Overcoming Taxane Resistance: Preclinical and Phase 1 Studies of Relacorilant, a Selective Glucocorticoid Receptor Modulator, with Nab-Paclitaxel in Solid Tumors

Pamela N. Munster[1], Andrew E. Greenstein[2], Gini F. Fleming[3], Erkut Borazanci[4], Manish R. Sharma[3], Joseph M. Custodio[2], Iulia Cristina Tudor[2], Hristina I. Pashova[2], Stacie Peacock Shepherd[2], Andreas Grauer[2], and Jasgit C. Sachdev[4]

ABSTRACT

Purpose: Chemotherapy resistance remains a major problem in many solid tumors, including breast, ovarian, and pancreatic cancer. Glucocorticoids are one potential driver of chemotherapy resistance as they can mediate tumor progression via induction of cell-survival pathways. We investigated whether combining the selective glucocorticoid receptor (GR) modulator relacorilant with taxanes can enhance antitumor activity.

Patients and Methods: The effect of relacorilant on paclitaxel efficacy was assessed in OVCAR5 cells *in vitro* and in the MIA PaCa-2 xenograft. A phase 1 study of patients with advanced solid tumors was conducted to determine the recommended phase 2 dose of relacorilant + nab-paclitaxel.

Results: In OVCAR5 cells, relacorilant reversed the deleterious effects of glucocorticoids on paclitaxel efficacy ($P < 0.001$). Compared with paclitaxel alone, relacorilant + paclitaxel reduced tumor growth and slowed time to progression in xenograft models (both $P < 0.0001$). In the heavily pretreated phase 1 population [median (range) of prior regimens: 3 (1–8), prior taxane in 75.3% (55/73)], 33% (19/57) of response-evaluable patients achieved durable disease control (≥16 weeks) with relacorilant + nab-paclitaxel and 28.6% (12/42) experienced longer duration of benefit than on prior taxane (up to 6.4×). The most common dose-limiting toxicity of the combination was neutropenia, which was manageable with prophylactic G-CSF. Clinical benefit with relacorilant + nab-paclitaxel was also associated with GR-regulated transcript-level changes in a panel of GR-controlled genes.

Conclusions: The observed preclinical, clinical, and GR-specific pharmacodynamic responses demonstrate that selective GR modulation with relacorilant combined with nab-paclitaxel may promote chemotherapy response and is tolerable. Further evaluation of this combination in tumor types responsive to taxanes is ongoing.

Introduction

Primary or acquired chemotherapy resistance, including resistance to taxanes, remains a major problem in many solid tumors. One potential mechanism of resistance is driven by glucocorticoids, which induce cell-survival pathways that may directly reduce chemotherapy efficacy. Endogenous glucocorticoid elevation has been reported in diverse cancer types, including breast, ovarian, squamous, cervical, and lymphomas (1–5), and is usually associated with adverse outcomes. The glucocorticoid receptor (GR) is expressed in many solid tumor types, including pancreatic and ovarian (6). High GR expression correlates with lower progression-free survival (PFS) in patients with ovarian cancer (7), and a gene signature based on GR-target genes is associated with elevated risk of early recurrence in breast cancer (8).

Glucocorticoids increase the expression of antiapoptotic genes such as serum glucocorticoid-regulated kinase 1 (*SGK1*) and dual specificity phosphatase 1 (*DUSP1*; refs. 9, 10). These genes reduce apoptosis via modulating *BCL2* and *FOXO3a* activities (11, 12). Preclinical studies in multiple solid tumor types, including pancreatic (13), ovarian (14, 15), prostate (16–18), and triple-negative breast cancer (19, 20), demonstrate that GR antagonism can suppress *SGK1* and *DUSP1* (15) and sensitize cells to chemotherapy-induced cytotoxicity. Even physiological cortisol levels can suppress tumor cell apoptosis, and GR antagonism can restore chemosensitivity and enhance platinum and taxane efficacy (13). These data provide a mechanistic rationale for combining a GR antagonist with chemotherapy in patients with solid tumors. Here, we report the results of preclinical studies and a phase 1 clinical trial (NCT02762981) exploring whether GR modulation can alter signaling pathways involved in cell survival to enhance tumor response to taxane therapy.

Nab-paclitaxel (Abraxane, nanoparticle albumin-coated paclitaxel) is approved for the treatment of breast cancer, non–small cell lung cancer, and pancreatic cancer. Unlike paclitaxel, nab-paclitaxel does not require pre-medication with corticosteroids (GR agonists) to reduce the risk of hypersensitivity reactions (21, 22), and is thus well suited for combination with a GR modulator. Data from a small study evaluating nab-paclitaxel with the non-selective GR antagonist mifepristone in 9 patients with metastatic breast cancer showed

[1]Department of Medicine (Hematology/Oncology), University of California San Francisco, San Francisco, California. [2]Corcept Therapeutics, Menlo Park, California. [3]Department of Medicine, the University of Chicago, Chicago, Illinois. [4]HonorHealth Research Institute, Scottsdale, Arizona.

Current address for M.R. Sharma: START Midwest, Grand Rapids, MI; current address for S.P. Shepherd, Fore Biotherapeutics, Philadelphia, PA; current address for A. Grauer, Federation Bio, South San Francisco, CA; and current address for J.C. Sachdev, Biosplice Therapeutics, San Diego, CA.

P.N. Munster and A.E. Greenstein contributed equally as co-authors of this article.

Corresponding Author: Pamela N. Munster, University of California, San Francisco, Box 1711, San Francisco, CA 94143. Phone: 415-502-3414; E-mail: Pamela.Munster@ucsf.edu

Clin Cancer Res 2022;28:3214–24

doi: 10.1158/1078-0432.CCR-21-4363

Translational Relevance

Chemotherapy resistance remains a key challenge in the treatment of solid tumors, and glucocorticoids can facilitate resistance by suppressing the apoptotic pathways (e.g., *BCL2* and *FOXO3a*) that cytotoxic agents, including taxanes, rely upon. The glucocorticoid receptor (GR) is expressed in many solid tumor types, including pancreatic and ovarian cancer, and higher GR expression correlates with lower median progression-free survival in certain solid tumors. Preclinical studies indicate that relacorilant, a selective GR modulator, may be able to restore chemosensitivity and enhance platinum and taxane efficacy by reversing cortisol's antiapoptotic effects. Here, we report further preclinical data as well as the results of a phase 1 study of relacorilant + nab-paclitaxel in patients with advanced solid tumors, including those with prior taxane exposure, which provide evidence that relacorilant may promote chemotherapy response.

response in 4/5 patients with tumors strongly positive for GR (22). As mifepristone also binds to the progesterone receptor, it is associated with undesirable side effects, including endometrial hypertrophy and the potential for vaginal bleeding. Relacorilant (CORT125134, Corcept Therapeutics), the potent GR modulator used in this study, selectively antagonizes GR ($K_i = 0.5$ nmol/L) and does not bind significantly to the androgen or progesterone receptors ($K_i > 10$ μmol/L; ref. 23).

The ability of relacorilant to antagonize GR activation was demonstrated in several preclinical studies (23). A study in healthy volunteers confirmed on-target pharmacological activity of relacorilant by preventing the effects of prednisone on immune-cell trafficking and expression of GR-controlled genes (24). Relacorilant monotherapy was well tolerated and safe in healthy volunteers (NCT03442621; ref. 24) and patients with Cushing syndrome (NCT02804750; ref. 25). Two phase 3 studies in patients with Cushing syndrome are ongoing (NCT03697109 and NCT04308590).

In the phase 1 dose-escalation study presented in this article, we investigated the safety, efficacy, tolerability, pharmacokinetics (PK), and pharmacodynamics of two different dosing regimens of relacorilant combined with nab-paclitaxel in solid tumors. Daily dosing of relacorilant was investigated for its continuous antagonism of GR-mediated chemotherapy resistance pathways and improved immune function through suppression of endogenous glucocorticoid activity. Higher doses of relacorilant administered intermittently with nab-paclitaxel were thought to yield higher GR antagonism around times of greatest chemotherapy exposure while improving tolerability (**Fig. 1**). A plain language summary of this article is available as Supplementary Fig. S1.

Patients and Methods

Clinical trial design

This phase 1, single-arm, open-label, multicenter study of relacorilant + nab-paclitaxel in patients with solid tumors (NCT02762981) was sponsored by Corcept Therapeutics, conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board at each participating center. Informed written consent was obtained from each participant or their guardian.

The primary objective of this study was to determine the MTD and development regimen of relacorilant + nab-paclitaxel in patients with solid tumors. Secondary objectives included characterization of the safety profile, PK, and pharmacodynamics of the combination and assessment of preliminary anticancer activity (best response by RECIST v1.1; ref. 26). A standard 3+3 dose-escalation design was used (**Fig. 1**). Nab-paclitaxel (60, 80, or 100 mg/m^2) was administered intravenously on days 1, 8, and 15 of each 28-day cycle until disease progression, unmanageable toxicity, or withdrawal from treatment. Continuous (daily) and intermittent (on the day before, day of, and day after nab-paclitaxel administration) dosing of relacorilant (100, 150, or 200 mg) were evaluated. Cycle 1 was preceded by a 1-week nab-paclitaxel lead-in and a 7-day relacorilant lead-in to evaluate for drug interactions (continuous dosing) and each 1-day lead-in of relacorilant with no nab-paclitaxel (intermittent dosing); see **Fig. 1** for details. On the basis of preliminary indications of efficacy, expansion cohorts for pancreatic ductal adenocarcinoma (PDAC) were enrolled.

Study participants

Patients (≥18 years) with any advanced or metastatic solid tumors who had disease progression with measurable or evaluable disease, for whom nab-paclitaxel was an appropriate therapy in the opinion of the investigator, were eligible for inclusion. Treatment with up to 3 prior lines of cytotoxic or myelosuppressive therapy in the advanced setting and previous nab-paclitaxel were allowed. Eastern Cooperative Oncology Group performance status of 0–1 as well as adequate renal, hepatic, and marrow function was required. Patients requiring treatment with chronic or frequently used oral corticosteroids (e.g., for rheumatoid arthritis or immunosuppression after organ transplantation) were excluded. Further inclusion and exclusion criteria can be found in the Supplementary Appendix.

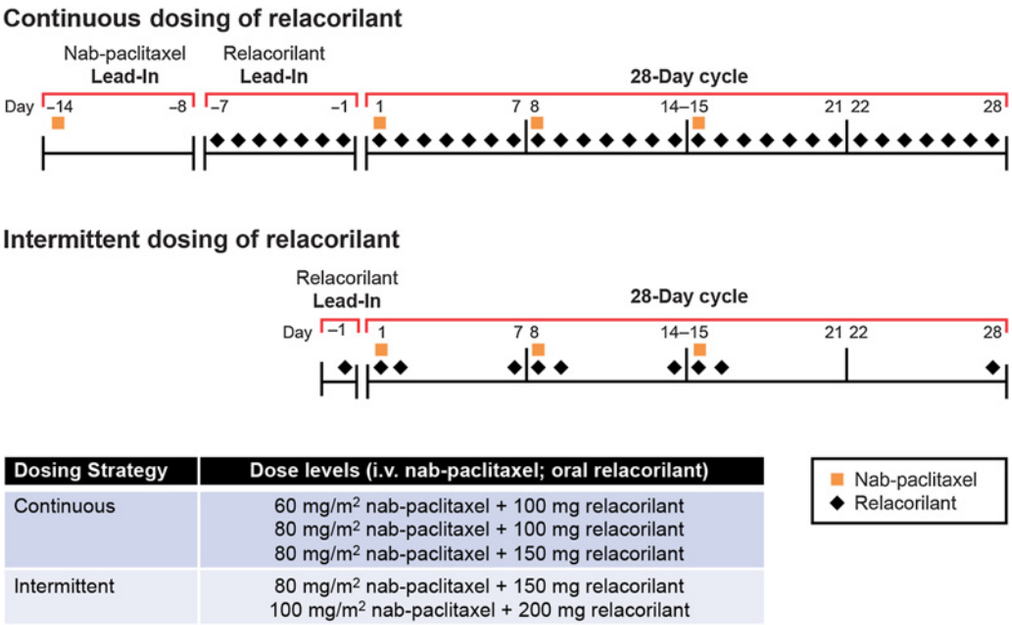
Assessments

Safety was assessed by the incidence of treatment-related AEs in all patients who had received at least 1 dose of relacorilant (safety population); the response-evaluable population included patients who had at least 1 post-baseline tumor assessment. Radiographic tumor assessments were performed at screening and every 6–8 weeks from cycle 1 day 1 (C1D1) per RECIST v1.1.

Dose-limiting toxicities (DLT) were assessed at each dose level from the first dose of relacorilant through the end of cycle 1. For hematologic events, DLTs were defined as grade 4 neutropenia lasting >7 days, grade ≥3 febrile neutropenia, grade 4 thrombocytopenia or grade ≥3 thrombocytopenia lasting >7 days or associated with grade ≥2 bleeding, and dose delay >7 days of scheduled chemotherapy secondary to myelosuppression. For non-hematologic events, any AE not attributable to disease or disease-related processes that was grade ≥3 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03 or that resulted in a dose omission or more than 1-week delay of nab-paclitaxel was considered a DLT.

PK

Plasma concentrations of relacorilant and nab-paclitaxel were determined by validated LC-MS/MS bioanalytical assays (MicroConstants). Primary PK parameters were estimated by noncompartmental analysis using Phoenix Winnonlin v8.2 (Certara). For continuous dosing, PKs were characterized after dosing with nab-paclitaxel alone (nab-paclitaxel lead-in day 1), after 7 days of dosing with relacorilant alone (relacorilant lead-in days 1 and 7), and after dosing with nab-paclitaxel + relacorilant during cycle 1 (days 1, 8, 9, and 15). For



Dosing Strategy	Dose levels (i.v. nab-paclitaxel; oral relacorilant)
Continuous	60 mg/m^2 nab-paclitaxel + 100 mg relacorilant 80 mg/m^2 nab-paclitaxel + 100 mg relacorilant 80 mg/m^2 nab-paclitaxel + 150 mg relacorilant
Intermittent	80 mg/m^2 nab-paclitaxel + 150 mg relacorilant 100 mg/m^2 nab-paclitaxel + 200 mg relacorilant

Figure 1.

Study design and dosing schedule for continuous and intermittent dosing of relacorilant + nab-paclitaxel. Starting doses were relacorilant 100 mg + nab-paclitaxel 80 mg/m^2 (continuous) and relacorilant 200 mg + nab-paclitaxel 100 mg/m^2 (intermittent). Relacorilant and nab-paclitaxel doses were escalated/de-escalated per Data Review Committee recommendation as shown, based on exposure and safety data.

intermittent dosing, PKs were characterized during treatment with the combination during cycle 1 only (days 1, 2, and 15).

Pharmacodynamics

GR-controlled genes were identified on the basis of a literature search and a separate healthy-volunteer study after systemic dosing with prednisone (NCT03335956). Probes specific to each identified gene were designed and generated by NanoString Technologies. Transcriptional effects were measured in whole blood at baseline and C1D15 in 46 patients. Whole blood was collected in Paxgene (Preanalytix) tubes. RNA was extracted and quantified on an nCounter Flex (NeoGenomics). Data were analyzed and adjusted *P* values (with Benjamini–Yekutieli FDR corrections) were determined in nSolver 4.0 (NanoString Technologies). Cross-validated random forest techniques were used to derive a gene signature that could predict clinical response (Ardigen SA, Krakow, Poland, Study WO5).

Statistical analysis

Baseline characteristics and safety data were assessed using descriptive summary statistics. For best-overall-response analysis, investigator-assessed response by RECIST v1.1 was determined and summarized. All statistical analyses were performed with SAS version 9.4 unless otherwise stated.

In vitro studies

In vitro studies in OVCAR5 cells were performed as previously described in (13). OVCAR5 cells (ATCC) were seeded in 96-well plates (Corning Costar Cat.# 3917) in media containing 2.5% FBS (Charles River Laboratories). After 48 hours, paclitaxel (Sigma-Aldrich) ± 100 nmol/L dexamethasone (Sigma-Aldrich) ± 450 nmol/L relacorilant were added. After another 72 hours, 100 μL of Cell Titer-Glo (Promega) reagent was added to each well and luminescence was quantified on the Synergy II microplate reader (BioTek). Data were normalized to controls, either equivalent volumes of dimethyl sulfoxide or empty wells. A non-parametric *t* test was conducted to compare normalized percentage of viability at 1,000 nmol/L paclitaxel, 100 nmol/L dexamethasone, ± 450 nmol/L relacorilant using Microsoft Excel. Charles River Laboratories study number: e533.

In vivo studies

Xenograft studies similar to those previously described in (13) were performed. Here, 3 doses of paclitaxel (7.5 mg/kg) were administered intravenously on days 8, 12, and 16. Animals were terminated when tumor volumes surpassed 1,250 mm^3 or at 65 days after tumor inoculation, whichever occurred first. Complete response (CR) was confirmed by hematoxylin and eosin–stained, formalin-fixed, paraffin-embedded tissue resected from the site of injection with no visible tumor cells at the end of study. Tumor growth inhibition (TGI%) was calculated using the formula:

$$\mathrm{TGI\%} = (1 - [T_i - T_0]/[V_i - V_0]) \times 100,$$

where T_0 and V_0 are the mean volumes of the treatment and control groups at day 0, respectively, and T_i and V_i are the mean tumor volume of the treatment and control groups on day 23. The experimental protocol was approved by the Institutional Animal Care and Use Committee (IACUC) at CrownBio (study number P1847).

Data availability

The data generated in this study are not publicly available due to concerns regarding patient privacy and consent but are available upon reasonable request from the corresponding author.

Raw data for **Figs. 1** and **3** of this article were generated at Charles River Laboratories (**Fig. 1B** and **C**), Crown Bio (**Fig. 1D** and **E**),

Neogenomics (**Fig. 3A**, **C**, and **D**), and Ardigen (**Fig. 3B** and **E**). Derived data supporting the findings presented in these figures are available from the corresponding author upon request.

Results

Preclinical studies

Effects of cortisol on cell survival and immune-related pathways are summarized in (13, 27–30). *In vitro*, glucocorticoid (100 nmol/L dexamethasone) decreased the cytotoxic activity of paclitaxel in OVCAR5 cells (**Fig. 2B**). Although the IC_{50} value of paclitaxel was not significantly affected by relacorilant, the maximum efficacy (as quantified by percentage viability) was improved. Relacorilant dose dependently reversed the effects of glucocorticoid, reducing the number of residual viable cells at the maximum paclitaxel dose (1,000 nmol/L) from 38.9% to 23.3% ($P < 0.001$; **Fig. 2C**)

Relacorilant has been shown to promote apoptosis and improve the activity of diverse cytotoxic agents, including 7.5 mg/kg paclitaxel, in multiple xenograft studies (13). To determine whether the combination of relacorilant and paclitaxel is additive or synergistic, the 2 agents were combined such that the activity of each agent alone could be clearly distinguished from the combination. MIA PaCa-2 xenografts (**Fig. 2D**) were treated with 1 cycle (3 doses) of paclitaxel with or without continuous relacorilant ($n = 10$/group). Although 7.5 mg/kg paclitaxel is active in this model when administered for 21+ days (13), the 3 doses administered here (vertical lines) did not significantly slow tumor growth. Relacorilant alone showed no efficacy. The combination, however, reduced both tumor growth and time to progression ($P < 0.0001$; quantified as time to tumor volume ≥400 mm^3) when compared with either agent alone. After 23 days of dosing, TGI was 34.3% for paclitaxel alone, 2% for relacorilant alone, and 92.6% for the combination. Relacorilant + paclitaxel also resulted in 1 histologically confirmed CR, as compared with 0 in the monotherapy groups. The efficacy of the combination was greater than the sum of both agents alone, underscoring the synergy observed for this combination *in vivo*.

Clinical study participants

Eighty-five patients with advanced solid tumors, who had progressed on and/or did not tolerate multiple previous lines of chemotherapy, were enrolled (Supplementary Fig. S1). Seventy-three patients received at least 1 dose of relacorilant, 57 were evaluable for

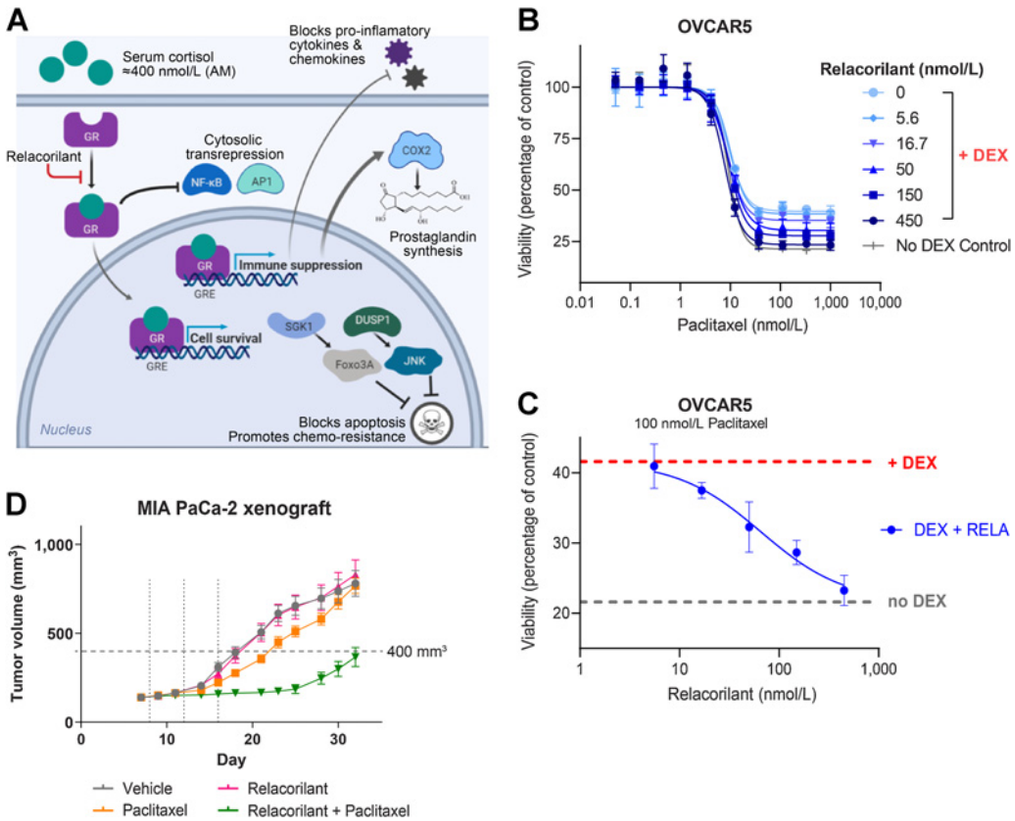


Figure 2.

GR antagonism overcomes resistance to taxanes. **A,** Cortisol promotes cell survival by deactivating apoptotic pathways induced by paclitaxel (27). Immunosuppressive effects of cortisol are also depicted (28). **B,** In OVCAR5 cells, DEX reduces paclitaxel cytotoxicity and relacorilant restores paclitaxel maximum efficacy (nonparametric *t* test comparing viability at 1,000 nmol/L paclitaxel with DEX ± 450 nmol/L relacorilant $P < 0.001$, $n = 4$/data point). **C,** Similarly, DEX increases the fraction of drug-tolerant cells when added to paclitaxel in OVCAR5 cells. Addition of relacorilant to paclitaxel + DEX decreases the fraction of drug-tolerant cells in a dose-dependent manner (mean ± SD shown, $n = 4$/data point). **D,** In a pancreatic cancer xenograft, the combination of relacorilant (30 mg/kg) + paclitaxel (7.5 mg/kg) reduces tumor growth and time to progression ($n = 10$ mice/group). Dashed vertical lines indicate days of paclitaxel administration (mean ± SEM shown). DEX, dexamethasone; RELA, relacorilant.

Table 1. Patient baseline characteristics.

	Continuous dosing				Intermittent dosing				
	PDAC	Ovarian cancer	Other solid tumors	Total	PDAC	Ovarian cancer	Other solid tumors	Total	Total
Safety population, *n*	34	5	15	54	3	9	7	19	73
Age (y), mean (SD)	61.6 (10.3)	43.8 (16.4)	59.0 (14.1)	59.2 (12.9)	67.0 (10.0)	58.2 (10.2)	61.9 (14.0)	60.9 (11.5)	59.7 (12.5)
Sex, female, *n* (%)	15 (44.1%)	5 (100%)	13 (86.7%)	33 (61.1%)	3 (100%)	9 (100%)	5 (71.4%)	17 (89.5%)	50 (68.5%)
Prior lines of cancer therapy, mean (SD)	2.6 (1.0)	4.0 (1.2)	3.9 (2.2)	3.1 (1.5)	3.7 (1.5)	4.0 (1.3)	3.6 (1.6)	3.8 (1.4)	3.3 (1.5)
Prior taxane, *n* (%)	26 (76.5%)	5 (100%)	10 (66.7%)	41 (75.9%)	3 (100%)	9 (100%)	2 (28.6%)	14 (73.7%)	55 (75.3%)
Response evaluable, *n*	26	4	11	41	1	9	6	16	57
Prior taxane, *n* (%)	20 (76.9%)	4 (100%)	7 (63.6%)	31 (75.6%)	1 (100%)	9 (100%)	1 (16.7%)	11 (68.8%)	42 (73.7%)
Dose-limiting toxicity evaluable, *n*	23	4	10	37	3	6	5	14	51

Note: Cancer types in the other solid tumors group included breast (3/15, 20.0%), triple-negative breast cancer or melanoma (2/15, 13.3% each), and pancreatic, sarcoma, cervical, and rectal cancer (1/15, 6.7% each). Ovarian cancer includes fallopian tube or primary peritoneal cancer.

response, and 51 were evaluable for DLTs (**Table 1**). Thirty-seven (50.7%) patients had PDAC and 14 (19.2%) had ovarian cancer (including fallopian tube or primary peritoneal cancer). Reasons for ending treatment are shown in Supplementary Table S1. Dose reductions of relacorilant or nab-paclitaxel were reported in 14 and 17 patients, respectively. AEs leading to dose reduction were rash, anorexia, colitis, fatigue, hyperbilirubinemia, and mucositis for relacorilant and peripheral neuropathy, anorexia, decreased neutrophil count, diarrhea, fatigue, febrile neutropenia, and mucositis for nab-paclitaxel.

PK

As relacorilant is a strong CYP3A4 inhibitor (31) and nab-paclitaxel is metabolized by CYP3A4 (32, 33), the potential for drug–drug interactions was evaluated. Mean PK parameters for nab-paclitaxel 80 mg/m^2 alone or combined with relacorilant 100 mg were measured on lead-in day 1 and C1D8, respectively. Relacorilant levels were similar whether administered alone or with nab-paclitaxel. In contrast, nab-paclitaxel exposures were increased by coadministration with relacorilant compared with nab-paclitaxel alone [AUC 4,550 (%CV 97) vs. 2,530 (%CV 28) ng*h/mL). The increase in nab-paclitaxel exposure was observed in all examined relacorilant dose levels and dosing schedules. Nab-paclitaxel 80 mg/m^2 in combination with relacorilant was found to approximate 100–125 mg/m^2 nab-paclitaxel monotherapy.

Safety

Fifty-four study participants (74.0%) experienced at least 1 adverse event (AE) of grade ≥3. No significant differences in AE profile were observed between continuous and intermittent dosing. The most common AEs of grade ≥3 were neutropenia (21.9%), anemia (9.6%), abdominal pain (8.2%), hyponatremia (6.9%), hypophosphatemia (6.9%), mucosal inflammation (6.9%), febrile neutropenia (5.5%), pleural effusion (5.5%), and vomiting (5.5%; **Table 2**). AEs that were considered DLTs are also listed in **Table 2**. Dermatological AEs (any grade) included skin disorders (40/73, 54.8%; including rash, maculopapular rash, acne, acneiform dermatitis, dry skin, pruritic rash, pruritus, cellulitis, and skin abrasion in ≥2 patients) and skin hyperpigmentation (19/73, 26.0%; skin disorders/hyperpigmentation combined: 42/73; 57.5%). Skin disorders and hyperpigmentation led to drug withdrawal or dose interruption in 2/73 (2.7%) and 7/73 (9.6%) patients, respectively. Acne was experienced by 11/73 (15.1%), leading to a dose reduction in 1/73 (1.4%). Acneiform skin conditions were treated with topical corticosteroids and cellulitis with antibiotics.

Forty study participants (54.8%) experienced a serious AE, including 8 that led to death (4 related to disease progression; 1 each of urosepsis in the setting of neutropenia, large bowel obstruction secondary to disease progression, respiratory failure, and transfusion-related acute lung injury). In 9 patients (12.3%), serious AEs were considered related to relacorilant (**Table 2**).

Neutropenia with nab-paclitaxel dose delay >7 days and febrile neutropenia were the most common DLTs at the starting dose levels (continuous: relacorilant 100 mg + nab-paclitaxel 80 mg/m^2; intermittent: relacorilant 200 mg + nab-paclitaxel 100 mg/m^2). As a result, primary prophylaxis with G-CSF became mandatory in later cohorts and one or both study drug doses were de-escalated, with later re-escalation in the continuous arm. Initially, prophylactic growth-factor use was restricted during cycle 1 per protocol and patients who received G-CSF were replaced for DLT assessment. Before prophylactic growth-factor was required, 9/26 (34.6%) patients had grade ≥3 neutropenia and 3/26 (11.5%) had febrile neutropenia. Of these, 1 patient died of urosepsis in the setting of neutropenia and in 1 patient the outcome of febrile neutropenia was not reported (patient discharged into hospice and later lost to follow-up); the other patients recovered. Two patients in these cohorts received prophylactic G-CSF (allowed but not required by protocol); 1 of them developed grade 4 neutropenia and recovered. After prophylactic growth factor was required, 6/47 (12.8%) patients had grade ≥3 neutropenia, 1/47 (2.1%) had febrile neutropenia, and all recovered.

Among the 7 patients with reported systemic steroid use while enrolled in the study, steroid use occurred either before the first or after the last dose of relacorilant in 4 patients. One instance of systemic steroid use for AE treatment (grade 2 colitis; relacorilant and nab-paclitaxel interrupted during steroid treatment) was reported; 1 patient received steroid for 1 day while on study drug due to urticaria, pruritis, and shortness of breath; and in 1 patient, as-needed steroid use to manage allergy to iodine contrast was reported. Best overall response in these 3 patients was CR, progressive disease (PD), and stable disease (SD), respectively.

Clinical activity

Across all cohorts, 1 best overall response of CR (1.8%, patient with ovarian cancer), 8 partial responses (PR; 14.0%), and 28 patients with SD (49.1%) were reported (**Fig. 3A**). No significant difference in

Table 2. Treatment-emergent grade ≥3 AEs, DLTs, and treatment-emergent relacorilant-related AEs with relacorilant + nab-paclitaxel occurring in >5% of the safety population.

	Continuous dosing							Intermittent dosing					
	100 mg/ 60 mg/m^2 (n = 14)		100 mg/ 80 mg/m^2 (n = 34)		150 mg/ 80 mg/m^2 (n = 6)		Total (n = 54)	150 mg/ 80 mg/m^2 (n = 14)		200 mg/ 100 mg/m^2 (n = 5)		Total (n = 19)	Total (N = 73)
Serious AEs, *n* (%)	6 (42.9)		18 (52.9)		5 (83.3)		29 (53.7)	8 (57.1)		3 (60.0)		11 (57.9)	40 (54.8)
Relacorilant-related serious AEs	2 (14.3)		4 (11.8)		1 (16.7)		7 (13.0)	1 (7.1)		1 (20.0)		2 (10.5)	9 (12.3)
	Grade ≥3	**DLT**	**Grade ≥3**	**DLT**	**Grade ≥3**	**DLT**		**Grade ≥3**	**DLT**	**Grade ≥3**	**DLT**		
Grade ≥3 AEs occurring in >5% of the safety population, *n* (%)													
Patients reporting at least 1 grade ≥3 AE	9 (64.3)	—	24 (70.6)	—	5 (83.3)	—	38 (70.4)	11 (78.6)	—	5 (100)	—	16 (84.2)	54 (74.0)
Neutropenia	1 (7.1)	0	6 (17.7)	3	1 (16.7)	0	8 (14.8)	4 (28.6)	0	4 (80.0)	3	8 (42.1)	16 (21.9)
Anemia	1 (7.1)	0	2 (5.9)	0	0	0	3 (5.6)	3 (21.4)	0	1 (20.0)	0	4 (21.1)	7 (9.6)
Abdominal pain	2 (14.3)	0	3 (8.8)	0	0	0	5 (9.3)	1 (7.1)	0	0	0	1 (5.3)	6 (8.2)
Hyponatremia	1 (7.1)	0	2 (5.9)	0	0	0	3 (5.6)	1 (7.1)	0	1 (20.0)	0	2 (10.5)	5 (6.9)
Hypophosphatemia	1 (7.1)	0	1 (2.9)	0	1 (16.7)	0	3 (5.6)	1 (7.1)	0	1 (20.0)	0	2 (10.5)	5 (6.9)
Mucosal inflammation	1 (7.1)	0	2 (5.9)	0	0	0	3 (5.6)	1 (7.1)	1	1 (20.0)	0	2 (10.5)	5 (6.9)
Febrile neutropenia	0	0	3 (8.8)	3	1 (16.7)	1	4 (7.4)	0	0	0	0	0	4 (5.5)
Pleural effusion	2 (14.3)	0	0	0	1 (16.7)	0	3 (5.6)	1 (7.1)	0	0	0	1 (5.3)	4 (5.5)
Vomiting	0	0	1 (2.9)	0	1 (16.7)	0	2 (3.7)	2 (14.3)	0	0	0	2 (10.5)	4 (5.5)
Relacorilant-related grade ≥3 AEs occurring in >5% of the safety population, *n* (%)													
Patients reporting at least 1 relacorilant-related grade ≥3 AE	6 (42.9)	—	10 (29.4)	—	2 (33.3)	—	18 (33.3)	3 (21.4)	—	4 (80.0)	—	7 (36.8)	25 (34.3)
Neutropenia	1 (7.1)	—	3 (8.8)	—	1 (16.7)	—	5 (9.3)	2 (14.3)	—	2 (40.0)	—	4 (21.1)	9 (12.3)

Note: Doses are expressed as relacorilant/nab-paclitaxel.
Abbreviations: AE, adverse event; DLT, dose-limiting toxicity.

efficacy was observed between the intermittent and continuous dosing regimens. Median PFS was 2.3 months [95% confidence interval (CI), 2.0–3.2] in patients with PDAC, 4.6 months (95% CI, 3.7–N/A) in patients with ovarian cancer, and 5.2 months (95% CI, 2.8–8.4) in patients with other solid tumors.

Durable disease control ≥16 weeks was observed in 19/57 (33.3%) response-evaluable patients (9/19 with CR or PR; **Fig. 3B–D**). Forty-two of 57 patients (73.7%) had received prior taxane therapy, which ended either at completion (if adjuvant) or due to relapse or progression, and 12/42 (28.6%) experienced longer duration of benefit on relacorilant + nab-paclitaxel than on prior taxane (**Fig. 3E**).

Three patients with PDAC who had previously progressed on taxane treatment achieved 1.9–3.6x longer duration of benefit (1 PR, 2 SDs) on relacorilant + nab-paclitaxel than on their prior taxane-based therapy. Two additional PRs with longer duration of treatment were observed: 1 patient with acinar pancreatic cancer (33 weeks, 4.5x prior taxane); 1 patient with human papillomavirus–positive squamous cell carcinoma of the vulva (SCC HPV$^+$) who had progressed on prior taxane and experienced progression in one lung lesion on relacorilant + nab-paclitaxel at 56 weeks (4.1x longer duration than on prior taxane). The lesion was radiated, and the patient continued treatment with relacorilant + nab-paclitaxel beyond the data cutoff date of the study as part of an investigator-sponsored study due to continued clinical benefit (46+ months on treatment since enrollment). One patient with triple-negative breast cancer and 1 with uveal melanoma experienced SD with longer duration of treatment than with prior taxane [1.8x longer (completed prescribed prior taxane regimen) and 5.5x longer (progressed on prior taxane)]. One patient with ovarian cancer had received taxane in the metastatic setting and experienced 6.4x longer duration of treatment on relacorilant + nab-paclitaxel than on prior taxane-containing regimen.

Pharmacodynamics

RNA profiling was conducted in whole blood from 46 patients before and after treatment with relacorilant + nab-paclitaxel. Transcriptional effects of relacorilant were pronounced, with large and consistent effects on multiple transcripts. On-target suppression of known GR-controlled genes from baseline to C1D15 was observed across 46 patients (e.g., *ptgs2*, which codes for COX2; FDR-adjusted $P < 0.001$; **Fig. 4A**). Genes encoding candidate-immunomodulatory drug targets (including *cxcl8*, *ptger4*, and *ido1*; $P < 0.001$) were among the most highly suppressed.

GR expression, assessed by CLIA-validated IHC in archival tumor specimens provided by patients, was consistently high in ovarian and pancreatic tumor cells (H-score range 80–300, no difference between PDAC and ovarian cancer). Changes in serum hormone levels, including cortisol and testosterone, which are commonly reported for the GR antagonist mifepristone (34), were not observed with relacorilant.

In a separate healthy-volunteer study, 148 GR-regulated genes were identified that are significantly induced by the GR agonist prednisone (4 hours post single 25-mg dose, NCT03335956). The majority of these genes were reduced from baseline to C1D15 in 50% or more of patients receiving relacorilant + nab-paclitaxel in the solid tumor phase 1 study (**Fig. 4B**).

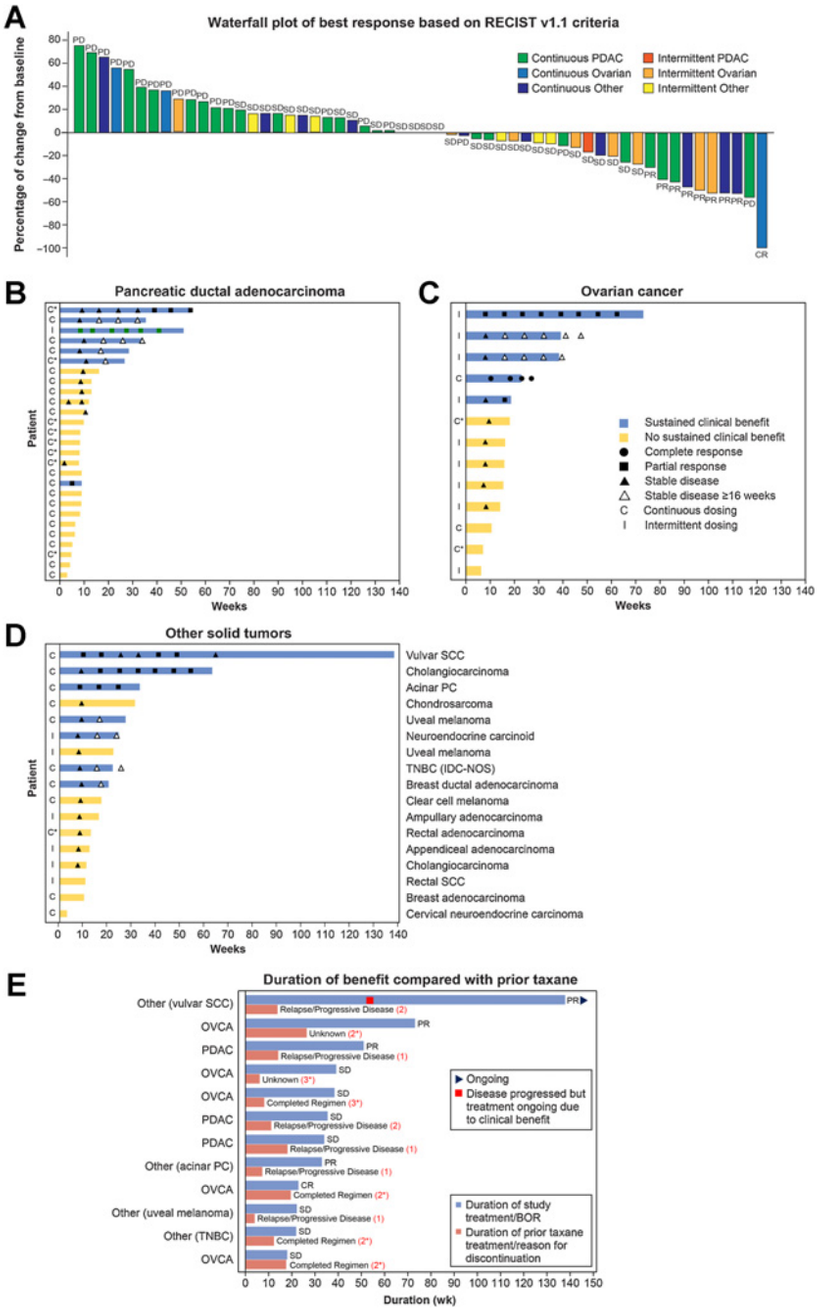


Figure 3.

Best overall response by RECIST (**A**), sustained clinical benefit (CR, PR, or SD ≥16 weeks) in response-evaluable patients (**B**–**D**) and longer duration of benefit compared with prior taxane (**E**; achieved in 12 patients). Seven of 27 (25.9%) patients with PDAC, 5/13 (38.5%) patients with ovarian cancer, and 7/17 (41.2%) patients with other solid tumors achieved durable disease control (CR, PR, or SD ≥16 weeks). In patients with ovarian cancer, the reason for ending the previous (adjuvant) taxane treatment was often completion of the regimen rather than relapse/progression. Duration is summarized for all patients with longer duration of response than on the immediately preceding taxane regimen; all patients except for 1 patient with ovarian cancer had disease control ≥16 weeks. Acinar PC, acinar pancreatic cancer; C, continuous dosing (100–200 mg relacorilant + 80–100 mg/m^2 nab-paclitaxel); C*, continuous dosing (100 mg relacorilant + 60 mg/m^2 nab-paclitaxel); CR, complete response; I, intermittent dosing (100–200 mg relacorilant + 80–100 mg/m^2 nab-paclitaxel); I*, continuous dosing (100 mg relacorilant + 60 mg/m^2 nab-paclitaxel); OVCA, ovarian cancer, including fallopian tube or primary peritoneal cancer; SCC, squamous cell carcinoma; TNBC (IDC-NOS), triple-negative breast cancer (invasive ductal carcinoma not otherwise specified). Prior taxane agent: (i) Nab-paclitaxel; (ii) Paclitaxel; (iii) Docetaxel; (*) Adjuvant or neoadjuvant therapy.

To determine whether GR antagonism was associated with clinical response, changes in GR-regulated genes were linked to best overall response by RECIST. CD163, a marker of myeloid cells, and IGF2R, which are typically induced by prednisone, were suppressed by relacorilant and showed deeper suppression in patients with clinical benefit (CR or PR; **Fig. 4C** and **D**). Cross-validated random-forest methods were applied to determine whether initial changes in gene expression could predict patients with best overall response of SD or better. A gene set was identified that could predict best overall response with significant sensitivity and specificity [receiver operating characteristic (ROC) AUC, 0.82 ± 0.12; **Fig. 4E**]. This model included patients with any tumor type receiving relacorilant + nab-paclitaxel across both regimens. A gene set was also identified that could predict durable disease control ≥16 weeks (ROC AUC 0.75 ± 0.16, not shown). These results suggest that GR antagonism, as measured by GR-regulated transcript level changes from baseline to C1D15, was correlated with (and predictive of) response to relacorilant + nab-paclitaxel.

Discussion

In vitro studies combining relacorilant with cytotoxic therapy presented here and in the literature (13), as well as the *in vivo* studies in the MIA PaCa-2 cell line presented here suggest that GR antagonism

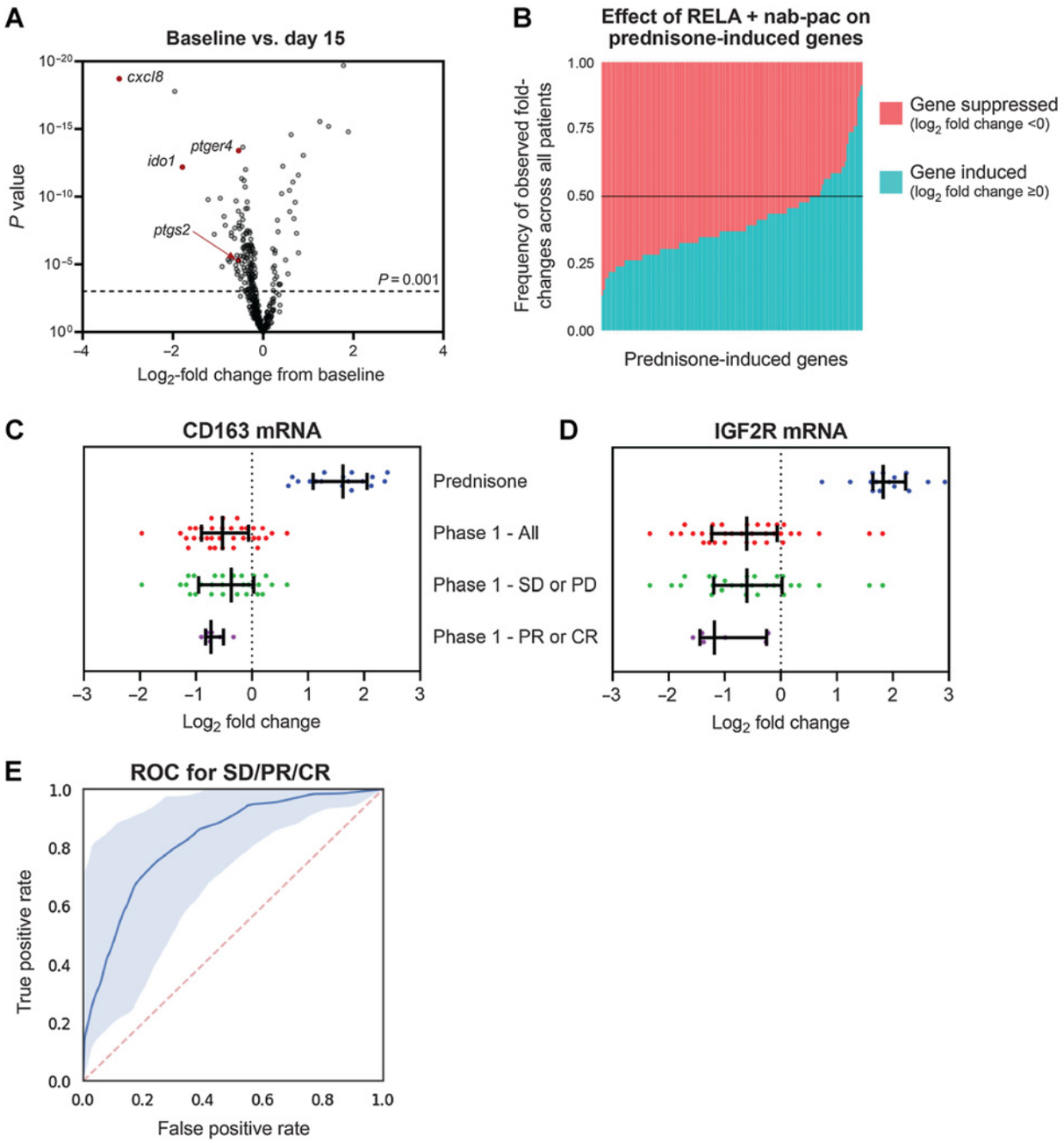


Figure 4.

GR-regulated genes are suppressed by relacorilant + nab-paclitaxel. **A,** RNA profiling was conducted in whole blood from phase 1 study participants treated with relacorilant + nab-paclitaxel ($n = 46$). Fold change and *P* value were calculated by comparing RNA counts between baseline and C1D15. Suppression of GR-controlled (*ptgs2*) and candidate-immunomodulatory drug target genes (*cxcl8, ptger4*, and *ido1*) was observed. **B,** 148 genes that are induced by prednisone in a separate healthy-volunteer study were also frequently suppressed after relacorilant + nab-paclitaxel treatment. **C** and **D,** Examples of two genes induced by prednisone that were suppressed in patients with solid tumors treated with relacorilant + nab-paclitaxel, particularly those with a PR or CR. Mean with 95% confidence intervals are shown in black bars. **E,** Gene signature predicting patients with best overall response of SD or better. Area under the receiver operating characteristic (ROC) curve, 0.82 ± 0.12. RELA, relacorilant.

can alter intracellular signaling pathways involved in cell survival and promote apoptosis in response to taxane treatment. On the basis of these findings, a phase 1 study of relacorilant + nab-paclitaxel was conducted in patients with advanced solid tumors. Limited duration of response was expected because of advanced tumor stage, disease burden, and several lines of prior therapy, including taxanes (suggesting chemotherapy resistance). Relacorilant demonstrated encouraging clinical activity and appeared to enhance sensitivity to taxanes in patients with metastatic PDAC, ovarian cancer, and other solid tumors. The combination was safe and well tolerated.

As a strong CYP3A4 inhibitor, relacorilant has the potential to inhibit nab-paclitaxel metabolism, which may result in increased nab-paclitaxel exposure. On the basis of available exposure and safety data, starting doses of 80 mg/m^2 nab-paclitaxel in combination with 100 mg of relacorilant (continuous dosing) or 150 mg relacorilant (intermittent dosing) were chosen, with dose titration based on tolerability. No substantial differences in efficacy or safety profiles were observed between the 2 dosing strategies. Both strategies continue to be evaluated in later-stage clinical trials, including a randomized phase 2 study of relacorilant + nab-paclitaxel in patients with platinum-resistant ovarian cancer (NCT03776812).

The observed clinical activity of relacorilant + nab-paclitaxel may be linked to modulation of glucocorticoid-controlled genes leading to enhanced or prolonged nab-paclitaxel activity. Durable disease control ≥16 weeks was observed in 33.3% of patients (median of 3 prior regimens; range, 1–8), including 25.9% of patients with PDAC and 38.5% of patients with ovarian cancer. Historical response rates are typically 0% in third-line PDAC and <15% in third-line ovarian cancer (35–37). In 12 (28.6%) patients who had received prior taxane therapy, duration of treatment was up to 6.4-fold longer on relacorilant + nab-paclitaxel than on prior taxane. GR-specific pharmacodynamic responses consistent with GR antagonism were observed in whole blood and were more pronounced in patients with clinical benefit. This observation suggests that GR antagonism was achieved, GR signaling plays a role in the response to nab-paclitaxel, and relacorilant contributes to the observed therapeutic response. These results support the hypothesis that relacorilant contributes to overcoming resistance to nab-paclitaxel and warrants further clinical studies in select tumor types.

Overall, safety and tolerability were acceptable with adverse events reflecting the advanced disease state, treatment history of the patients, and concurrent treatment with nab-paclitaxel. Neutropenia was the most common grade ≥3 AE of relacorilant + nab-paclitaxel, and the observed rate appears to be in line with expectations for the stage and prior therapies of the enrolled patients. Notably, nab-paclitaxel carries a boxed warning for neutropenia, which is more frequent in patients with multiple prior lines of chemotherapy (38). Furthermore, neutropenia is not seen with relacorilant monotherapy in other indications (24). In response to the observed dose-limiting neutropenia, primary prophylaxis with G-CSF became mandatory in later cohorts, reducing the frequency of neutropenia. Prophylaxis with G-CSF will be considered in later studies of relacorilant + nab-paclitaxel.

Reported nab-paclitaxel AEs also include sensory or peripheral neuropathy, fatigue/asthenia, myalgia/arthralgia, anemia, nausea, infections, and diarrhea (33), which overlaps significantly with the most common AEs observed with relacorilant + nab-paclitaxel. In this study, dermatological AEs (e.g., rashes, skin hyperpigmentation, and acne) were reported with greater frequency than expected with nab-paclitaxel alone. Cases of hyperpigmentation appear to occur more commonly in patients with darker skin (39). Most reactions were tolerable, leading to withdrawal or drug interruption in 2 and 7 patients for skin disorders and hyperpigmentation, respectively. Although some resembled dermatological AEs previously observed with taxane treatment, others, in particular hyperpigmentation, were considered related to relacorilant and will be further evaluated.

Because of their action as GR agonists, systemic steroids beyond physiological doses were generally not used concomitant with relacorilant administration. Of 7 patients with systemic steroids reported as concomitant medication while enrolled in the study, only one instance of a patient receiving a single dose of steroid while on relacorilant is documented. Best overall response in this patient was PD.

The recommended phase 2 starting dose was identified as relacorilant 100 mg (continuous dosing) or 150 mg (intermittent dosing) with nab-paclitaxel 80 mg/m^2 in 28-day cycles, based on safety, tolerability, PK, drug–drug interactions, and pharmacodynamic activity. Although the MTD was not identified in this study, both regimens were well tolerated.

Study limitations include the small number of patients in some cohorts and non-dose differences between the cohorts, for example, G-CSF use, drug lead-in, and tumor type. The gene set previously described in **Fig. 4** was not predefined and should, therefore, be considered exploratory for future predictive assay development. The effects of nab-paclitaxel or G-CSF alone on pharmacodynamics should be explored in future studies. Study goals included determining the recommended phase 2 starting dose, safety of the combination, and preliminary efficacy signals to inform future studies. However, the study was not designed to identify a preferred dosing regimen (intermittent or continuous relacorilant) or to show efficacy in specific tumor types. Furthermore, this study was not designed to characterize the contribution of relacorilant to the overall effect of relacorilant + nab-paclitaxel. Future studies of the combination, including a nab-paclitaxel–only comparator arm, may help answer this question.

Conclusions

The efficacy observed with relacorilant + nab-paclitaxel supports the hypothesis that GR antagonism may delay or overcome resistance to taxanes and enhance chemotherapy efficacy, a finding that warrants further clinical evaluation. Further studies in platinum-resistant ovarian cancer and other tumors are ongoing.

Authors' Disclosures

A.E. Greenstein reports other support from Corcept Therapeutics outside the submitted work, as well as employment and stock ownership in Corcept Therapeutics and stock ownership in Gilead (March/April 2020). In addition, A.E. Greenstein also reports patents for WO 2021/163058 issued, WO 2021/154750 issued, WO 2021/076565 pending, and WO 2020/132046 pending. G.F. Fleming reports other support from Corcept Therapeutics during the conduct of the study; G.F. Fleming also reports other support from Roche and Syros, as well as personal fees from GSK, Iovance, Sermonix, Compugen, Celldex, Plexxicon, AstraZeneca, Molecular Templates, CytomX, Astellas, and K Group Beta outside the submitted work. E. Borazanci reports grants from Corcept Therapeutics during the conduct of the study, as well as consulting for Vivacitus, Nanology, TD2, and BioNtech. M.R. Sharma reports other support from Corcept Therapeutics during the conduct of the study. J.M. Custodio reports other support from Corcept Therapeutics during the conduct of the study, as well as a patent 11,285,145 issued. I.C. Tudor reports employment with Corcept Therapeutics. S.P. Shepherd reports employment with Corcept Therapeutics during the conduct of the study, as well as stock ownership in Abbott, AbbVie, and BridgeBio; S.P. Shepherd also reports a patent for US11234971B2 issued and licensed to Corcept Therapeutics and a patent for US20200197373A1 issued and licensed to Corcept Therapeutics. A. Grauer reports other support from Corcept Therapeutics outside the submitted work, as well as employment with Corcept Therapeutics. J.C. Sachdev reports other support from Corcept Therapeutics during the conduct of the study; J.C. Sachdev also reports personal fees from Pfizer, Tempus, Immunomedics, Ipsen Pharmaceuticals, Novartis Pharmaceuticals, and AstraZeneca, as well as grants from Merck, Pfizer, Tesaro/GSK, Plexxikon, Abbvie, Bolt Biotherapeutics, ImmuneSensor, Sermonix, Syros, Aduro, and Agenus outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

P.N. Munster: Conceptualization, data curation, supervision, methodology, project administration, writing–review and editing. **A.E. Greenstein:** Conceptualization, data curation, formal analysis, supervision, methodology, writing–original draft, project administration, writing–review and editing. **G.F. Fleming:** Conceptualization, data curation, supervision, methodology, project administration, writing–review and editing. **E. Borazanci:** Conceptualization, data curation, supervision,

methodology, project administration, writing–review and editing. **M.R. Sharma:** Conceptualization, data curation, supervision, methodology, project administration, writing–review and editing. **J.M. Custodio:** Conceptualization, data curation, supervision, methodology, project administration, writing–review and editing. **I.C. Tudor:** Conceptualization, data curation, supervision, methodology, project administration, writing–review and editing. **H.I. Pashova:** Conceptualization, data curation, formal analysis, supervision, methodology, project administration, writing–review and editing. **S.P. Shepherd:** Conceptualization, data curation, supervision, methodology, project administration, writing–review and editing. **A. Grauer:** Conceptualization, data curation, formal analysis, supervision, methodology, writing–original draft, project administration, writing–review and editing. **J.C. Sachdev:** Conceptualization, data curation, supervision, methodology, project administration, writing–review and editing.

Acknowledgments

The studies reported in this article were funded by Corcept Therapeutics. The authors thank Thaddeus Block for clinical trial oversight and for initiating this study and Dorothy D. Nguyen and Grace Mann for their contributions to data interpretation. The authors acknowledge medical writing support by Tina K. Schlafly, an employee of Corcept Therapeutics, and Danielle L. Ippolito of MedVal Scientific (funded by Corcept Therapeutics). The authors reviewed and approved the final version.

The publication costs of this article were defrayed in part by the payment of publication fees. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

Note

Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Received December 17, 2021; revised April 1, 2022; accepted May 16, 2022; published first May 18, 2022.

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