Impact of Relacorilant, a Selective Glucocorticoid Receptor Antagonist, on the Immunosuppressive Effects of Endogenous Cortisol

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BACKGROUND

CORTISOL

- Cortisol, a glucocorticoid (GC), regulates a wide range of processes, including the suppression of T-cell activation, pro-inflammatory cytokine secretion, and immune cell trafficking, by binding to the glucocorticoid receptor (GR).
  - GR is expressed in most human cells and is particularly abundant in immune cells.
- Elevated GC activity has been implicated in the pathophysiology of multiple cancer types, including breast, ovarian, squamous cell, and cervical, as well as lymphomas [1-5], and is associated with poor treatment outcomes.
  - Patients administered synthetic GC prior to immune checkpoint inhibitor (ICI) therapy experienced worse outcomes across multiple oncology indications [6-8].
  - Similarly, patients with adrenocortical cancer (ACC) and excess systemic GC less frequently benefitted from pembrolizumab than ACC patients with normal GC levels [9, 10].
- The degree of immune suppression by endogenous GC and the resulting consequences for anti-tumor immune response are not fully understood.
  - Normal morning serum cortisol ranges are high enough (276–552 nM) that GR activation is expected, which is critical for normal physiology.
  - However, GR activation at physiological levels also suppresses T-cell function, including the IFNγ and TNFα pathways, and alters the cellular composition of blood, depleting lymphocytes and increasing myeloid cell abundance.

RELACORILANT: A SELECTIVE GR ANTAGONIST

- Relacorilant (CORT125134, Corcept Therapeutics) is a selective cortisol modulator that:
  - binds GR (K<1 nM),
  - antagonizes GR in cells (EC_{50} = 7.2 nM), and
  - does not bind to the androgen and progesterone receptors (K>10 μM) [11].
- In a Phase 1/2 study in patients with solid tumors (CORT125134-550, NCT02762981), relacorilant demonstrated clinical activity in combination with nab-paclitaxel [12].
- Phase 2 and 3 studies with relacorilant in combination with nab-paclitaxel in patients with solid tumors are underway.
- ► In this poster, we present in vitro, in vivo, and clinical studies that suggest that relacorilant can reverse the immunosuppressive effects of endogenous GC, making it well-suited for combination with an ICI.

METHODS

IN VITRO AND IN SILICO STUDIES

- Immune cell markers and GR expression were assessed by immunohistochemistry (IHC) in 10 triple-negative breast cancer (TNBC) and 2 melanoma samples.
- GR transcript was correlated with PD-L1 and other immune-related transcripts in data accessed from The Cancer Genome Atlas (TCGA, www.cancer.gov/tcga). Cellular abundance was calculated using xCell [13].
- The effects of GC and relacorilant were assessed in human peripheral blood mononuclear cells (PBMCs) from 4 donors stimulated with αCD3 + IL-12; 400 nM cortisol and 300 nM relacorilant were used. T-cell activation was measured by FACS and cytokine secretion by immunoassay.

IN VIVO STUDIES

- In a syngeneic model, EG7 tumor-bearing mice (n = 10 per group) were treated with either vehicle or αPD1 (mouse surrogate RMP1-14) ip QSD +/- relacorilant once daily for 25 days. Mice were not treated or handled in any way intended to alter normal GC.
- Cytokines were measured by Luminex in terminal sera.

CLINICAL STUDIES

- A Phase 1/2, single-arm, non-randomized, open-label, multicenter trial in patients with solid tumors was performed to determine the preliminary efficacy of relacorilant + nab-paclitaxel (CORT125134-550, NCT02762981).
- Healthy volunteer data from a Phase 1 study were analyzed for comparison (CORT125134-120, NCT03508635).
- Whole blood was collected in PAXgene® tubes and RNA was quantified using nCounter® FLEX (NanoString).
- Lymphocyte and neutrophil abundance were determined using standard differential complete blood-count tests and the neutrophil-to-lymphocyte ratio (NLR) was calculated as the absolute neutrophil count divided by the absolute lymphocyte count.
- Cytokines were assessed by immunoassays in EDTA plasma.

RESULTS

GR EXPRESSION IS ASSOCIATED WITH TUMOR INFILTRATION OF EFFECTOR AND REGULATORY IMMUNE CELLS

- Tumor GR expression was assessed via IHC in 10 TNBC and 2 melanoma cases.
  - In both tumor types, T-cell infiltration, marked by the expression of CD3, positively correlated with tumor GR expression (Figure 1 and Figure 2A).
  - Tumor GR expression was also positively correlated with FOXP3+ (a marker of regulatory T-cells [Treg] that suppress effector function), PD1+ (a common ICI target that suppresses effector function), and CD57+ cells (a marker of natural killer cells) (Figure 2B-D).
- Analysis of transcriptomics data from TCGA showed that GR expression also correlated with markers of immunosuppressive cells.
  - A positive correlation of GR and programmed death-ligand 1 (PD-L1) expression was observed (R=0.25, P<0.001), with particularly strong correlations in adrenal (R=0.48, P<0.001), bladder (R=.45, P<0.001), and pancreatic cancers (R=0.46, P<0.001) (Figure 3A).

- In melanomas:
  - Positive correlations between GR and CD8+ cytotoxic T-cells (R=0.24, P<0.001), Tregs (R=0.29, P<0.001), and T-helper type 2 (Th2) cells (R=0.2, P<0.001) were observed (Figure 3B–D).
  - Negative correlations between GR and T-helper type 1 (Th1) cells were observed (R=–0.36, P<0.001) (Figure 3E).

RATIONALE #1 FOR COMBINING ICI'S WITH RELACORILANT

- Immune infiltration and PD-L1 expression have been associated with improved response to ICI [14].
  - Tumors with these features also show high expression of GR, the target of relacorilant.
- Suppression of tumor-infiltrating CD3+ T-cells may be reversed with relacorilant.

Figure 1. Immunohistochemical Staining of a TNBC Tumor Sample.
Quantification of GR is shown in the upper panel (green, yellow, and red indicating increasing intensity), while CD3-expressing cells (T-cells) are highlighted on the bottom (positive cells marked in green).

Figure 2. Correlation Between Tumor GR Expression and Cell Infiltration.
Analysis is shown in 10 TNBC and 2 melanoma cases. H-scores were used to quantify tumor GR expression in IHC.

Figure 3. Correlation Between GR Expression, PD-L1 Expression, and Immune Cell Infiltrate.
Analysis is based on data accessed via TCGA. (A) Correlation of GR and PD-L1 expression, with correlations within adrenal, bladder, and pancreatic cancers highlighted on the right. (B-E) Correlations of GR expression with infiltration of CD8+, Treg, Th1, and Th2 cells in cutaneous melanoma.

RELACORILANT RESTORES T-CELL ACTIVATION INHIBITED BY CORTISOL IN HUMAN PBMCS

- To understand the molecular consequences of GC activity on T-cell activation, the effects of cortisol and relacorilant were assessed in human PBMCs (Figure 4).
  - T-cells were stimulated by addition of αCD3 + IL-12, and stimulation was assessed by profiling of cell surface markers on CD4+ and CD8+ T-cells as well as secreted pro-inflammatory cytokines.
  - Cortisol (400 nM) suppressed nearly all effects of stimulation by αCD3 + IL-12 while relacorilant (300 nM) restored nearly all effects of stimulation that were suppressed by cortisol.
    - Expression of CD137, a costimulatory immune checkpoint molecule, on CD8+ cells was induced by stimulation, suppressed by cortisol, and restored by relacorilant (P<0.001, Figure 4A).
      - Similar effects were observed with PD-1, LAG3, CTLA-4, and TIGIT surface expression on both CD4+ and CD8+ T-cells (data not shown).
    - The cytokines TNFα and IFNγ were also induced by stimulation, suppressed by cortisol, and restored by relacorilant (P=0.006 and P=0.05, respectively, Figure 4B and C).
      - Similar effects were observed for IL-1β, IL-6, and IL-2 (data not shown).

RATIONALE #2 FOR COMBINING ICI'S WITH RELACORILANT

- Activated T-cells that secrete pro-inflammatory cytokines are primary mediators of the anti-tumor immune response.
- T-cell activation and cytokine secretion are suppressed by physiological concentrations of cortisol.
- Relacorilant can reverse the effect of cortisol, restoring activation and cytokine secretion.

Figure 4. PBMC Activation Upon Stimulation With αCD3 + IL-12.

RELACORILANT PROMOTES CHECKPOINT INHIBITOR RESPONSE IN SYNGENEIC MOUSE MODEL

- The combination of a PD-1 antagonist antibody (αPD1, an ICI) and relacorilant was assessed in the EG7 tumor model.
- While relacorilant or αPD1 alone had no significant effect in this model, their combination potently suppressed tumor growth (P=0.007, Figure 5A).
  - By day 14, 80% (8/10) of mice in the αPD1 arm had tumors larger than 1800 mm³ compared to 20% (2/10) in the αPD1 + relacorilant group.
- The αPD1 + relacorilant group also showed significantly improved tumor control and survival probability compared to αPD1 alone (Figure 5B and C).
  - An assessment of individual tumor-volume trajectories confirmed better tumor control between days 10–20 in the αPD1 + relacorilant group compared to αPD1 alone (Figure 6).
- Relacorilant alone significantly decreased circulating IL-10, an anti-inflammatory cytokine, compared to vehicle (P=0.002, Figure 7).

RATIONALE #3 FOR COMBINING ICI'S WITH RELACORILANT

- Relacorilant + αPD1 was more effective than αPD1 alone in a syngeneic mouse model.
- Relacorilant alone decreased circulating IL-10, an anti-inflammatory cytokine, in mice.

Figure 5. Efficacy of αPD1 + Relacorilant in Syngeneic Mouse Model.
Tumor control was defined as tumor volume <1800 mm³.

Figure 6. Individual Tumor Volumes in Syngeneic Mouse Model.

Figure 7. Serum IL-10 Concentration for Vehicle and Relacorilant in Syngeneic Mouse Model.

TRANSCRIPTIONAL AND HEMATOLOGICAL EFFECTS OF RELACORILANT SUGGEST IMPROVED IMMUNE ACTIVITY IN PHASE 1/2 STUDY IN PATIENTS WITH SOLID TUMORS

- RNA profiling was conducted in whole blood from patients with advanced solid tumors (predominantly pancreatic and ovarian cancer) treated with relacorilant + nab-paclitaxel (n = 46). Fold change and P value were calculated by comparing RNA counts between baseline and cycle 1 day 15 (C1D15) (Figure 8).
  - Relacorilant + nab-paclitaxel suppressed the expression of canonical GR-controlled genes (ptgs2, P<0.001), confirming on-target antagonism of GR.
  - Genes encoding candidate-immunomodulatory drug targets (including cxcl8, ptger4, idol; P<0.001) were also suppressed.

Figure 8. Suppression of GR-Controlled and Candidate-Immunomodulatory Drug Target Genes in a Phase 1/2 Solid Tumor Study of Relacorilant + Nab-Paclitaxel.

Relacorilant Normalizes Elevated Neutrophil-to-Lymphocyte Ratio (NLR) in Patients with Solid Tumors

- Lower NLR is associated with improved outcomes on ICI [15].
  - NLR elevations in cancer patients have been reported, but the physiological drivers are unclear.
- A higher mean baseline NLR was observed in patients with solid tumors compared with healthy subjects (Figure 9, left).
- Relacorilant significantly reduced the NLR in patients with solid-tumor patients with elevated baseline NLR (>3) but not in patients with normal NLR at baseline (Figure 9, middle and right).
- These data suggest that elevated GC activity may contribute to high NLR, and relacorilant can normalize the NLR in some cancer patients.

Figure 9. Effects of Relacorilant + Nab-Paclitaxel on NLR.
Healthy volunteer data taken from the Phase 1 study; patient data from the Phase 1/2 solid tumor study. Solid tumor patients with elevated NLR (>3) are shown in red; patients with normal NLR are shown in blue.

Immune Activation and Antagonism of GC Activity by Relacorilant in a Patient with Complete Response

- In the Phase 1/2 solid tumor study, complete response per RECIST 1.1 was observed in one patient with ovarian cancer during treatment with relacorilant + nab-paclitaxel.
  - The patient's NLR declined from 5.5 (elevated) to 2.5 (normal) during the 7-day relacorilant lead-in preceding the first treatment cycle (Figure 10A).
  - The NLR improvement was accompanied by a reduction in GR-controlled transcripts ptgs2 and dusp1 over day 15. The abundance of these transcripts increased above baseline as the disease later progressed, treatment with relacorilant was discontinued, and dexamethasone was eventually administered (Figure 10B).
  - Plasma IFNγ slightly increased, while IL-10 decreased in this patient (Figure 10C).
  - A decrease in T_{reg} and an increase in CD3+, CD4+, and CD8+ were observed early in treatment (Figure 10D).

Figure 10. Biomarkers in a Patient with Ovarian Cancer with Complete Response on Relacorilant + Nab-Paclitaxel Therapy.

Figure 11. Plasma and Whole Blood Trends in Patients with Durable Benefit.

Relacorilant Improves Immune Activity in Patients with Durable Response

- In a subset of patients (n = 11, Table 1), durable clinical response was observed.
  - These durable responses are notable given prior treatment history with nab-paclitaxel and historic data in similar patients.
- Evidence of an immune response to relacorilant + nab-paclitaxel in these patients is indicated by the following observations (Figure 11).
  - Circulating blood counts: Increase in T-cell count (P=0.06), decrease in T_{reg} (P=0.06), and decrease in NLR (P=0.006 and P=0.02 on days 8 and 15).
  - Plasma cytokine levels: Increase in IFNγ (P=0.03) and decrease in IL-10 (P=0.03).
  - Whole blood RNA counts: Decreased expression of ptgs2 early in treatment (Figure 11, P=0.008).

Table 1. Summary of Remarkable Responders.
The patient with complete response described above is highlighted in bold type.

Cancer Type	Best Response	Duration of Benefit (weeks)	Progressed on Prior Taxane?
Ovarian—High-grade serous	**CR**	**23**	**No—Adjuvant**
Vulvar	PR	109	Yes
Ovarian—Primary peritoneal	PR	70	No—Adjuvant
Cholangiocarcinoma	PR	59	No
PDAC	PR	54	No
PDAC	PR	50	Yes
Acinar pancreatic	PR	32	Yes
Ovarian—Low-grade serous	SD	39	No—Adjuvant
Ovarian—Low-grade serous	SD	38	Yes
PDAC	SD	37	Yes
PDAC	SD	33	Yes

CR, complete response; PDAC, pancreatic ductal adenocarcinoma, PR, partial response; SD, stable disease.

CONCLUSIONS

- GR is abundantly expressed in human tumors and immune cells, and high GR expression is associated with high immune infiltrate and PD-L1 expression.
- Physiological concentrations of cortisol broadly suppress human PBMC activation in vitro.
  - Relacorilant, a potent, selective cortisol modulator that antagonizes GR, reverses this suppression.
- In the EG7 mouse model, relacorilant promotes αPD1 activity.
  - Consistent with the effects observed in isolated human PBMCs, the ability of relacorilant to promote T-cell function and pro-inflammatory cytokine secretion was corroborated in this model.
- Evidence of T-cell activation by relacorilant was also observed in solid-tumor patients with sustained response in a Phase 1/2 solid tumor study.
  - In this study, relacorilant suppressed GR-inducible genes and reduced the NLR.
- These findings support the hypothesis that relacorilant can reverse immune suppression by endogenous GC in solid tumor cancers.
- Clinical studies with immune checkpoint inhibitors and relacorilant are planned (eg, CORT125134-551, NCT04373265).

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RATIONALE #4 FOR COMBINING ICI'S WITH RELACORILANT

- High GC activity may be the cause of elevated NLR in some cancer patients.
- This Phase 1/2 solid tumor study suggests that NLR, T_{reg}, IL-10, and transcription of GR-target genes may be decreased, while IFNγ and T-cells may be increased by relacorilant + nab-paclitaxel.
- These immune effects have been associated with improved response to ICI.

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