Abstract 440

Rucaparib for Recurrent, Locally Advanced or Metastatic Urothelial Carcinoma: Results From ATLAS, a Phase 2, Open-label Trial

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INTRODUCTION

- Enhanced understanding of the molecular characteristics of metastatic urothelial carcinoma (UC) will provide insight into potentially efficacious treatments for patients with the disease
- Rucaparib is a potent, oral, small-molecule inhibitor of poly(ADP-ribose) polymerase (PARP)[1] approved in the United States and the European Union for the treatment of patients with a deleterious *BRCA* mutation (germline and/or somatic)–associated recurrent ovarian cancer and for maintenance treatment of patients with recurrent ovarian cancer who achieved a complete or partial response to platinum-based chemotherapy, regardless of homologous recombination deficiency (HRD) status[2,3]
- We hypothesized that a subset of urothelial tumors might be susceptible to PARP inhibition
  - A high proportion of urothelial tumors may exhibit HRD (ie, have a deleterious alteration in a gene involved in homologous recombination and/or high genomic loss of heterozygosity [LOH])[4,5]
  - Rucaparib has also demonstrated benefit in patients with tumors that are homologous recombination proficient[6]
- ATLAS (NCT03397394) was an international, open-label, phase 2 study designed to evaluate the efficacy and safety of rucaparib monotherapy treatment in patients with locally advanced, unresectable, or metastatic UC previously treated with 1 or 2 anticancer systemic regimens (**Figure 1**)

METHODS

Figure 1. ATLAS Trial Schema

Screening

Within 28 days of first dose of rucaparib

Key eligibility criteria
- ≥18 years of age
- Locally advanced unresectable UC or mUC
  - Patients with or without tumors associated with HRD*
- Measurable disease per RECIST v1.1
- Confirmed radiographic progression after 1 or 2 prior treatments (eg, platinum-based chemotherapy, immune checkpoint inhibitor, and/or clinical trial) for advanced/metastatic disease
- ECOG PS 0 or 1
- No prior PARP inhibitor treatment
- Adequate organ function
- Mandatory tumor tissue collected ≤28 days before the first dose of rucaparib or archival tumor tissue collected ≤6 months before rucaparib treatment, with no intervening antitumor therapy

Treatment

28-day cycle

Rucaparib 600 mg BID (N=97)

- Until radiographic disease progression, unacceptable toxicity, or other reason for discontinuation
- Patients receiving clinical benefit may continue treatment beyond progression

Analyses†

Primary
- Investigator-assessed objective response‡ in all patients
  - Investigator-assessed objective response in patients with tumors that are HRD-positive*

Secondary
- Duration of response
- Progression-free survival
- Overall survival
- Safety
- Pharmacokinetics

Exploratory
- Association between DDR pathway genes and rucaparib sensitivity

Post hoc
- Clinical benefit rate (CR, PR, or SD lasting ≥16 wks)

*Tumor HRD status determined by the percentage of genomic loss of heterozygosity in a tumor sample before efficacy analysis. †Tumor assessments and blood sample collection for circulating tumor DNA every 8 weeks for up to 18 months; then every 12 weeks thereafter; plasma samples were collected for trough level pharmacokinetic analysis of rucaparib 1 hour before the morning dose on day 1 of cycles 2, 3, and 4. ‡RECIST v1.1 criteria were used to document radiographic response.
BID, twice daily; CR, complete response; DDR, DNA damage repair; ECOG PS, Eastern Cooperative Oncology Group performance status; HRD, homologous recombination deficiency; mUC, metastatic urothelial carcinoma; PARP, poly(ADP-ribose) polymerase; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; UC, urothelial carcinoma.

- Tumor HRD status was determined using the DX1 next-generation sequencing assay from Foundation Medicine (Cambridge, MA, USA); genomic LOH ≥10% was prespecified as the cutoff to categorize tumor samples as HRD-positive (**Figure 2**)
  - Sequencing results were also used to further understand the genomic characteristics of metastatic UC and explore the deleterious DNA damage response (DDR) gene alterations that may be associated with rucaparib sensitivity in this disease
- Efficacy analysis was performed using the intent-to-treat (ITT) population (all patients who received at least 1 dose of rucaparib) and the subgroups based on tumor HRD status

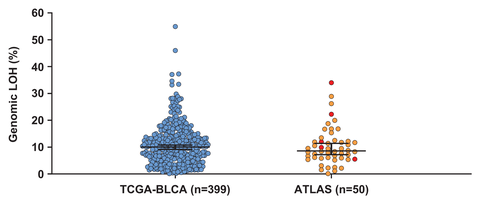
RESULTS

- Between June 1, 2018, and April 9, 2019, 97 patients were enrolled

Genomic Analyses

- Tumor samples were obtained from 76/97 patients (78.4%); most tissue samples were recently obtained (≤6 months; 67/76 [88.2%])
- LOH was determined for 50/97 patients (51.5%); median genomic LOH in ATLAS was similar to that found in The Cancer Genome Atlas - Urothelial Bladder Carcinoma (TCGA-BLCA) dataset (**Figure 2**)[5]
- Median tumor mutational burden score was 6.3 (n=60) and all ATLAS samples with known status were microsatellite stable (n=59)

Figure 2. Genomic LOH in TCGA-BLCA Dataset[5] and Tumor Tissue Samples From Patients Enrolled into the ATLAS Study



In ATLAS, LOH was determined for 50 of 97 patients; LOH could not be determined for 47 patients because a tumor sample was not provided, or the quantity/quality of the sample was insufficient for assessment. Red circles in the ATLAS dataset highlight samples with deleterious alterations in DDR pathway genes *BRCA1*, *BRCA2*, *PALB2*, or *RAD51C*. Bars represent median and 95% CI.
CI, confidence interval; DDR, DNA damage repair; LOH, loss of heterozygosity; TCGA-BLCA, The Cancer Genome Atlas - Urothelial Bladder Carcinoma.

Patients

- In total, 20 patients were categorized as HRD-positive based on the prespecified LOH cutoff (**Table 1**)

Table 1. Baseline Characteristics

	HRD subgroup[a]			
	Positive (n=20)	Negative (n=30)	Indeterminate[b] (n=47)	Overall (N=97)
Age, median (range), y	71 (39–87)	66 (47–85)	66 (50–85)	66 (39–87)
Male, n (%)	11 (55.0)	27 (90.0)	38 (80.9)	76 (78.4)
Race, n (%)				
White	18 (90.0)	24 (80.0)	32 (68.1)	74 (76.3)
Black or African American	0	2 (6.7)	1 (2.1)	3 (3.1)
Other	0	1 (3.3)	2 (4.3)	3 (3.1)
Unknown	2 (10.0)	3 (10.0)	12 (25.5)	17 (17.5)
ECOG PS, n (%)				
0	6 (30.0)	9 (30.0)	14 (29.8)	29 (29.9)
1	13 (65.0)	20 (66.7)	32 (68.1)	65 (67.0)
2	0	1 (3.3)[c]	1 (2.1)[c]	2 (2.1)[c]
Missing	1 (5.0)	0	0	1 (1.0)
Histology, n (%)				
Urothelial	14 (70.0)	25 (83.3)	30 (63.8)	69 (71.1)
Urothelial with variant	5 (25.0)	2 (6.7)	7 (14.9)	14 (14.4)
Unknown	1 (5.0)	3 (10.0)	10 (21.3)	14 (14.4)
Tumor location, n (%)				
Bladder (lower tract)	17 (85.0)	22 (73.3)	38 (80.9)	77 (79.4)
Upper tract	3 (15.0)	8 (26.7)	9 (19.2)	20 (20.6)
No. of prior therapies, n (%)				
1	11 (55.0)	16 (53.3)	26 (55.3)	53 (54.6)
2	9 (45.0)	14 (46.7)	21 (44.7)	44 (45.4)
Prior therapies, n (%)[d]				
Cisplatin-based chemotherapy	13 (65.0)	20 (66.7)	24 (51.1)	57 (58.8)
Carboplatin-based chemotherapy	5 (25.0)	8 (26.7)	21 (44.7)	34 (35.1)
Immune checkpoint inhibitor	14 (70.0)	23 (76.7)	34 (72.3)	71 (73.2)
Time from prior systemic therapy, n (%)				
<3 months	16 (80.0)	19 (63.3)	27 (57.5)	62 (63.9)
≥3 months	4 (20.0)	11 (36.7)	20 (42.6)	35 (36.1)
De novo metastases, n (%)	12 (60.0)	6 (20.0)	12 (25.5)	30 (30.9)
Visceral metastases	9 (45.0)	20 (66.7)	23 (48.9)	52 (53.6)
Liver metastases	9 (45.0)	12 (40.0)	14 (29.8)	35 (36.1)
No. of Bellmunt risk factors, n (%)[e]				
0	4 (20.0)	6 (20.0)	8 (17.0)	18 (18.6)
1	8 (40.0)	10 (33.3)	23 (48.9)	41 (42.3)
2	7 (35.0)	11 (36.7)	14 (29.8)	32 (33.0)
3	1 (5.0)	3 (10.0)	2 (4.3)	6 (6.2)

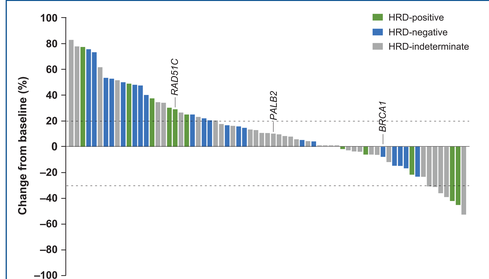
Data cutoff: January 18, 2020.
[a]Based on ≥10% genomic LOH cutoff. [b]Tumor sample was either not received or not evaluable for percentage of genomic LOH because of insufficient tissue volume, low tumor content, inadequate DNA extraction, or the sample did not meet quality control metrics resulting in reduced sequencing specificity. [c]Patients had an ECOG PS score of 1 at screening but were classified with an ECOG PS score of 2 at baseline. [d]Categories are not mutually exclusive. [e]Bellmunt risk factors include an ECOG PS score >0, a hemoglobin level <10 g/dL, and presence of liver metastases.[7]
ECOG PS, Eastern Cooperative Oncology Group performance status; HRD, homologous recombination deficiency; LOH, loss of heterozygosity.

- As of the January 18, 2020 data cutoff, all 97 patients had discontinued treatment; the most common reasons for discontinuation were radiographic or clinical disease progression (72/97 [74.2%]) and an adverse event (9/97 [9.3%])

Efficacy Outcomes

- There were no confirmed responses per RECIST v1.1 (0%; 95% CI, 0%–3.8%) among the 95 evaluable patients with measurable disease at baseline
- However, reductions in tumor size were observed in a number of patients (**Figure 3**), and 27/95 patients (28.4%) had a best response of stable disease
  - A similar proportion of patients had a best response of stable disease across the HRD subgroups (HRD-positive, 4/19 [21.1%]; HRD-negative, 7/29 [24.1%]; HRD-indeterminate, 15/47 [31.9%])

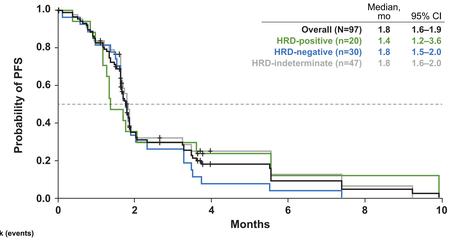
Figure 3. Investigator-Assessed Best Response in Target Lesions Per RECIST v1.1 in the ITT Population



Data cutoff: January 18, 2020.
Only patients with measurable disease at baseline and at least 1 post-baseline tumor assessment (n=69) were included in the analysis.
Each bar represents data from a single patient. Zero percent change from baseline is shown as 0.5% for visual clarity.
Patients identified with tumors containing deleterious alterations in select DDR genes are noted adjacent to the patient's bar in the figure.
DDR, DNA damage repair; HRD, homologous recombination deficiency; ITT, intent to treat; RECIST, Response Evaluation Criteria in Solid Tumors.

- The 16-week clinical benefit rate was 12.6% (12/95) in the ITT population, 15.8% (3/19) in the HRD-positive subgroup, 6.9% (2/29) in the HRD-negative subgroup, and 12.8% (6/47) in the HRD-indeterminate subgroup
- Median PFS was 1.8 months (95% CI, 1.6–1.9) in the ITT population, and was similar across HRD subgroups (**Figure 4**)

Figure 4. Kaplan-Meier Estimates of Progression-Free Survival as Assessed by the Investigator in the Overall ITT Population and by HRD Subgroup



At risk (events)						
Overall	97 (0)	26 (54)	8 (66)	4 (70)	2 (72)	0 (74)
HRD-positive	20 (0)	6 (11)	2 (13)	1 (14)	1 (14)	0 (15)
HRD-negative	30 (0)	9 (18)	2 (25)	1 (26)	0 (27)	
HRD-indeterminate	47 (0)	11 (25)	4 (28)	2 (30)	1 (31)	0 (32)

Data cutoff: January 18, 2020.
ITT, intent to treat; HRD, homologous recombination deficiency.

Safety

- The safety population included 97 patients who received at least 1 dose of rucaparib (**Table 2**); median (range) treatment duration was 1.8 (0.1–10.1) months

Table 2. Most Frequent (≥10% of Patients) Treatment-Emergent Adverse Events of Any Grade in the Safety Population

	Safety population (N=97)	
TEAE	Any grade, n (%)[a]	Grade ≥3, n (%)
Any TEAE	95 (97.9)	71 (73.2)
Asthenia/fatigue	56 (57.7)	8 (8.2)
Nausea	41 (42.3)	1 (1.0)
Anemia/decreased hemoglobin	35 (36.1)	20 (20.6)
Decreased appetite	28 (28.9)	2 (2.1)
Thrombocytopenia/decreased platelets	22 (22.7)	11 (11.3)
Vomiting	22 (22.7)	1 (1.0)
Blood creatinine increased	21 (21.6)	1 (1.0)
Constipation	21 (21.6)	3 (3.1)
Malignant neoplasm progression	19 (19.6)	19 (19.6)
ALT/AST increased	17 (17.5)	5 (5.2)
Dysgeusia	16 (16.5)	0
Dyspnea	13 (13.4)	3 (3.1)
Weight decreased	13 (13.4)	0
Diarrhea	12 (12.4)	1 (1.0)
Urinary tract infection	12 (12.4)	4 (4.1)
Abdominal pain	11 (11.3)	1 (1.0)
Hypophosphatemia	11 (11.3)	6 (6.2)
Dehydration	10 (10.3)	2 (2.1)
Insomnia	10 (10.3)	0
Pyrexia	10 (10.3)	1 (1.0)

Visit cutoff date: January 18, 2020.
[a]No incidence of myelodysplastic syndrome or acute myeloid leukemia was reported.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Pharmacokinetics

- Mean (coefficient of variation) trough plasma concentration of rucaparib was 2150 ng/mL (81%; n=46) at day 29, 1730 ng/mL (66%, n=18) at day 57, and 2000 ng/mL (62%; n=11) at day 85 of treatment; pharmacokinetic exposures were comparable with data from patients with other tumor types[8]

Genomic Characteristics

- Deleterious alterations in DDR pathway genes thought to be associated with PARP inhibitor activity (*BRCA1, BRCA2, RAD51C*, and *PALB2*) were relatively infrequent in tumor samples with sequencing data (6/64 [9.4%]) (**Table 3**)

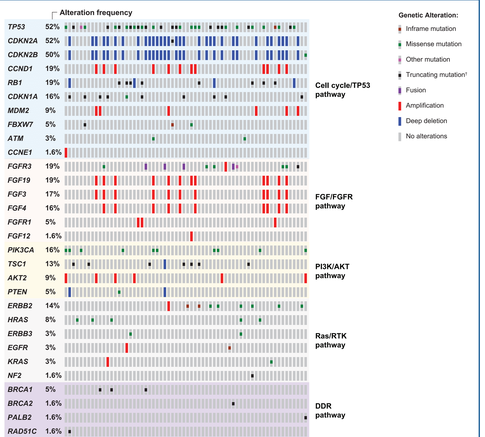
Table 3. Summary of Genetic Alterations in Tumor Tissue Samples and Tumor Responses in Patients With a DDR Gene Mutation

Patient	Gene[a]	Deleterious alteration	Zygosity	Germline status[b]	% LOH	TMB	Best change % SLD
1	*BRCA1*	V409fs*3	Heterozygous	Germline	9.9	13.9	–7.8
2	*BRCA1*	E23fs*17	Heterozygous	Germline	12.0	5.0	N/A[c]
3	*RAD51C*	E218fs*33	Unknown[d]	Somatic	34.0	3.8	29.1
4	*BRCA1*	Rearrangement (truncating)	Not reported[e]	Not reported[e]	22.3	6.3	N/A[c]
5	*BRCA2*	Rearrangement (truncating)	Not reported[e]	Not reported[e]	5.6	6.3	N/A[c]
6	*PALB2*	Rearrangement (truncating)	Not reported[e]	Not reported[e]	Unknown[d]	16.4	10.2

[a]Deleterious somatic and germline alterations in the following DDR genes are shown: *BRCA1, BRCA2, PALB2*, or *RAD51C*. [b]Germline/somatic status has been inferred using a research-use only algorithm that has not been analytically validated. [c]Not evaluable due to lack of data comparing baseline and post-treatment scans. [d]Valid data could not be generated. [e]Zygosity and germline/somatic status were not reported for gene rearrangements.
DDR, DNA damage repair; LOH, loss of heterozygosity; N/A, not applicable; SLD, sum of the longest diameter; TMB, tumor mutational burden.

- In ATLAS, alterations in the cell cycle pathway, receptor tyrosine kinase pathway, and *FGF/R* genes (**Figure 5**) were consistent with those observed in the TCGA-BLCA dataset[5]
  - Most ATLAS patient samples exhibited alterations in *TP53* (33/64 [51.6%])
  - Frequent *FGF/R* amplifications were identified
  - Co-occurrence of *FGF* and *CCND1* amplifications were often observed; *CDKN2A* and *CDKN2B* deletions were also commonly seen together

Figure 5. Genetic Alterations in Select Pathways Among Patients Enrolled in ATLAS



Oncoprint generated from 64 tumor samples with sequencing data. Shown here are those samples containing at least one deleterious alteration in the genes listed. Percentages shown indicate the gene alteration frequencies.
*Only *FGFR1* and *FGFR3* alterations were identified in ATLAS samples; no *FGFR2* alterations were observed. †Includes truncating rearrangements.
DDR, DNA damage repair.

CONCLUSIONS

- In this analysis of data from ATLAS, there were no confirmed responses per RECIST v1.1; a best response of stable disease was observed in 28.4% of patients, with no difference in the proportion of patients between the HRD-positive and HRD-negative subgroups
  - The trial was discontinued because preliminary efficacy results at the time of the first interim efficacy analysis did not meet protocol-defined continuance criteria, suggesting that monotherapy with rucaparib may not provide a meaningful clinical benefit to unselected patients with recurrent, metastatic UC
- The safety profile and pharmacokinetics of rucaparib in metastatic UC were consistent with that observed in patients with recurrent ovarian cancer, prostate cancer, and other solid tumors[2,3,8-10]
- Genomic profiling of ATLAS tissue samples provides expanded insight into the molecular characterization of metastatic UC
  - Median genomic LOH and deleterious gene alterations observed in the ATLAS dataset were similar to those in the TCGA-BLCA dataset,[5] which consisted largely of untreated primary bladder tumors

REFERENCES

1. Robillard et al. *Cancer Res*. 2017;77:abst 2475.
2. Rubraca® (rucaparib) tablets [prescribing information]. Boulder, CO: Clovis Oncology, Inc; 2018.
3. Rubraca® (rucaparib) tablets [summary of product characteristics]. Swords, Ireland: Clovis Oncology Ireland Ltd.; 2019.
4. Teo et al. *Clin Cancer Res*. 2017;23:3610-8.
5. The Cancer Genome Atlas. https://cancergenome.nih.gov/. Accessed January 20, 2020.
6. Coleman et al. *Lancet*. 2017;390:1949-61.
7. Bellmunt et al. *J Clin Oncol*. 2010;28:1850-5.
8. Shapiro et al. *Clin Pharmacol Drug Dev*. 2019;8:107-18.
9. Kristeleit et al. *Clin Cancer Res*. 2017;23:4095-106.
10. Abida et al. *Ann Oncol*. 2019;30:abst 846PD.

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