PREOPERATIVE OLAPARIB IN EARLY-STAGE ENDOMETRIAL CANCER (EC): A WINDOW OF OPPORTUNITY TRIAL TO EVALUATE THE PARP INHIBITION EFFECT, TARGETING CELL CYCLE-RELATED PROTEINS (POLEN STUDY)

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BACKGROUND

- Olaparib (AZD2281, KU-0059436) is a poly ADP ribose polymerase (PARP) inhibitor. Previous studies have shown relevant clinical activity as single agent in ovarian, breast and prostate cancers with BRCA1/2 mutations.
- However, little is known about the activity of PARP inhibitors in Endometrial Carcinoma (EC).
- The aim of this study is **to identify pharmacodynamic and pharmacogenetic biomarkers associated with a short term exposure to olaparib** in type I primary EC patients (pts).

TRIAL DESIGN

- Multicenter, single arm, window of opportunity preoperative trial in **women with type I primary EC candidate to primary surgery.**
- Major eligibility criteria are: **(Table 1)**.
  1) pts aged ≥18 years with histologically confirmed type I primary EC;
  2) who have not received prior anticancer therapies for current disease and
  3) adequate organ function and performance status
- Patients receive a **28 days course of olaparib tablets, 300 mg twice daily** before surgery.

- All patients will be followed for 28 days from the last administered study dose **(Table 2)**. Management of olaparib related toxicity and dose modifications are described in **Table 3**. It is recommended that patients who require treatment with inhibitors or inducers of CYP3A4 are not treated within the trial to ensure their safety and the efficacy of olaparib **(Table 4)**.

- The trial uses an exact single stage design. The primary endpoints are the significant inhibition of cyclin D1, Ki67 and active caspase 3 activity in post-treatment against pre-treatment.
- We define significant inhibition in a patient if she shows ≥50% histoscore reduction, with a 95% confidence that it is not due to chance compared to the variation among the baseline values in all the sample. These pts are considered responders.
- The inhibition rate below which the treatment is considered inactive is 5%. The inhibition rate above which the treatment warrants further exploration is 35%; with type I and II errors of 5%, the sample size is 36 pts, with ≥6 pts with significant inhibition as threshold.

- The secondary objectives are summarize in **(Table 5)**. Pharmacokinetic data will be modelled with non-compartmental analysis.
- The study was approved by the IRB from 5 participating sites in Spain **(Figure 1)**.
- Thirteen women have been recruited for the trial since study start on February 2016. The expected end of accrual will be on February 2017 **(Figure 2)**.

Trial registration number: NCT02506816; EudraCT: 2015-001156-30.

Table 1. Selection criteria

A) Inclusion Criteria:			
1.	Women ±18 years with histologically-confirmed type I primary endometrial carcinoma (EC).*	2.	WHO performance status ≤ 2.
3.	Adequate organ and bone narrow function, resolution of all toxic effects of prior therapy or surgical procedures	4.	Signed informed consent, including consent to tissue collection and blood samples as specified by the protocol.

* Diagnosis biopsy must contain 3-12 mg of tumor cellularity/stroma (Tumor: 5-20 mm) and this will be checked in the central laboratory for this trial. If tumor cellularity/stroma is inadequate, one re-biopsy with adequate tumor cellularity/stroma will be mandatory before study entry.

B) Exclusion Criteria:			
1.	Prior anticancer therapies for the current EC.	2.	Patients, who have had a major surgery or significant traumatic injury ≤ 4 weeks of start of study drug.*
3.	Prior treatment with any investigational drug ≤ 4 weeks.	4.	Patients receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent. **
5.	Patients who have received immunization with attenuated live vaccines ≤ 1 week.	6.	Patients who have any severe and/or uncontrolled medical conditions. ***
7.	Patients with an active, bleeding diathesis.	8.	Female patients who are pregnant or breast feeding, or adults of reproductive potential who are not using effective birth control methods.
9.	History of noncompliance to medical regimens.	10.	Patients unwilling to or unable to comply with the protocol.

* Patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia) or patients that may require major surgery during the course of the study must to be also excluded.
** Procedures allowed: corticosteroids with a daily dosage equivalent to prednisone ≤ 20 mg; patients receiving corticosteroids on a stable dosage regimen for a minimum of 4 weeks prior the study entry and topical or inhaled corticosteroids.
*** - Symptomatic congestive heart failure of New York heart Association Class III or IV.
- Unstable angina pectoris, myocardial infarction within 6 months of start of study drug.
- Serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease severely impaired lung function.
- Uncontrolled diabetes as defined by fasting serum glucose >1.5 x ULN Active (acute or chronic).
- Uncontrolled severe infections.

Table 2. Study Schedule

Study Procedures	SCREENING Day (-14) -Day 0	BASELINE Day (-7) -Day 0	THERAPY PERIOD Day 1 – Day 28 (+/-5 days)	SURGERY or TC-biopsy Day 29 (+/-5 days)	FOLLOW UP 28 days after last drug dose
Olaparib treatment		300 mg twice daily			
Clinical and safety (CTCAE v 4.1) assessments		X	D1, D7, D14, D21, D28		X
Imaging assessment		X			
Experimental laboratory (Sampling collection):					
Pharmacokinetic-pharmacodynamic samples***.			D1*, D7, D14, D28 **		
Biopsy of tumor tissues	X			X	

* Before and after 1st dose; ** Before surgery. *** Plasma samples for pharmacokinetic evaluation will be collected from each patient on days 1 (before first dose of olaparib and 1 to 4 hours after the first dose), day 7 (1 to 4 hours after olaparib dose), day 14 (1 to 4 hours after olaparib dose) and the day of surgery (1 to 4 hours before).

Table 3. Summary of dose modifications during the study

Type of event	Adverse reaction	Dose delay or interruption	Dose reduction
Non Hematologic	G3-4	As needed for up to 7 days. If longer, the medical monitor must be informed.	If more interruptions are considered inadequate: 1 dose level reduction Dose reduction schedule: Starting dose: 600 mg/d 1st level: 500 mg/d 2nd level: 400 mg/d 3rd level: Discontinue
	New or worsening pulmonary symptoms	It is recommended the discontinuation of olaparib and to initiate an assessment process.	
Hematologic	G3-4 Anemia G3-4 Neutropenia* G3-4 Leucopenia* G3-4 Febrile neutropenia*	As needed for up to 7 days. If longer, permanently discontinued.	If more interruptions restart with 1 dose level reduction Dose reduction schedule: Starting dose: 600 mg/d 1st level: 500 mg/d 2nd level: 400 mg/d 3rd level: Discontinue
	G3 Thrombocytopenia	Interrupted for up to 7 days	-Restart with 1st level reduction (500 mg/d) -If other episode, permanently discontinued.
	G4 Thrombocytopenia	Permanently discontinued	
Unrelated to toxicity	Any	As short as possible. If olaparib treatment cannot be restart within 7 days the case should be discussed with the medical monitor.	

*Before and after 1st dose; ** Before surgery.

Table 4. Prohibited therapies

Therapies	Prohibited drugs or therapies
CYP3A4	Strong inhibitors: ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir.
	Strong inducers: phenitoyn, rifampicin, rifapentine, rifabutin, carbamazepine, phenobarbital, nevirapine and hypericum perforatum (St. John's wort).
	Moderate inducer: modafenil
Attenuated live vaccines	Not allowed within 1 week before or during olaparib treatment.
Colony stimulating factor granulocyte (G-CSF)	Primary prophylaxis not allowed.
Concomitant antineoplastic therapies	Not allowed.

Table 5. Study objectives and Outcomes

Primary objective:	Primary outcome:
To identify biomarker changes associated to short exposure to olaparib as potential predictors of activity in EC.	The primary endpoints are the significant inhibition of cyclin D1, Ki67 and active caspase 3 activity in post-treatment against pre-treatment.*
Secondary objectives	**Secondary outcomes**
- Pharmacodynamic / Pharmacogenetic:	
• To correlate changes induced by AZD2281 with types of EC and tumour biomarkers. • To estimate predictive value of histological type and tumor biomarkers. • To estimate predictive role of microsatellite instability and PTEN loss in clinical tumor changes and PARP inhibition. • To correlate clinical tumor changes with several targets of PARP inhibition.	• DNA repair: PARP, PARP-1, pHistone 2AX • Mitosis: pHistone 2AX • Angiogenesis (VEGF, HIF-1alpha) • Apoptosis (NFkB p65, p50) • Mutations and deletions (PTEN, MLH-1, MSH-2, MSH-6, PMS-2) • Microsatellity instability
- Pharmacokinetic:	
• To quantify AZD2281 levels in human tissues. • To explore the correlation between intratumoral AZD2281 concentrations with plasma PK parameters and molecular alterations. • To compare intratumoral AZD2281 concentrations with those present in healthy tissues.	• Olaparib blood levels. • Drug tumoral tissue levels on day 28 of the treatment. • Drug healthy tissue levels on day 28 of the treatment.
- Pharmacokinetic-dynamic	
• To further explore the use of Pharmacokinetic-dynamic modelling (PBMC modelling) as surrogate pharmacodynamic marker of AZD2281 activity in endometrial tumors. • To establish a kinetic-dynamic modelling, based on the status of the variables of time (t), concentration (C) in blood and in tissue, and molecular effect (E).	
- Safety:	
• To estimate the tolerability to AZD2281 throughout the study and up to 28 days after the last dose of AZD2281.	• Common terminology criteria for adverse events (CTCAE) v.4

* The activity was measured in terms of histological score: Hscore= 1x(%light staining) + 2x(%moderate staining) + 3x(%strong staining).

Figure 1. Participant cities and sites in Spain

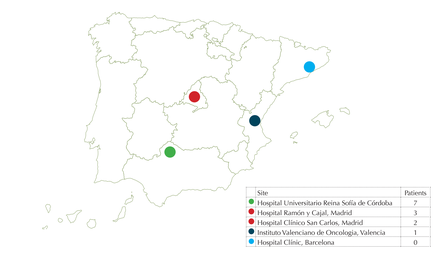
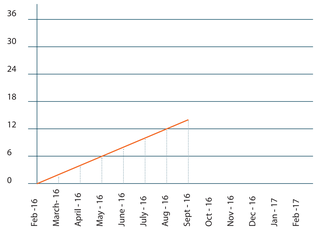


Figure 2. Enrollment evolution on 20/09/2016 (n=13)



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