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A PHASE 1/2 STUDY OF RELACORILANT + NAB-PACLITAXEL IN PATIENTS WITH SOLID TUMORS: THE DOSE-FINDING PHASE

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INTRODUCTION

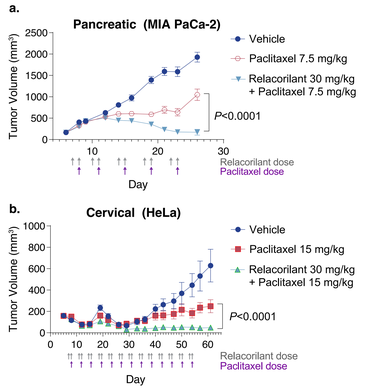
CORTISOL MODULATION AND CANCER BIOLOGY

- High rates of glucocorticoid receptor (GR) expression have been shown in several solid tumor types including pancreatic, ovarian, and triple-negative breast cancer (TNBC)[1,2]
- GR has been shown to be involved in chemotherapy resistance in tumor cells, with stimulation of GR shown to reduce chemotherapy sensitivity and blockade of GR shown to enhance chemotherapy sensitivity[3,4]
- GR activation inhibits apoptosis leading to reduced chemotherapy efficacy[5,6]
- Preclinical studies across multiple tumor types have shown that GR antagonists can enhance the efficacy of chemotherapy[3,4,6-8]
- GR expression and/or signaling is correlated with poor prognosis in breast,[8] endometrial,[9] and ovarian[10] cancers
- Clinical data in patients with TNBC have shown that treatment with mifepristone, a competitive GR antagonist, was tolerable when used with nab-paclitaxel (nab-pac)[11] and eribulin[12]

RELACORILANT: A SELECTIVE GLUCOCORTICOID RECEPTOR ANTAGONIST

- Relacorilant (CORT125134) is a selective cortisol modulator that potently binds GR (K_i <1 nM), inhibits GR in cells (half-maximal inhibition of 7.2 nM), and does not bind to the androgen receptor or the progesterone receptor (K_i >10 μM)[13]
- *In vitro* studies demonstrated significant inhibition of CYP2C8 and CYP3A4 and modest inhibition of CYP2D6, CYP2C9, and CYP3A5[13]
- In pancreatic (MIA PaCa-2, **Figure 1a**) and cervical (HeLa, **Figure 1b**) xenograft models, relacorilant in combination with paclitaxel was significantly (*P*<0.0001) more effective at reducing tumor growth than paclitaxel alone

Figure 1. Relacorilant in combination with paclitaxel inhibits pancreatic (MIA PaCa-2) (a) and cervical (HeLa) (b) xenograft tumor growth



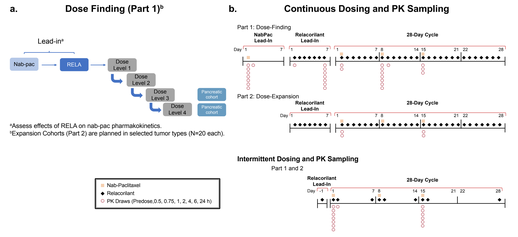
In the pancreatic model, complete regression (no measurable tumor) was observed in 4/10 animals in the relacorilant + paclitaxel group vs. no complete regressions in the other treatment groups.
Data represent the mean + SEM.

METHODS

STUDY DESIGN

- The study objective was to determine the maximum tolerated dose (MTD) and recommended phase 2 dose of relacorilant when administered with nab-pac, and to evaluate the safety, pharmacokinetics (PK), and clinical activity of the combination
- Eligible patients enrolled in a standard "3+3" dose escalation design to evaluate two dosing schedules for relacorilant (**Figure 2a**). Expansion cohorts in specific tumor types are permitted. A cohort with pancreatic cancer is enrolling patients
  - Due to potential drug-drug interactions that may increase the exposure to nab-pac, the starting dose of nab-pac in the continuous-dosing regimen was 80 mg/m² in combination with relacorilant
  - To assess for drug-drug interactions, continuous dosing has a lead-in period before the start of the combination (**Figure 2b**). The starting dose in dose level 1 was as follows:
    1) Continuous: 100 mg relacorilant once daily with 80 mg/m² nab-pac on Days 1, 8, and 15 of a 28-day cycle
    2) Intermittent: 100 mg/m² nab-pac on Days 1, 8, and 15 of a 28-day cycle with relacorilant 200 mg the day before, day of, and day after nab-pac
  - As the study progressed, use of G-CSF to control neutropenia, which has been the most common dose-limiting toxicity (DLT), expanded
    1) In the initial cohorts, G-CSF was allowed during the DLT evaluation period only if required to manage toxicity. Prophylactic G-CSF use was not allowed to avoid confounding the assessment of toxicity
    2) In later cohorts, G-CSF was allowed per standard practice, including optional prophylactic use in patients with a high risk of neutropenia
    3) Due to continued DLTs of neutropenia, mandatory prophylactic G-CSF is now required in all patients. Patients receive at least one injection of G-CSF the day after nab-pac, including the nab-pac lead-in

Figure 2. Study design (a), dosing, and PK sampling (b)



PATIENT ELIGIBILITY

Key inclusion criteria

- Consented patients ≥18 years of age with advanced or metastatic solid tumors who have disease progression
- Treated with up to 3 prior lines of cytotoxic or myelosuppressive therapy in the advanced setting. Previous nab-pac is allowed
- ECOG (Eastern Cooperative Oncology Group) Performance Status 0-1
- Adequate renal, hepatic, and marrow function
- Measurable or evaluable disease (dose escalation cohorts)
- For patients enrolled in the pancreatic cohort, key inclusion criteria are:
  - Histologically confirmed diagnosis of pancreatic adenocarcinoma. Patients with pancreatic neuroendocrine tumors, lymphoma of the pancreas, or ampullary cancer are not eligible
  - CA19-9 (or CEA, CA-125 in non-CA 19-9 elevated tumors) measured within 14 days prior to first dose of study drug
  - Metastatic (non-irradiated) lesion that is measurable by RECIST v1.1

Key exclusion criteria

- Requirement for treatment with chronic or frequently used oral corticosteroids for medical conditions or illnesses (eg, rheumatoid arthritis, immunosuppression after organ transplantation)

Assessments

- Patients were to provide either archived tumor tissue or pretreatment tumor biopsy if available for immunohistochemistry (IHC) staining for GR status
- DLTs were identified at each dose level to determine MTD
- Tumor assessments were performed at screening and every 6-8 weeks from Cycle 1 Day 1 with confirmation of tumor response performed within 4 weeks per RECIST v1.1
  - Ovarian, fallopian tube, or primary peritoneal cancer tumors also included CA-125 assessment and response per GCIG criteria

RESULTS

- A total of 35 patients were enrolled and treated in the study between May 24, 2016 and March 10, 2018
  - Demographics and baseline characteristics of patients treated with both nab-pac and relacorilant are shown in **Table 1**
  - Sixteen (46%) patients had pancreatic cancer and 9 (26%) had ovarian cancer

Table 1. Baseline demographic and clinical characteristics

	Continuous N=25	Intermittent N=10	Total N=35
Age, mean (range) years	56.8 (18–81)	61.8 (46–79)	58.3 (18–81)
Female, n (%)	18 (72)	8 (80)	26 (74.3)
Race, n (%)			
White	22 (88)	6 (60)	28 (80)
Black	3 (12)	2 (20)	5 (14.3)
Asian	0 (0)	2 (20)	2 (5.7)
Carcinoma type, n (%)			
Pancreatic	13 (52)	3 (30)	16 (45.7)
Ovarian (including primary peritoneal cancer)	5 (20)	4 (40)	9 (25.7)
Cervical	1 (4)	0 (0)	1 (2.9)
Breast (ER/PR+ / HER2-)	3 (12)	0 (0)	3 (8.6)
Other[a]	3 (12)	3 (30)	6 (17.1)
ECOG, n (%)			
0	7 (28)	5 (50)	12 (34.3)
1	18 (72)	5 (50)	23 (65.7)
Time from initial diagnosis to date of first study treatment, mean years (range)	2.8 (0–8)	4.8 (1–11)	3.3 (0–11)
No. of prior therapies, mean (range)[b]	3.4 (1–8)	4.4 (2–6)	3.7 (1–8)
Prior chemotherapy, n (%)			
Taxanes	21 (84)	8 (80)	29 (82.9)
Platinum salts	18 (72)	7 (70)	25 (71.4)

[a]Includes rectal and vulvar (continuous) and neuroendocrine and prostate (intermittent); [b]All prior therapies, including adjuvant therapy.

DOSE ESCALATION AND DLTs

- To date, 3 continuous cohorts and 2 intermittent cohorts have been enrolled
- DLTs occurring during the first treatment cycle are shown in **Table 2**. Neutropenia with dose delay >7 days and febrile neutropenia have been the most common DLTs. Due to dose-limiting neutropenia, mandatory prophylactic G-CSF is now being used in both the ongoing continuous and intermittent cohorts. G-CSF was not mandatory earlier in the study because of the concern that G-CSF could have confounded the assessment of DLTs

Table 2. Dosing cohorts and DLTs

Relacorilant/ Nab-pac Dosage	G-CSF	Evaluable Patients	Patients with DLTs	DLT (grade)
Continuous				
100/80	Only if required for toxicity management	7	2	Neutropenia (3) with dose delay >7 days and rash (3) Febrile neutropenia (3)
100/80	Per PI discretion	4	2	Febrile neutropenia (3), thrombocytopenia (4), hand/foot syndrome (3), and mucositis (3) Neutropenia (4) with dose delay >7 days
100/60	Prophylactic	5[a]	0	None
100/80 (ongoing)	Prophylactic	0	0	None
Intermittent				
200/100	Per PI discretion	3	1	Urosepsis (5)
150/80	Per PI discretion	5	1	Mucositis (3)
150/80 (ongoing)	Prophylactic	0	0	None

[a]One patient in this cohort experienced neutropenia requiring G-CSF support after the cut-off date of March 10, 2018. Per the DRC recommendation, a new cohort is being evaluated with mandatory G-CSF.

SAFETY

- To date, 31% of patients have discontinued treatment due to adverse events (7/25 continuous, 4/10 intermittent). Forty nine percent have discontinued due to progressive disease (15/25 continuous, 2/10 intermittent)
- Treatment-emergent adverse events (TEAEs) considered related to relacorilant or the combination that occurred in ≥10% of all patients who received a dose of relacorilant through March 10, 2018 are reported in **Table 3**
- Four patients experienced an adverse event of neutropenia and 1 of febrile neutropenia

Table 3. Relacorilant drug-related TEAEs reported in ≥10% of all patients who received at least 1 dose of relacorilant

	Continuous N=25		Intermittent N=10		Total N=35	
TEAEs	All Grades	≥G3	All Grades	≥G3	All Grades	≥G3
N (%) of Patients with Relacorilant Related TEAE	21 (84)	8 (32)	10 (100)	6 (60)	31 (89)	14(40)
Fatigue	6 (24)	1 (4)	3 (30)	0	9 (26)	1 (3)
Nausea	6 (24)	0	2 (20)	0	8 (23)	0
Rash	6 (24)	1 (4)	2 (20)	0	8 (23)	1 (3)
Skin hyperpigmentation	4 (16)	1 (4)	3 (30)	0	7 (20)	1 (3)
Neutropenia	3 (12)	2(8)	3 (30)	3 (30)	6 (17)	5 (14)
Vomiting	6 (24)	0	0	0	6 (17)	0
Constipation	3 (12)	0	2 (20)	0	5 (14)	0
Decreased appetite	4 (16)	0	1 (10)	0	5 (14)	0
Diarrhea	3 (12)	0	1 (10)	0	4 (11)	0
Neuropathy peripheral	2 (8)	0	2 (20)	0	4 (11)	0

- Preliminary data indicate that nab-pac exposure is increased with relacorilant at doses of 100-150 mg once daily

PK DATA AND CLINICAL ACTIVITY

Figure 3a. Mean (±SD) relacorilant concentration versus time profiles in patients following once-daily oral administration of 100 mg relacorilant with and without coadministration of 80 mg/m² nab-pac

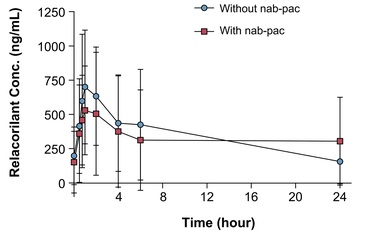


Figure 3b. Nab-pac $AUC_{0\text{-}24}$ in patients following once-weekly IV infusions of nab-pac at 80 mg/m² with and without coadministration of 100 mg relacorilant

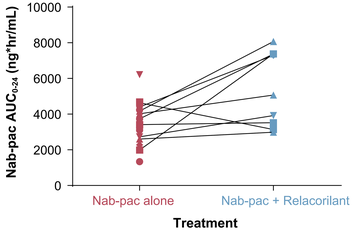
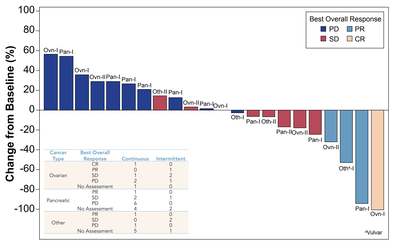
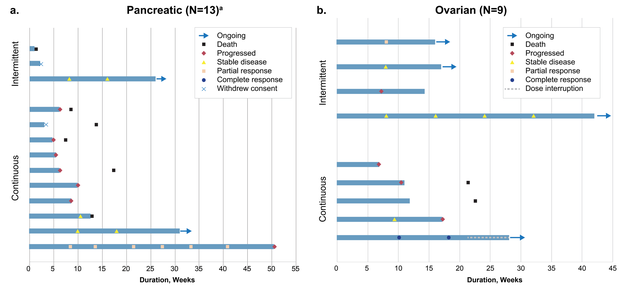


Figure 4. Best response in 22 evaluable patients per RECIST v1.1



Pan=Pancreatic Cancer; Ovn=Ovarian Cancer; Oth=Other Cancer
I=Continuous; II=Intermittent

Figure 5. Duration of disease control and response by tumor type: Pancreatic cancer (a) and ovarian cancer (b)



[a]Three patients discontinued during the lead-in period.

Table 4. Response and glucocorticoid receptor immunohistochemistry summary in all patients with available tissue[a]

Cancer Type	Prior Taxane	Time to Progression (days)	RECIST (PR, CR, SD, PD)	Dose: RELA (mg)/Nab-Pac (mg/m²)	GR IHC		
					% positive cells	% at 2+ or above	H- Score
Ovarian[b]	Y	294[c]	SD	200/100	100	100	300
Pancreatic	N	42[c]	Too early	100/60	100	100	290
Ovarian[b]	Y	119[c]	SD	150/80	100	100	290
Pancreatic[b]	Y	182[c]	SD	150/80	100	100	290
Pancreatic	Y	49[c]	Too early	100/60	100	100	270
Pancreatic	Y[d]	43	PD	100/60	99	90	269
Ovarian	Y	196[c]	CR	100/80	95	80	225
Pancreatic[b]	Y[d]		Withdrew	150/80	100	80	210
Pancreatic	Y[d]	353	PR	100/80	90	60	180
Pancreatic	Y	42[c]	Too early	100/60	90	60	180
Pancreatic	Y	60	PD	100/60	80	60	150
Pancreatic	N	43	PD	100/60	70	40	120
Pancreatic	Y[d]	38	PD	100/80	50	20	80
Pancreatic	Y[d]	217[c]	SD	100/80	60	25	60
TNBC	Y[d]		No assessment; withdrew	100/80	0	0	0

[a]Includes only those patients with sufficient archived tumor tissue available for analysis; [b]Denotes intermittent dosing of relacorilant; [c]Patient still on study and has not progressed; [d]Taxane refractory; disease progression within 6 months of taxane treatment.

- For the patients that had completed at least one cycle of therapy and GR IHC was complete, all had detectable GR expression
- Six patients experienced durable clinical benefit (SD, PR, or CR for >6 months; **Table 4**; green font), including 2 patients with pancreatic cancer previously refractory to taxane therapy. All patients with durable clinical benefit had ≥60% GR positive cells

CONCLUSIONS

- Neutropenia was the most significant treatment-related adverse event and is manageable with mandatory prophylactic G-CSF
- Continuous and intermittent dose-finding cohorts are ongoing. Preliminary data indicate that relacorilant can increase the exposure to nab-pac
- An efficacy signal was observed in refractory patients with pancreatic and ovarian cancers. A cohort of patients with metastatic pancreatic cancer is enrolling at the dose level at which clinical benefit has been observed (relacorilant 100 mg daily; nab-pac 80 mg/m²). Results at this dose level are not presented here
- These results support further evaluation of the regimen. The study is ongoing with expansions being considered, including in ovarian cancer and TNBC

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ACKNOWLEDGEMENTS

This study was funded by Corcept Therapeutics. Funding for design, and production support was provided by Corcept Therapeutics to MedVal Scientific Information Services, LLC. The authors thank Mark R. Vogel for writing assistance, Sherry Tong for project management, Amy Plodek for data management, and Harvey Kushner and Terri Leung for statistical analysis.

Clinicaltrials.gov: NCT02762981