Selective Glucocorticoid Receptor Modulation Reveals a New Role for CLEC10A in Patients With Solid Tumors

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Disclosure Information

Grace Mann

I have the following relevant financial relationships to disclose:

Employee of:	Corcept Therapeutics
Consultant for:	N/A
Speaker's Bureau for:	N/A
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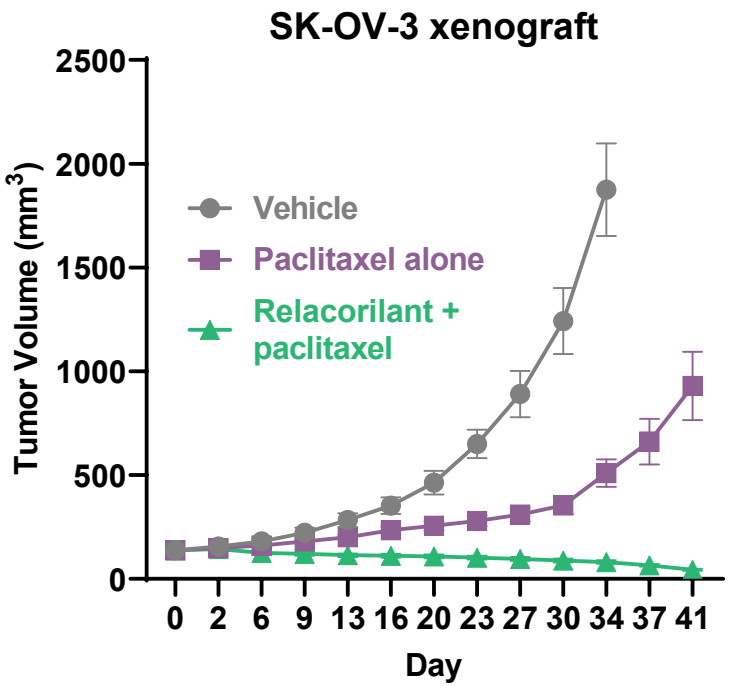
My additional financial relationship disclosures are: N/A

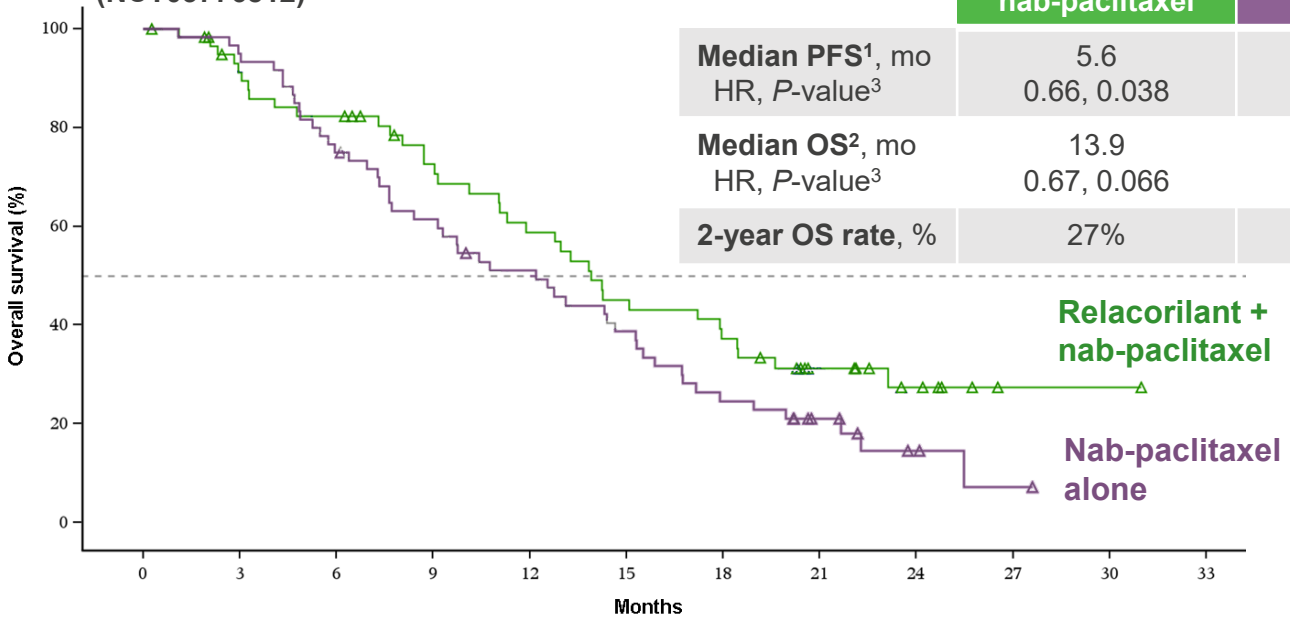
Selective Glucocorticoid Receptor Modulators (SGRMs) Can Enhance Chemotherapy Efficacy

- GR activation by endogenous cortisol can induce genes that suppress chemotherapy-mediated apoptosis
- The SGRM relacorilant selectively antagonizes the GR to enhance chemotherapy efficacy



Ovarian Cancer Phase 2 Study[1,2]
(NCT03776812)

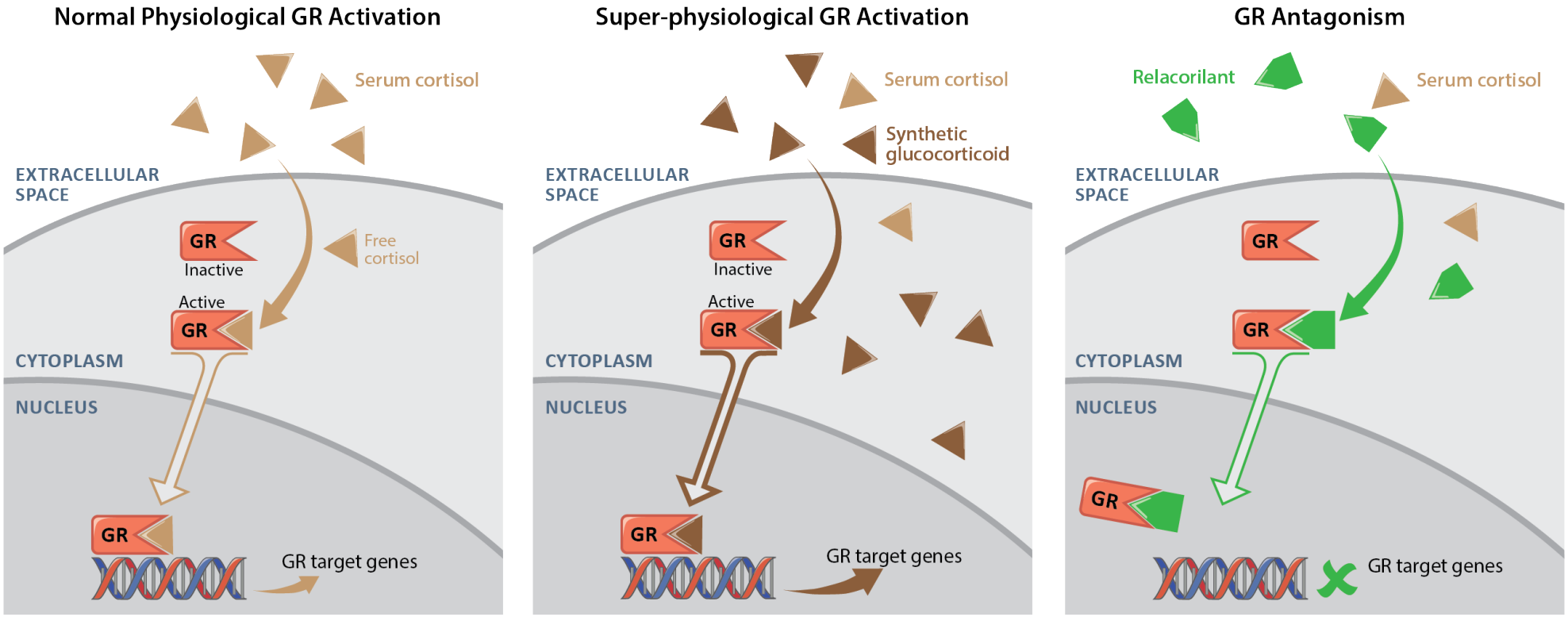
	Intermittent relacorilant + nab-paclitaxel	Nab-paclitaxel
Median PFS[1], mo HR, *P*-value[3]	5.6 0.66, 0.038	3.8 –
Median OS[2], mo HR, *P*-value[3]	13.9 0.67, 0.066	12.2 –
2-year OS rate, %	27%	14%



GR, glucocorticoid receptor; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SGRM, selective glucocorticoid receptor modulator.
[1]Colombo N, et al. *Ann Oncol.* 2021;32(suppl 5):7210. [2]Colombo N, et al. *J Clin Oncol.* 2022;40(suppl 17):LBA5503. [3]*P*-values not adjusted for multiplicity; relacorilant dosed intermittently; confirmatory phase 3 study underway (ROSELLA; NCT05257408).

Objective: Identify Biomarkers of GR Activity

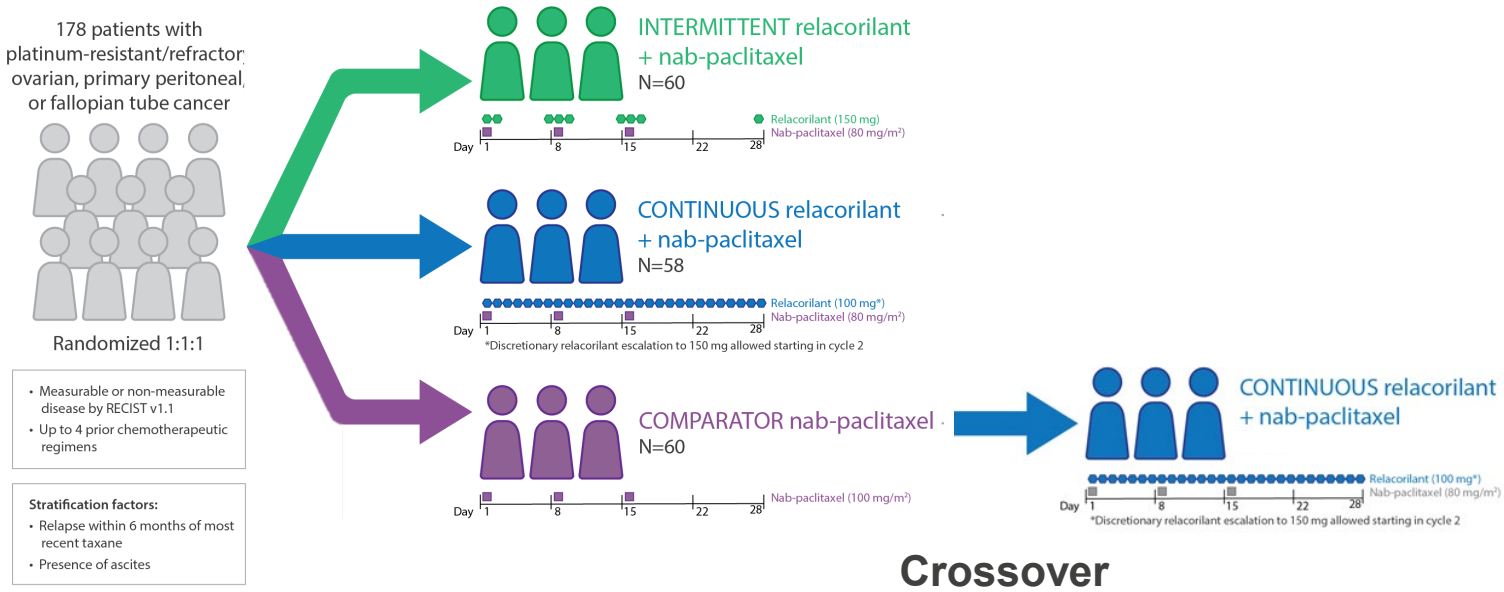
- The effects of short-term, super-physiological glucocorticoids on cells and tissue have been characterized
- We used oral relacorilant to probe the GR activities of endogenous cortisol in blood



GR, glucocorticoid receptor.

Discovery Data Set: Phase 2 Study in Patients With Platinum-resistant Ovarian Cancer (NCT03776812)

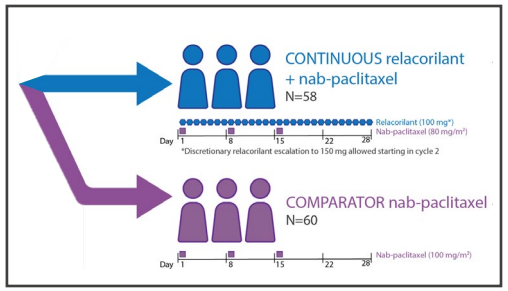
- A randomized, controlled, 3-arm study of relacorilant + nab-paclitaxel vs. nab-paclitaxel alone[1,2]
- Crossover post-progression: Nab-paclitaxel alone to continuous relacorilant + nab-paclitaxel
- RNA analysis in whole blood:
  - Proprietary NanoString panel of 444 candidate GR-target genes
  - Assessed gene changes at baseline and after 2 weeks of treatment
  - Crossover:
    - Assessed within-patient changes on nab-paclitaxel alone vs. relacorilant + nab-paclitaxel

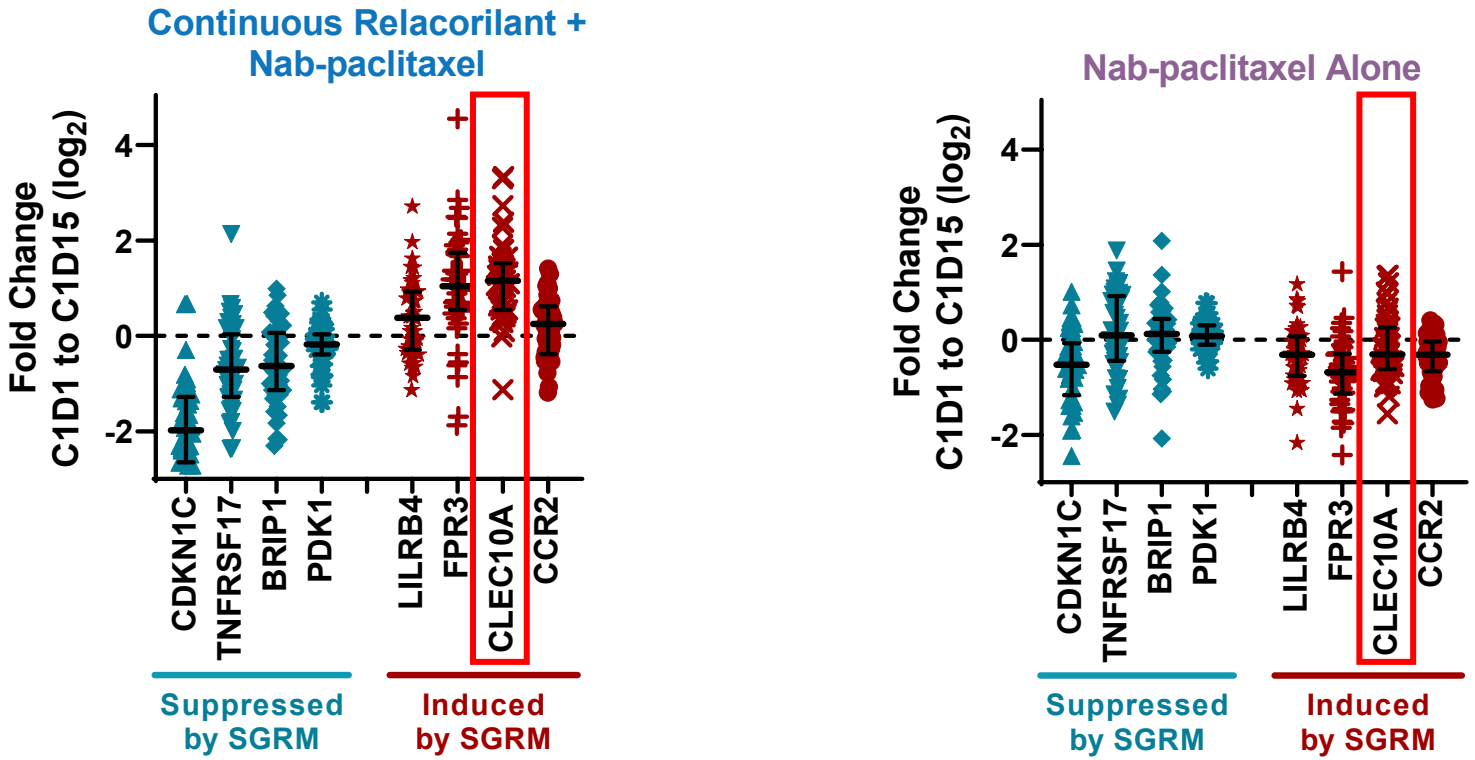


Data from the intermittent relacorilant + nab-paclitaxel arm are not included in this analysis. GR, glucocorticoid receptor.
[1]Colombo N, et al. *Ann Oncol.* 2021;32(suppl 5):7210. [2]Colombo N, et al. *J Clin Oncol*. 2022;40(suppl 17):LBA5503.

Identified Genes Affected by Relacorilant + Nab-paclitaxel, but not Nab-paclitaxel Alone

- Showing the **4 most suppressed** and the **4 most induced** genes by relacorilant
  - Testing the fold change in each gene between treatment arms resulted in $P<0.05$

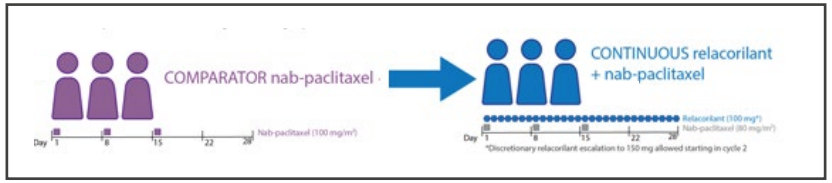


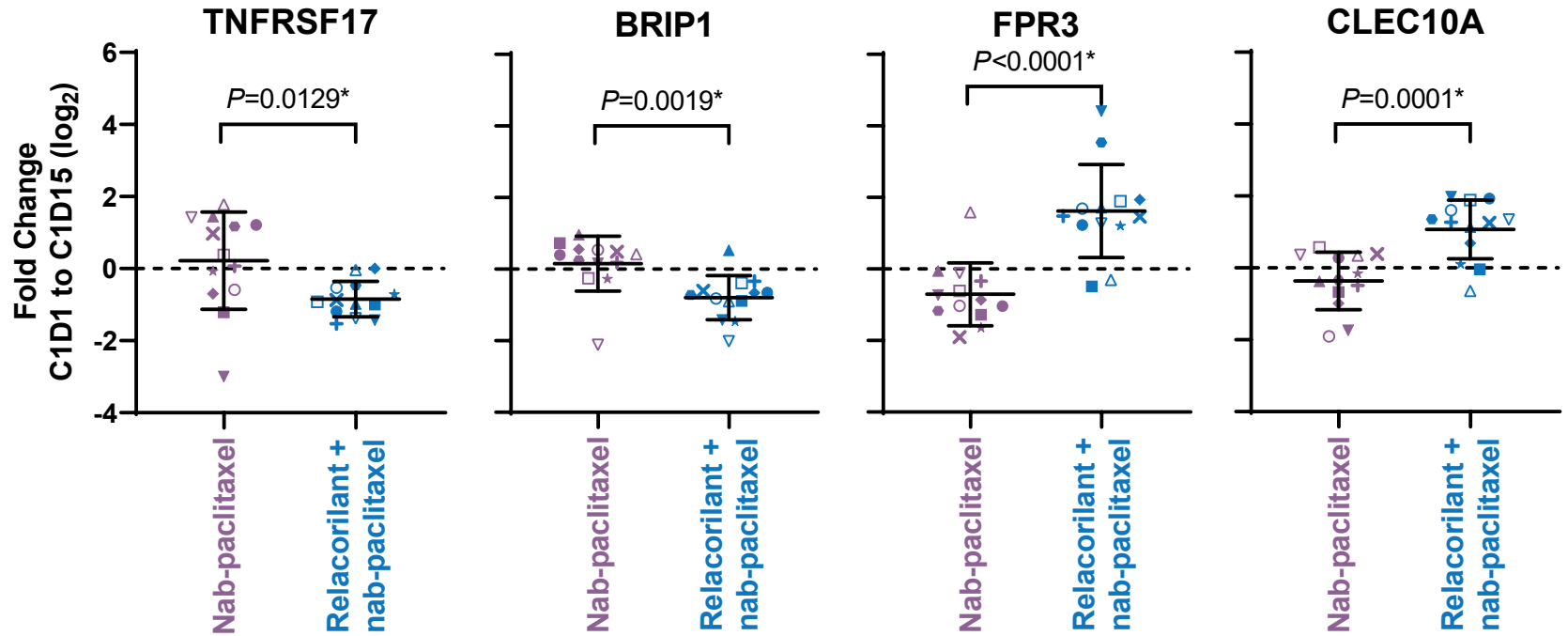


C1D1, cycle 1 day 1; C1D15, cycle 1 day 15. SGRM, selective glucocorticoid receptor modulator.

Crossover Analysis Confirms That These Genes Are Modulated by Relacorilant

- Genes were not altered on nab-paclitaxel alone
- Significant modulation observed after crossover to continuous relacorilant + nab-paclitaxel
- Confirms that these genes are markers of GR activity





* *P*-values not adjusted for multiplicity. Crossover analysis included n=13 patients. GR, glucocorticoid receptor.

Modulation of GR Activity Markers Confirmed in Other Solid Tumor Types: Pancreatic Ductal Adenocarcinoma (NCT04329949)

- A single-arm, open-label study of relacorilant + nab-paclitaxel in patients with metastatic PDAC[1]
- Effect of relacorilant on gene panel confirmed

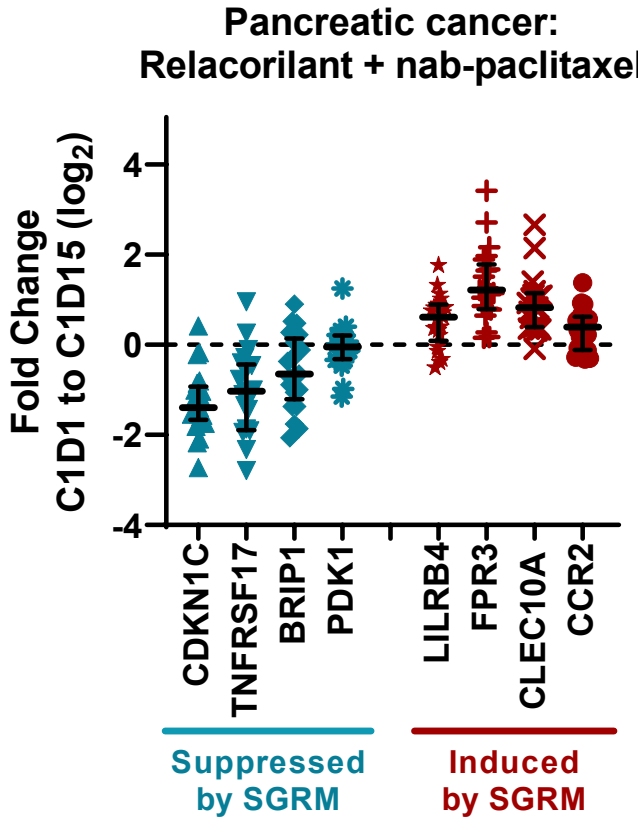
Patient population:
- Histologically confirmed mPDAC
- 2 to 4 prior lines of therapy
- Prior gemcitabine- and fluoropyrimidine-based therapy

Relacorilant (100 mg) + Nab-paclitaxel (80 mg/m^2)

(n=43)

Completed 12 weeks of treatment‡ or discontinued due to PD or toxicity

Interim analysis

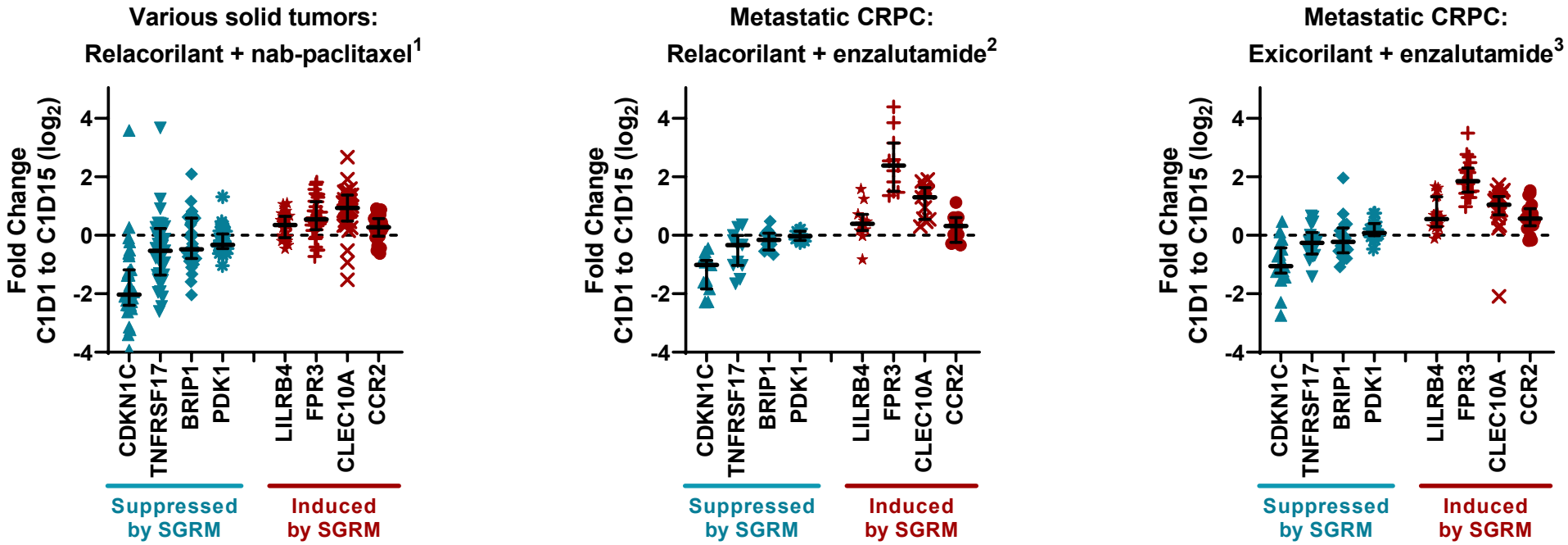


GR, glucocorticoid receptor; ORR, objective response rate; PD, progressive disease; mPDAC, metastatic pancreatic ductal adenocarcinoma; SGRM, selective glucocorticoid receptor modulator.

[1] E. Borazanci et al. *J Clin Oncol* 2022;40(16_suppl):4140–4140.

Modulation of GR Activity Markers Confirmed in Other Solid Tumor Types (NCT02762981, NCT03674814, NCT03437941)

- Similar pattern of change were observed across distinct:
  - Disease types
  - Concomitant medications (G-CSF, nab-paclitaxel, enzalutamide)
  - Selective GR modulators (relacorilant, exicorilant)

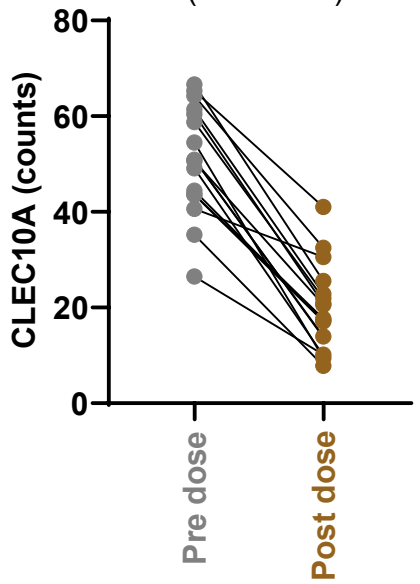


CRPC, castration-resistant prostate cancer; G-CSF, growth-colony stimulating factor; GR, glucocorticoid receptor.
[1]P. Munster et al. *Clin Cancer Res*. 2022;28(15):3214–3224. [2]NCT03674814. [3]M. Morris et al. Poster 145, presented at: *ASCO GU Cancers Symposium 2023,* Feb. 16–18, 2023; San Francisco, CA.

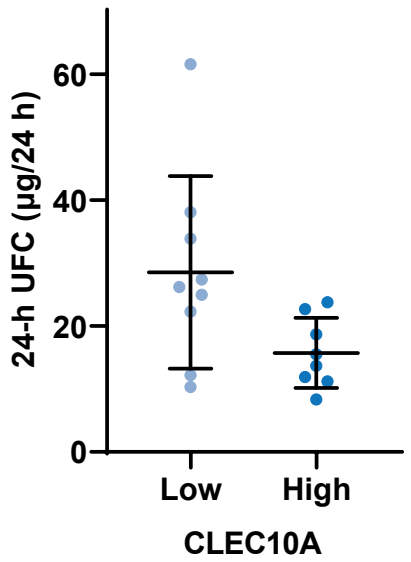
CLEC10A: A Particularly Sensitive Marker of GR Activity

- CLEC10A is strongly decreased by GR agonists and strongly increased by relacorilant
  - In healthy volunteers[1], the GR agonist prednisone rapidly decreased CLEC10A
  - In a mCRPC study[2], low baseline CLEC10A was associated with high baseline 24-hour urinary free cortisol

Effect of Prednisone on CLEC10A
(*P*<0.0001)



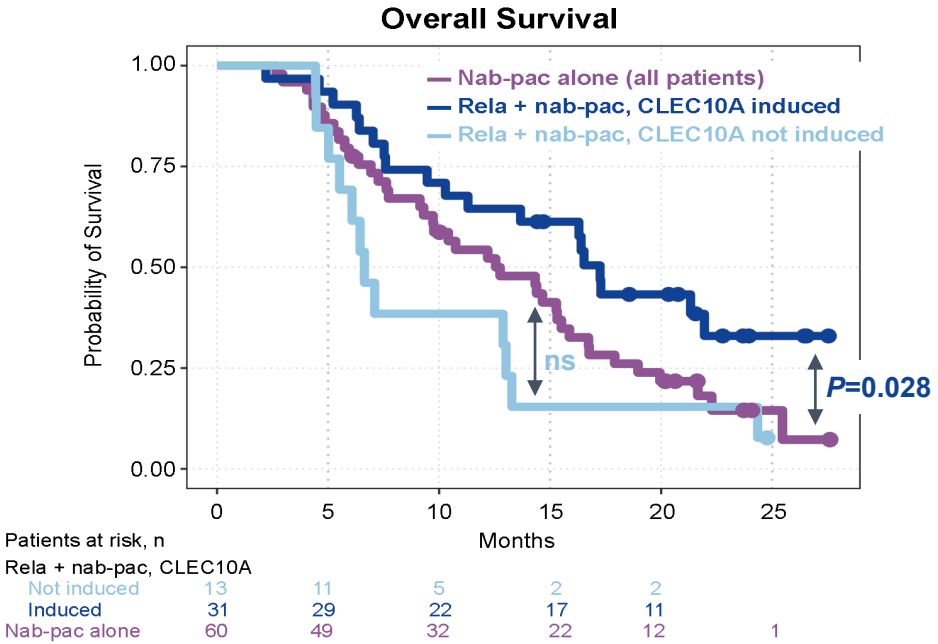
Baseline UFC vs. CLEC10A
(*P*=0.037)



GR, glucocorticoid receptor; mCRPC, metastatic castration-resistant prostate cancer; UFC, urinary free cortisol.
[1]Healthy volunteer study (NCT03335956); CLEC10A assessed pre- and 4-h post 25 mg prednisone. [2]M. Morris et al. Poster 145, presented at: *ASCO GU Cancers Symposium 2023,* Feb. 16–18, 2023; San Francisco, CA.

CLEC10A Induction by Relacorilant Is Associated With Longer Overall Survival in Patients With Ovarian Cancer

- In a post-hoc, exploratory analysis, patients treated with relacorilant + nab-paclitaxel[1] with CLEC10A induction experienced improved OS compared to nab-paclitaxel alone
  - No significant difference from nab-paclitaxel alone observed in patients receiving relacorilant + nab-paclitaxel without induction in CLEC10A
- This suggests that GR modulation by relacorilant is associated with clinical benefit



	Relacorilant + nab-paclitaxel vs. nab-paclitaxel alone	
	CLEC10A induced	CLEC10A not induced
Log rank *P*-value	0.028	0.26
Median OS		
Nab-paclitaxel alone	12.2	12.2
Relacorilant + nab-paclitaxel	17.2	6.6
HR vs. nab-paclitaxel alone	0.55	1.44

[1]Exploratory, post-hoc analysis in the ovarian cancer phase 2 study (NCT03776812). GR, glucocorticoid receptor; HR, hazard ratio; nab-pac, nab-paclitaxel. OS, overall survival; rela, relacorilant.

Conclusions

- We identified reliable indicators of GR activity in whole blood RNA.
- Consistent pharmacodynamic effects were observed in multiple tumor types.
- CLEC10A was a particularly sensitive marker of GR activity.
  - CLEC10A is induced by SGRMs and suppressed by synthetic and endogenous glucocorticoids.
- CLEC10A increase was associated with longer OS in patients with ovarian cancer treated with the SGRM relacorilant + nab-paclitaxel.
  - This suggests a possible association between GR modulation and clinical benefit.
- These studies confirm that systemic GR activity in patients with a range of solid tumors can be modulated pharmacologically and provide new insights into the systemic functions of the GR in humans.

GR, glucocorticoid receptor; RNA, ribonucleic acid; OS, overall survival; SGRM, selective glucocorticoid receptor modulator.

Thank you!

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- the investigators, and
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