ATARI TRIAL SUMMARY

PROTOCOL TITLE	ATARI: **AT**r inhibitor in combination with olaparib/durvalumab in gynaecological cancers with **ARI**d1A loss or no loss
TARGET DISEASE	Relapsed gynaecological cancer
STUDY DESIGN	A multi-centre, open-label, multiple two-stage parallel cohorts, phase II clinical trial for relapsed gynaecological cancers
PRIMARY OBJECTIVES	To determine whether ceralasertib has clinical activity as measured by RECIST 1.1 objective response rate as a single agent and in combination with olaparib /durvalumab in patients with ARID1A-deficient ('loss') and no loss relapsed gynaecological cancers
SECONDARY OBJECTIVES	1. To evaluate the disease control rate using RECIST version 1.1 and duration of disease control 2. To evaluate the progression free survival 3. To evaluate the Time to Progression (TTP) 4. To evaluate the proportion of patients free of progression at 6 months 5. To assess the safety and tolerability of ceralasertib as monotherapy and in combination with olaparib/durvalumab in ARID1A loss and no loss relapsed gynaecological cancers 6. To evaluate Overall Survival (OS)
EXPLORATORY OBJECTIVES	• To assess maximum percentage change in the sum of target lesions between baseline and while on treatment and percentage change over time • To evaluate GCIG (CA125) objective response rate in CA125 evaluable ovarian cancer patients • To investigate the correlation between potential tumour and/or circulating biomarkers of clinical activity with ceralasertib monotherapy, and the ceralasertib/olaparib and ceralasertib/durvalumab combination, in gynaecological cancers and objective response rate, disease control rate and progression free survival
TRIAL POPULATION	Patients with relapsed ovarian, endometrial and endometriosis-related clear cell carcinomas (Cohorts 1A-B & 2) or other relapsed gynaecological cancers (endometrioid, carcinosarcoma, cervical carcinoma) (Cohort 3) or relapsed endometrial carcinomas (Cohorts 4 & 5)
RECRUITMENT TARGET	Ten patients will enter each cohort at the corresponding Stage 1. Depending on response rate, up to 19 further patients per cohort may be entered in the corresponding Stage 2. The total number of patients entered to the trial will be min 60 – max 174
TREATMENT REGIMEN	**Cohort 1A:** ARID1A-deficient relapsed ovarian, endometrial and endometriosis-related clear cell carcinomas: • ceralasertib monotherapy: 160mg ceralasertib tablets BD day 1 to day 14, oral administration in a 28 day cycle **Cohort 1B:** (if no activity shown in Cohort 1A) ARID1A-deficient relapsed ovarian and endometrial clear cell carcinomas: • ceralasertib + olaparib: 160mg ceralasertib tablets OD day 1 to day 7 + 300mg olaparib tablets BD, continuous days 1-28, oral administration

	Cohort 2: ARID1A-expressed relapsed ovarian, endometrial and endometriosis-related clear cell carcinomas: • ceralasertib + olaparib: 160mg ceralasertib tablets OD day 1 to day 7 + 300mg olaparib tablets BD, continuous days 1-28, oral administration **Cohort 3:** Other relapsed gynaecological cancers (endometrioid, carcinosarcoma, cervical carcinoma): • ceralasertib + olaparib: 160mg ceralasertib tablets OD day 1 to day 7 + 300mg olaparib tablets BD, continuous days 1-28, oral administration **Cohort 4:** ARID1A-deficient relapsed endometrial cancers (serous, clear cell, endometrioid, carcinosarcoma): 28-day cycle – ceralasertib + durvalumab • 240mg ceralasertib tablets PO BD day 1 to day 7, 1500mg durvalumab IV infusion, once, day 8 **Cohort 5**: ARID1A-expressed relapsed endometrial cancers (serous, clear cell, endometrioid, carcinosarcoma): 28-day cycle – ceralasertib + durvalumab • 240mg ceralasertib tablets PO BD day 1 to day 7, 1500mg durvalumab IV infusion, once, day 8 In all cohorts, continuous treatment until disease progression (assessed by RECIST 1.1), unacceptable toxicity, withdrawal of consent or if the investigator decides it is not in the best interest of the patient to continue. Patients will be assessed by CT scan every 8 weeks with assessment of response by RECIST v1.1.
PRIMARY ENDPOINT	Best overall objective response rate as defined by RECIST version 1.1 for each cohort separately.
SECONDARY ENDPOINTS	1. Disease control rate using RECIST version 1.1 2. Duration of disease control using RECIST version 1.1 3. Progression Free Survival 4. Time to Progression (TTP) 5. Proportion free of progression at 6 months 6. Safety and tolerability, graded according to NCI-CTCAE version 5 7. Overall survival
EXPLORATORY ENDPOINTS	• Maximum percentage change in the sum of target lesions between baseline and while on treatment and percentage change over time • Response rate according to GCIG CA125 criteria in CA125 evaluable ovarian cancer patients • Correlation between potential tumour and/or circulating biomarkers of clinical activity with ceralasertib monotherapy, and the ceralasertib/ olaparib and ceralasertib/durvalumab combination, in gynaecological cancers and objective response rate, disease control rate and progression free survival

FOLLOW UP	Patients will be followed up at thirty days after the last dose of study drug/s for safety and then every three months for survival status (or until withdrawal of consent for further follow up). Patients who discontinued treatment prior to disease progression will be followed up every 8 weeks in the first year and every 12 weeks thereafter until disease progression or commencement of new treatment.

TRIAL SCHEMA

Figure 1: