Title: ATARI trial: ATR inhibitor in combination with olaparib in gynaecological cancers with ARID1A loss or no loss (ENGOT/GYN1/NCRI)

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Abstract

Background

ARID1A loss-of-function mutations have been reported in gynaecological cancers including rarer subtypes such as clear cell. Preclinical studies indicate *ARID1A*-mutant cancers display sensitivity to ATR inhibition whilst tumours without *ARID1A* mutations may be sensitive to ATR inhibitors in combination with PARP inhibitors.

Primary Objective

To determine whether the ATR inhibitor, ceralasertib, has clinical activity as a single agent and in combination with PARP inhibitor, olaparib, in patients with ARID1A-'loss' and 'no loss' clear cell carcinomas and other relapsed gynaecological cancers.

Study Hypothesis

ARID1A-deficient clear cell carcinoma of the ovary or endometrium is sensitive to ATR inhibition, whilst the combination of ATR and PARP inhibition has activity in other gynaecological tumours, irrespective of ARID1A status.

Trial Design

ATARI (ENGOT/GYN1/NCRI) is a multi-centre, international, proof-of-concept, phase II, parallel cohort trial assessing ceralasertib activity as a single agent and in combination with olaparib in ARID1A-stratified gynaecological cancers.

Patients with relapsed ovarian/endometrial clear cell carcinoma with ARID1A loss receive ceralasertib monotherapy (Cohort 1A). Relapsed ovarian/endometrial clear cell carcinoma

patients with no ARID1A loss (Cohort 2) or patients with other histological subtypes (endometrioid, carcinosarcoma, cervical) (Cohort 3) receive combination therapy (olaparib/ceralasertib). Treatment continues until disease progression.

Major Inclusion/Exclusion Criteria

Patients with histologically confirmed recurrent clear cell (ovarian, endometrial or endometriosis-related), endometrioid (ovarian, endometrial or endometriosis-related), cervical (adenocarcinomas or squamous) or carcinosarcomas (ovarian or endometrial) are eligible. Patients progressing after ≥ 1 prior platinum with evidence of measurable (RECIST v1.1) radiological disease progression since last systemic anti-cancer therapy and prior to trial entry are eligible. Previous ATR or PARP inhibitor treatment is not permissible.

Primary Endpoint

Best overall objective response rate (RECIST v1.1).

Sample Size

A minimum of 40 and a maximum of 116.

Estimated Dates for Completing Accrual and Presenting Results

ATARI is open to recruitment in the UK and France, Canadian participation is anticipated.

Trial Registration

NCT0405269

Introduction

Cervical, endometrial and ovarian cancers represent the 4th, 6th and 8th most commonly diagnosed malignancies amongst women globally[1]. Despite high initial response rates to treatment with a combination of surgery and chemotherapy, many patients relapse. The majority of patients that relapse will receive multiple lines of therapy; despite these, diminishing treatment-free intervals are common as is the development of resistant disease indicating a great unmet need amongst these patients.

Ovarian, endometrial and cervical carcinomas have several clinicopathologically distinct histological subtypes with patients diagnosed with recurrent/metastatic clear cell, carcinosarcoma or cervical cancer displaying the worst outcomes. Recurrent/metastatic ovarian clear cell carcinoma (OCCC) and endometrial clear cell carcinomas are associated with a poor prognosis and resistance to standard cytotoxic chemotherapy[2].

To date, a number of therapeutic strategies have been trialled in an attempt to improve the outcomes for women diagnosed with OCCC. the NiCCC (ENGOT-0V36) clinical trial, in which patients with clear cell carcinoma were randomized to receive nintedanib, an oral VEGFR, PDGFR and FGFR inhibitor or standard-of-care chemotherapy, failed to demonstrate a statistically significant progression free survival (PFS) or overall survival (OS) benefit[3]. Another therapeutic avenue of interest is immune checkpoint blockade. Phase II studies of programmed cell death protein 1 (PD-1) and Programmed death-ligand 1 (PD-L1) inhibitors have noted durable responses in patients with clear cell histology[4,5]. The PD-L1 inhibitor pembrolizumab (Keytruda, MSD) in OCCC is currently being evaluated (NCT03425565).

Loss of function mutations in the tumour suppressor gene *ARID1A* (AT-rich interactive domain-containing protein 1A) leading to a loss of protein expression are a frequent observation in both ovarian and endometrial carcinomas of clear cell and endometroid histology (Table 1). ARID1A (AT-rich interactive domain-containing protein 1A) along with its paralog ARID1B are components of the cBAF complex[6]. Loss of ARID1A has been shown to result in aberrant cell cycle control[7]. ARID1A is recruited to double-strand DNA breaks (DSBs) via its interaction with Ataxia telangiectasia and Rad3-related (ATR). Recruitment of ARID1A to DSBs facilitates efficient processing of DNA ends, producing single stranded DNA which becomes coated in replication protein A (RPA) thereby sustaining the DNA damage signal and promoting cycle arrest[8]. A number of novel therapeutic strategies are currently being trialled for ARID1A defective cancers including PARP (poly[ADP-ribose] polymerase) inhibitors (NCT03682289), PI3K (phosphatidylinositol-3-kinase) inhibitors (NCT03842228) and BRD4 (Bromodomain-containing protein 4)(NCT03297424) inhibitors alongside ATR inhibitors (NCT03682289).

ATR is a serine-threonine kinase that plays an essential role in the DNA damage response, detecting single stranded DNA, a common intermediate formed when replication forks stall[9]. Williamson *et al* previously demonstrated that small molecule inhibitors of ATR (ATRi) selectively kill tumour cells with defects in the ARID1A. This novel synthetic lethal effect was evident in OCCC cell lines with naturally occurring endogenous *ARID1A* mutations, tumour cell line xenografts and tumour cell line xenografts derived from *ARID1A* mutant endometrial cancer[10]. Mechanistically, it has been shown that the topoisomerase enzyme, TOP2A, is localised to DNA in an ARID1A-dependent manner and in the absence of ARID1A function, complex chromosomal structures which form during DNA replication which are normally

resolved by TOP2A, fail to be processed prior to mitosis[11]. ATR inhibition in ARID1A defective cells thus activates DNA damage pathways, increases complex chromosomal structures such as anaphase bridges, large scale genomic rearrangements and ultimately causes cell death[10].

The *BRCA*ness phenotype is not a feature of OCCC; tumours of this subtype do not frequently carry mutations in homologous recombination-associated genes, are resistant to platinum-based chemotherapy and lack the genomic scars characteristic of HR-deficiency. Nevertheless, as previously discussed, ARID1A-deficient cancers, such as OCCC display evidence of an impaired DNA damage response and sensitivity to ATRi[10]. *In vitro*, silencing of ATR has been shown to enhance the cytotoxic effect of Poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi)[12]. In part, this synergistic interaction has been attributed to the abrogation of ATR-mediated cell cycle checkpoints in response the DNA-damaging effects of PARPi[13]. Furthermore, ATR inhibition has been shown to overcome PARPi resistance in *BRCA1* and *BRCA2* mutant cancer cells through both impeding BRCA1-independent loading of *RAD51* at DNA double strand breaks and restoring degradation of stalled replication forks[14].

The ATARI clinical trial (ATr Inhibitor in Combination with Olaparib in Gynaecological Cancers with ARId1A Loss or no Loss, NCT04065269) is the first clinical trial which aims to test the hypothesis that ARID1A-defective ovarian and endometrial clear cell carcinomas are more sensitive to ATR inhibition. To date, trials aiming to exploit the specific vulnerabilities of ARID1A-defective tumours, have stratified patients according to their mutation status. However, in ATARI, based on the work by *Khalique et al*, loss of protein expression, as determined by immuno-histochemistry, will be used to stratify patients, followed by retrospective mutation analysis[15]. Building on the pre-clinical data which demonstrates

synergy between ATR and PARP inhibition, the combination will be tested in patients with evidence of ARID1A expression (i.e., assumed to be wild-type for *ARID1A*).

Methods

Trial Design

The ATARI clinical trial is an international, academic-sponsored phase II clinical trial in which patients with ovarian and endometrial clear cell carcinoma, along with other rare gynaecological tumours are treated with the ATRi, ceralasertib (AstraZeneca), with or without the PARPi olaparib (Lynparza, AstraZeneca) (Figure 1).

The intention is to recruit patients from 18 centres in total (up to 6 per country) in the United Kingdom, France and Canada. ATARI is sponsored by The Institute of Cancer Research, with central coordination led by the ICR Clinical Trials & Statistics Unit (ICR-CTSU). International participation is coordinated via ARGACY-GINECO (France) and Princess Margaret Hospital Consortium (PMHC) in Canada.

All patients have histological confirmation of clear cell carcinoma by central review following registration and prior to trial entry. Assessment of ARID1A status occurs centrally via immunohistochemistry using archival or fresh tissue biopsies obtained at registration[15]. Tumours sequenced outside of ATARI, with confirmed ARID1A loss of function mutation may be eligible for trial entry without repeat IHC assessment if testing performed in an appropriate laboratory (GCLP or CLIA accredited).

Cohort 1A patients are those with clear cell carcinomas (ovarian, endometrial or endometriosis-related) and demonstrable ARID1A loss. Cohort 1A patients receive ceralasertib monotherapy (160mg tablets BD days 1-14 in a 28-day cycle). If no activity is observed in this cohort, Cohort 1B will open, with the same patient population receiving ceralasertib plus olaparib in combination (160mg ceralasertib tablets OD days 1-7 and 300mg olaparib tablets BD continuous in a 28-day cycle). Patients with clear cell carcinomas (ovarian, endometrial or endometriosis-related) with no ARID1A loss enter Cohort 2 and patients with other relapsed gynaecological sub-types enter Cohort 3, irrespective of ARID1A status. Both Cohort 2 and Cohort 3 patients receive combination therapy (160mg ceralasertib tablets OD days 1-7 and 300 mg olaparib tablets BD continuous in a 28-day cycle).

Each cohort will recruit patients independently with 10 patients per cohort included in the formal interim analysis at the end of Stage 1. If >1 responses are observed an additional 19 patients will be recruited into the cohort in Stage 2. Cohorts 1A/1B, 2 and 3 will be evaluated separately at Stage 1 and Stage 2.

In all cohorts, trial treatment continues until disease progression, unacceptable toxicity, withdrawal of consent or investigator decision that continued treatment is not in the best interest of the patient. Patients are assessed at D1 of each cycle (safety bloods, toxicity assessment) with additional visits at C1D7, C1D15 and C2D15. Tumour imaging and response assessment occurs every 8 weeks.

The trial is funded by AstraZeneca, with additional support provided by The Lady Garden Foundation, and is endorsed by Cancer Research UK.

Participants

Eligible patients are those with histologically confirmed progressive or recurrent gynaecological carcinomas of the following histological sub-types:

- Clear cell (ovarian, endometrial or endometriosis-related)
- Endometrioid (ovarian, endometrial or endometriosis-related)
- Cervical (adenocarcinomas or squamous)
- Carcinosarcomas (ovarian or endometrial)

Patients who have progressed after ≥1 prior platinum containing regimen are eligible, with evidence of measurable (RECIST v1.1) radiological disease progression since the last systemic anti-cancer therapy and prior to trial entry. Patients previously receiving ATR or PARP inhibitor treatment are excluded.

Trial Objectives and Endpoints

Primary Objective

The primary objective of ATARI is 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 in patients with ARID1A-deficient ('loss') and no loss relapsed gynaecological cancers.

Primary Endpoint

The primary endpoint is best overall objective response rate (complete or partial response) as defined by RECIST version 1.1. All objective responses reported locally will be centrally reviewed to confirm response.

Secondary Objectives

To evaluate:

- Disease control rate (RECIST v1.1) and duration of disease control
- Progression Free Survival (PFS)
- Time to Progression
- Proportion of patients free of progression at 6 months
- Safety and tolerability of ceralasertib as monotherapy and in combination with olaparib in ARID1A loss and no loss relapsed gynaecological cancers
- Overall survival

Exploratory Objectives

- To assess best percentage change in the sum or target lesions between baseline and while on treatment and percentage change over time
- Evaluate GCIG (CA125) objective response rate in CA125 evaluable ovarian cancer patients
- Investigate the correlation between potential tumour and/or circulating biomarkers of clinical activity with ceralasertib monotherapy and the ceralasertib/olaparib combination in gynaecological cancers and objective response rate, disease control rate and PFS

Sample Size

The total number of patients entered into the trial will be a minimum of 40 and a maximum of 116. Each of the parallel cohorts has been designed following an optimal Simon 2-stage design to early discard whether ceralasertib monotherapy or in combination with olaparib shows <10% anti-tumour activity (p=0.01, highest response rate observed in clear cell carcinosarcoma), and powered to show activity over 30% (p1=0.3, clinically meaningful to explore further). Assuming one-sided 5% alpha and 80% power, 10 patients will be recruited into each cohort at Stage 1. If none or 1 responses are observed, recruitment into the cohort will stop and action taken according to Figure 1. If more than 1 response is observed, 19 additional patients will be recruited in the corresponding cohort into Stage 2. If more than 5 responses are observed overall for the specific cohort at the end of Stage 2, it will be considered that the treatment given in that cohort has shown anti-tumour activity of at least 30% and warrants further investigation. If 5 or less responses are observed at the end of Stage 2, action is taken according to Figure 1.

Interim Analysis

The trial is monitored by an Independent Data Monitoring and Steering Committee (IDMSC) who meet every 6 months to oversee the safety of trial participants, monitor data produced by the trial and oversee progress of the trial towards its interim and overall objectives.

The formal interim analysis will be conducted at the end of Stage 1 for each of the stratified cohorts and assessed according to the Simon 2-stage design as described above. Stage 1

analysis will be triggered once the target number of evaluable patients has been achieved and after a minimum follow-up of 16 weeks for the last patient entered into the cohort (unless progression status is known sooner).

The IDMSC will monitor recruitment rate regularly and advise whether halting or pausing recruitment following accrual of 10 patients in each cohort in preparation for interim analysis. If recruitment into one cohort is slow, seamless recruitment into stage 2 would be preferred. Over-recruitment into Stage 2 will be closely monitored; patients who become unevaluable will be replaced.

Statistical Methods

Primary analysis of the primary endpoint and key secondary endpoints for each cohort will be triggered once the target number of evaluable patients have had a minimum follow-up of 24 weeks (unless progression status can be ascertained earlier). Analysis will be presented by stratified cohort.

Best overall response and disease control rates will be summarised by number of cases and proportions, reported with exact 95% confidence intervals (CI). For time to event endpoints Kaplan Meier graphs and median survival time with 95% CI will be presented.

Translational approach

The translational component of ATARI aims to generate data that could help develop how ATR inhibitors are used in the context of clear cell carcinomas and other gynecological cancers. Sequencing of DNA extracted from archival tissue and optional pre-treatment and post-progression biopsies where available, will be performed to investigate genetic determinants of ATR inhibitor response and resistance. Plasma samples will be collected from all patients for the duration of study enrolment in order to evaluate whether biomarkers of ATR inhibitor response can be detected in circulating tumour DNA (ctDNA). Two targeted sequencing panels will be employed to capture known genetic determinants of both ATRi and PARPi resistance in ctDNA.

Discussion

ATARI is the first clinical trial aiming to determine if the preclinical data showing a synthetic lethal interaction between the tumour suppressor gene *ARID1A* and *ATR* translates in to improved outcomes for patients specifically with ovarian and endometrial clear cell carcinoma. The utility of ARID1A protein expression together with mutation status will help determine those patients with functional loss of ARID1A and thus will act as a framework for future clinical trials. The inclusion of the olaparib/ceralasertib combination therapy arm, based on preclinical hypotheses, will investigate whether the two classes of DDR inhibitors have the potential to provide clinical activity worth further exploration. The cohort of non-clear cell, rare gynaecological cancers provides the opportunity to assess the combination of ATR and PARP inhibition in a further cohort of patients with limited treatment options. Results from the translational work within this trial will aid both the validation of known

biomarkers and identify novel biomarkers of ATR inhibitor response and resistance. The results of the ATARI trial will provide the first indication of whether there is clinical activity of ATR inhibitors in clear cell carcinomas and other rare gynaecological cancers according to ARID1A status. These results will help shape future trials and has the potential to change the standard of care in the future for women with rare gynaecological cancers.

Contributors: SB initiated the project, NP and JB contributed statistical input into the study design, RN, SK and CJL provided translational input. AA, KV and JT provided histopathology input and translational support. SB, JS, NP and CT drafted and refined the manuscript. All authors have read and approved the manuscript.

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Ethical Review: This study has been reviewed and approved by the London – South East Research Ethics Committee (19/LO/1082)

367 Table 1. ARID1A mutation and expression in gynaecological cancers

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	ARID1A gene mutation	**ARID1A loss of expression**
Ovarian clear cell carcinoma	35-75% (median 52%)	15 - 75% (median 45%)
Ovarian endometroid carcinoma	30-63% (median 47%)	31 - 55% (median 45%)
Endometrial clear cell carcinoma	17%	20-26% (median 21%)
Endometrial endometroid carcinoma	40-55% (median 46%)	19-34% (median 26%)
Cervical adenocarcinoma	17%	9-31% (median 12%)
Cervical squamous cell carcinoma	7%	7-16% (median 12%)
Endometrial carcinosarcoma	20%	-
Ovarian carcinosarcoma	80%	-

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