

# ATLAS: A Phase 2, Open-Label Study of Rucaparib in Patients with Locally Advanced 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 antitumor activity through a mechanism called synthetic lethality in tumors with homologous recombination (HR) deficiency (HRD) (Figure 1)<sup>1-3</sup>
  - Rucaparib also decreased tumor growth in mouse xenograft models of human cancer with or without deficiencies in *BRCA4*
- In multiple tumor types, the presence of HRD and/or genome-wide loss of heterozygosity (LOH; a specific type of DNA damage indicative of HRD) are associated with response to PARP inhibitors, such as rucaparib<sup>5-7</sup>
- To explore the potential utility of rucaparib in urothelial cancer, The Cancer Genome Atlas<sup>8</sup> muscle-invasive bladder cancer dataset was investigated for genomic evidence of HRD
- Results from the analysis indicated that many urothelial tumors have high genomic LOH (Figure 2)
- In the recurrent ovarian cancer setting, both LOH high and LOH low patients benefited from rucaparib treatment<sup>6</sup>
- These data suggest that the PARP inhibitor rucaparib may have activity in patients with locally advanced, unresectable or metastatic urothelial cancer, regardless of tumor HRD status

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

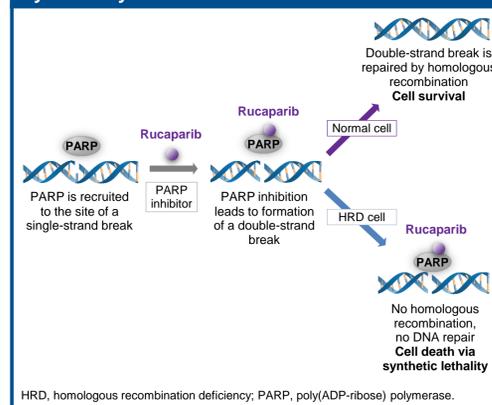
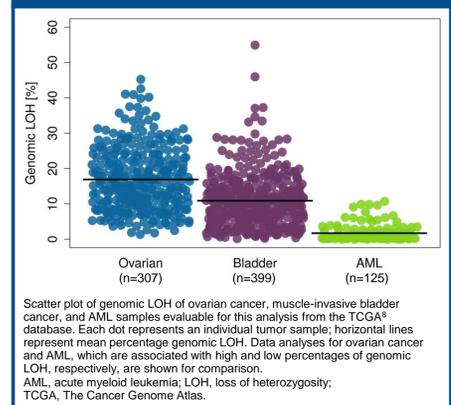


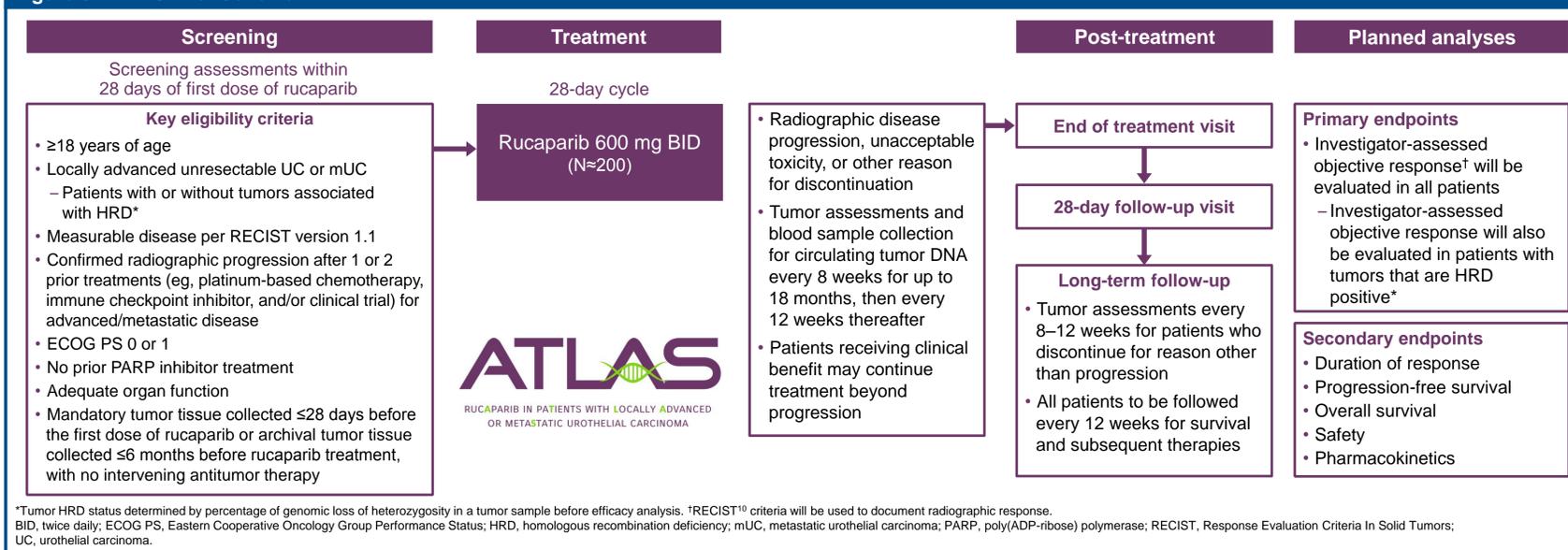
Figure 2. Genomic LOH in Bladder, Ovarian, and AML Tumors



## 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 systemic regimens (Figure 3)<sup>9</sup>
  - Eligible patients are not required to have tumors associated with HRD, because rucaparib may potentially benefit patients with HR-proficient or HR-deficient tumors
- 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 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 one-sided 5% significance level if the true response rate for rucaparib is 20%

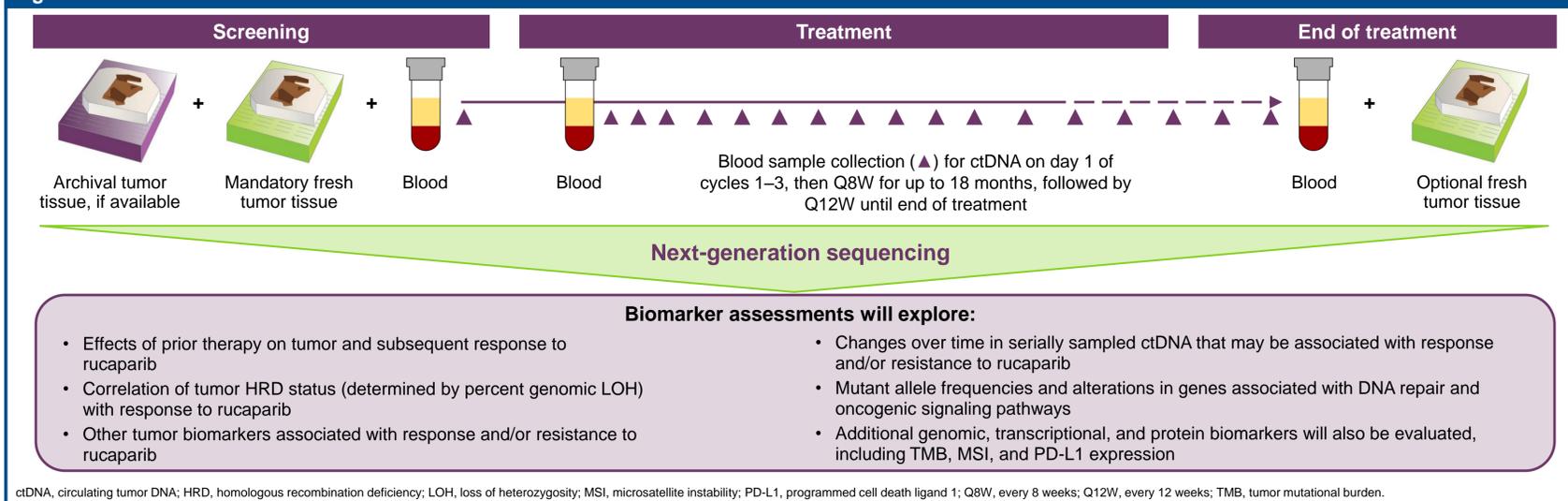
Figure 3. ATLAS Trial Schema



## BIOMARKER ASSESSMENT

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

Figure 4. ATLAS Biomarker Assessments Schedule



## Tumor Tissue Collection and Analyses

- Tumor tissue samples to be collected:
  - Archival (required, if available)
  - Screening (mandatory)
  - Treatment discontinuation (optional)
- Tumor tissue samples will be analyzed 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
  - Tumor mutational burden (TMB)
  - Microsatellite instability (MSI)
- Tumors 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):
  - At screening
  - Day 1 of cycles 1-3, then every 8 weeks for up to 18 months, followed by every 12 weeks until the end of treatment
  - At treatment discontinuation
- Circulating tumor DNA extracted from blood will be profiled by Foundation Medicine using the FoundationACT™ NGS assay, which analyzes a panel of 67 cancer-related genes

Results from NGS testing of tumor 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 tumor 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 enrollment is 200 patients at ≈65 sites in 6 countries
- There are 41 sites currently enrolling in the United States (Figure 5)

Figure 5. US Sites Participating in ATLAS



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