case reports

Phase Ib SEASTAR Study: Combining Rucaparib and Sacituzumab Govitecan in Patients With Cancer With or Without Mutations in Homologous Recombination Repair Genes

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JCO Precis Oncol 6:e2100456.

INTRODUCTION

Tumors characterized by homologous recombination deficiency, including *BRCA1/2*-mutated cancers, are sensitive to inhibition of poly(ADP-ribose) polymerases (PARPs), enzymes that regulate DNA repair.[1,2] In tumor cells with mutated homologous recombination repair (HRR) genes, PARP inhibition synergizes with homologous recombination deficiency leading to synthetic lethality because of accumulated DNA damage.[2,3]

Rational combinations designed to increase DNA damage and reliance on HRR are promising strategies for increasing sensitivity to PARP inhibitors, although overlapping toxicities, such as myelosuppression, suggest a need for more selective and rational targeted agents.[2,4-6] In human tumor cell lines, topoisomerase 1 (Topo1) inhibitors, including irinotecan and topotecan, have demonstrated synergy with PARP inhibitors.[4,5] Since PARP1 is required for the clearance of Topo1-DNA cleavable complexes, PARP inhibition may augment Topo1-mediated DNA damage or delay repair.[7,8] PARP inhibition has been shown to potentiate the cytotoxicity of SN-38, the active metabolite in irinotecan and topotecan, in mismatch repair-deficient and repair-proficient cell lines.[9] Furthermore, combination of a PARP inhibitor with topotecan or irinotecan in early clinical studies delayed repair of Topo1-mediated DNA damage, but also demonstrated challenges with overlapping hematologic and/or gastrointestinal toxicities.[10,11]

The phase Ib SEASTAR study (ClinicalTrials.gov identifier: NCT03992131) was designed to evaluate the safety, tolerability, and preliminary efficacy of the PARP inhibitor rucaparib in combination with other anticancer agents. Rucaparib is approved in the United States and European Union for treatment or maintenance treatment of patients with recurrent ovarian cancer (OC),[12,13] and in the United States for patients with metastatic castration-resistant prostate cancer,[12] and is under investigation in patients with solid tumors harboring mutations in HRR genes.[14] Arm B of the SEASTAR study investigated the combination of rucaparib with sacituzumab govitecan (SG), a conjugate of SN-38 with a humanized antibody targeting Trop-2 (trophoblast cell-surface antigen-2), a cell surface antigen overexpressed in epithelial cancers that has been linked to aggressive disease and poor prognosis. Targeted delivery of SN-38 to cancer cells through an antibody-drug conjugate (ADC) is a rational and effective strategy for combination therapy with a PARP inhibitor by potentially reducing off-target and additive toxicity.[15,16] SG is approved in the United States for the treatment of patients with metastatic triple-negative breast cancer (TNBC) and urothelial cancer (UC),[17] and has shown preliminary antitumor activity in other cancer types.[18] Here, we report the results for six patients who received the combination of rucaparib and SG in arm B of the SEASTAR study.

METHODS

Study Design and Patients

The phase Ib open-label, parallel-arm SEASTAR study was approved by local and/or national institutional review boards and performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Council for Harmonisation. All patients provided written informed consent for participation. The primary aim of the study was to determine the maximum tolerated dose and recommended phase II dose; investigator-assessed objective response rate was a key secondary end point.

Arm B enrolled adult patients (≥ 18 years) with previously treated, locally advanced or metastatic TNBC or UC; or relapsed, platinum-resistant OC. Patients with advanced, recurrent, or metastatic solid tumors with documented evidence of a deleterious alteration in *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, and/or *RAD51D* were also eligible. Genomic alterations were identified by local testing or through central next-generation sequencing of tumor tissue or baseline plasma by Foundation Medicine (Cambridge, MA). Prior PARP

ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on December 13, 2021 and published at ascopubs.org/journal/po on February 9, 2022: DOI https://doi.org/10.1200/PO.21.00456

TABLE 1. Summary of Patient Demographics, Disease History, and Best Response

Patient No.	Demographics	Tumor Type	Deleterious HRR Mutation[a]	No. of Prior Regimens[b]	Prior PARP Inhibitor (treatment duration)	Best Response[c] (duration)
Cohort 1: starting dose 300 mg rucaparib twice a day plus 6 mg/kg IV SG						
1	Asian female, age 56 years	Metastatic granulosa cell OC	Not detected	5	No	SD (36.3+ weeks)
2	White female, age 60 years	Metastatic, high-grade EC	*BRCA1*, N1355fs*10	3	Frontline single-agent niraparib maintenance[d] (9.5 months)	Confirmed PR (12.0 weeks)
3	White male, age 63 years	Metastatic, transitional cell UC	*BRCA2*, E2846fs*22	3	No	SD (13.3 weeks)
Cohort 2: starting dose 300 mg rucaparib once daily plus 6 mg/kg IV SG						
4	White female, age 69 years	Metastatic, high-grade serous OC	Not detected	3	Second-line single-agent niraparib[e] (6 weeks)	Confirmed PR (17.1 weeks)
5	White female, age 57 years	Metastatic TNBC	*BARD1*, M584fs*7	8	Eighth-line veliparib plus dinaciclib[e] (5 weeks)	Confirmed PR (14.0 weeks)
6	White female, age 50 years	Metastatic TNBC	Not detected	6	No	SD (24.3 weeks)

Abbreviations: *BARD1*, BRCA-associated ring domain protein 1; *BRCA1*, BRCA1 DNA repair associated; *BRCA2*, BRCA2 DNA repair associated; EC, endometrial cancer; HRR, homologous recombination repair; IV, intravenous; OC, ovarian cancer; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; UC, urothelial cancer.

[a]Genomic alterations were identified by local testing or through central next-generation sequencing of baseline plasma or tumor tissue by Foundation Medicine (Cambridge, MA). See Supplemental Table 2 in the Data Supplement for a detailed description of local testing. The detected *BRCA1/2* mutations are well-characterized germline mutations in the ClinVar database: *BRCA1* N1355fs*10[19] and *BRCA2* E2846fs*22.[20] On the basis of the low allele frequency detected by next-generation sequencing of plasma samples, the *BARD1* mutation was likely somatic in origin.

[b]Includes regimens from all treatment settings (neoadjuvant, adjuvant, maintenance, and metastatic), but does not include radiotherapy.

[c]RECIST version 1.1.

[d]Best response of SD and subsequently progressed with prior PARP inhibitor therapy.

[e]Best response of PD with prior PARP inhibitor therapy.

inhibitor treatment was allowed, but patients previously treated with irinotecan, topotecan, or any derivative were excluded. Additional inclusion and exclusion criteria are included in the Protocol.

Study Treatment and Assessments

This study used a standard 3 + 3 dose escalation design, with a starting dose of 300 mg rucaparib twice a day (cohort 1) or 300 mg rucaparib once daily (cohort 2) in combination with 6 mg/kg SG administered intravenously (IV), on days 1 and 8 of a 21-day cycle. Dose-limiting toxicities (DLTs) were evaluated in cycle 1. Treatment interruptions and/or dose reductions were permitted for rucaparib (in 100-mg decrements) or SG (by 25% dose reduction) in the event of toxicity. Growth factor administration was permitted for treatment of toxicity when clinically indicated. Prophylactic administration of growth factors was allowed after the DLT evaluation period. Response was assessed per RECIST, version 1.1 (v1.1). Detailed descriptions of predefined DLTs, management of adverse events (AEs), and safety and efficacy assessments are included in the Protocol.

RESULTS

Six patients were enrolled in two dose cohorts (n = 3 each). Patients in cohort 1 received a starting dose of 300 mg rucaparib twice a day plus 6 mg/kg IV SG on days 1 and 8 of each cycle; cohort 2 received 300 mg rucaparib once daily plus 6 mg/kg IV SG on days 1 and 8 of each cycle (Table 1). All patients had metastatic solid tumors, including TNBC (n = 2), OC (n = 2), endometrial (n = 1), and UC (n = 1). Two patients had a known deleterious *BRCA1* or *BRCA2* gene mutation at enrollment, and one patient had a deleterious *BARD1* mutation detected in circulating tumor DNA at baseline using central plasma testing. Patients received a median of 4 prior regimens (range, 3-8), with three patients previously receiving a PARP inhibitor (Fig 1).

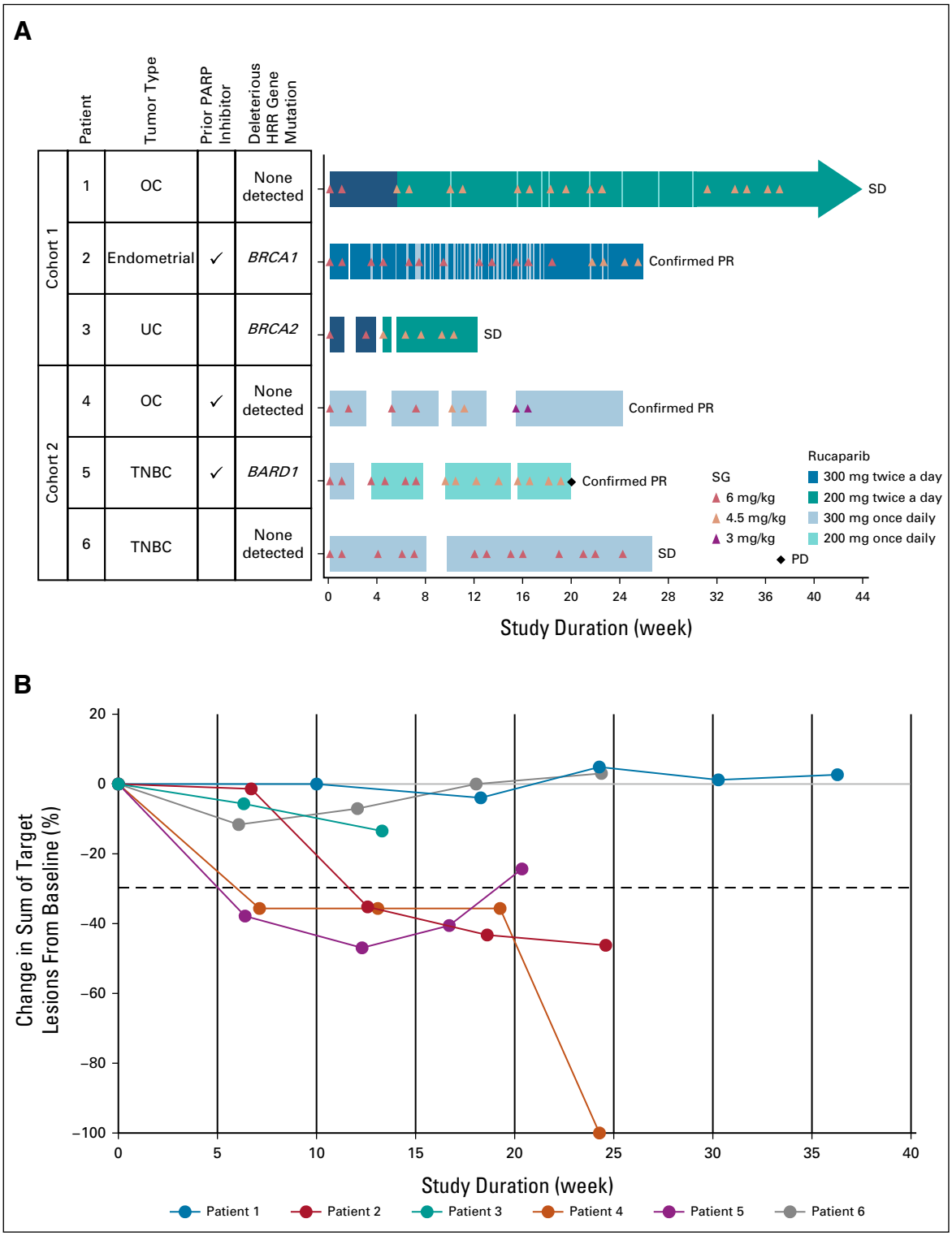

FIG 1. Overview of efficacy and treatment with rucaparib plus SG. (A) Duration of treatment and best overall response. Arrowhead denotes ongoing treatment as of the August 11, 2020, data cutoff date. (B) Change in tumor volume over time for each patient. Dotted line indicates the threshold for partial response (30% decrease from baseline). Because of the COVID-19 pandemic, SG was withheld after cycle 6 for patient 1. SG was then discontinued during cycle 11 at the patient's request. SG was withheld after cycle 4 for patient 4 because of the pandemic. *BARD1*, BRCA-associated ring domain protein 1; *BRCA1*, BRCA1 DNA repair associated; *BRCA2*, BRCA2 DNA repair associated; HRR, homologous recombination repair; OC, ovarian cancer; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; UC, urothelial cancer.

TABLE 2. TEAEs and Treatment-Related Adverse Events Reported in > 20% of Patients (≥ 2 patients)

TEAEs	Any Grade, No. (%)	Treatment-Related, Any Grade, No. (%)	Grade ≥ 3, No. (%)	Treatment-Related, Grade ≥ 3, No. (%)
Any TEAE	6 (100)	6 (100)	5 (83.3)	5 (83.3)
Neutropenia/ANC decreased	6 (100)	6 (100)	5 (83.3)	5 (83.3)
Diarrhea	5 (83.3)	4 (66.7)	0	0
ALT/AST increased	4 (66.7)	2 (33.3)	0	0
Asthenia/fatigue	4 (66.7)	3 (50.0)	0	0
Dyspnea	3 (50.0)	1 (16.7)	1 (16.7)	0
Hyponatremia	3 (50.0)	1 (16.7)	0	0
Nausea	3 (50.0)	3 (50.0)	0	0
Thrombocytopenia/platelet count decreased	3 (50.0)	3 (50.0)	1 (16.7)	1 (16.7)
Vomiting	3 (50.0)	3 (50.0)	0	0
Abdominal pain	2 (33.3)	0	0	0
Alopecia	2 (33.3)	2 (33.3)	0	0
Anemia	2 (33.3)	2 (33.3)	1 (16.7)	0
Constipation	2 (33.3)	0	0	0
Hypokalemia	2 (33.3)	0	0	0
Hypomagnesemia	2 (33.3)	0	0	0
Hypophosphatemia	2 (33.3)	2 (33.3)	0	0
Mucosal inflammation	2 (33.3)	2 (33.3)	0	0
Pruritus	2 (33.3)	2 (33.3)	0	0
Stomatitis	2 (33.3)	1 (16.7)	0	0
Upper respiratory tract infection	2 (33.3)	0	0	0
WBC count decreased	2 (33.3)	2 (33.3)	2 (33.3)	2 (33.3)

Abbreviations: ANC, absolute neutrophil count; TEAE, treatment-emergent adverse event.

Two of three patients in cohort 1 experienced DLTs of grade 4 neutropenia. No DLTs were observed in cohort 2, although grade 3/4 neutropenia led to 1- to 2-week delays in starting cycle 2 in all three patients. All patients experienced at least one treatment-emergent AE (TEAE) (Table 2). The most common TEAEs were neutropenia/decreased absolute neutrophil count (ANC) (n = 6), diarrhea (n = 5), increased ALT/AST (n = 4), and asthenia/fatigue (n = 4). Grade ≥ 3 TEAEs were reported in five patients; those reported in ≥ 2 patients were neutropenia/decreased ANC (n = 5) and decreased WBC count (n = 2), all considered treatment-related. Genotypic analysis of *ABCC2*, *SLCO1B1*, and *UGT1A1*[21,22] showed no clear trends relating patient genotype and toxicity (Data Supplement, Supplemental Table 1). With management of TEAEs via treatment interruption, dose reduction, and/or granulocyte colony-stimulating factor support, all patients continued treatment for ≥ 12 weeks, with a mean (±standard deviation) exposure of 25.7 ± 10.5 weeks for rucaparib and 22.1 ± 9.3 weeks (7.3 ± 2.9 cycles) for SG (Fig 2). As of the cutoff date of August 11, 2020, one patient with OC in cohort 1 (patient 1) remained on rucaparib for 44+ weeks (having discontinued SG after week 37 [cycle 11]).

All patients had an investigator-assessed best response of RECIST v1.1 stable disease or better (Fig 1). Three patients had a confirmed RECIST v1.1 partial response (Fig 3); all three patients were previously treated with a PARP inhibitor until disease progression (two with niraparib monotherapy, and one with veliparib plus dinaciclib), including one patient with no known deleterious HRR gene mutation (Table 1). No reversion mutations in HRR genes were identified in these three patients by central testing.

DISCUSSION

The results from this case series suggest that rucaparib plus SG has promising antitumor activity in patients with advanced solid tumors, including PARP inhibitor–exposed patients with tumors with and without HRR gene mutations. Although submaximal doses of SG and rucaparib were combined, decreases in ANC levels were observed. DLTs because of neutropenia were not unexpected, given the known toxicity profiles of Topo1 and PARP inhibitors.[12,15,23-25] In a previous study in advanced epithelial cancers, 33% of patients experienced grade ≥ 3 neutropenia with SG monotherapy.[15] Combinations of topotecan or irinotecan with olaparib or irinotecan-based

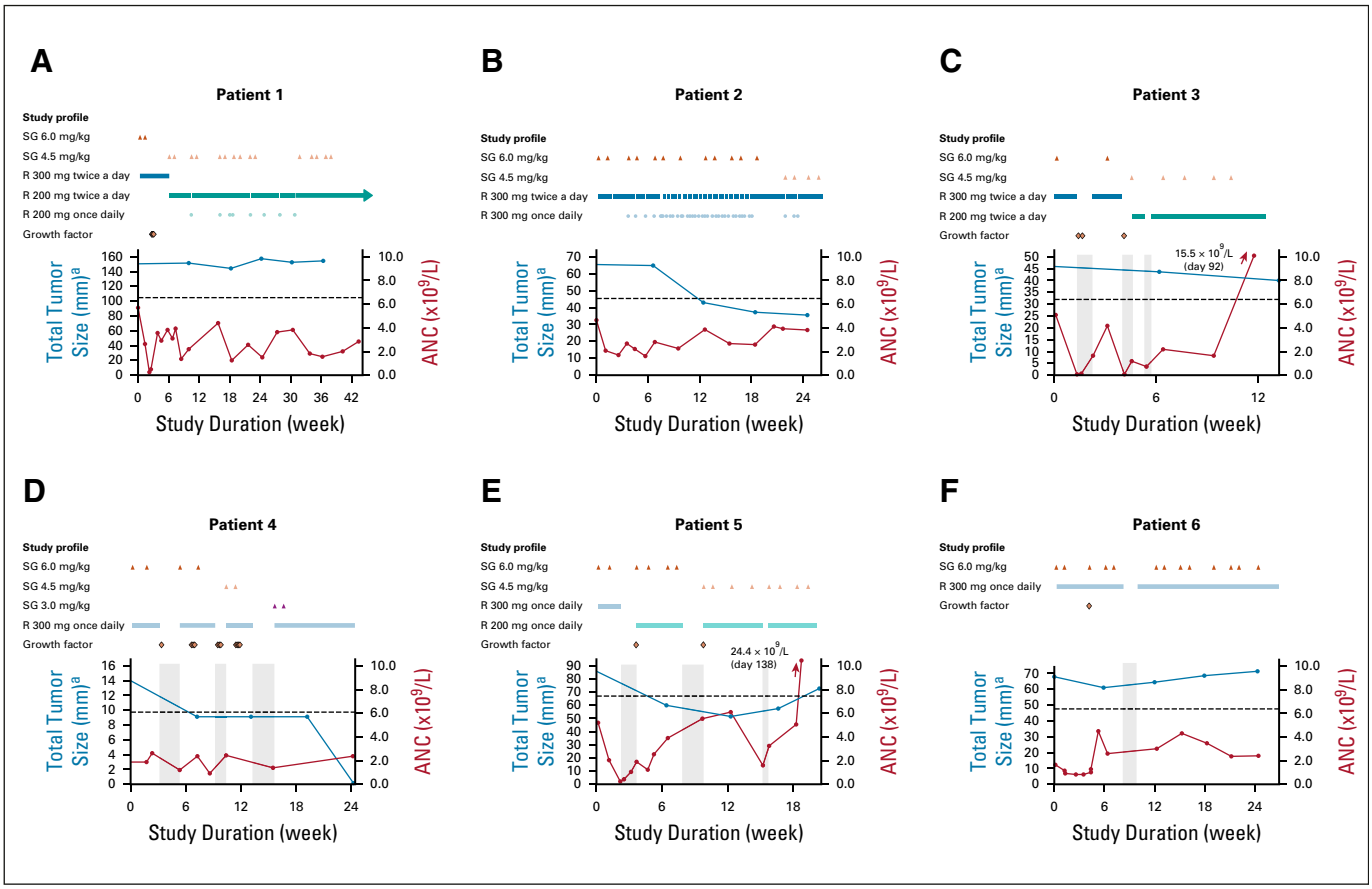

FIG 2. Investigator-assessed tumor response and ANC over the course of treatment. A timeline is included for each patient showing treatment interruptions (gray bars) and dose reductions of oral rucaparib (twice a day or once daily) and SG (administered intravenously on days 1 and 8 of a 21-day cycle), as well as administration of growth factors. Dotted line indicates the threshold for partial response (30% decrease from baseline). ANC, absolute neutrophil count; R, rucaparib; SG, sacituzumab govitecan. [a]Evaluated per RECIST v1.1.

chemotherapy with veliparib resulted in hematologic DLTs or severe toxicities and are no longer in development.[26-28] Although *UGT1A1* genotype has been linked to elevated rates of neutropenia and diarrhea with irinotecan or SG[15,22,29-31] and neutropenia with rucaparib plus irinotecan,[32] the results from this study did not show any clear relationships with such toxicities. However, correlations may have been limited by the small number of patients in this series.

In patients treated with SG monotherapy, neutropenia is typically managed with a combination of treatment interruptions, dose reductions, or granulocyte colony-stimulating factor administration.[17] By applying similar strategies in this study, all patients were able to continue therapy and had a best response of RECIST v1.1 stable disease or better. Antitumor activity in a patient with prior PARP inhibitor treatment without HRR mutation is notable, given the current unmet clinical need in identifying rational combinations capable of enhancing the efficacy of PARP inhibitor therapy in a broader range of patients beyond those harboring HRR-mutant tumors.[2,6]

In summary, the results from the SEASTAR study provide proof-of-concept clinical evidence supporting further development of PARP inhibitors in combination with ADCs carrying Topo1-inhibitor payloads. Importantly, recent data suggest that a pulse-dosing schedule of rucaparib plus irinotecan allows for long-term tolerability and has demonstrated encouraging efficacy in patients with tumors harboring *ATM* mutations.[32] Combination of other Trop-2–directed ADCs, such as datopotamab deruxtecan,[18] with more selective PARP inhibitors, such as the PARP1-targeted inhibitor AZD5305,[33] may also improve tolerability. Although no optimal recommended phase II dose was established in the current study, these data suggest that combination trials are warranted to investigate intermittent dosing of PARP inhibitors together with SG or other ADCs to reduce myelosuppression and optimize antitumor efficacy; future research may also help clarify the relative contributions of each agent to the observed antitumor activity.

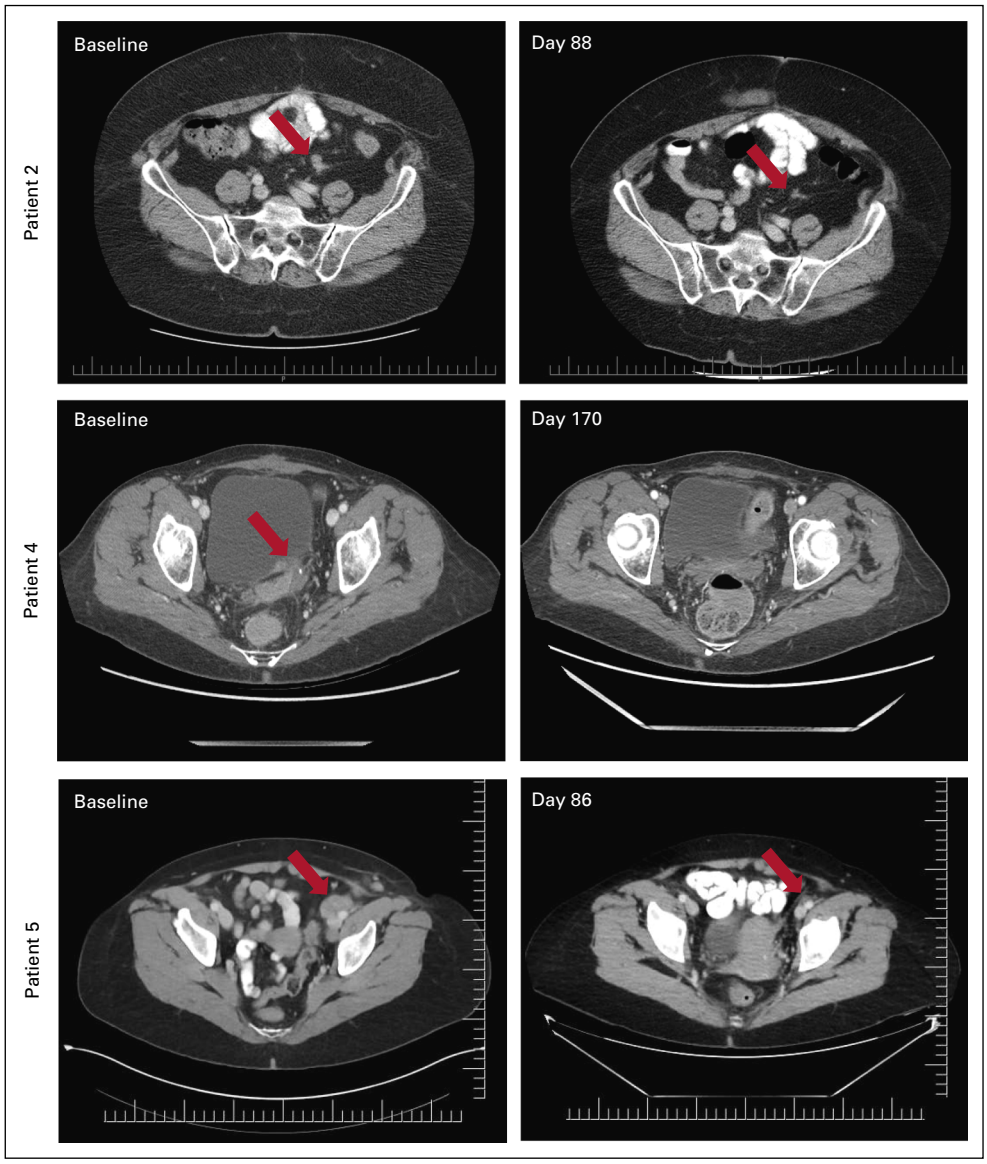

FIG 3. Representative computed tomography scans showing confirmed RECIST version 1.1 partial responses. Patient 2 had an overall 46.2% reduction in endometrial cancer tumor burden at day 88, including a 41.2% decrease in diameter of the small, left pelvic mesenteric nodule shown. Patient 4 experienced complete regression of a 1.4-cm serosal ovarian cancer metastatic implant in the posterior bladder wall by day 170. Patient 5 had a 68.6% reduction in diameter of the left iliac lymph node lesion shown here at day 86 and an overall best response of 47.1% reduction in triple-negative breast cancer tumor burden.

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PRIOR PRESENTATION

Presented in part at the European Society for Medical Oncology Virtual Congress 2020, September 17, 2020.

SUPPORT

Funded by Clovis Oncology Inc and was designed by the sponsor. Medical writing and editorial support were funded by Clovis Oncology and provided by Melanie Styers and Leslie Mitchell of Verascity Science. T. A. Y. is supported by MD Anderson Cancer Center Support grant (NIH/NCI P30 CA016672), the US Department of Defense Ovarian Cancer Research Program (OC200482), and the V Foundation Clinical Scholar Program (VC2020-001). T.A.Y. and E.E.D. acknowledge support from MD Anderson Cancer Center Support Grant No. NIH/NCI P30 CA016672, Clinical Translational Science Award No. 1UL1 TR003167, Cancer Prevention Research Institute of Texas Precision Oncology Decision Support Core RP150535, and Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy. G.I.S. is supported by the Dana-Farber/Harvard Cancer Center Support Grant No. (NIH/NCI P30 CA006516). T.A.Y. also acknowledges support from the US Department of Defense Ovarian Cancer Research Program (OC200482) and the V Foundation Clinical Scholar Program (VC2020-001).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Research Funding: Pfizer (Inst), Genentech (Inst), Bayer (Inst), Immune Design (Inst), Vertex (Inst), Millennium (Inst), Puma Biotechnology (Inst), Tensha Therapeutics (Inst), Covidien (Inst), Novartis (Inst), Cellceutix (Inst), Sanofi (Inst), Cyclacel (Inst), Mirati Therapeutics (Inst), AstraZeneca (Inst), GlaxoSmithKline (Inst), Lilly (Inst), Aileron Therapeutics (Inst), PharmaMar (Inst), PTC Therapeutics (Inst), Roche (Inst), CanBas (Inst), Tesaro (Inst), Merck Serono (Inst), Sierra Oncology (Inst), Syros Pharmaceuticals (Inst), Curis (Inst), Merck (Inst), Array BioPharma (Inst), Seattle Genetics (Inst), Clovis Oncology (Inst), Exelixis (Inst), Boehringer Ingelheim (Inst), Esperas Pharma (Inst), Amgen (Inst), Bristol Myers Squibb (Inst), AstraZeneca (Inst)
Patents, Royalties, Other Intellectual Property: Patent No.: 9872874, Title: Dosage regimen for sapacitabine and seliciclib Issue Date: January 23, 2018, Provisional Patent No.: 62/538,319, Title: Compositions and methods for predicting response and resistance to CDK4/6 inhibition, Filed: July 28, 2017
Travel, Accommodations, Expenses: Lilly, Pfizer, Bicycle Therapeutics, G1 Therapeutics, Sierra Oncology, Bayer

No other potential conflicts of interest were reported.

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