ACR-368, a CHK1/2 Kinase Inhibitor, in Patients With Relapsed or Refractory Desmoplastic Small Round Cell Tumor: Phase I/II Trial Results

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ABSTRACT

PURPOSE We hypothesized that ACR-368 (prexasertib) would be active in desmoplastic small round cell tumor (DSRCT) because of favorable responses in preclinical models.

METHODS Preclinical work identified ACR-368 activity in DSRCT, and a phase I/II trial of ACR-368 and irinotecan in patients 12 months and older with relapsed/refractory DSRCT was conducted. The primary objectives were determination of recommended phase II dose (RP2D) and best overall response rate (ORR) at the RP2D in DSRCT, with ≥3 of 16 responses considered promising.

RESULTS Preclinical data confirmed ACR-368 as potentially therapeutic in DSRCT, and 19 patients were enrolled in a subsequent clinical trial. Treatment was well tolerated, and cytopenias were managed using growth factors. Fifteen of 19 patients, including five of six achieving PR, had previously received irinotecan. The estimated ORR at the RP2D was 23% (lower boundary one-sided 90% CI, 9%), exceeding the unpromising rate of 5%. In addition, three patients with DSRCT had a PR at doses other than the RP2D, bringing the ORR for all doses (n = 19) to 32% (90% CI, 15% to 53%). The median overall survival was 19 months (95% CI, 13 to 36).

CONCLUSION The RP2D of ACR-368 with irinotecan by age group is ACR-368 105 or 150 mg/m² once on day 1 (>21 years or ≤21 years, respectively) and irinotecan 15 mg/m² once daily for 5 days in 21-day cycles for both groups. The study met its primary objective to consider ACR-368 and irinotecan promising in DSRCT and, to our knowledge, is the first incorporating a targeted therapy to achieve this magnitude of response.

ACCOMPANYING CONTENT

- Appendix
- Data Sharing Statement
- Protocol

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BACKGROUND

Desmoplastic small round cell tumor (DSRCT) is an ultrarare and aggressive cancer initially described in 1995,[1] which predominantly affects adolescent and young adult biological males. The exact incidence of DSRCT is poorly defined but has been categorized as ultrarare with <1 per 1,000,000.[2] The 5-year overall survival (OS) from retrospective series ranges from 11%[3] to 28%,[4,5] and the median OS from 16 to 37 months.[6] Recurrence despite high-intensity, multimodality therapy is common,[7,8] and new therapies to improve outcomes for patients with DSRCT are urgently required.

Checkpoint kinase proteins 1 (CHK1) and 2 (CHK2) are conserved serine/threonine kinases and are key effectors in eukaryotic cells exposed to genotoxic stress. CHK1 is activated by DNA damage and plays a key role in the intra-S and G2/M checkpoints that slow DNA replication and limit mitotic entry, respectively. Inhibition of CHK1 abrogates the DNA damage response (DDR) checkpoint, allowing cells that have sustained DNA damage to prematurely enter mitosis and undergo mitotic catastrophe because of incompletely replicated chromosomes.[9] Thus, it is postulated that CHK1 inhibition alone can generate DNA damage and induce mitotic catastrophe.

ACR-368 (formerly LY2606268 and also known as prexasertib) blocks phosphorylation of CHK proteins disrupting DNA replication, inducing DNA damage, and preventing DNA repair, leading eventually to mitotic catastrophe because of the presence of unresolved DNA breaks.[10] Histologic subtypes with high levels of replication stress and/or defects in

CONTEXT

Key Objective

Desmoplastic small round cell tumor (DSRCT) is an orphan disease with an abysmal outcome, and there have been few clinical trials dedicated toward improving outcomes for this disease. In this trial, we sought to answer if DNA damage response inhibition using a checkpoint kinase 1 inhibitor, ACR-368, in combination with irinotecan was a safe and effective strategy for the treatment of DSRCT.

Knowledge Generated

The combination of ACR-368 with irinotecan was safe, met the predefined criteria to be determined as promising, and achieved the highest overall response rate for relapsed and refractory DSRCT thus far reported. To our knowledge, this is the first trial of a targeted agent for DSRCT achieving meaningful radiographic responses and one of only several studies ever conducted with a specific focus on this disease.

Relevance *(P.L. Kunz)*

DSRCT is an ultra-rare and aggressive cancer with limited therapies and few prospective clinical trials. ACR-368 (prexasertib) blocks phosphorylation of CHK proteins disrupting DNA replication, inducing DNA damage, and preventing DNA repair. This study demonstrates that the combination of ACR-368 with irinotecan was safe and achieved the highest reported overall response rate for relapsed and refractory DSRCT. The results are promising and warrant investigation of ACR-368 in future clinical trials.*

Plain Language Statement *(M. Lewis)*

DSRCT is a rare fast-growing cancer with few treatments. ACR-368 (prexasertib) stops DNA replication, causing DNA damage, and leading to death of cancer cells. This study demonstrates that the combination of ACR-368 with irinotecan, a standard chemotherapy, was safe and achieved high shrinkage rates. The results are promising will hopefully lead to studies of ACR-368 in future clinical trials.†

*Relevance section written by *JCO Oncology Advances* Editor-in-Chief Pamela L. Kunz, MD.
†Plain Language Summary written by *JCO Oncology Advances* Associate Editor Mark Lewis, MD.

DNA damage repair pathways may therefore be susceptible to CHK1 inhibition.[11]

Clinically, ACR-368 has been previously studied as monotherapy[12-16] and in combination with other agents[17-19] and with concomitant radiation therapy[20] in multiple solid tumor histologies. A recommended phase II monotherapy dose (RP2D) for adult patients was established as 105 mg/m^2 every 14 days[12] although a subsequent study conducted by the Children's Oncology Group confirmed an acceptable RP2D of 150 mg/m^2 once every 14 days for patients 21 years and younger.[21] Response rates of up to 33% were noted in cohorts driven by biomarkers such as BRCA wild-type status,[15] but development has been hindered by overall underwhelming response rates and concern regarding tolerability of combination therapy because of myelosuppression.[22,23]

METHODS

Cell Culture

Cells were cultured in RPMI media with 10% FBS, 100 U/mL penicillin, and 100 mg/mL streptomycin and maintained at 37°C in 5% CO_2. The JN,[24] BER,[25] and DSRCT-SK2[24] cell lines were provided by Dr M.L. and were authenticated by confirmation of the presence of a EWSR1-WT1 fusion by RT-PCR and short tandem repeat DNA genotype analysis.[26]

Cell Line Screen

Cells were plated using a Multidrop Combi from Thermo Scientific at a density of 2,000 cells per well in a 25-μL volume in a 384-well format. Cell viability was analyzed using CellTiter-Glo Assay (Promega #G7571; Promega, Madison, WI). Luminescence was measured at 300 ms using a Cytation Imaging Reader by BioTek (Santa Clara, CA). Each treatment was performed in triplicate, averaged, and normalized to control to determine relative viability.

Animal Studies

Approximately 8-week-old athymic female mice were injected with 10-15 million BER cells in Matrigel. Animals were dosed with ACR-368 subcutaneously 15 mg/kg twice daily for 3 days followed by a treatment break of 4 days as had been previously established.[27,28] All experiments were performed in accordance with institutional guidelines and under an approved protocol from The Memorial Sloan Kettering

Cancer Center (MSK) Institutional Animal Care and Use Committee.

Clinical Trial Patient Eligibility

Eligible patients had relapsed or refractory DSRCT or RMS histologically confirmed at MSK, were 1 year or older with adequate organ function according to protocol definitions (Protocol), had RECIST measurable disease, and could have had any number of previous lines of therapy, including irinotecan (ClinicalTrials.gov identifier: NCT04095221). Given the preponderance of patients with DSRCT enrolled and because there was no primary efficacy end point studied in patients with RMS, this article describes the experience of patients with DSRCT only.

The trial was approved by the Institutional Review Board of MSK. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Council on Harmonization Guidelines on Good Clinical Practice, and all patients provided written informed consent before enrollment.

Study Design and Interventions

In the dose-escalation phase of the protocol, patients received ACR-368 and irinotecan in 21-day cycles (Table 1), were monitored for dose-limiting toxicities (DLTs), had extent of disease scans every two cycles (6 weeks), and were allowed to continue therapy if they did not experience DLTs, other unacceptable toxicity, or disease progression. In the dose-escalation phase, patients received ACR-368 on day 1 and irinotecan on days 1-5 or days 1-10 of a 21-day cycle (Table 1). The dose of ACR-368 in levels 2 and 2A differed depending on age because of recommended phase II monotherapy dose trials previously established in adult and pediatric patients[15,21] and not based on predicted age-based differences in pharmacokinetics or disease biology. The trial was closed before completion because of discontinuation of ACR-368 supply during the period spanning the outlicense of ACR-368 from Eli Lilly and Company to Acrivon Therapeutics, Inc.

When it was deemed safe and feasible, optional research biopsies for patients 18 years or older were offered during the screening period (14 days before the start of protocol therapy) and within 3 days after the second dose of ACR-368 although only one patient older than 18 years agreed to these analyses.

End Points and Evaluations

The primary objectives were the determination of the RP2D of ACR-368 in combination with irinotecan in the phase I portion and efficacy as assessed by best overall response rate (ORR) according to RECIST 1.1 in the phase II portion. Patients underwent computed tomography (CT) of the chest, abdomen, and pelvis with intravenous and oral contrast or CT of the chest without contrast and MR of the abdomen and pelvis with contrast for disease evaluation.

Toxicity was assessed using NCI Common Terminology Criteria for Adverse Events version 5.

Secondary objectives included assessing time to progression and OS in treated patients, and correlative/exploratory objectives included correlating tumor genomic profiling with response.

Statistical Considerations

A 3 + 3 dose-escalation schema was followed, and the RP2D was defined as the highest dose level associated with not more than one DLT of six patients. A response rate of 30% was designated as positive and worthy of further investigation for evaluation of the primary objective. These metrics were chosen given a retrospective series evaluating pazopanib in 29 patients with DSRCT whose disease had progressed on standard chemotherapies, reporting one patient with a partial response, one patient with a complete response, and 16 patients (55%) with stable disease (SD),[29] and one open-label phase II study evaluating ganitumab in patients with metastatic Ewing sarcoma and DSRCT (16 patients with DSRCT included), which reported an overall response rate of 6%.[30] Additional data regarding treatment in the relapsed and refractory setting are primarily limited to anecdotal case reports[31-33] and small retrospective series[34-36] supporting the null and positive response rates as above.

An exact, single-stage, phase II design was used for the dose expansion portion of the protocol to distinguish between an unpromising ORR of 5% and a promising ORR of 30%, with a target one-sided type-I error of 10% and a power of 90%.

TABLE 1. Dose Levels

Age ≤21 Years			Age >21 Years		
Dose Level	ACR-368	Irinotecan	Dose Level	ACR-368	Irinotecan
1 (starting)	80 mg/m^2 once on day 1	15 mg/m^2 once daily × 10 days	1 (starting)	80 mg/m^2 once on day 1	15 mg/m^2 once daily × 10 days
2	150 mg/m^2 once on day 1	15 mg/m^2 once daily × 10 days	2	105 mg/m^2 once on day 1	15 mg/m^2 once daily × 10 days
2A	150 mg/m^2 once on day 1	15 mg/m^2 once daily × 5 days	2A	105 mg/m^2 once on day 1	15 mg/m^2 once daily × 5 days
21-day cycles					

Sixteen patients treated at the RP2D were required, and if three responses were documented in 16 treated patients, the regimen would be deemed promising. The true one-sided type-I error of this design was 0.04 (power = 90%). Patients treated at the RP2D in the dose-escalation portion of the protocol were included in the dose expansion portion.

RESULTS

Preclinical Efficacy

To investigate the possible antitumor effects of DDR inhibitors in DSRCT and other solid tumors occurring in younger patients, a screen using a 26-agent panel relevant to the DDR pathway and four cytotoxic chemotherapy agents in six histologies (34 cell lines) was performed. ACR-368 demonstrated notable activity in multiple histologies including two DSRCT cell lines (JN-DSRCT, DSRCT-SK2) and was confirmed as an agent of interest for further testing (Fig 1A).

ACR-368 was next tested in a cell line–derived xenograft model using the BER cell line. Statistically significant tumor regression was demonstrated and sustained after drug removal after 28 days. Immunohistochemical analysis of tumors after 21 days of exposure to ACR-368 resulted in a statistically significant reduction in Ki67 and induction of cleaved caspase 3/7 (Fig 1B).

To further confirm activity and spur clinical trial development, ACR-368 was thereafter tested in three unique DSRCT PDX models where exquisite sensitivity, again sustained after drug exposure, was noted (Fig 1C).

Given these favorable results, a phase I/II, single-institution, investigator initiated clinical trial was planned. We hypothesized that the topoisomerase I inhibitor, irinotecan, would be tolerable and provide an exogenous source of DNA damage in combination with ACR-368, leading to a clinically relevant therapeutic combination.

Patient Characteristics

Nineteen patients with DSRCT were enrolled from December 2019 to October 2021 (Fig 2, Table 1) coincident with the COVID-19 pandemic. Only 13 of 16 planned patients were enrolled at the RP2D because of early study closure, and all 13 were evaluable for the phase II efficacy end point. Most patients were male (n = 15, 79%), consistent with the overall incidence of DSRCT by sex. Patients ranged in age from 15 to 45 (mean 27) years. Patients had received a median of three (range, 1-8) lines of previous therapy, 63% (n = 12) had previous surgery, and 53% (n = 10) had previous whole abdominopelvic radiation therapy. A majority of patients (n = 15, 79%) had previously received irinotecan with a median of 8 (range, 1-26) months since previous irinotecan exposure. For those with previous irinotecan exposure, 14 (93%) had experienced SD or partial response followed by progression (either while receiving or after receiving the agent), whereas one patient (6%) had progressive disease (PD) at the first evaluation while receiving the agent. No patients were responding to irinotecan at the time of enrollment on study.

Toxicity and Recommended Phase II Dosing

No protocol-defined dose-limiting toxicities were observed during the study (Protocol). The RP2D was ACR-368 105 or 150 mg/m² once on day 1 (>21 years or ≤21 years, respectively) and irinotecan 15 mg/m² once daily for 5 days in 21-day cycles (dose level 2A). The doses of ACR-368 differed by age because of the RP2 monotherapy doses established in the published literature.[12,21] The regimen was overall well tolerated, with the most common adverse events being cytopenias (Table 2). There were no episodes of grade 3 or 4 diarrhea. On dose levels 1 and 2, both of which administered 10 days of irinotecan 15 mg/m² once daily, all patients experienced grade 4 neutropenia between days 7 and 9 of cycle 1. This hematologic toxicity was deemed most closely related to ACR-368 as it was out of proportion to what is experienced even with higher doses of irinotecan[37] and was consistent with previous experiences with CHK1/2 inhibition.[18,21,38] This nadir resulted in incomplete administration of days 6-10 of irinotecan pending investigator discretion and overall clinical course although none of these events met criteria for protocol-defined dose-limiting toxicity. Therefore, dose level 2A with only 5 days of irinotecan was added to assist with potential toxicity and ease of use on which patients received ACR-368 105 or 150 mg/m² once daily on day 1, pegfilgrastim on day 5, and romiplostim subcutaneously once weekly to a maximum of 10 mcg/kg as clinically indicated.[39] Examples of these interventions mitigating myelosuppression are shown in Appendix Figure A1. Only two episodes of febrile neutropenia, both of which were uncomplicated, were noted throughout the trial.

Efficacy

Despite early study closure (only 13 of 16 planned patients enrolled at the RP2D), the protocol met its primary objective achieving a 23% ORR at the RP2D (three partial responses, 90% CI, 7% to 49%) and a 32% ORR (six partial responses, 90% CI, 15% to 53%) at all dose levels (Fig 3A, Table 3). Five of six patients achieving partial response had experienced previous progression of disease while receiving or after treatment with irinotecan at a median interval since irinotecan exposure of 8 months (range, 3-26; Table 4, Fig 2). Four of six patients achieving partial response had previously experienced progression of disease while receiving irinotecan-containing regimens at intervals of 4, 3, 9, and 26 months before entry onto the current trial, respectively. One patient achieving partial response had received irinotecan and temozolomide during two time periods during the first of which she had experienced clinical benefit, but during the second of which 8 months before clinical trial entry she had experienced progression of disease. One patient who achieved a partial response had not received irinotecan previously.

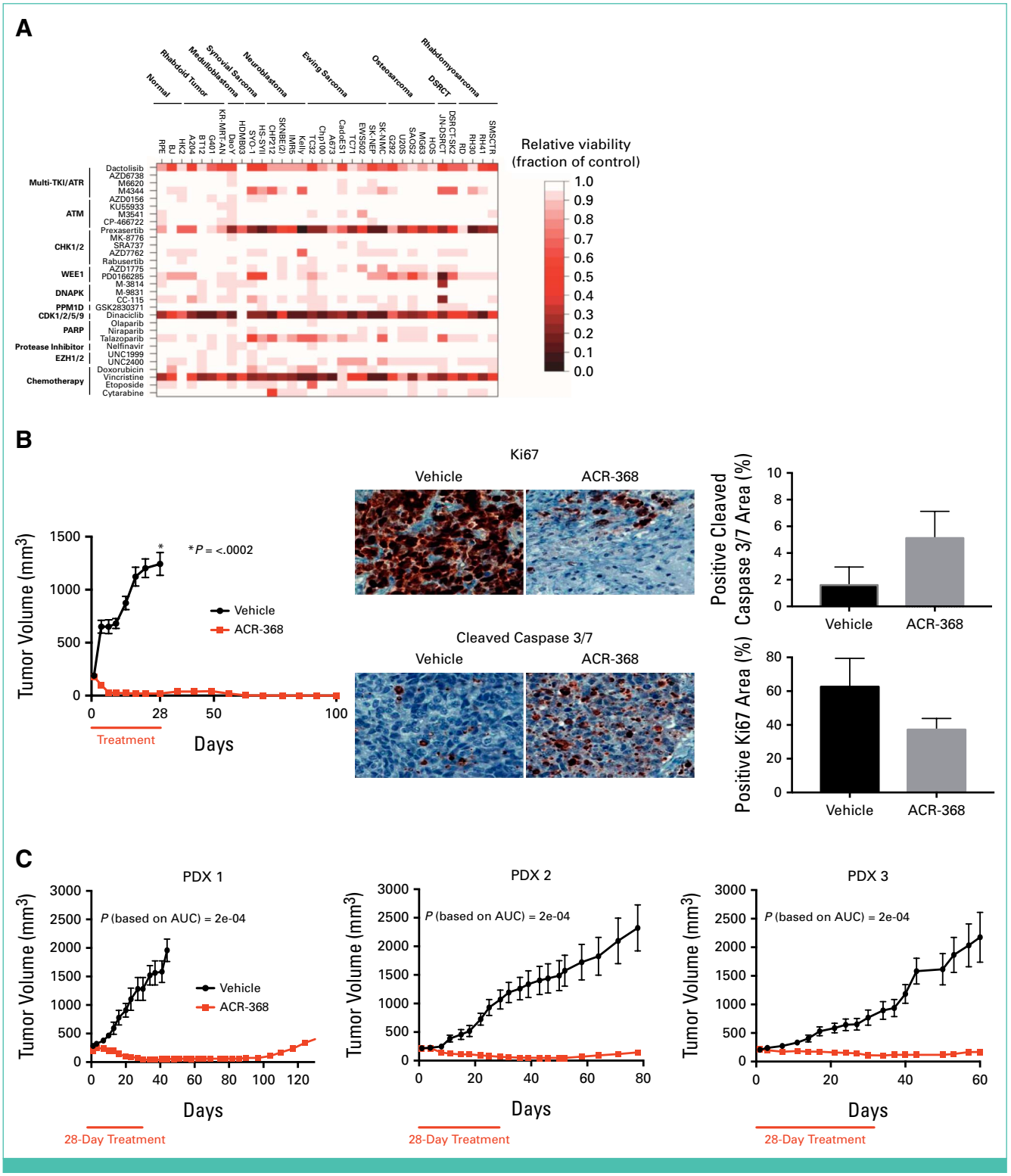

FIG 1. Desmoplastic small round cell tumor in vitro and in vivo models are sensitive to ACR-368. (A) Results from a large-scale screen of DNA-damage response and chemotherapeutic agents are depicted as a heat map using relative viability as a fraction of a negative control and confirm the sensitivity of DSRCT cell lines to Chk1/2 inhibitor ACR-368. (B) A cell line–derived xenograft model showed complete and sustained response to ACR-368 15 mg/kg administered subcutaneously twice daily for 3 days on followed by 4 days of rest. IHC analyses reveal reduction in Ki67 and induction of cleaved caspase 3/7 in tumors treated with ACR-368 for 21 days. (C) Three unique patient-derived xenograft models showed exquisite sensitivity to treatment with ACR-368 using the same schedule described in (B), with sustained regression even after withdrawal of ACR-368 after 28 days of therapy. DSRCT, desmoplastic small round cell tumor.

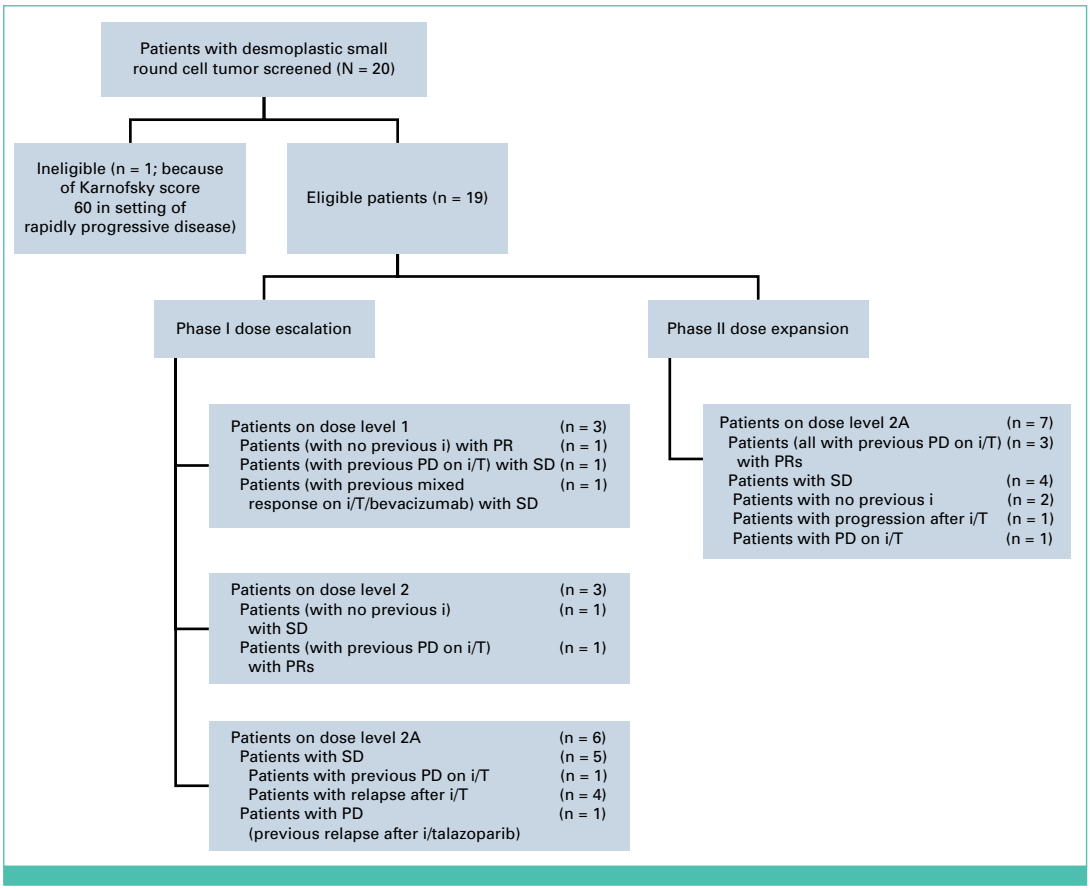

FIG 2. CONSORT diagram. i, irinotecan; PD, progressive disease; PR, partial response by RECIST criteria; SD, stable disease; T, temozolomide.

Only one patient experienced PD as their best response because of the presence of new lesions, and the 12 remaining patients all experienced SD although one of these patients was removed from protocol therapy after the first imaging time point because of physician choice given concern for progression by positron emission tomography imaging. At data cutoff, the median PFS for all treated patients was 6.2 months (Fig 3C) and the median OS was 19 months (Fig 3D).

Participants remained on therapy for a median of nine cycles or 27 weeks of therapy (range, 2-43 cycles for 6-129 weeks; one patient ongoing at the time of data cutoff; Fig 3B).

Although not initially allowed per protocol, nor a protocol-defined end point, one patient previously deemed to have unresectable disease was able to undergo surgical debulking after 14 cycles of treatment and continued to receive treatment postoperatively (21 additional cycles at the time of data cutoff), with continuous stability of modest volume residual disease.

Molecular Profiling

Sixteen and six of 19 patients had corresponding targeted hybridization capture next-generation sequencing (MSK-IMPACT)[40] and whole-genome sequencing and RNA-sequencing (WGS; RNA-seq) results[41] from at least one time point, respectively, matched to germline controls.

Targeted next-generation sequencing did not reveal recurrent findings correlating with treatment response, and WGS and RNA-seq data were too sparse for interpretation.

TABLE 2. Adverse Effects (n = 19 patients)

Dose Level	1				2				2A				Total, No. (%)
Grade	1	2	3	4	1	2	3	4	1	2	3	4	
Neutropenia				3				3	2		2	8	18 (95)
Thrombocytopenia			1	1			2				1	5	10 (53)
Anemia	2		1		1	1	1		1	2	2		11 (58)
Diarrhea	1	1			1	1							4 (21)
Fatigue	1	2			2	3			1	2			11 (58)
Nausea	1	1			3				2	2			9 (47)
Febrile neutropenia							1				1		2 (11)
AST increased	1				2		1		6	1	1		12 (63)
ALT increased	1					2	2		6	1	1		13 (68)
Bilirubin increased										1			1 (5)
Creatinine increased									1				1 (5)

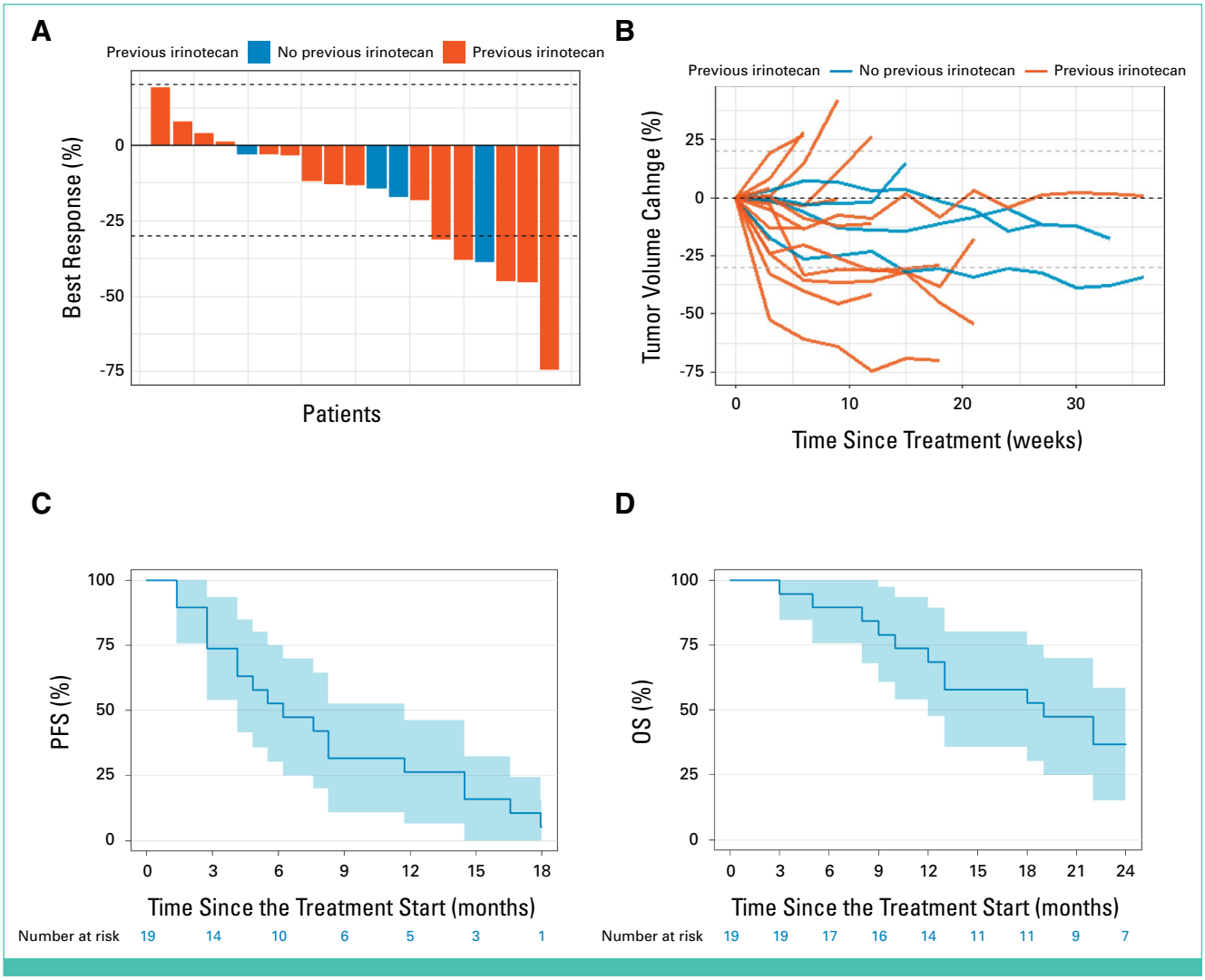

FIG 3. Tumor responses in patients with DSRCT. (A) Waterfall plot depicting best volumetric tumor response while receiving ACR-368 and irinotecan treatment, stratified by previous irinotecan and no previous irinotecan exposure. (B) Spider plot depicting volumetric tumor response over time (weeks) while receiving ACR-368 and irinotecan. (C and D) PFS and OS of clinical trial enrollees. DSRCT, desmoplastic small round cell tumor; OS, overall survival; PFS, progression-free survival.

DISCUSSION

In this signal-seeking phase I/II study, treatment with ACR-368 and irinotecan resulted in notable and durable antitumor activity in patients with heavily pretreated relapsed and refractory DSRCT, despite significant previous exposure to and significant dose reductions from traditional schedules of irinotecan. The protocol met its primary objective achieving

TABLE 3. Responses in Patients With Desmoplastic Small Round Cell Tumor by Dose Level and Previous Irinotecan Exposure

Characteristic	Overall (n = 19)[a]	1 (n = 3)[a]	2 (n = 3)[a]	2A (n = 13)[a]	No Previous Irinotecan (n = 4)	Previous Irinotecan (n = 15)
Best response						
PR	6 (32)	1 (33)	2 (67)	3 (23)	1 (25)	5 (33)
SD	11 (58)	2 (67)	1 (33)	8 (62)	3 (75)	8 (53)
CBR (PR + SD)	17 (89)	3 (100)	3 (100)	11 (85)		
SD[b]	1 (5)	0 (0)	0 (0)	1 (8)	0 (0)	1 (7)
PD	1 (5)	0 (0)	0 (0)	1 (8)	0 (0)	1 (7)

Abbreviations: CBR, clinical benefit rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a]No. (%).
[b]SD = RECIST SD but removed from trial treatment because of clinical progression of disease.

TABLE 4. Patient Characteristics

Dose Level	Overall (n = 19)[a]	1 (n = 3)[a]	2 (n = 3)[a]	2A (n = 13)[a]
Biological sex				
Female	4 (21)	0 (0)	1 (33)	3 (23)
Male	15 (79)	3 (100)	2 (67)	10 (77)
Age, years				
≤18	6 (32)	0 (0)	1 (33)	5 (38)
18-39	9 (47)	2 (67)	1 (33)	5 (38)
>39	4 (21)	1 (33)	1 (33)	3 (23)
No. of previous lines of therapy				
1	2 (11)	0 (0)	0 (0)	2 (15)
2	7 (37)	2 (67)	3 (100)	2 (15)
3	6 (32)	1 (33)	0 (0)	5 (38)
4	1 (5)	0 (0)	0 (0)	1 (8)
5	1 (5)	0 (0)	0 (0)	1 (8)
6	1 (5)	0 (0)	0 (0)	1 (8)
8	1 (5)	0 (0)	0 (0)	1 (8)
Previous irinotecan	15 (79)	2 (67)	2 (67)	11 (85)
No previous irinotecan	4 (215)	1 (33)	1 (33)	2 (15)
Interval in months since previous irinotecan	8 (1-26)	4 (2-5)	4 (3-4)	13 (1-26)
Previous surgery	12 (63)	1 (33)	2 (67)	9 (69)
Previous focal irradiation	6 (32)	1 (33)	0 (0)	5 (38)
Previous WAP irradiation	10 (53)	0 (0)	2 (67)	8 (62)
Best response				
PR	6 (32)	1 (33)	2 (67)	3 (23)
SD	12 (63)	2 (67)	1 (33)	9 (69)
PD	1 (5)	0 (0)	0 (0)	1 (8)
Best response (%)	−13.5 (−74.7 to 19.2)	−13.1 (−38.7 to 3.6)	−31.3 (−74.7 to 17.4)	−12.1 (−45.6 to 19.2)
No. of cycles	9.0 (2-43)	7.0 (4-24)	12.0 (12-21)	8.0 (2-43)

Abbreviations: PD, progressive disease; PR, partial response; SD, stable disease; WAP = whole abdomen/pelvis.
[a]No. (%); median (minimum-maximum).

at least three responses at the RP2D despite enrolling only 13 of 16 planned patients at the RP2D because of out-licensing of ACR-368. Furthermore, there were three additional responders in the study overall, yielding an overall response rate of 32%. This is, to our knowledge, the first clinical trial evaluating an investigational compound in DSRCT to achieve a response rate of this magnitude.

An additional dose level (3; ACR-368 105 or 150 mg/m² once on day 1 [>21 years or ≤21 years] and irinotecan 15 mg/m² once daily for 3 days in 14-day cycles) had been considered but was not pursued despite a lack of DLTs experienced at dose level 2A given concern for possible dose-limiting myelosuppression with more frequent ACR-368 administration and a clinical environment significantly affected by the COVID-19 pandemic. However, the presented data suggest that these toxicities can be well managed with diligent growth factor support rendering this agent, even in combination with irinotecan, well tolerated overall (Appendix Fig A1). Given this established experience, it is likely that more frequent administration would be feasible and tolerable, potentially increasing antitumor effect. Similarly, these combination toxicity data can facilitate the clinical testing of additional relevant combinations in future trials. Given that patients with DSRCT do not exhibit biomarkers of sensitivity to DDR inhibitors established in malignancies occurring in older adults such as microsatellite instability; *BRCA1/2*, *PALB2*, and *RAD51C/D* mutations, signature 3; or other syndromes associated with homologous recombination repair deficiencies, the mechanism rendering sensitivity to ACR-368 remains uncertain. Given the established evidence of fusion oncoproteins such as EWSR1:FLI1 which underlies Ewing sarcoma resulting in replication stress,[42] we can hypothesize that DSRCT's pathognomonic EWSR1:WT1 fusion might be exhibiting a similar effect and rendering sensitivity to ACR-368. Rich correlative assessments in future clinical trials will be critical including such as elements expression levels of the recombinase piggyBac transposable element–derived 5 (PGBD5)[43] and formation of R-loops.[44] Future clinical work for ACR-368 and similar agents in DSRCT will also benefit from continuous exploration of combination therapies including antibody-drug conjugates,

other cellular therapy agents with targets relevant to the surfaceome of DSRCT, radiation therapy, and, most importantly, successful intercalation into a frontline backbone of rigorous, high-intensity therapy.

There have been very few clinical trials completed with specific attention to desmoplastic small round cell tumor because of its ultrarare status, inadequately understood biology, and overall dismal outcomes. In addition, DSRCT occurs predominantly in adolescent and young adult patients, a cohort which suffers from distinct psychosocial challenges and generally low clinical trial enrollment[45] further complicating systematic interrogations. However, this study proves that histology-specific, signal-seeking trials in orphan cancers are feasible and useful and can achieve rapid accrual even in the face of barriers such as the COVID-19 pandemic.

Limitations of our study include its small size, the absence of a comparator group, and the concomitant use of an active chemotherapy agent confounding interpretation of the efficacy of ACR-368. The doses of irinotecan administered on this trial were lower than those used in standard regimens with the primary intention of providing an additional source of DNA damage rather than tumor efficacy on its own. Traditional irinotecan-containing regimens often contain between 200[46] and 250 mg/m^2/cycle,[47,48] compared with 150 mg/m^2/cycle on dose level 2 (although irinotecan was often truncated because of neutropenia as described above) and 75 mg/m^2/cycle at the RP2D of dose level 2A. Finally, five of six patients achieving partial responses on this trial had previously progressed while receiving irinotecan-containing regimens (Fig 2), all at higher doses than were administered in this trial.

In conclusion, ACR-368 with irinotecan was tolerable and clinically active in a population of patients with heavily pretreated DSRCT, despite previous irinotecan exposure in most patients. This positive signal resulting in clinical benefit for these patients with currently incurable disease is encouraging and should be further investigated in additional clinical trials.

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A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/OA-24-00095. Individual data that underlie the results reported in this article will be available after deidentification upon appropriate (methodologically sound proposal) request to the corresponding author upon publication. Relevant portions of the study protocol are provided as a supplement to this article.

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APPENDIX

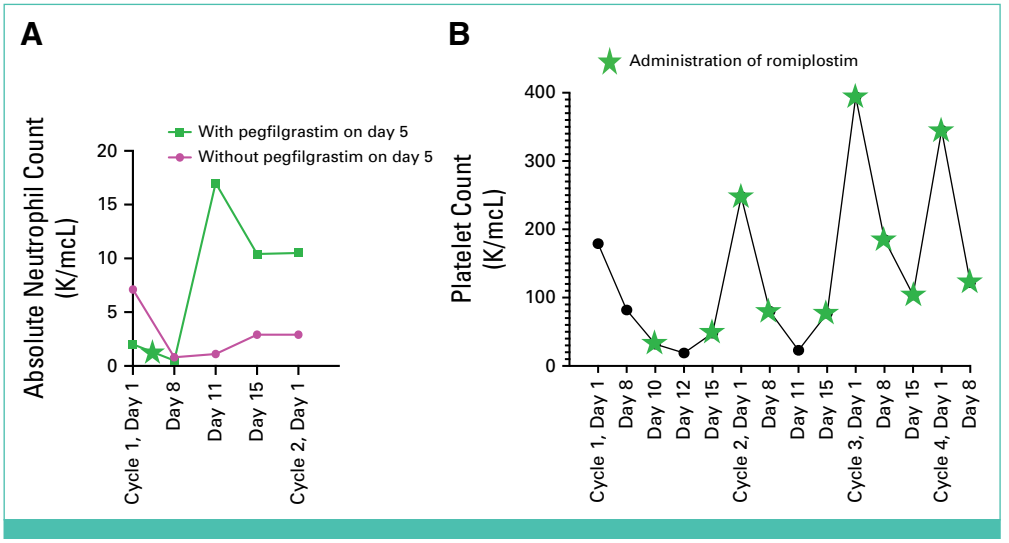

FIG A1. Successful management of myelosuppression because of ACR-368 with growth factors. (A) Neutropenic and (B) thrombocytopenic nadirs experienced in a single patient after exposure to ACR-368 were successfully managed with pegfilgrastim administration at approximately day 5 of each cycle and romiplostim administered once a week.