Phase 1 study of ceratalasertib in combination with AZD5305 in patients with advanced/metastatic ovarian cancer previously treated with PARP inhibitors

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Background

- PARP inhibitors in combination with PARP inhibitors are a standard of care for patients with ovarian cancer and have demonstrated notable efficacy, particularly in patients with BRCA1 or BRCA2 mutation-positive (BRCA2+) or other homologous recombination deficiency (HRD) positive tumours.
- Although many of the patients are initially sensitive to PARP inhibitors, some patients may eventually develop resistance.
- Aneis telangiectasia and RAD-related protein (ATR) is a key enzyme that responds to DNA replication stress, arresting cell cycle progression to allow time for repair of damaged DNA.

- Combination of ATR and PARP inhibitors has shown to overcome resistance to PARP inhibitors in PARP inhibitor-resistant cell lines and patient-derived xenograft (PDx) models.
- Ceratalasertib, a selective and potent ATR inhibitor (Figure 1) in combination with the PARP inhibitor, has demonstrated activity in patients with BRCA1 or BRCA2, PARP inhibitor-resistant ovarian cancer in the CAPRI study (NCT02433424).
- Despite demonstrating encouraging preliminary efficacy in combination with clinicians, the dose and duration of ceratalasertib treatment is limited by haematological toxicity.

- Compared with approved PARP inhibitors, which target both PARP1 and PARP2, AZD5305 in combination with ceratalasertib has demonstrated durability of tumour regression in PDX models of PARP inhibitor-resistant, PARP1 mutation-positive advanced or metastatic breast, prostate, or HRD positive breast and ovarian cancer.
- Furthermore, AZD5305 in combination with ceratalasertib has demonstrated durable tumour regression in PDX models of PARP inhibitor-resistant, breast and ovarian cancer.

Thus, combination treatment with AZD5305 and ceratalasertib may provide a better overall survival.

Compared with approved PARP inhibitors, which target both PARP1 and PARP2, AZD5305 in combination with ceratalasertib has demonstrated durable tumour regression in PDX models of PARP inhibitor-resistant, breast and ovarian cancer.
- The module will include dose-escalation (Part A) and dose-expansion (Part B) cohorts.

• Patients will continue to receive ceratalasertib in combination with AZD5305 as long as they are continuing to show clinical benefit, or until objective disease progression, unacceptable toxicity, withdrawal of consent or another treatment discontinuation criterion is met, at which point both ceratalasertib and AZD5305 treatment will be discontinued.

Figure 2. Study design

Key inclusion criteria
- Age ≥18 years.
- Recurrent platinum-sensitive, high-grade, epithelial ovarian, fallopian tube or primary peritoneal cancer (including serous or endometrioid histology).
- Prior treatment with PARP inhibitors with no intervening chemotherapy between PARP inhibitor treatment and study enrolment.

Key exclusion criteria
- Known hypersensitivity to PARP inhibitors including AZD5305.
- A known hypersensitivity to ceratalasertib or any excipient of the product.
- Prior treatment with PARP inhibitors with no intervening chemotherapy between PARP inhibitor treatment and study enrolment.
- Part B only: Known or suspected mutations (germline or somatic) in BRCA1, BRCA2, PALB2, or ATM.
- Part B only: Known hypersensitivity to PARP inhibitors including AZD5305.

Key exclusion criteria
- A diagnosis of ataxia telangiectasia.
- Prior exposure to an ATR inhibitor.
- A known hypersensitivity to ceratalasertib or any excipient of the product.
- Known hypersensitivity to PARP inhibitors including AZD5305.

Primary objectives
- Part A: Safety and tolerability of ceratalasertib in combination with AZD5305, in order to determine the maximum tolerated dose (MTD) and/or select a recommended Phase 2 dose.

Secondary objectives
- Assess the anti-tumour activity of ceratalasertib in combination with AZD5305 in terms of objective response rate, percentage change in tumour size, duration of response, and progression-free survival according to Response Evaluation Criteria in Solid Tumours v1.1.
- Characterise the pharmacokinetics of ceratalasertib in combination with AZD5305.

Exploratory objectives
- Assess pharmacodynamic biomarker changes which may include functional ATR inhibition, circulating tumour DNA and circulating tumour cells.
- Assess mechanisms of PARP inhibitor resistance.

References: