, Nop56, Nop58, and NHP2L1 Original method based on RT-qPCR) *(JJ Diaz Lab, Centre Léon Bérard*
2.4 To define the rRNA methylation status, using a subset of sites located in functional regions of ribosomes (18S-27, 18S-627 and 18S-1490 in DC)	
2.5 To perform the detection of components of rRNA methylation in patients' blood samples	Blood samples pre-treatment and 8 weeks after treatment initiation ELISA: fibrillarin (circulating anti-FBL autoantibody) on serum (500µL) *(JJ Diaz Lab, Centre Léon Bérard)*

13.2 Tracking circulating DNA to monitor treatment response (Frenel JS Lab)

13.2.1 Rationale

Circulating tumor DNA (ctDNA) isolated from blood of cancer patients is a double-stranded DNA molecule, naked and fragmented. It is released into the plasma by necrotic or apoptotic tumor cells and represents an alternative source of tumor DNA, easily accessible and assessable repeatedly. Such "liquid biopsy" can characterize real-time tumor genetic profile and its evolution during the natural evolution of the disease (45).
Proof-of-concept studies have shown that sequencing ctDNA can reveal important information on tumor-related genetic alterations relevant to oncogenesis and cancer progression, tumor heterogeneity, and mechanisms of response and resistance to therapy for a given patient (45-47). Of relevance, the EMA has recently authorized the prescription of gefitinib, an EGFR inhibitor, based on the detection of EGFR mutations in the cDNA of patients whose tumor is not analyzable. Very recently, Fresnel et al. have shown in a population of phase I trial patients that the molecular changes at ctDNA mutation level during targeted therapies were associated with time to disease progression by RECIST criteria (48).

13.2.2 Biosamples collection

Collection of biosamples during on-treatment period is critical for assessing drug effect and is mandatory for all study participants.

Type of Biological samples	Timing of collection	Details
Blood samples	• Week 1 Day 1 pre-dose • Week 4 Day 1 pre-dose • Week 8 Day 1 pre-dose • EOT and/or At time or relapse	2*8mL EDTA per timepoint for immediate freezing and subsequent ctDNA isolation for molecular analyses

13.2.3 Objective and type of analysis

The objectives of this translational part are

- To follow the evolution of the mutations identified in circulating tumoral DNA (ctDNA) and to evaluate the correltation with efficacy endpoints.
- To compare the type of mutations identified before study drug initiation and at time of relapse using ctDNA.

Following cDNA extraction from plasma using the QUIAGENTM kit, cDNA will be quantified using the Quant-iT™ Pico-Green® double-stranded DNA (dsDNA) Assay Kit (Invitrogen, Carlsbad, CA) and SynergyHT microplate reader (Biotek). A panel of genes of interest (including at least TP53, PIK3CA, FBXW7, PP2RI1, PIK3R1, CDH4, PTEN, CTNNB1, ARID1A, KRAS, FGFR2, ESR1, 30kb) will be set up using the Webinterface : https://www.ampliseq.com/browse.action. A IonTorrent PGM platfrom will be used. A digital

PCR platform will be used to follow the mutation over time during the treatment period (Quantstudio®).

13.3 PK analysis of AZD2014

The following blood samples will be withdrawn for patients randomized in Arm A in order to analyse the PK parameters of AZD2014 in collaboration with AstraZeneca.

Type of Biological samples	Timing of collection	Details
Blood samples	Week 1 Day 1: pre-dose, 2h and 6-8 hours later Week 2 Day 1: pre-dose, 2h and 6-8 hours later	4mL K_2EDTA See Appendix 08

13.4 Impact of the treatment with AZD2014 on circulating NK cell phenotype and function.

The Centre International de Recherche en Infectiologie (CIRI, INSERM U1111 – CNRS UMR5308) study the role of the mTOR pathway in Natural Killer cells. These innate immune cells take part in the anti-tumoral response, displaying in particular strong anti-metastatic activity. Using a murine model, the CIRI recently demonstrated that mTOR activity is tightly correlated to NK cell anti-tumoral activity (Marçais et al, Elife 2017). In addition, the CIRI obtained preliminary data showing that treatment of breast cancer patients with an inhibitor of mTORC1 affects circulating NK cell differentiation and functions.
The CIRI now would like to test the impact of the treatment with AZD2014, an inhibitor of both mTORC1 and mTORC2, on circulating NK cell phenotype and function. To this aim, they would need 10ml of fresh blood collected on EDTA tubes before (Baseline) and 8 weeks after the beginning of the treatment. The CIRI will perform ficoll separation to obtain PBMCs on which they will perform their tests. They will first perform an in depth phenotyping of the NK cell population using multi-parametric flow cytometry (>20 parameters measured). This will be coupled and correlated to the measure of the basal activity of the mTOR pathway in these cells using phospho-flow cytometry (pS6, pAkt S473, pSTAT5) as well as the measure of NK cell effector functions following stimulation (2 stimulation types, 4 readouts).

Type of Biological samples	Timing of collection	Details
Blood samples	Week 1 Day 1: pre-dose Week 8 Day 1: pre-dose	2 * 5 ml EDTA tubes immediately send to the CIRI :Antoine Marçais, Centre International de Recherche en Infectiologie (CIRI), Lyon

XIV. TRIAL ORGANIZATION AND COMMITEES

14.1 Sponsor

The Centre Leon Berard is the Sponsor for this study.

14.2 Data monitoring committee (DMC)

The DMC will be constituted by the sponsor and will be composed of statisticians and clinical experts. This committee will review each event that could modify the benefit risk ratio. Results of the planned interim analysis for efficacy will be discussed by the DMC as well to provide recommendations to the sponsor and to the steering committee. Additional meetings may be organized at any time if an event occurs or on members' request.

14.3 Steering committee

The Steering committee will be composed of the coordinating investigator and representatives of the coordinating center. The Steering Committee has primary responsibility for the general organization of the trial and makes any major decision recommended by the DMC. Meetings are scheduled every 4 months from the beginning of the trial. Additional meetings may be called at any time on request by one or more members.

On an ongoing basis, the Steering Committee will review all SAE/SUSAR, Severe toxicities and related Grade ≥ 3 AEs as well as:

- Potential amendment
- Results of interim safety analyses
- Study continuation and possibility to recruit additional patients (increase of the required sample size) in case a lot of patients will be non-evaluable before the primary endpoint evaluation.

The Steering committee is also empowered to propose the inclusion (or non-inclusion) of any participating center. It will be regularly informed of the accrual rate of inclusion and of any emergent problems and will review the activity and safety data at the end of the study.

14.4 Imaging Review committee

The central review committee, composed of radiologists from Centre Léon Bérard, will review each radiological tumor assessment from baseline to disease progression on a timely manner.

XV. DATA COLLECTION & MANAGEMENT

The study will be coordinated by the coordinating center of Leon Berard Cancer Center in France (DRCI of Centre Leon Berard).

15.1 Site Set-up

All sites will be required to sign appropriate contracts with the Sponsor prior to participation. In addition all participating Investigators will be asked to sign the necessary agreements and supply a current CV with evidence of recent GCP training to the Sponsor. All members of the site research team will also be required to sign a Site Signature and Delegation Log which lists the range of duties that have been delegated to them for the trial. This should be counter-signed by the Principal Investigator and returned to the Sponsor.

Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, AE reporting, collection and reporting of data, and record keeping.

Sites will be provided with an Investigator Master File and a Pharmacy File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The Sponsor must be informed immediately of any change in the site research team.

15.2 Data entry and data management

All the data concerning the patients will be recorded in the eCRF throughout the study. SAE reporting will be also paper-based by e-mail and/or Fax.

Data entry will be performed online by investigators and authorised staff based on source documents and signed electronically by the principal investigator. The investigator is responsible to ensure accuracy, completeness and timeliness of the data reported in the eCRFs.

An audit trail will record all the initial data entries and the changes made (reason for change, time and date of entry and change; user name of person who made entry and change). A patient file will be validated after no more inconsistency is detected by the program.

The database will be locked after all queries are solved, and after data review and final validation (blind-review meeting).

15.3 Study monitoring

The sponsor will perform the study monitoring and will help the investigators to conduct the study in compliance with the clinical trial protocol, Good Clinical Practices (GCP) and local law requirements.

At regular intervals during the clinical trial, the investigational site will be contacted, through monitoring visits, by a representative of the coordinating center (i.e. the study monitor) to review study progress, Investigator and patient compliance with clinical trial protocol, and any emergent problems. These monitoring visits could include, but not be limited, to review of the following aspects: patient informed consent, patient recruitment and follow-up, Serious Adverse Event documentation and reporting, Critical events documentation and reporting, AE documentation, investigational product allocation, patient compliance with the study treatments, investigational product accountability, concomitant therapy use and quality of data. It is the responsibility of the Investigator to maintain adequate and accurate eCRFs for each enrolled patients.

All staff, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information.

The study monitor will ask the investigator to modify any erronate, forgotten or unclear data. All the modifications will be explained (if necessary), dated and signed. If the data are modified by another person than the investigator, the authorisation of this person will be documented.

A monitoring report will be written on each visit. This will document the progress of the clinical trial and give an account of all emergent problems.

15.4 Audit and inspections

For the purpose of ensuring compliance with the Clinical Trial Protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that auditors/inspectors are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

XVI. ETHICAL AND REGULATORY ASPECTS

16.1 Ethical principles

This Clinical Trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for Good Clinical Practice (GCP). Those Investigators participating as leaders in this trial, including National Coordinators, will receive compensation for their time but will receive no financial profit from their activities related to the trial.

16.2 Laws and regulations

This Clinical Trial will be conducted in compliance with French and European laws and regulations, as well as any applicable guidelines. The trial will be registered on www.clintrials.gov and on other sites, as appropriate.

16.3 Informed consent

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial, including the written information given approval/favorable opinion by the Institutional Review Board/Ethics Committee (IRB/EC).

Prior to a patient's participation in the clinical trial, the written Informed Consent Form should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.

16.4 Data protection

Personal data will be collected and processed in accordance with Regulation (EC) No 45/2001 and national data protection legislation implementing Regulation (EU) 2016/679 (General Data Protection Regulation).

The Coordinating center (DRCI, Leon Berard Cancer Center) committed to the Commission Nationale de l'Informatique et des Libertés (CNIL) to comply to the reference methodology 1 (*Méthodologie de Référence MR-001*): statement registered under #1994173 the 27/09/2016.

The personal data processing from this clinical trial falls within the scope of the MR-001.

Arrangements to comply with the applicable rules on the protection of personal data are implemented by the Sponsor and coordinating center, including but not limited to:

- Personal data are collected and processed for the sole purpose of this clinical trial;
- Contracts signed between sites, Investigators and Sponsor include clauses on personal data protection;
- Patients will be identified by a code number and their initials excluding any directly identifying personal data. The matching list is kept on the site by the Investigator;

- All the data concerning the patients will be recorded in the eCRF throughout the study. Data entry will be performed online by Investigators and authorised staff only. Access to the eCRF is protected with personal access codes;
- Access to the personal data, under Sponsor's responsibility and within the legal frame, is restricted to the Sponsor and persons acting on its behalf, Investigators and their team as well as persons in charge of quality assurance and Sponsor's study monitors under required conditions;
- Consent for the future use of the data collected in the course of this study for research programs in the scientific field is also sought. Patients will be informed that such consent can be rescinded and they can exercise their right to oppose at any time
- Patients will be fully informed in the ICF on the study related personal data colleting and processing (nature, purpose, data recipients, use of already collected data in case of study exclusion or withdrawal of consent), their right of access, rectification, erasure, restriction of processing data, data portability and opposition. The Investigator is the contact person on those matters.
- According to GDPR, patients can also contact the Data Protection Officer (DPO) of Centre Léon Bérard in order to obtain information concerning their data processing during the study course. The DPO can be contacted using the following email address: dpd@lyon.unicancer.fr.
- In case the patient is not satisfied by the reply provided, she can contact the CNIL using the following link: https://www.cnil.fr/.
- If the patient retrieves his/her consent, the data and results obtained before the consent withdrawal will be kept in the database and analyzed. No further data will be collected.

16.5 Biological samples collection, storage and furture use

Biological samples from clinical trial subjects will be collected, stored and used in the future in compliance with the applicable rules, including but not limited to:

- Contracts signed between sites, Investigators and Sponsor include clauses on collection, storage and future use of biological samples from clinical trial subjects,
- Only qualified personnel will perform the collection in compliance with the protocol and specific study procedures detailed in the Lab book,
- Biological samples will be analyzed and stored in approved laboratories; traceability will be insured,
- Patients will be fully informed in the ICF on the study related biological samples collection (nature, purpose, recipients, use of already collected samples in case of study exclusion or withdrawal of consent) and a specific consent for the future use of those samples for research programs in the same field is also sought; they will be informed that such consent can be rescinded at any time.

16.6 Institutional Review Board/Independent Ethics Committee (IRB/EC)

The Clinical Trial Protocol will be submitted to the appropriate IRB/EC. The Clinical Trial (study number, Clinical Trial Protocol title and version number), the documents reviewed (Clinical Trial Protocol, Informed Consent Form, Investigator's Brochure, Investigator's CV, etc.) and the date of the review should be clearly stated on the written IRB/EC approval/favorable opinion.
During the Clinical Trial, any amendment or modification to the Clinical Trial Protocol should be submitted to the IRB/EC. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the Clinical Trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the IRB/EC.

16.7 Responsibilities of the sponsor

The Sponsor is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Clinical Trial Protocol as regards of ethics, Clinical Trial Protocol compliance, and integrity and validity of the data recorded on the eCRFs.
The responsibilities of the Sponsor are:

- To subscribe an insurance
- To register the trial and get an EudraCT number
- To submit the protocol to the Ethic Committee and Competent Authority and to inform them of any changes in the conduct of the study using written amendment form
- To send to investigators all information necessary to the research
- To declare to EMA (Eudravigilance database), Competent Authority, EC/IRB and principal investigators any suspected unexpected serious adverse reaction (SUSAR)
- To communicate the annual security report (DSUR) and the final report of the study to the Competent Authority, EC/IRB and to principal investigators
- To store study main documents during the minimal length as defined by the Good Clinical Practices, i.e. 15 years after the end of the research.

16.8 Responsibilities of the investigator

The Investigator is required to ensure compliance with all procedures required by the Clinical Trial Protocol, data collection and, more generally, Good Clinical Practices.
Under his responsibility, clinical research technicians provide administrative and logistic support to the study; assist in the auditing of source records and the documentation of CRFs.
The responsibilities of the Principal investigator are:

- To send his/her and others investigators' signed CV to the sponsor
- To identify Sub-Investigators to assist in the conduct of the Clinical Trial in accordance with the Clinical Trial Protocol and to define their responsibilities. All Sub-Investigators shall be appointed and listed in a timely manner.
- To perform patient recruitment after sponsor authorization,
- The responsibilities of all Investigators are:
    - To collect written informed consent form before enrolment of patients
    - To make sure of clinical trial protocol compliance, data collection and, more generally, GCP compliance
    - To complete CRF for each enrolled patient, to validate collected data in the eCRFs and if necessary to date, correct and sign DCF (Data Clarification Form).
    - To transmit the CRFs to the coordinating centre at the end of study

- To notify immediately any SAEs to the sponsor (contact: Ms A. Millaret)
- To accept potential visits of control by inspectors mandated by the sponsor or the competent authority
- To make sure that patients anonymity and confidentiality is respected
- To store data and identification of enrolled patients in accordance with current legislation, for a minimal length of 15 years after the end of the study

16.9 Confidentiality

All information disclosed or provided by the Sponsor, or produced during the Clinical Trial, including, but not limited to, the Clinical Trial Protocol, the CRFs, and the results obtained during the course of the Clinical Trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

The submission of the Clinical Trial Protocol and other necessary documentation to the Ethics Committee and/or competent authority is mandatory but the EC/CA members have the same obligation of confidentiality.
The Investigator and the Sub-Investigators shall use the information solely for the purposes of this Clinical Trial, to the exclusion of any use for their own or for a third party's account.
Furthermore, the Investigator and the Sponsor agree to adhere to the principles of personal data confidentiality in relation to the patients, Investigator and its collaborators involved in the study.

16.10 Property rights

All information and documents provided by the sponsor, as well as all the results/data which arise directly or indirectly from the clinical trial are the sole and exclusive property of the sponsor. The investigator shall not mention any information or the product in any application for a patent or for any other intellectual property rights.

16.11 Protocol amendments

Any modification of the protocol has to be agreed by the coordinating investigator and the sponsor in the form of a written amendment.
Any amendment which modifies significantly the patient's security, the objectives of the study or its scientific quality requires written approval/favourable opinion by CA/IRB/EC prior to its implementation unless there are overriding safety reasons.
In some instances, an amendment may require a change to the Informed Consent Form. The Investigator must receive a IRB/EC approval/favourable opinion concerning the revised Informed Consent Form prior to implementation of the change and patient’s signature should be collected again if necessary.

16.12 Insurance

The sponsor has subscribed an insurance policy in compliance with local laws covering its responsibility for all the participants for any injury that might be caused by the clinical trial. The insurance of the Sponsor does not relieve the Investigator and the collaborators from maintaining their own liability insurance policy.

XVII. REPORTING AND PUBLICATIONS

A clinical study report will be prepared under the responsibility and according to the standards of the sponsor, provided that all CRFs have been completed. It will include the study objectives, the methodology, statistical analysis and raw data listings, and the conclusions of the study. It will also include all the list of AE that occurred during the study and data concerning all the patients included in the study. It will be submitted to the coordinating investigator for review and signature. The clinical study report will be prepared and will be available for health authorities within one year after the end of the study.

The manuscript of the publication will be prepared within the 6 months following the publication of the final clinical study report by the principal investigator, or upon agreement.

Investigators are informed that the sponsor reserves all rights to data generated from this study. Written approval from the sponsor must be obtained prior to any publication or presentation of data from this study.

The sponsor is not allowed to use investigator's name in any publication without a prior written consent. The investigator is not allowed to use sponsor's name in any publication without a prior written consent.

The principal investigator agrees to publish the results. No publication can be done without the principal investigator and the Sponsor approval; the funding source will be mentioned in the acknowledgments section. The final decision for the publication of the study will be taken by the principal investigator, statisticians and the sponsor.

Any publication or communication (oral or written) will be defined by mutual agreement between the investigators according to international guidelines (http://www.icmje.org/). All the authors who participated actively to the conception of the study, its development and writing of results will be cited, i.e.:

- The principal investigator, the co-investigator, and all investigators who have included and followed patients. The order of citation will be established according to the number of inclusions in the study.
- The contributors of the coordinating centre team (DRCI-SponsorShip Unit) who participated in the drafting of the protocol and the statistical analysis of the study.
- The Centre Léon Bérard will be cited as Sponsor of the study.
- Specific publication policies with the funding source and AstraZeneca are specified in the Clinical trial Agreements.

APPENDICES

APPENDIX 1 - ECOG Performance Status

Patients will be graded according to the ECOG Performance Status scale and criteria as described below:

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50 % of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5: 649-655, 1982

APPENDIX 2 - RECIST 1.1

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228-47 (http://www.eortc.be/recist/documents/RECISTGuidelines.pdf

Bogaerts J, Ford R, Sargent D, et al. Individual patient data analysis to assess modifications to the RECIST criteria. *Eur J Cancer* 2009;45:248-60

APPENDIX 3 - Creatinine Clearance

Formule MDRD (Modification of the Diet in Renal Disease) (Levvey, 2000)

$186.3 \times (\text{créatininémie en µmol/L} / 88.4)^{-1.154} \times \text{âge}^{-0.203}$ (x 0,742 si sexe féminin)

Formule de Cockroft & Gault (1976)

[(140 - âge) x poids / créatininémie en µmol/L)] x k (avec k = 1,04 chez la femme).

La formule de Cockroft est de moins en moins utilisée compte-tenu de son inexactitude chez les sujets âgés et les sujets en surpoids notamment. Par exemple, chez le sujet âgé, cette formule sous-estime la fonction rénale, pouvant conclure à tort au diagnostic d'insuffisance rénale.

APPENDIX 4 - National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE)

Refer to NCI CTC AE v.4.0 online at the following NCI website:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_v40.

Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.

When 2 criteria are available for similar toxicities, the one resulting in the more severe grade should be used.

The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.

An accurate baseline prior to therapy is essential.

Common Terminology Criteria for Adverse Events v4.0
(Publish Date June 14, 2010)

APPENDIX 5 - Restricted CYP and transporter related co-medications

Before study start use **potent or moderate inhibitors or inducers of CYP3A4/5, CYP2C8, Pgp (MDR1) and BCRP or the drug transporters Pgp (MDR1) and BCRP** is not permitted within the appropriate wash-out periods before the first dose of study treatment until at least after Cycle 1
.
Examples of such substances are shown in below in Table 5.1, Table 5.2, Table 5.3 and Table 5.4.

The appropriate wash-out periods for each CYP and transporter enzyme inhibitor or inducer are indicated in Table 5.1 and Table 5.2. For the sensitive or narrow therapeutic range substrates indicated in Table 5.3 and Table 5.4 the appropriate wash-out period is a minimum of 5 x reported half-life.

S**hort term administration** of such substances **during a study** may be permitted after the end of Cycle 1 under the following circumstances:

- If a patient requires short-term administration of a drug that is a potent or moderate **CYP3A4/5, Pgp (MDR1) or BCRP nhibitor** (see Table 5.1) this could be permitted but may increase exposure to study drug which must be withheld for 3 days prior to the first dose and not restarted until at least the concomitant therapy has been discontinued and the appropriate washout period has elapsed.

- If a patient requires short-term administration of a drug that is a potent or moderate **CYP3A4/5, Pgp (MDR1) or BCRP inducer** (see Table 5.2) this could be permitted but could lead to lower levels of study drug and a potential reduction in clinical efficacy

- If a patient requires short term administration of restricted **substrates of OATP1B1, OATP1B3, MATE 1 or MATE2K** AZD2014 should be withheld for 3 days prior to the first dose and not restarted until the concomitant therapy has been discontinued and the appropriate washout period (at least 5 x elimination half-life) has elapsed.

The lists of CYP and transporter inhibitors, inducers and substrates are not exhaustive and the absence of a drug from these lists does not imply that its combination with AZD2014 is safe.

Information on any treatment in the 4 weeks prior to starting study treatment and all concomitant treatments given during the study with reasons for the treatment should be recorded. If medically feasible, patients taking regular medication, with the exception of potent or moderate inhibitors or inducers of CYP3A4/5, Pgp (MDR1) or BCRP should be maintained on it throughout the study period.

Table 5.1 Examples of Cytochrome P450 CYP and transporter inhibitor/inducer restrictions

Transporter Enzymes	Potent or moderate inhibitors / inducers	Minimum wash-out period
CYP3A4/5 Strong competitive inhibitors	grapefruit juice, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, saquinovir, telithromycin, troleandomycin and voriconazole	1 week
CYP3A4/5 Strong time dependent inhibitors	bocepravir, clarithromycin, cobicistat, danoprevir, elvitegravir, LCL161, lopinavir, mibefradil, posaconazole, ritonavir, telaprevir and tipranivir	2 weeks
CYP3A4/5 Strong inhibitors (classification unknown)	Conivaptan	1 week
CYP3A4/5 Moderate competitive inhibitors	amprenavir, aprepitant, atazanavir, cimetidine, cyclosporine, fluconazole, imatinib and netupitant	1 week
CYP3A4/5 Moderate time dependent inhibitors	ACT-178882, casopitant, crizotinib, darunavir, diltiazem, erythromycin, ledipasvir, lomitapide, tofisopam and verapamil	2 weeks
	FK1706	half-life not found
CYP3A4/5 Moderate inhibitors (classification not known)	ciprofloxacin and dronedarone	1 week
	Schisandra sphenanthera	half-life not found
CYP3A4/5 Strong inducers	carbamazepine, phenytoin, rifabutin, rifampicin and St. John's Wort	3 weeks
	enzalutamide and phenobarbital	5 weeks
	mitotane	114 weeks
	avasimibe	half-life not found
CYP3A4/5 Moderate inducers	bosentan, genistein, lersivirine, lopinavir, modafinil, nafcillin, ritonavir, semagacestat, thioridazine and tipranavir	1 week
	etravirine	2 weeks
	efavirenz	3 weeks
	talviraline	half-life not found

Table 5.2 Examples of potent or moderate Pgp (MDR1) and BCRP transporter enzyme inhibitors and inducers

Transporter Enzymes	Potent or moderate inhibitors / inducers	Minimum wash-out period
Pgp (MDR1) inhibitors	dronedarone, erythromycin, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, ritonavir, quinidine and verapamil	1 week
	Vorapawer	10 weeks
	valspodar (PSC 833)	half-life not found
Pgp (MDR1) inducers	Carbamazepine and rifampin	3 weeks
BCRP inhibitors	atazanavir, cyclosporine, lopinavir, ritonavir and tipranavir	1 week
BCRP inducers	none included on reference databases	

- References:
  - University of Washington database
  - Expert Opin. Drug Metab. Toxicol. (2013) 9(6):737-751
- Potent inhibitor (yielding AUC ratio ≥5)
- Moderate inhibitor (yielding AUC ratio ≥ 2 and <5)
- Potent inducers (AUC decreased by ≥ 80% or CL increased by more than 5fold (400%)
- Moderate inducers (AUC decreased by 50 - 80% or CL increased by more than 2-5 fold (100 - 400%)

Table 5.3 Examples of In Vivo Substrates Transporters

Transporters	Sensitive CYP substrates
OATP (1B1 or 3)	bosentan, fexofenadine, glybutride, pitavastatin, pravastatin, **repaglinide**, rosuvastatin, s
MATE (1 or 2K)	Cisplatin

- Substrates in bold type have a narrow therapeutic index
- Reference: Expert Opin. Drug Metab. Toxicol. (2013) 9(6):737-751

APPENDIX 6 - SPC of Arimidex (anastrozole)

The current version is available on the French drug database website:

http://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=62303214&typedoc=R

APPENDIX 7 - Actions required in case of increases in liver biochemistry and evaluation of Hy's Law

7.1- Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.
As per FDA guidance, discontinuation of treatment and further evaluation of drug induced liver injury should be considered if not otherwise explained by underlying malignant disease:

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN **and** (TBL >2xULN **or** INR >1.5)

ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.
The Investigator participates, together with Sponsor clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).
The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

7.2- Definition

Potential Hy's Law (PHL)
Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).
Hy's Law (HL)
AST or ALT ≥ 3x ULN together with TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.
For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

7.3- Identification of Potential Hy's Law (PHL) cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:
• ALT ≥ 3xULN
• AST ≥ 3xULN
• TBL ≥ 2xULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to Sponsor representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

• Notify the Sponsor representative

• Request a repeat of the test (new blood draw) by the central laboratory

• Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

• Determine whether the patient meets PHL criteria (see 7.2 Definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

• Notify the Sponsor representative

• Determine whether the patient meets PHL criteria (see 7.2 Definition) by reviewing laboratory reports from all previous visits

• Promptly enter the laboratory data into the laboratory CRF

7.4- Follow-up

Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

• Inform the Sponsor representative that the patient has not met PHL criteria

• Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

• Notify the Sponsor representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

• Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated

• Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.

• Complete the three Liver CRF Modules as information becomes available

• If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

7.5- Review and assessment of Potential Hy's Law (PHL) cases

The instructions in this Section should be followed for all cases where PHL criteria are met.
No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The Sponsor will be involved in this review together with other subject matter experts as appropriate.
According to the outcome of the review and assessment, the Investigator will follow the instructions below:
If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

• If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF

• If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the IMP:
• Report an SAE (report term 'Hy's Law') according to Protocol processes.

- The 'Medically Important' serious criterion should be used if no other serious criteria apply

- As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

• Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

• Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

APPENDIX 8 - Processing of PK blood samples

Tubes to be used : 8 mL EDTA whole blood for AZD2014 PK-analysis

Sample handling :

To be centrifuged within 30 minutes of collection at 1500g for 10 minutes.

- Plasma should be taken off immediately using a clean transfer pipette and aliquoted into 1 clean, sterile 2 ml cryovial.
- Tubes will be labelled with site name, date, time-point, study day/visit, and patient study number.
- Aliquots should be frozen within 1 hour of collection at -70°C (alternatively -20°C if -70°C not available)

Refer to Lab manual for details.

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