Glucocorticoid Receptor Expression and Activity in a Phase 2 Ovarian Cancer Trial of the Glucocorticoid Receptor Modulator Relacorilant in Combination With Nab-Paclitaxel

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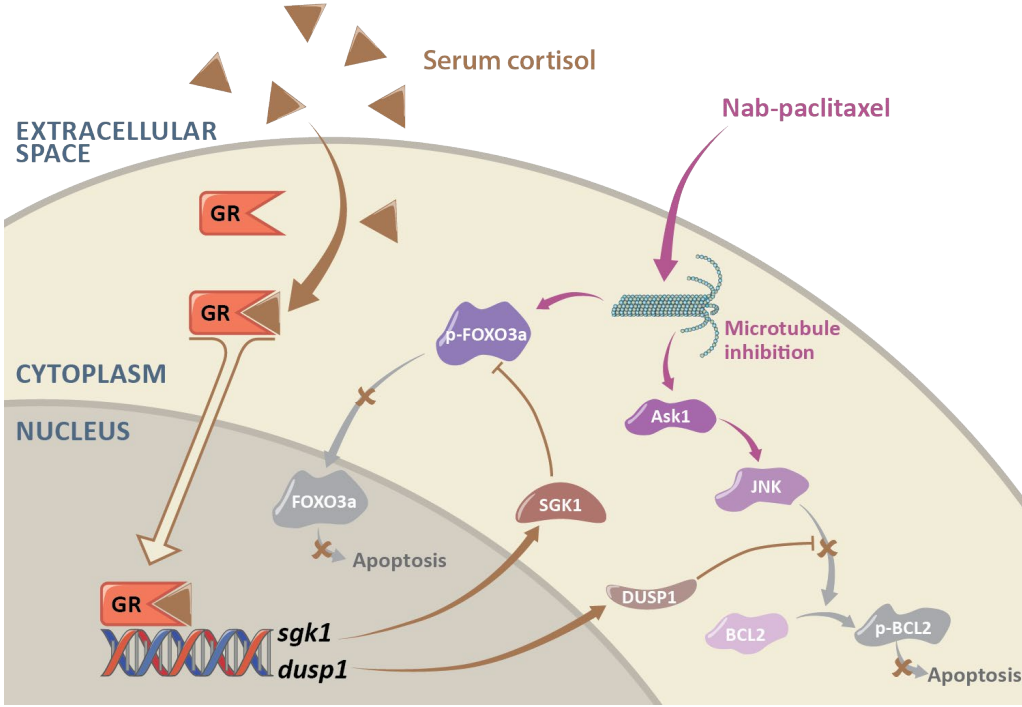
DECLARATION OF INTERESTS

Prof. Lorusso received/performed:

- A consulting/advisory role for PharmaMar, Merck Serono, Novartis
- A speakers bureau role for AstraZeneca, Clovis Oncology, PharmaMar, and Tesaro/GSK
- Travel/accommodations/expenses from AstraZeneca, Clovis Oncology, PharmaMar, Roche, and Tesaro/GSK
- Expert testimony on behalf of Clovis Oncology
- Honoraria from AstraZeneca, Clovis Oncology, Genmab, Immunogen, Merck, Roche, and Tesaro/GSK
- Research funding (to institution) from Clovis Oncology, Merck, PharmaMar, and Tesaro/GSK, Corcept Theraputics, MSD

Cortisol Activity in Ovarian Cancer

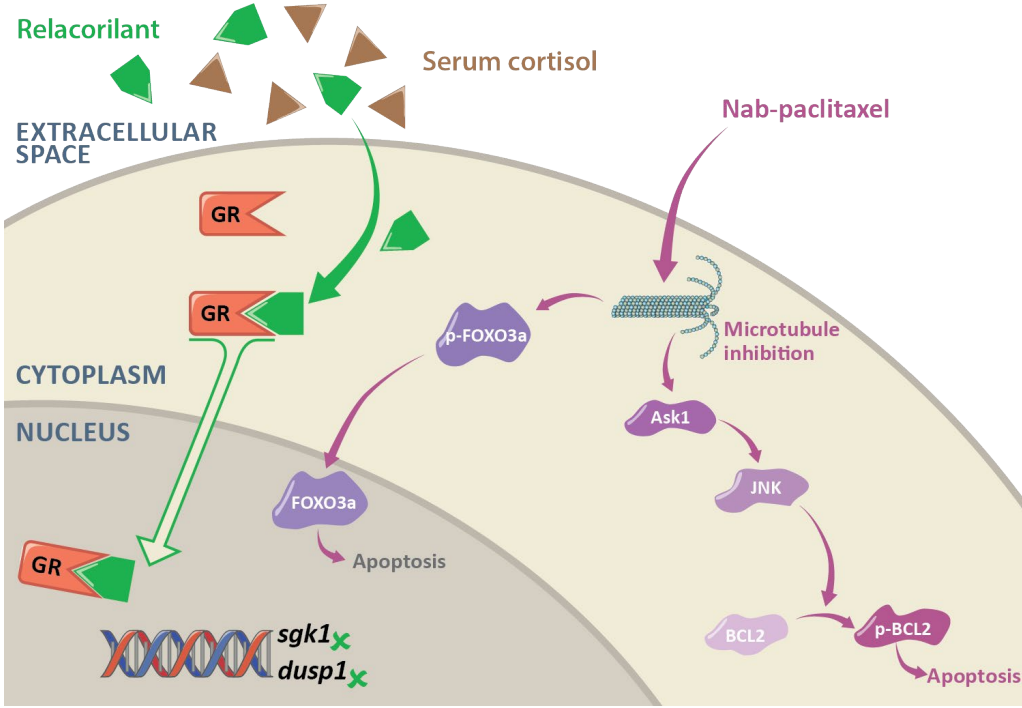
- **Cortisol** activity at the glucocorticoid receptor (GR) reduces chemotherapy efficacy by suppressing apoptotic pathways utilized by cytotoxic agents, such as nab-paclitaxel
- **High GR expression** is associated with poor prognosis and reduced chemotherapy response in ovarian cancer[1]



[1] Veneris et al. *Gynecol Oncol.* 2017;146:153–60.

Cortisol Activity in Ovarian Cancer

- **Cortisol** activity at the glucocorticoid receptor (GR) reduces chemotherapy efficacy by suppressing apoptotic pathways utilized by cytotoxic agents, such as nab-paclitaxel
- **High GR expression** is associated with poor prognosis and reduced chemotherapy response in ovarian cancer[1]
- **Relacorilant** is a non-steroidal, oral, selective GR modulator (SGRM) that antagonizes the effects of endogenous cortisol
- Preclinical and phase 1 clinical data suggested an additive effect of relacorilant + nab-paclitaxel[2,3]



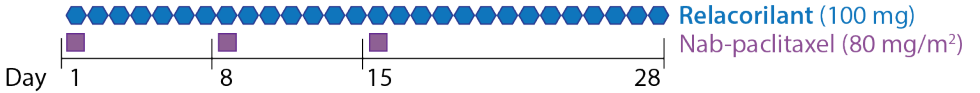
[1] Veneris et al. *Gynecol Oncol.* 2017;146:153–60. [2] Greenstein & Hunt. *Oncotarget.* 2021;12: 1243–55. [3] Munster et al. *Clin Cancer Res.* 2022;28:3214–24.

Relacorilant + Nab-paclitaxel in Platinum-resistant/refractory Ovarian Cancer

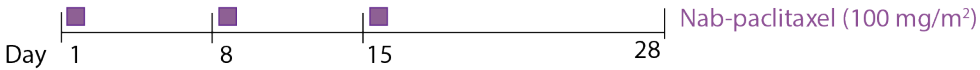
Phase 2 Study Design and Key Findings[1]

INTERMITTENT **relacorilant** + nab-paclitaxel (N=60)

CONTINUOUS **relacorilant** + nab-paclitaxel (N=58)



COMPARATOR nab-paclitaxel (N=60)



PFS, progression-free survival; DOR, duration of response; OS, overall survival; HR, hazard ratio; INTERM, intermittent; CONT, continuous; COMP, comparator. [1] NCT03776812; [2] Colombo et al. ESMO 2021, Abstract 7210; [3] Colombo et al. ASCO 2022, Abstract LBA5503

INTERMITTENT Relacorilant + Nab-paclitaxel[2,3]

- Improved PFS and DOR
- Trended toward improved OS
- Showed no additional toxicity

compared to nab-paclitaxel only

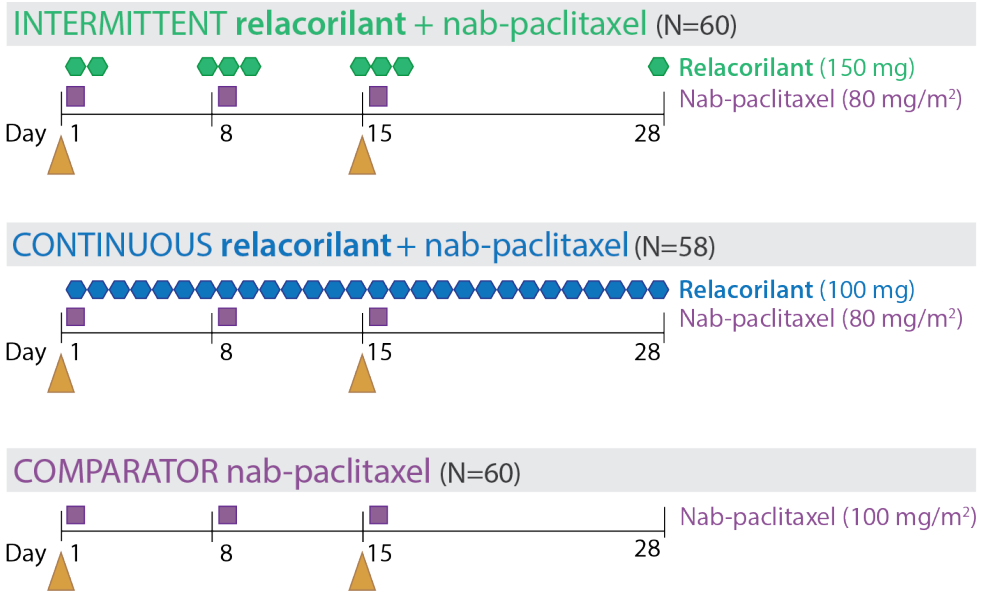
	Median PFS, mo (95% CI)	HR vs Comparator (95% CI)	Log-rank *P* vs Comparator
INTERM	**5.6** (3.7, 7.2)	**0.66** (0.44, 0.98)	**0.038**
CONT	5.3 (3.8, 5.6)	0.83 (0.56, 1.22)	0.329
COMP	3.8 (3.5, 5.4)	N/A	N/A

PFS analysis; data cutoff March 22, 2021. *P*-values are nominal, no multiplicity adjustment applied.

Domenica Lorusso, MD, PhD

Relacorilant + Nab-paclitaxel in Platinum-resistant/refractory Ovarian Cancer

Phase 2 Study Design and Key Findings[1]



Biomarker objectives included:

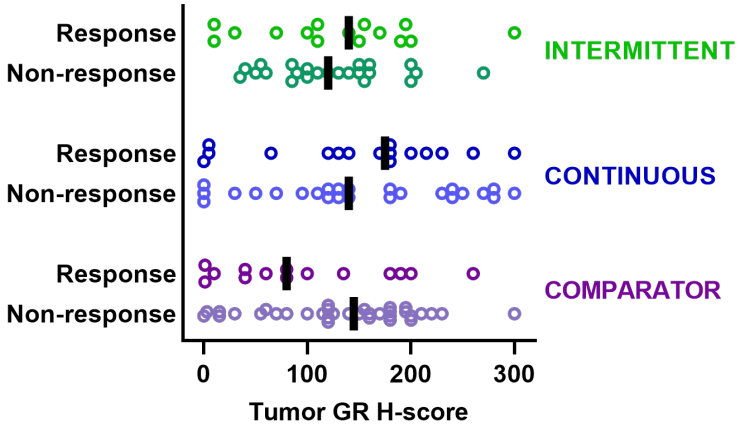
- Determine if tumor GR expression is associated with response
  - Baseline archival or recent biopsies analyzed by IHC
- Determine if GR target genes are modulated in blood

▲ Pharmacodynamic samples collected pre-dose on cycle 1 day 1 & day 15

[1] NCT03776812; GR, glucocorticoid receptor; IHC, immunohistochemistry.

Tumor GR Expression Was Associated With Clinical Response

Best Overall Response by RECIST v1.1

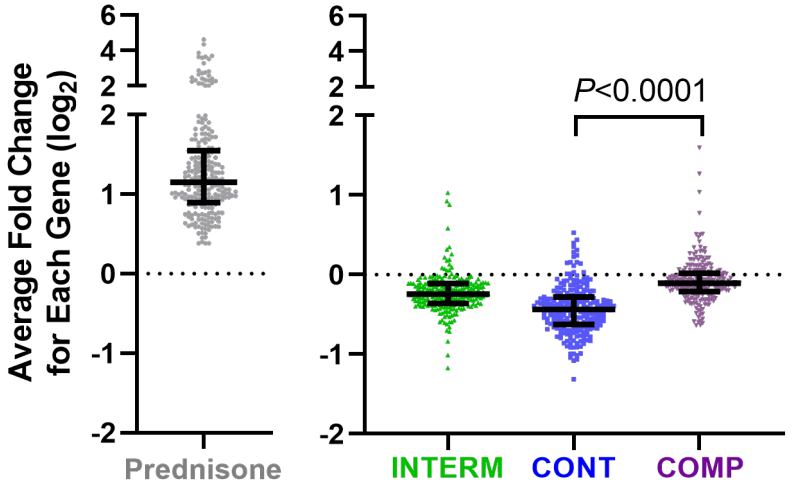


- GR was detectable (H-score ≥1) in 93% (122/131) of patients
- High tumor GR expression (H-score ≥100) was observed in 68% (89/131) of patients
  - Benefit of relacorilant was analyzed in this subset because response to chemotherapy is especially poor[1]
- In patients with high tumor GR expression, relacorilant treatment improved ORR compared to nab-paclitaxel only

	ORR in Patients With:	
	High Tumor GR Expression, n/N (%)	**Low Tumor GR Expression,** n/N (%)
Relacorilant + Nab-paclitaxel (continuous + intermittent combined)	23/57 (40.4%)	8/25 (32.0%)
Nab-paclitaxel only	6/32 (18.8%)	8/17 (47.1%)
χ^2 *P*-value	0.037	>0.05, ns

[1] Veneris et al. *Gynecol Oncol.* 2017;146:153–60. CLIA-validated IHC assay using standard H-score methods (0–300). GR, glucocorticoid receptor; Response- CR or PR; Non-response- SD or PD; IHC, immunohistochemistry; ORR, objective response rate; ns, not significant.

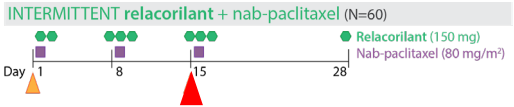
GR-inducible Genes Are Suppressed by Relacorilant



- 237 GR-inducible genes were identified in a previous study in the blood of healthy volunteers[1]

Ovarian Cancer Phase 2 Study[2]

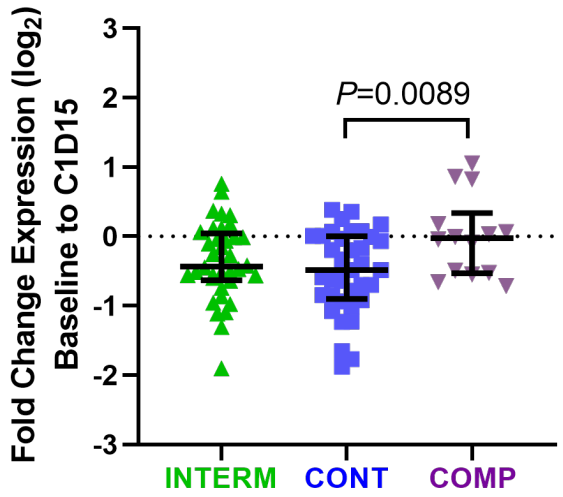
- 168/237 GR-inducible genes were suppressed in the nab-paclitaxel-only arm
- Significantly more GR-inducible genes (220/237) were suppressed after continuous dosing of relacorilant
- Intermittent dosing of relacorilant showed a similar but muted trend compared to continuous dosing
  - Maximal gene modulation was not captured in this arm, possibly due to the sample collection timing (just a single relacorilant dose on day 14, after 4 days of relacorilant washout)



[1] NCT03335956, 17 healthy volunteers. Induction observed 4 h post a single dose of prednisone (25 mg).
[2] NCT03776812, all subjects with both C1D1+C1D15 samples collected per protocol

Canonical GR Target Genes Are Suppressed by Relacorilant

Example: Serum and glucocorticoid regulated kinase 1 (SGK1)



- A well-established GR-inducible gene
- Plays an important role in the cellular stress response and is involved in the regulation of cell survival
- Similar trends observed in other GR-inducible genes
- Intermittent dosing of relacorilant showed similar but muted trend compared to continuous dosing

GR, glucocorticoid receptor.

Conclusions

- GR expression was abundant in the ovarian tumors evaluated in this study
  - High GR expression (observed in 68% of tumors) was associated with low ORR to nab-paclitaxel alone (18.8%) but with increased ORR in patients treated with relacorilant + nab-paclitaxel (40.4%)

- Suppression of GR-inducible genes indicated GR antagonism by relacorilant in blood and confirmed that GR signaling can be modulated in patients with ovarian cancer

- A randomized phase 3 study of nab-paclitaxel + intermittently dosed relacorilant vs nab-paclitaxel monotherapy is ongoing to confirm the clinical benefit in patients with platinum-resistant ovarian cancer (NCT05257408)
  - The study will also test GR-inducible gene modulation after 3 consecutive doses of relacorilant (on day 17)

GR, glucocorticoid receptor; ORR, objective response rate.

Thanks to all Those who Contributed to This Study!

The study patients and their families

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