Preliminary Results from TRITON2: A Phase 2 Study of Rucaparib in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Associated with Homologous Recombination Repair (HRR) Gene Alterations

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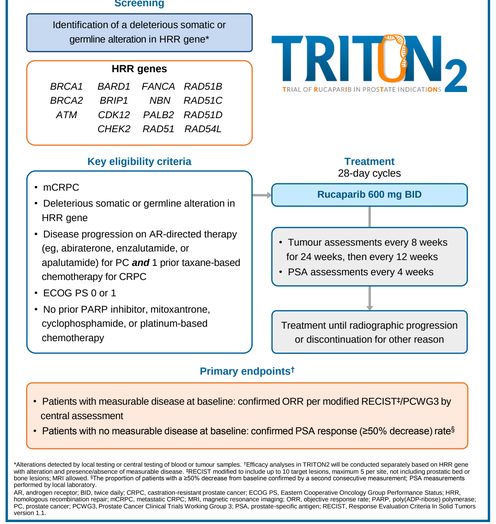
INTRODUCTION

- There are limited treatment options available for patients with mCRPC following androgen receptor (AR)–directed therapy and taxane chemotherapy[1,2]
- In metastatic prostate cancer, up to 25% of patients harbour a deleterious germline and/or somatic alteration in *BRCA1*, *BRCA2*, *ATM*, or other HRR gene[3-5]
- In cells with HRR deficiency, inhibition of poly(ADP-ribose) polymerase (PARP) results in cell death via synthetic lethality[6-8]
- Preclinical and limited clinical data have shown that PARP inhibitors have antitumour activity in HRR-deficient prostate cancer
  - In preclinical studies, rucaparib demonstrated activity in prostate cancer cell lines with reduced levels of *BRCA1*, *BRCA2*, or *ATM*[9]
  - In the phase 2 study TOPARP-A (NCT01682772), 16 of 49 (33%) evaluable patients with mCRPC progressing on ≥1 prior chemotherapy responded to olaparib treatment, using a composite endpoint of radiographic, prostate-specific antigen (PSA), or circulating tumour cell response; of the 16 responders, 14 had a tumour alteration in *BRCA1* (n=1), *BRCA2* (n=7), *ATM* (n=4), or other HRR gene (n=2)[10]
- Here we present interim data from TRITON2 (CO-338-052; EudraCT 2016-003162-13; NCT02952534), a phase 2, international, multicentre, open-label study evaluating rucaparib in patients with mCRPC associated with an HRR gene alteration

METHODS

- Eligible patients were screened for the presence of a deleterious germline or somatic alteration in *BRCA1*, *BRCA2*, *ATM*, or other prespecified HRR gene[11] (**Figure 1**)
  - Deleterious alterations were defined as protein-truncating mutations, large protein-truncating rearrangements, splice site mutations, deleterious missense mutations, and homozygous deletions
- Enrolled patients received oral rucaparib 600 mg twice daily (BID)

Figure 1. TRITON2 Trial Schema

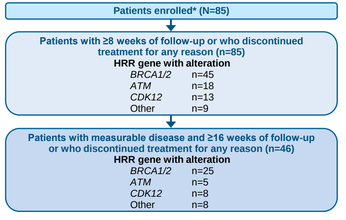


*Alterations detected by local testing or central testing of blood or tumour samples. †Efficacy analyses in TRITON2 will be conducted separately based on HRR gene with alteration and presence/absence of measurable disease. ‡RECIST modified to include up to 10 target lesions, maximum 5 per site, not including prostatic bed or bone lesions; MRI allowed. §The proportion of patients with a ≥50% decrease from baseline confirmed by a second consecutive measurement; PSA measurements performed by local laboratory.
AR, androgen receptor; BID, twice daily; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HRR, homologous recombination repair; mCRPC, metastatic CRPC; MRI, magnetic resonance imaging; ORR, objective response rate; PARP, poly(ADP-ribose) polymerase; PC, prostate cancer; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1.

RESULTS

- Enrolment is ongoing in TRITON2
- As of 16 April 2018, 85 patients were enrolled in TRITON2 (**Figure 2**; **Table 1**)
  - At the visit cutoff date (29 June 2018), median duration of follow-up was 5.7 months (range, 2.6–16.4 months)

Figure 2. Efficacy Populations



*Enrolment cutoff date: 16 April 2018.
HRR, homologous recombination repair; PSA, prostate-specific antigen.

Table 1. Baseline Demographics

Characteristic	By HRR gene with alteration: *BRCA1/2* (n=45)	*ATM* (n=18)	*CDK12* (n=13)	Other[a] (n=9)	Overall (N=85)
Age, median (range), y	71 (50–88)	72.5 (62–84)	64 (49–79)	72 (60–86)	71 (49–88)
Race, n (%)					
White	35 (77.8%)	12 (66.7%)	6 (46.2%)	5 (55.6%)	58 (68.2%)
Black or African American	4 (8.9%)	3 (16.7%)	1 (7.7%)	1 (11.1%)	9 (10.6%)
Unknown	6 (13.3%)	3 (16.7%)	6 (46.2%)	3 (33.3%)	18 (21.2%)
ECOG PS, n (%)					
0	16 (35.6%)	10 (55.6%)	6 (46.2%)	1 (11.1%)	33 (38.8%)
1	28 (62.2%)	8 (44.4%)	7 (53.8%)	7 (77.8%)	50 (58.8%)
≥2	1 (2.2%)	0	0	1 (11.1%)	2 (2.4%)
Baseline PSA, median (range), ng/mL	52.0 (3.5–4782.0)	59.3 (9.2–4350.0)	57.7 (23.3–2966.5)	54.0 (8.8–798.8)	54.0 (3.5–4782.0)
Gleason score ≥8, n (%)	33 (73.3%)	6 (33.3%)	13 (100%)	6 (66.7%)	58 (68.2%)
No. prior CRPC therapies, median (range)[b]	2 (2–7)[c]	3 (2–6)	3 (2–4)	2 (2–4)	2 (2–7)[c]
Prior therapies, n (%)[d]					
Abiraterone	25 (55.6%)	16 (88.9%)	9 (69.2%)	8 (88.9%)	58 (68.2%)
Enzalutamide	33 (73.3%)	14 (77.8%)	12 (92.3%)	4 (44.4%)	63 (74.1%)
Abiraterone and enzalutamide	14 (31.1%)	12 (66.7%)	8 (61.5%)	3 (33.3%)	37 (43.5%)
Docetaxel	43 (95.6%)	17 (94.4%)	11 (84.6%)	8 (88.9%)	79 (92.9%)
Cabazitaxel	4 (8.9%)	4 (22.2%)	2 (15.4%)	1 (11.1%)	11 (12.9%)
Sipuleucel-T	6 (13.3%)	4 (22.2%)	1 (7.7%)	0	11 (12.9%)
Radium	5 (11.1%)	4 (22.2%)	0	1 (11.1%)	10 (11.8%)
Metastases, n (%)[d]					
Bone	40 (88.9%)	17 (94.4%)	10 (76.9%)	7 (77.8%)	74 (87.1%)
Nodal	28 (62.2%)	5 (27.8%)	11 (84.6%)	8 (88.9%)	52 (61.2%)
Visceral	19 (42.2%)	4 (22.2%)	4 (30.8%)	1 (11.1%)	28 (32.9%)
Hepatic	8 (17.8%)	2 (11.1%)	1 (7.7%)	1 (11.1%)	12 (14.1%)
Measurable disease at baseline (per investigator), n (%)					
Yes	27 (60.0%)	5 (27.8%)	8 (61.5%)	8 (88.9%)	48 (56.5%)
No	18 (40.0%)	13 (72.2%)	5 (38.5%)	1 (11.1%)	37 (43.5%)
Gene alteration status, n (%)					
Germline	15 (33.3%)	5 (27.8%)	0	0	20 (23.5%)
Somatic	30 (66.7%)	10 (55.6%)	0	0	40 (47.1%)
Not available	0	3 (16.7%)	13 (100%)	9 (100%)	25 (29.4%)

Visit cutoff date: 29 June 2018.
[a]Includes 2 patients with an alteration in *FANCA*, and 1 patient each with an alteration in *BRIP1*, *CHEK2*, *NBN*, *PALB2*, *RAD51*, *BRIP1/CHEK2*, or *CHEK2/CDK12*. [b]Does not include luteinizing hormone-releasing hormone analogues, first-generation antiandrogens, hormones, corticosteroids, bone-targeted agents, haematopoietic growth factors, or docetaxel given for hormone-sensitive disease. [c]Data unavailable for 1 patient. [d]Categories are not mutually exclusive.
CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HRR, homologous recombination repair; PSA, prostate-specific antigen.

Radiographic Response in Patients with Measurable Disease

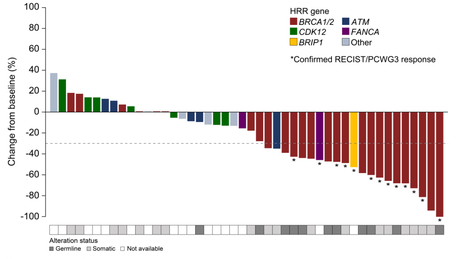
- Of patients with a *BRCA1/2* alteration and measurable disease at baseline, 44.0% (11/25) had a confirmed objective response by investigator assessment (**Table 2**; **Figure 4**)
- A confirmed objective response by investigator assessment was also observed in 1 patient with a *BRIP1* alteration and 1 patient with a *FANCA* alteration (**Table 2**)

Table 2. Confirmed Investigator-Assessed ORR in Evaluable Patients

Characteristic	By HRR gene with alteration: *BRCA1/2* (n=25)	*ATM* (n=5)	*CDK12* (n=8)	Other (n=8)
ORR, n (%) [95% CI][a]	11 (44.0%) [24.4–65.1]	0 [0.0–52.2]	0 [0.0–36.9]	2 (25.0%) [3.2–65.1]
Complete response, n (%)	0	0	0	0
Partial response, n (%)	11 (44.0%)	0	0	2 (25.0%)[b]
Stable disease, n (%)	9 (36.0%)	4 (80.0%)	5 (62.5%)	5 (62.5%)
Progressive disease, n (%)	4 (16.0%)	1 (20.0%)	2 (25.0%)	1 (12.5%)
Not evaluable, n (%)	1 (4.0%)	0	1 (12.5%)	0

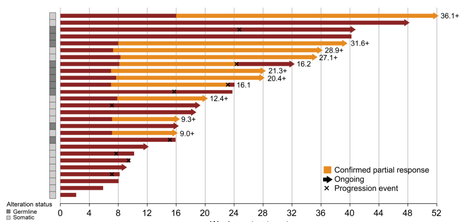
Visit cutoff date: 29 June 2018.
Includes patients who had measurable disease at baseline per the investigator and ≥16 weeks of follow-up or who discontinued treatment.
[a]Per modified RECIST/PCWG3 criteria.
[b]One patient had a *BRIP1* alteration and 1 patient had a *FANCA* alteration.
CI, confidence interval; HRR, homologous recombination repair; ORR, objective response rate; PCWG3, Prostate Cancer Clinical Trials Working Group 3; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1.

Figure 3. Best Change from Baseline in Sum of Target Lesions (n=46)



Visit cutoff date: 29 June 2018.
Includes patients with measurable disease at baseline and ≥1 postbaseline scan. Each bar represents a single patient; patients with no change from baseline are shown as 0.5% for visual clarity. The dotted line indicates the threshold for partial response (30% decrease from baseline).
HRR, homologous recombination repair; PCWG3, Prostate Cancer Clinical Trials Working Group 3; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

Figure 4. Treatment Duration and Duration of Radiographic Response in Patients with a *BRCA1/2* Alteration and Measurable Disease at Baseline (n=27)



Visit cutoff date: 29 June 2018. Values shown represent duration of confirmed response; ongoing responses are indicated with a +.
Each bar represents time on treatment for 1 patient; ongoing radiographic responses are displayed to the visit cutoff date.

PSA Response

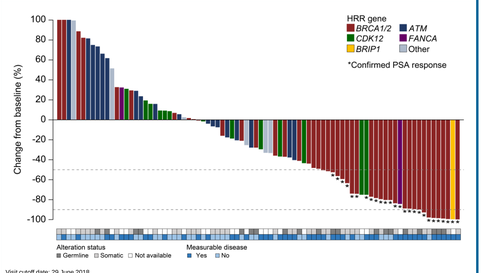
- Among patients with a *BRCA1/2* alteration, 51.1% (23/45) had a confirmed PSA response (**Table 3**)
- A confirmed PSA response was also observed in 1 patient with a *CDK12* alteration, 1 patient with a *BRIP1* alteration, and 1 patient with a *FANCA* alteration (**Table 3**)

Table 3. Confirmed PSA Response Rates

PSA response rate	By HRR gene with alteration, n/N (%) [95% CI]: *BRCA1/2*	*ATM*	*CDK12*	Other
All evaluable patients	23/45 (51.1%) [35.8–66.3]	0/18 (0%) [0.0–18.5]	1/13 (7.7%)[a] [0.2–36.0]	2/9 (22.2%)[b] [2.8–60.0]
With measurable disease	17/27 (63.0%) [42.4–80.6]	0/5 (0%) [0.0–52.2]	1/8 (12.5%)[a] [0.3–52.7]	2/8 (25.0%)[b] [3.2–65.1]
With no measurable disease	6/18 (33.3%) [13.3–59.0]	0/13 (0%) [0.0–24.7]	0/5 (0%) [0.0–52.2]	0/1 (0%) [0.0–97.5]

Visit cutoff date: 29 June 2018.
Includes patients who had ≥8 weeks of follow-up or who discontinued treatment.
[a]This patient did not demonstrate a confirmed objective radiographic response.
[b]One patient with a *BRIP1* alteration and 1 patient with a *FANCA* alteration; both patients demonstrated a confirmed objective radiographic response.
CI, confidence interval; HRR, homologous recombination repair; PSA, prostate-specific antigen.

Figure 5. Best Change from Baseline in PSA (n=84)



Visit cutoff date: 29 June 2018.
Includes all patients with ≥1 postbaseline PSA measurement. Each bar represents a single patient; patients with no change from baseline are shown as 0.5% for visual clarity. The upper dotted line indicates a 50% decrease from baseline PSA and the lower dotted line indicates a 90% decrease from baseline PSA. PSA increases for the 3 leftmost patients were 231%, 183%, and 126%; bars were capped at 100% for visual clarity.
HRR, homologous recombination repair; PSA, prostate-specific antigen.

- Enrolment of patients with a *CDK12* alteration has been halted per protocol based on the lack of responses observed in these patients to date

Safety

- In the safety population (defined as all patients who received ≥1 dose of rucaparib; N=85), median treatment duration in the overall population was 3.7 months (range, 0.5–12.9 months)
  - Median treatment duration in patients with a *BRCA1/2* alteration was 4.4 months (range, 0.5–12.0 months)

Table 4. Summary of TEAEs

	Overall safety population (N=85), n (%)
At least 1 TEAE	81 (95.3%)
At least 1 TEAE grade ≥3	45 (52.9%)
Treatment interruption and/or dose reduction due to TEAE	45 (52.9%)
Treatment interruption due to TEAE	41 (48.2%)
Dose reduction due to TEAE	25 (29.4%)[a]
TEAE leading to discontinuation	5 (5.9%)[b]
Death due to TEAE	1 (1.2%)[c]

Visit cutoff date: 29 June 2018.
[a]The most common were asthenia/fatigue (8.2%), anaemia/decreased haemoglobin (7.1%), thrombocytopenia/decreased platelet count (5.9%), and nausea (4.7%). [b]One patient each (1.2%) discontinued due to anaemia/decreased haemoglobin, asthenia/fatigue, decreased appetite, and general physical health deterioration; 1 patient (1.2%) discontinued due to TEAEs of asthenia/fatigue, decreased appetite, and weight loss. [c]Due to disease progression.
TEAE, treatment-emergent adverse event.

Table 5. Most Common (≥10%) TEAEs of Any Grade in All Patients Regardless of Causality

	Overall safety population (N=85): Any grade, n (%)	Grade ≥3, n (%)
Asthenia/fatigue	38 (44.7%)	4 (4.7%)
Nausea	36 (42.4%)	3 (3.5%)
Anaemia/decreased haemoglobin	24 (28.2%)	13 (15.3%)
Decreased appetite	24 (28.2%)	3 (3.5%)
Constipation	19 (22.4%)	1 (1.2%)
ALT/AST increased	18 (21.2%)	4 (4.7%)
Vomiting	17 (20.0%)	0
Diarrhoea	16 (18.8%)	1 (1.2%)
Arthralgia	11 (12.9%)	1 (1.2%)
Dizziness	11 (12.9%)	0
Back pain	10 (11.8%)	2 (2.4%)
Oedema peripheral	10 (11.8%)	0
Weight decreased	10 (11.8%)	0
Dysgeusia	9 (10.6%)	0
Dyspnoea	9 (10.6%)	0
Haematuria	9 (10.6%)	3 (3.5%)

Visit cutoff date: 29 June 2018.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Pharmacokinetic (PK) Data

- Data for trough rucaparib plasma concentration were collected from 79 patients enrolled as of the 16 April 2018 enrolment cutoff date
- The plasma concentration of rucaparib in men enrolled in TRITON2 was comparable to that observed in women with ovarian cancer also treated with rucaparib 600 mg BID[12]

CONCLUSIONS

- Rucaparib has encouraging antitumour activity in patients with a deleterious alteration in *BRCA1* or *BRCA2*
  - Among evaluable patients with a *BRCA1/2* alteration, 44.0% (11/25) had a confirmed radiographic response and 51.1% (23/45) had a confirmed PSA response
- Two patients with *BRIP1* or *FANCA* alterations also had confirmed radiographic and PSA responses
- Confirmed radiographic responses have not yet been observed in patients with *ATM* or *CDK12* gene alterations
  - Some reductions in target lesion diameters and PSA measurements have been observed in these patients
- Preliminary safety and PK data for rucaparib in men with mCRPC are consistent with those observed in patients with ovarian cancer and other solid tumours[13-17]
- Based on initial data from TRITON2, on 2 October 2018, the U.S. Food and Drug Administration granted Clovis Oncology Breakthrough Therapy designation for rucaparib as a monotherapy treatment of adult patients with *BRCA1/2*-mutated mCRPC who have received at least 1 prior AR-directed therapy and taxane-based chemotherapy[18]
- Enrolment in TRITON2 is ongoing, and the safety and efficacy of rucaparib as treatment for patients with mCRPC associated with an HRR gene alteration continues to be evaluated

REFERENCES

1. Parker et al. *Ann Oncol.* 2015;26:vi69-77.
2. NCCN Clinical Practice Guidelines in Oncology. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed 10 October 2018.
3. Robinson et al. *Cell.* 2015;161:1215-28.
4. Pritchard et al. *N Engl J Med.* 2016;375:443-53.
5. Abida et al. *JCO Precis Oncol.* 2017;1:1-16.
6. O'Connor. *Mol Cell.* 2015;60:547-60.
7. Lee et al. *Ann Oncol.* 2014;25:32-40.
8. Scott et al. *J Clin Oncol.* 2015;33:1397-406.
9. Nguyen et al. *Cancer Res.* 2017;77(13 suppl):abst 2476.
10. Mateo et al. *N Engl J Med.* 2015;373:1697-708.
11. Chowdhury et al. ESMO 2018. Abst 795PD.
12. Shapiro et al. *Clin Pharmacody Drug Dev.* 2018 [Epub ahead of print].
13. Kristeleit et al. *Clin Cancer Res.* 2017;23:4095-106.
14. Swisher et al. *Lancet Oncol.* 2017;18:75-87.
15. Coleman et al. *Lancet.* 2017;390:1949-61.
16. Rubraca (rucaparib) tablets [prescribing information]. Boulder, CO: Clovis Oncology, Inc.; 2018.
17. Rubraca (rucaparib) tablets [summary of product characteristics]. Boulder, CO: Clovis Oncology, Inc.; 2018.
18. Clovis Oncology. https://ir.clovisoncology.com/investors-and-news/news-releases/press-release-details/2018/Clovis-Oncology-Receives-Breakthrough-Therapy-Designation-for-Rubraca-rucaparib-for-Treatment-of-BRCA12-Mutated-Metastatic-Castration-Resistant-Prostate-Cancer-mCRPC/default.aspx. Accessed 10 October 2018.

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Please also see the ESMO 2018 poster presenting tissue and plasma screening results from the TRITON2 and TRITON3 studies

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