ATLAS: A Phase 2, Open-Label Study of Rucaparib in Patients with Locally Advanced (Unresectable) or Metastatic Urothelial Carcinoma

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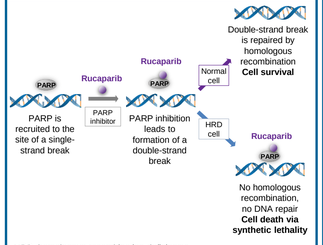
INTRODUCTION

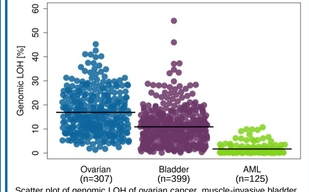
- There are limited treatment options for patients with metastatic urothelial carcinoma who have progressed following treatment with platinum (cisplatin or carboplatin)–based chemotherapy and/or immune checkpoint inhibitor therapy
- Poly(ADP-ribose) polymerase (PARP) inhibitors are approved in ovarian and breast cancer; however, there are limited data on the activity of PARP inhibitors in urothelial cancer
- Nonclinical studies have shown that the PARP inhibitor rucaparib has antitumour activity through a mechanism called synthetic lethality in tumours with homologous recombination (HR) deficiency (HRD) (**Figure 1**)[1–3]
  - Rucaparib also decreased tumour growth in mouse xenograft models of human cancer with or without deficiencies in *BRCA*[4]
- Predictive biomarkers associated with HRD and sensitivity to PARP inhibitors include *BRCA1/2* mutations and tumour genomic loss of heterozygosity (LOH)[5,6]
  - Genomic LOH is a specific type of DNA damage indicative of HRD and sensitivity to PARP inhibitors
- To explore the potential utility of rucaparib in urothelial cancer, The Cancer Genome Atlas[7] muscle-invasive bladder cancer dataset was investigated for genomic evidence of HRD
- Results from the analysis indicated that many urothelial tumours have high genomic LOH (**Figure 2**)
- In the recurrent ovarian cancer setting, both LOH high and LOH low patients benefited from rucaparib treatment[6]
- These data suggest that the PARP inhibitor rucaparib may have activity in patients with locally advanced (unresectable) or metastatic urothelial cancer, unselected for tumour HRD status

Figure 1. Schematic of Rucaparib-Induced Cytotoxicity in Cells with HRD



HRD, homologous recombination deficiency; PARP, poly(ADP-ribose) polymerase.

Figure 2. Genomic LOH in Bladder, Ovarian, and AML Tumours

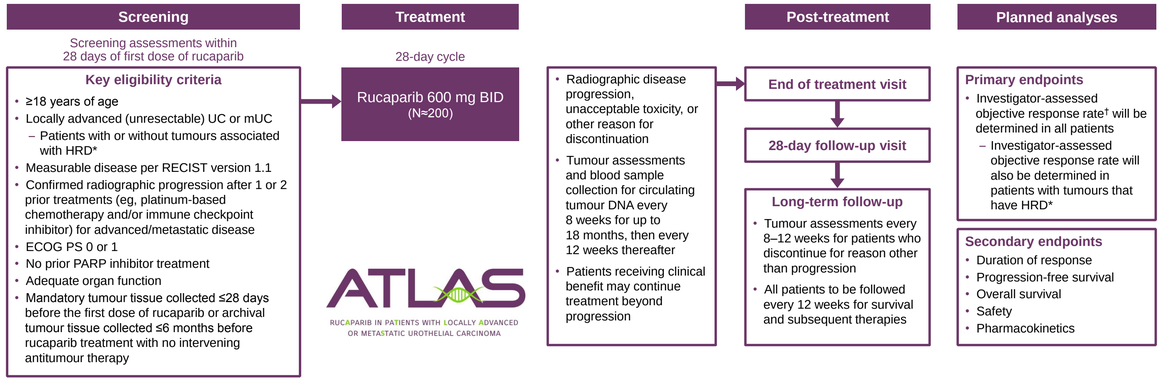


Scatter plot of genomic LOH of ovarian cancer, muscle-invasive bladder cancer, and AML samples evaluable for this analysis from the TCGA† database. Each dot represents an individual tumour sample; horizontal lines represent mean percentage genomic LOH. Data analyses for ovarian cancer and AML, which are associated with high and low percentages of genomic LOH, respectively, are shown for comparison. AML, acute myeloid leukaemia; LOH, loss of heterozygosity; TCGA, The Cancer Genome Atlas.

ATLAS TRIAL OVERVIEW

- ATLAS (CO-338-085; EudraCT 2017-004166-10; NCT03397394) is an international, open-label, phase 2 trial evaluating single-agent rucaparib (600 mg twice daily) as treatment for locally advanced (unresectable) or metastatic urothelial carcinoma previously treated with 1 or 2 anticancer treatments for advanced/metastatic disease (**Figure 3**)[8]
  - **Eligible patients are not required to have tumours associated with HRD because rucaparib may potentially benefit patients with HR-proficient or HR-deficient tumours**
- Approximately 200 patients will be enrolled
  - Two interim analyses are planned after data are available for 60 and 120 patients
- **Primary objective:** to evaluate objective response rate in the intent-to-treat and molecularly defined HRD-positive populations
- **Secondary objectives:** evaluation of duration of response, progression-free survival, overall survival, safety and tolerability, and steady-state pharmacokinetics of rucaparib
- The trial has >90% power to reject the null hypothesis (P=0.10) at a 5% significance level if the true response rate for rucaparib is 20%

Figure 3. ATLAS Trial Schema

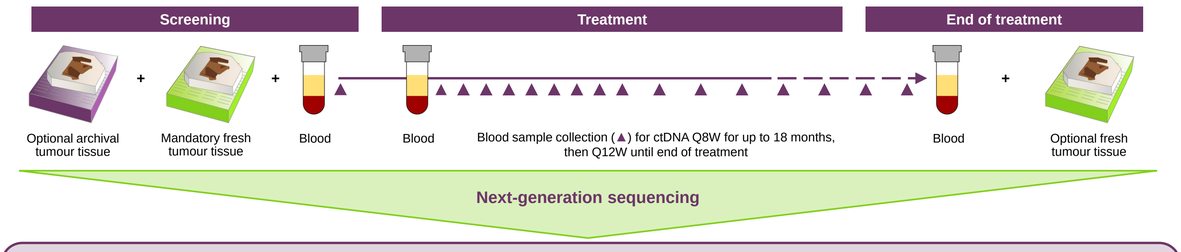


*Tumour HRD status determined by percentage of genomic loss of heterozygosity in a tumour sample before efficacy analysis. †RECIST[9] criteria will be used to document radiographic response.
BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HRD, homologous recombination deficiency; mUC, metastatic urothelial carcinoma; PARP, poly(ADP-ribose) polymerase; RECIST, Response Evaluation Criteria In Solid Tumors; UC, urothelial carcinoma.

BIOMARKER ASSESSMENT

- The ATLAS trial is enrolling biomarker unselected patients, with the goal of identifying and optimising predictive biomarkers of rucaparib sensitivity and resistance (**Figure 4**)
  - Collecting these samples also allows for the comprehensive characterisation of tumour evolution

Figure 4. ATLAS Biomarker Assessments Schedule



Biomarker assessments will explore:

- Effects of prior therapy on tumour and subsequent response to rucaparib
- Correlation of tumour HRD status (determined by percent genomic LOH) with response to rucaparib
- Other tumour biomarkers associated with response and/or resistance to rucaparib
- Changes over time in serially sampled ctDNA that may be associated with response and/or resistance to rucaparib
- Mutant allele frequencies and alterations in genes associated with DNA repair and oncogenic signalling pathways
- Additional genomic, transcriptional, and protein biomarkers will also be evaluated, including TMB, MSI, and PD-L1 expression

ctDNA, circulating tumour DNA; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; MSI, microsatellite instability; PD-L1, programmed death ligand-1; Q8W, every 8 weeks; Q12W, every 12 weeks; TMB, tumour mutational burden.

Tumour Tissue Collection and Analyses

- Tumour tissue samples to be collected:
  - Archival (optional)
  - Screening (mandatory)
  - Treatment discontinuation (optional)
- Tumour tissue samples will be analysed by Foundation Medicine (Cambridge, MA) using the DX1 next-generation sequencing (NGS) assay. The readouts of this assay include:
  - Alterations in a panel of 310 cancer-related genes
  - Genomic LOH
  - Tumour mutational burden (TMB)
  - Microsatellite instability (MSI)
- Tumours will also be evaluated for expression of the immune regulatory protein PD-L1 using the 22C3 (Agilent) and SP142 (Ventana) immunohistochemistry assays at HistoGeneX (Wilrijk, Belgium)

Blood Sample Collection and Analyses

- Blood samples to be collected (mandatory):
  - Screening
  - Every 8 weeks for 18 months, then every 12 weeks until the end of treatment
  - Treatment discontinuation
- Circulating tumour DNA extracted from blood will be profiled by Foundation Medicine using the FoundationACT™ NGS assay, which analyses a panel of 67 cancer-related genes

Results from NGS testing of tumour samples will be made available to the investigators

TRIAL SUMMARY

- The international, open-label, phase 2 trial ATLAS aims to assess the safety and efficacy of single-agent rucaparib in patients with locally advanced (unresectable) or metastatic urothelial carcinoma, irrespective of tumour HRD status, who have progressed after 1 or 2 prior anticancer treatments for advanced/metastatic disease
- The translational research aspects of the ATLAS trial will assess the association between biomarkers and response and resistance to rucaparib
- The target enrolment is 200 patients at ≈65 sites in 6 countries (**Figure 5**)

Figure 5. Countries Participating in ATLAS

France
Germany
Italy
Spain
United Kingdom
United States

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