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Rucaparib + Sacituzumab Govitecan: Initial Data From the Phase 1b/2 SEASTAR Study (NCT03992131)

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SUMMARY

- **Initial encouraging signs of antitumour activity were seen with the combination of rucaparib + sacituzumab govitecan in patients with advanced solid tumours (n=6), including patients with prior poly(ADP-ribose) polymerase inhibitor exposure and without a deleterious homologous recombination repair gene mutation (Figure 2)**
- **Despite early toxicities, all 6 patients continued treatment, with treatment-emergent adverse events effectively managed with dose modification and/or growth factor support**
- **Further evaluation of the combination is warranted**

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Supplementary Material
Also available at:
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PRESENTING AUTHOR DISCLOSURE

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INTRODUCTION

- Preclinically, poly(ADP-ribose) polymerase (PARP) inhibitors such as rucaparib and DNA topoisomerase I (TOP1) inhibitors such as irinotecan have shown highly synergistic antitumour effects, but clinical development has been hampered by overlapping toxicities[1-5]
  - Tumour-targeted delivery of a TOP1 inhibitor may reduce systemic toxicity of the combination
  - Sacituzumab govitecan is an antibody-drug conjugate composed of an anti-Trop-2 antibody coupled to the active metabolite of irinotecan (SN-38) via a proprietary hydrolysable linker[6]
- Here, we describe the safety, tolerability, and preliminary efficacy of rucaparib + sacituzumab govitecan from the SEASTAR study, an open-label, parallel-arm study of the PARP inhibitor rucaparib in combination with other anticancer agents

METHODS

- For the phase 1b portion, eligible patients had metastatic triple-negative breast cancer, urothelial cancer, or platinum-resistant ovarian cancer; patients with another solid tumour type with a deleterious mutation in a homologous recombination repair (HRR) gene (*BRCA1, BRCA2, PALB2, RAD51C*, or *RAD51D*) were also eligible
- Prior treatment with a PARP inhibitor was allowed; patients previously treated with irinotecan, topotecan, or any derivative in any formulation were excluded
- A 3+3 design was used, with a starting dose of rucaparib 300 mg orally twice daily + sacituzumab govitecan 6 mg/kg intravenously on days 1 and 8 of a 21-day cycle in cohort 1
- Dose-limiting toxicities (DLTs) were assessed during cycle 1 (see Supplementary Material)
- Haematopoietic growth factor support was allowed except during the DLT period
- The primary endpoints of phase 1b were the incidence of grade 3 or 4 treatment-emergent adverse events (TEAEs) and number of participants who experienced a DLT
  - A key secondary endpoint was investigator-assessed objective response per Response Evaluation Criteria In Solid Tumors, version 1.1 (RECIST)

RESULTS

- Six patients were enrolled in 2 dose cohorts; demographics, disease history, and on-study findings for each patient are shown in **Figure 1**
- Two of 3 patients in cohort 1 experienced dose-limiting grade 4 neutropenia during cycle 1
- In cohort 2, the rucaparib starting dose was reduced from 300 mg twice daily to 300 mg once daily; grade 3/4 neutropenia led to the delay of cycle 2 by 1–2 weeks in all 3 patients
- All 6 patients were able to continue treatment for at least 12 weeks, with TEAEs managed through treatment interruption, dose reduction, and/or growth factor support
  - One patient remains on treatment as of the data cutoff date (11 Aug 2020)
- Summaries of safety and efficacy data are shown in the **Table** and **Figure 2**, respectively
- All patients had a best response of stable disease or better
- Three patients had a confirmed partial response; all 3 patients had been previously treated with a PARP inhibitor (2 niraparib, 1 veliparib) until disease progression
  - Two responders did not have a known deleterious HRR gene mutation: 1 patient had metastatic, triple-negative breast cancer (**Figure 3; Supplementary Material**) and 1 patient had metastatic, high-grade serous ovarian cancer

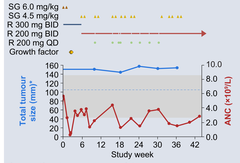
Figure 1. SEASTAR Patients Receiving Rucaparib + Sacituzumab Govitecan

COHORT 1 - starting dose: 300 mg BID rucaparib + 6 mg/kg IV sacituzumab govitecan

PATIENT 1

Demographics and disease history
- Asian, female, age 56 years
- Metastatic, granulosa cell ovarian cancer
- No HRR gene mutation detected
- Five prior anticancer regimens

Study profile



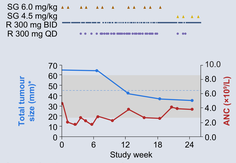
Investigator-assessed tumour response
- SD (duration: 36.3+ weeks)

Grade ≥2 TEAEs
- Grade 2: abdominal cramping, diarrhoea, fatigue, hair loss, intermittent hyponatraemia
- Grade 3: *Clostridium difficile* infection
- Grade 4: neutropenia (DLT)

PATIENT 2

Demographics and disease history
- White, female, age 60 years
- Metastatic, high-grade endometrial cancer
- *BRCA1* gene mutation
- Three prior anticancer regimens
  - One prior PARP inhibitor (1st-line maintenance with single-agent niraparib)

Study profile



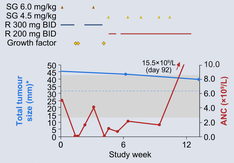
Investigator-assessed tumour response
- Confirmed PR (duration: 12.0 weeks)

Grade ≥2 TEAEs
- Grade 2: diarrhoea, eye infection

PATIENT 3

Demographics and disease history
- White, male, age 63 years
- Metastatic, transitional cell urothelial carcinoma
- *BRCA2* gene mutation
- Three prior anticancer regimens

Study profile



Investigator-assessed tumour response
- SD (duration: 13.3 weeks)

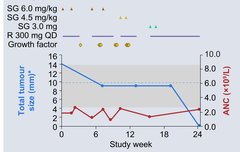
Grade ≥2 TEAEs
- Grade 2: flu-like symptoms, generalised muscle weakness, hypophosphataemia, low bicarbonate
- Grade 3: anaemia, cholecystitis
- Grade 4: leukopenia, neutropenia (DLT)

COHORT 2 - starting dose: 300 mg QD rucaparib + 6 mg/kg IV sacituzumab govitecan

PATIENT 4

Demographics and disease history
- White, female, age 69 years
- Metastatic, high-grade serous ovarian cancer
- No HRR gene mutation detected
- Three prior anticancer regimens
  - One prior PARP inhibitor (2nd-line treatment with single-agent niraparib)

Study profile



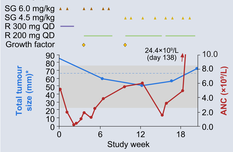
Investigator-assessed tumour response
- Confirmed PR (duration: 17.1 weeks)

Grade ≥2 TEAEs
- Grade 2: constipation, depression, diarrhoea, dyspnoea, fatigue, GERD, mucositis, neuropathy, sinusitis, swelling in left axilla
- Grade 3: leukopenia, thrombocytopenia
- Grade 4: neutropenia

PATIENT 5

Demographics and disease history
- White, female, age 57 years
- Metastatic, triple-negative breast cancer (invasive ductal carcinoma)
- No HRR gene mutation detected
- Eight prior anticancer regimens
  - One prior PARP inhibitor (8th-line treatment with veliparib + dinaciclib)

Study profile



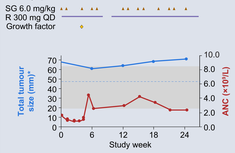
Investigator-assessed tumour response
- Confirmed PR (duration: 14.0 weeks)

Grade ≥2 TEAEs
- Grade 2: anaemia, anxiety, back pain, bilirubin increased, diarrhoea, fatigue, mucositis oral, nausea, thrombocytopenia
- Grade 3: dyspnoea, febrile neutropenia
- Grade 4: neutropenia, leukopenia

PATIENT 6

Demographics and disease history
- White, female, age 50 years
- Metastatic, triple-negative breast cancer (invasive ductal carcinoma)
- Not tested for HRR gene mutation
- Six prior anticancer regimens

Study profile



Investigator-assessed tumour response
- SD (duration: 24.3 weeks)

Grade ≥2 TEAEs
- Grade 3: neutropenia

Sacituzumab govitecan: 6 mg/kg; 4.5 mg/kg; 3 mg/kg
Rucaparib: 300 mg BID; 200 mg BID; 300 mg QD; 200 mg QD
Growth factor support; Ongoing on study
Total tumour size; Threshold for 30% decrease in total tumour size; Absolute neutrophil count; Normal range for neutrophil count (2.6 to 8.5×10⁹/L)

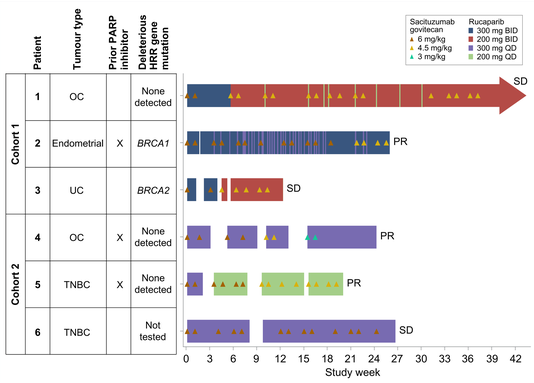
Data cutoff date: 11 Aug 2020.
*Evaluated per RECIST.
ANC, absolute neutrophil count; BID, twice daily; DLT, dose-limiting toxicity; GERD, gastro-oesophageal reflux disease; HRR, homologous recombination repair; IV, intravenous; LDTL, longest diameter of target lesions; PARP poly(ADP-ribose) polymerase; PR, partial response; QD, once daily; R, rucaparib; RECIST, Response Evaluation Criteria In Solid Tumors, version 1.1; SD, stable disease; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event.

Table. Most Common TEAEs (Reported in ≥3 Patients)

	Any grade n (%)	Grade ≥3 n (%)
Any TEAE	6 (100)	5 (83.3)
Neutropenia/ANC decreased	6 (100)	5 (83.3)
Diarrhoea	5 (83.3)	0
ALT/AST increased	4 (66.7)	0
Asthenia/fatigue	4 (66.7)	0
Dyspnoea	3 (50.0)	1 (16.7)
Hyponatraemia	3 (50.0)	0
Nausea	3 (50.0)	0
Thrombocytopenia/platelet count decreased	3 (50.0)	1 (16.7)
Vomiting	3 (50.0)	0

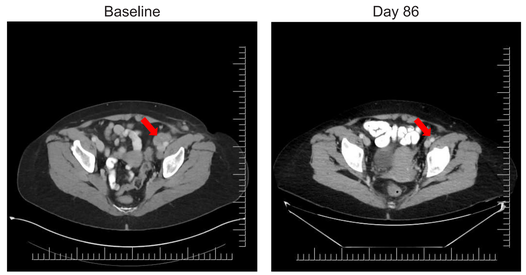
Data cutoff date: 11 Aug 2020.
ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Figure 2. Duration of Treatment



Data cutoff date: 11 Aug 2020.
BID, twice daily; HRR, homologous recombination repair; OC, ovarian cancer; PARP, poly(ADP-ribose) polymerase; PR, partial response; QD, once daily; RECIST, Response Evaluation Criteria In Solid Tumors, version 1.1; SD, stable disease; TNBC, triple-negative breast cancer; UC, urothelial cancer.

Figure 3. Representative Images of Confirmed Partial Response Observed in Patient with Metastatic TNBC (Patient 5)



TNBC, triple-negative breast cancer.