Relacorilant + Nab-Paclitaxel in Patients With Recurrent, Platinum-Resistant Ovarian Cancer: A Three-Arm, Randomized, Controlled, Open-Label Phase II Study

Nicoletta Colombo, MD[1,2]; Toon Van Gorp, MD, PhD[3]; Ursula A. Matulonis, MD[4]; Ana Oaknin, MD, PhD[5]; Rachel N. Grisham, MD[6]; Gini F. Fleming, MD[7]; Alexander B. Olawaiye, MD[8]; Dorothy D. Nguyen, MD[9]; Andrew E. Greenstein, PhD[9]; Joseph M. Custodio, PhD[9]; Hristina I. Pashova, PhD[9]; Iulia C. Tudor, PhD[9]; and Domenica Lorusso, MD, PhD[10]

DOI https://doi.org/10.1200/JCO.22.02624

ABSTRACT

PURPOSE Despite therapeutic advances, outcomes for patients with platinum-resistant/refractory ovarian cancer remain poor. Selective glucocorticoid receptor modulation with relacorilant may restore chemosensitivity and enhance chemotherapy efficacy.

METHODS This three-arm, randomized, controlled, open-label phase II study (ClinicalTrials.gov identifier: NCT03776812) enrolled women with recurrent, platinum-resistant/refractory, high-grade serous or endometrioid epithelial ovarian, primary peritoneal, or fallopian tube cancer, or ovarian carcinosarcoma treated with ≤4 prior chemotherapeutic regimens. Patients were randomly assigned 1:1:1 to (1) nab-paclitaxel (80 mg/m²) + intermittent relacorilant (150 mg the day before, of, and after nab-paclitaxel); (2) nab-paclitaxel (80 mg/m²) + continuous relacorilant (100 mg once daily); or (3) nab-paclitaxel monotherapy (100 mg/m²). Nab-paclitaxel was administered on days 1, 8, and 15 of each 28-day cycle. The primary end point was progression-free survival (PFS) by investigator assessment; objective response rate (ORR), duration of response (DOR), overall survival (OS), and safety were secondary end points.

RESULTS A total of 178 women were randomly assigned. Intermittent relacorilant + nab-paclitaxel improved PFS (hazard ratio [HR], 0.66; log-rank test $P = .038$; median follow-up, 11.1 months) and DOR (HR, 0.36; $P = .006$) versus nab-paclitaxel monotherapy, while ORR was similar across arms. At the preplanned OS analysis (median follow-up, 22.5 months), the OS HR was 0.67 ($P = .066$) for the intermittent arm versus nab-paclitaxel monotherapy. Continuous relacorilant + nab-paclitaxel showed numerically improved median PFS but did not result in significant improvement over nab-paclitaxel monotherapy. Adverse events were comparable across study arms, with neutropenia, anemia, peripheral neuropathy, and fatigue/asthenia being the most common grade ≥3 adverse events.

CONCLUSION Intermittent relacorilant + nab-paclitaxel improved PFS, DOR, and OS compared with nab-paclitaxel monotherapy. On the basis of protocol-prespecified Hochberg step-up multiplicity adjustment, the primary end point did not reach statistical significance ($P < .025$). A phase III evaluation of this regimen is underway (ClinicalTrials.gov identifier: NCT05257408).

ACCOMPANYING CONTENT

Article, p. 4790

Data Supplement

Protocol

Accepted May 23, 2023
Published June 26, 2023

J Clin Oncol 41:4779-4789

View Online Article

INTRODUCTION

Treatment of advanced epithelial ovarian cancer remains challenging. Even among patients who initially respond to platinum-based chemotherapy, most relapse within the first 3 years and eventually die of treatment-resistant disease.[1-3] Sequential single-agent chemotherapy is the standard therapeutic option for platinum-resistant/refractory disease,[4,5] but outcomes remain poor.[3,6]

One mechanism of chemotherapy resistance may be driven by glucocorticoids (GCs). Endogenous cortisol can promote tumor progression via suppression of the apoptotic pathways used by cytotoxic agents.[7] When cortisol activates

CONTEXT

Key Objective

Can selective glucocorticoid receptor modulation with relacorilant benefit patients with platinum-resistant ovarian cancer by restoring chemosensitivity and/or enhancing chemotherapy efficacy?

Knowledge Generated

Intermittently dosed relacorilant + nab-paclitaxel improved progression-free survival, duration of response, and overall survival compared with nab-paclitaxel monotherapy with minimal additional toxicity in patients with advanced, platinum-resistant/refractory ovarian cancer. Although the primary end point did not reach statistical significance ($P < .025$) on the basis of protocol-prespecified Hochberg step-up multiplicity adjustment, the strength of the results in this controlled study stimulated evaluating this regimen in a currently ongoing phase III trial (ClinicalTrials.gov identifier: NCT05257408).

Relevance *(B.G. Haffty)*

Recurrent platinum resistant ovarian cancer is a significant clinical issue. This randomized phase II trial of relacorilant + nab-paclitaxel provides promising data that paved the way for a confirmatory ongoing phase III trial.*

*Relevance section written by *JCO* Deputy Editor Bruce G. Haffty, MD.

the glucocorticoid receptor (GR), target genes are upregulated and suppress apoptosis pathways (Fig 1).[8,9] High GR expression in ovarian cancer is correlated with shorter progression-free survival (PFS),[10,11] and preclinical studies have shown that physiological cortisol levels suppress chemotherapy-mediated tumor cell apoptosis.[7,12]

Taxanes play a role in the treatment of epithelial ovarian cancer, both in the initial and recurrent settings. Weekly paclitaxel is a standard regimen in platinum-resistant disease. Nab-paclitaxel, a solvent-free, albumin-bound nanoparticle form of paclitaxel, was developed to avoid numerous toxicities, including hypersensitivity reactions.[13,14] Nab-paclitaxel has shown substantial single-agent activity in a phase II study of patients with platinum-resistant ovarian cancer.[15]

Preclinical and early-phase clinical trials indicate that relacorilant (CORT125134, Corcept Therapeutics Inc, Menlo Park, CA), an investigational, orally administered, selective GR modulator (SGRM), may be able to restore chemosensitivity and enhance chemotherapy efficacy by competitively antagonizing the antiapoptotic effects of cortisol.[7,12,16-18] Relacorilant potently binds GR, inhibits GR in cells, and does not bind to the androgen or progesterone receptors.[19] In preclinical studies, relacorilant suppressed antiapoptotic genes upregulated by GC[18] and restored paclitaxel-induced tumor cell apoptosis reduced by cortisol.[7,12] Although paclitaxel was used to establish this mechanism preclinically, relacorilant + nab-paclitaxel was evaluated clinically because of its better safety profile and lack of corticosteroid premedication. The activity of relacorilant + nab-paclitaxel is supported by a phase I/II study in patients with advanced solid tumors,[16] where 38% of treated patients with ovarian cancer experienced durable disease control (complete or partial response or stable disease for ≥16 weeks).

The present phase II trial was conducted to evaluate the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics of relacorilant + nab-paclitaxel in patients with platinum-resistant/refractory ovarian cancer compared with nab-paclitaxel monotherapy.

METHODS

Additional details can be found in the Data Supplement (Appendix, online only).

Study Design

This three-arm randomized, controlled, open-label, phase II study (ClinicalTrials.gov identifier: NCT03776812; Data Supplement [Fig S1]) was performed in accordance with the principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Council for Harmonisation, and local regulatory requirements. The Protocol (online only) was approved by the institutional review board or independent ethics committee at each investigative site. All patients or their legally authorized representatives provided written informed consent.

Patients were randomly assigned 1:1:1 to one of three treatment arms: (1) nab-paclitaxel 80 mg/m² + relacorilant 150 mg orally once on the day before, once the day of, and once the day after nab-paclitaxel (intermittent arm); (2) nab-paclitaxel 80 mg/m² + relacorilant 100 mg orally once daily (continuous arm); and (3) nab-paclitaxel 100 mg/m² (nab-paclitaxel monotherapy arm). Across all arms, nab-paclitaxel was administered by infusion once per day on days

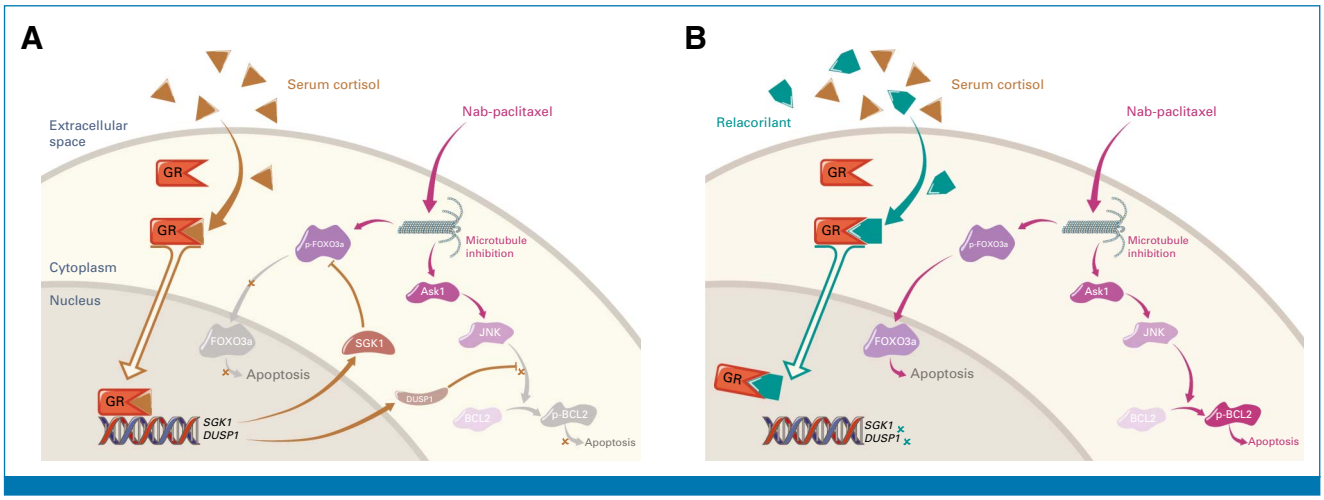

FIG 1. Effects of cortisol and relacorilant on pathways mediating nab-paclitaxel–induced tumor cell apoptosis. (A) By activating the GR, cortisol interferes with apoptotic processes, hence reducing the efficacy of chemotherapies. In the absence of cortisol, the GR is maintained in a transcriptionally inactive form in the cytosol. When bound to cortisol, GR translocates into the nucleus and modulates the expression of target genes such as *SGK1* and *DUSP1*. Microtubule inhibitors such as nab-paclitaxel induce tumor cell apoptosis via BCL2 and FOXO3a activities, but both pathways are impaired by GR target genes. (B) The selective GR modulator relacorilant antagonizes these effects of cortisol. As a result, the pathways required for nab-paclitaxel–induced tumor cell apoptosis are restored, and chemotherapy efficacy is enhanced. GR, glucocorticoid receptor.

1, 8, and 15 of each 28-day cycle. Random assignment was stratified by treatment-free interval from most recent taxane (relapse within 6 months *v* >6 months) and presence of ascites (yes/no). Prophylactic growth factor was required in the relacorilant-treated arms and by the investigator's standard practice in the nab-paclitaxel monotherapy arm.

Daily relacorilant was investigated to assess the benefit of sustained GR antagonism. Intermittent relacorilant was investigated on the basis of preclinical data indicating that sustained GR antagonism may not be required and that a higher relacorilant dose may yield greater GR antagonism around times of chemotherapy exposure.

The primary efficacy end point was PFS by investigator's assessment evaluated through two comparisons: each of the two relacorilant-treated arms versus the nab-paclitaxel monotherapy arm. Secondary end points included overall survival (OS), objective response rate (ORR), duration of response (DOR), best overall response (BOR), cancer antigen 125 (CA-125) response, safety, and PK. Baseline tumor GR expression, change from baseline in GR-target genes, and patient-reported outcomes (PROs) were exploratory end points.

Patient Population

Female patients (18 years or older) with recurrent, high-grade serous or endometrioid epithelial ovarian, primary peritoneal, or fallopian tube cancer or ovarian carcinosarcoma, for whom nab-paclitaxel was an appropriate treatment in the opinion of the investigator, were eligible to participate. To limit heterogeneity in the patient population, clear cell, mucinous, and borderline histologic subtypes were excluded. At least one prior line of platinum-based chemotherapy with platinum-free interval ≤6 months or disease progression during or immediately after platinum-based therapy was required. Patients with primary platinum-refractory disease were eligible. Measurable or nonmeasurable disease by RECIST v1.1 and ≤4 prior chemotherapeutic lines were allowed. Eastern Cooperative Oncology Group performance status 0 or 1 and adequate organ and bone marrow function were required. See the Data Supplement (Appendix) for key exclusion criteria.

Assessments

Radiographic tumor assessments (computed tomography or magnetic resonance imaging) were performed within 28 days before and every 8 weeks from cycle 1 day 1 until disease progression. Tumor response was assessed by the investigator using RECIST v1.1. ORR was calculated as the proportion of patients with measurable disease at baseline who achieved a BOR of complete or partial response. Response according to CA-125 using Gynecological Cancer InterGroup (GCIG) criteria was assessed within 14 days before and every 4 weeks from cycle 1 day 1 for the first 12 months of treatment.

PROs and quality-of-life assessments were collected in the safety population using three standard, validated instruments (FACT NFOSI-18,[20] EQ-5D-5L/VASc,[21] and PROMIS Physical Function[22-24]). PRO data are reported through cycle 6 day 1 as overall mean change from baseline (estimated using a longitudinal mixed-effects model), with a positive change reflecting improvement.

PK samples for relacorilant and nab-paclitaxel were collected on cycle 1 day 15 predose and 1, 2, 4, and 6 hours postdose.

Pharmacodynamic Analysis

Whole blood was collected predose (PreAnalytiX, Hombrechtikon, Switzerland) at baseline and cycle 1 day 15. RNA was extracted and quantified on an nCounter Flex (NeoGenomics, Fort Meyers, FL). A proprietary set of GR-related gene probes was designed and manufactured by NanoString Technologies (Seattle, WA). Data were analyzed using a Mann-Whitney test.

Fold change (FC) in expression for a panel of 239 GR-agonist—inducible genes was assessed in whole blood from baseline to cycle 1 day 15 (predose). For each gene, FC was averaged (1) for all patients who received study drug + growth-colony stimulating factor (G-CSF) in the nab-paclitaxel monotherapy arm, and (2) for those in the intermittent and continuous arms combined.

GR Immunohistochemistry

The CLIA-validated GR immunohistochemistry (IHC) assay was conducted on baseline archival formalin-fixed paraffin-embedded biopsies or resected tumor tissue. A χ^2 test was conducted to compare the expected frequency of RECIST v1.1 response in patients with an H-score ≥100 (a threshold selected on the basis of receiver operating characteristic analysis of the data set) to the observed response.

Statistical Analysis

Time-to-event end points were summarized using Kaplan-Meier methods. The stratified log-rank test was used to compare the treatment groups with respect to time-to-event variables. Primary estimates of the treatment differences were obtained using hazard ratios (HRs) and two-sided 95% CIs from stratified Cox regression models that included treatment as a covariate and by stratification variables used at random assignment. Two simultaneous comparisons were planned for the primary efficacy end point (PFS): each relacorilant-containing arm versus nab-paclitaxel monotherapy. The Hochberg step-up procedure was prespecified as a multiple adjustment procedure to determine statistical significance for the two PFS comparisons (either $P < .05$ for both comparisons or lowest $P < .025$). Response-rate end points were summarized as point and interval estimates and 95% CIs. All hypothesis tests presented here are nominal two-sided tests at a .05 level of significance; no multiplicity adjustment was applied. Data presented are based on the primary analysis for PFS (154 PFS events, data cutoff March 22, 2021) and final OS analysis (128 OS events, data cutoff March 7, 2022).

RESULTS

Patient Demographics and Disposition

From April 2019 to July 2020, 178 patients were enrolled at sites in Northern America and Europe (CONSORT diagram: Data Supplement [Fig S2]). Baseline and disease characteristics are presented in Table 1. In total, 177 of 178 (99.4%) patients had received prior taxane (one unknown). There were 36.5% of patients who were considered platinum refractory. Patients with primary platinum-refractory disease were overrepresented in the intermittent arm compared with other study arms. Across all arms, 59.0% of patients had received prior bevacizumab, and 36.5% had received poly (ADP-ribose) polymerase inhibitors. Fewer patients in the intermittent arm received prior bevacizumab than in the nab-paclitaxel monotherapy arm (51.7% *v* 61.7%).

The majority of patients discontinued treatment because of disease progression (71.8%) or adverse events (10.7%; Data Supplement [Fig S2]).

Efficacy

At the primary analysis (median follow-up of 11.1 months across arms), intermittent relacorilant improved PFS compared with nab-paclitaxel monotherapy with a HR of 0.66 (95% CI, 0.44 to 0.98; $P = .038$) and a median PFS of 5.6 months versus 3.8 months (Fig 2A). In the continuous arm, the median PFS was 5.3 months (HR, 0.83; 95% CI, 0.56 to 1.22; $P = .329$; Fig 2B). After multiplicity adjustment, the results for the primary end point (simultaneous testing of each relacorilant-treated arm *v* nab-paclitaxel monotherapy) did not meet statistical significance ($P < .025$).

Response to relacorilant + nab-paclitaxel is summarized in Table 2. Although ORRs were similar across study arms, DOR was significantly prolonged in the intermittent arm compared with nab-paclitaxel monotherapy.

At the predefined OS analysis (median follow-up of 22.5 months), HRs were 0.67 (95% CI, 0.43 to 1.03; $P = .066$) and 0.85 (95% CI, 0.56 to 1.29; $P = .447$) for the intermittent and continuous arms versus nab-paclitaxel monotherapy, respectively. The median OS was 13.9 (95% CI, 11.1 to 18.4), 11.3 (95% CI, 7.5 to 16.4), and 12.2 (95% CI, 7.7 to 15.3) months in the intermittent, continuous, and nab-paclitaxel monotherapy arms, respectively (Figs 2C and 2D).

BOR for CA-125 was evaluated in patients with an initial CA-125 level of at least 2× the upper limit of the reference range. CA-125 responses per GCIG criteria were observed in 34 of 53 (64.2%) patients in the intermittent, 32 of 51 (62.7%) patients in the continuous, and 28 of 52 (53.8%) patients in the nab-paclitaxel monotherapy arms.

Consistent PFS and OS benefit across multiple subgroups was observed in the intermittent arm versus nab-paclitaxel monotherapy (Data Supplement [Figs S3 and S4]), including greater improvement in OS in patients who had received 1-3 prior lines of anticancer therapy, including bevacizumab, and who did not have primary platinum-refractory disease (OS HR, 0.38 [95% CI, 0.17 to 0.82]; median OS, 17.9 months [95% CI, 12.8 to not reached] *v* 12.6 months [95% CI, 6.4 to 15.3]; Data Supplement [Table S1 and Fig S5]).

TABLE 1. Baseline Characteristics for the Study Population

Characteristic	Intermittent Relacorilant (150 mg) + Nab-Paclitaxel (80 mg/m^2; n = 60)	Continuous Relacorilant (100 mg) + Nab-Paclitaxel (80 mg/m^2; n = 58)	Nab-Paclitaxel Monotherapy (100 mg/m^2; n = 60)	Overall (N = 178)
Age, median (range), years	60 (38-81)	60 (45-75)	61.5 (41-81)	61 (38-81)
Platinum refractory,[a] No. (%)	23 (38.3)	20 (34.5)	22 (36.7)	65 (36.5)
Primary platinum refractory,[b] No. (%)	7 (11.7)	3 (5.2)	1 (1.7)	11 (6.2)
No. of prior systemic anticancer therapies,[c] median (range)	2.5 (1-4)	3 (1-5)	3 (1-4)	3 (1-5)
No. of prior chemotherapies, median (range)	2 (1-4)	2 (1-4)[d]	2 (1-4)	2 (1-4)[d]
≥4 prior lines of therapy,[c] No. (%)	7 (11.7)	15 (25.9)	9 (15.0)	31 (17.4)
Bevacizumab, No. (%)	31 (51.7)	37 (63.8)	37 (61.7)	105 (59.0)
PARP inhibitor, No. (%)	18 (30.0)	27 (46.6)	20 (33.3)	65 (36.5)
Molecular profiling[b]				
BRCA1(+), n/N (%)	5/42 (11.9)	4/42 (9.5)	7/48 (14.6)	16/132 (12.1)
BRCA1 unknown, n/N (%)	1/42 (2.4)	0/42 (0.0)	1/48 (2.1)	2/132 (1.5)
BRCA2(+), n/N (%)	1/36 (2.8)	3/39 (7.7)	3/39 (7.7)	7/114 (6.1)
BRCA2 unknown, n/N (%)	1/36 (2.8)	1/39 (2.6)	1/39 (2.6)	3/114 (2.6)
Presence of ascites,[e,f] No. (%)	16 (26.7)	15 (25.9)	16 (26.7)	47 (26.4)
Treatment-free interval from most recent taxane, No. (%)				
Relapse within 6 months[e,g]	29 (48.3)	29 (50.0)	29 (48.3)	87 (48.9)
≤6 months[h]	30 (50.0)	26 (44.8)	27 (45.0)	83 (46.6)
>6 to ≤12 months	6 (10.0)	12 (20.7)	14 (23.3)	32 (18.0)
>12 months	23 (38.3)	20 (34.5)	19 (31.7)	62 (34.8)
Missing	1 (1.7)	0	0	1 (0.6)
Measurable disease at baseline, No. (%)	56 (93.3)	54 (93.1)	53 (88.3)	163 (91.6)
Histology, No. (%)				
High-grade serous	56 (93.3)	53 (91.4)	57 (95.0)	166 (93.3)
Endometrioid	0	1 (1.7)	1 (1.7)	2 (1.1)
Carcinosarcoma	1 (1.7)	0	1 (1.7)	2 (1.1)
Mixed	1 (1.7)	1 (1.7)	1 (1.7)	3 (1.7)
Others	1 (1.7)	1 (1.7)	0	2 (1.1)

NOTE. Intermittent relacorilant dosed once on the day before, once the day of, and once the day after nab-paclitaxel infusion. Continuous relacorilant dosed once daily. Nab-paclitaxel dosed once per day on days 1, 8, and 15 of each 28-day cycle.

Abbreviations: EDC, electronic data capture; IxRS, interactive voice/web response system; PARP, poly (ADP-ribose) polymerase.

[a]Defined as progression during or within 1 month from last platinum treatment.

[b]Retrospectively collected and available in a subset of the study population only.

[c]Chemotherapy, myelosuppressive therapy, and molecularly targeted agents.

[d]EDC data for one patient updated after the primary analysis data cutoff date.

[e]Stratification factor.

[f]As assessed by investigator at random assignment.

[g]Per data collected in IxRS, used for stratification.

[h]Per data collected in EDC, updated after random assignment.

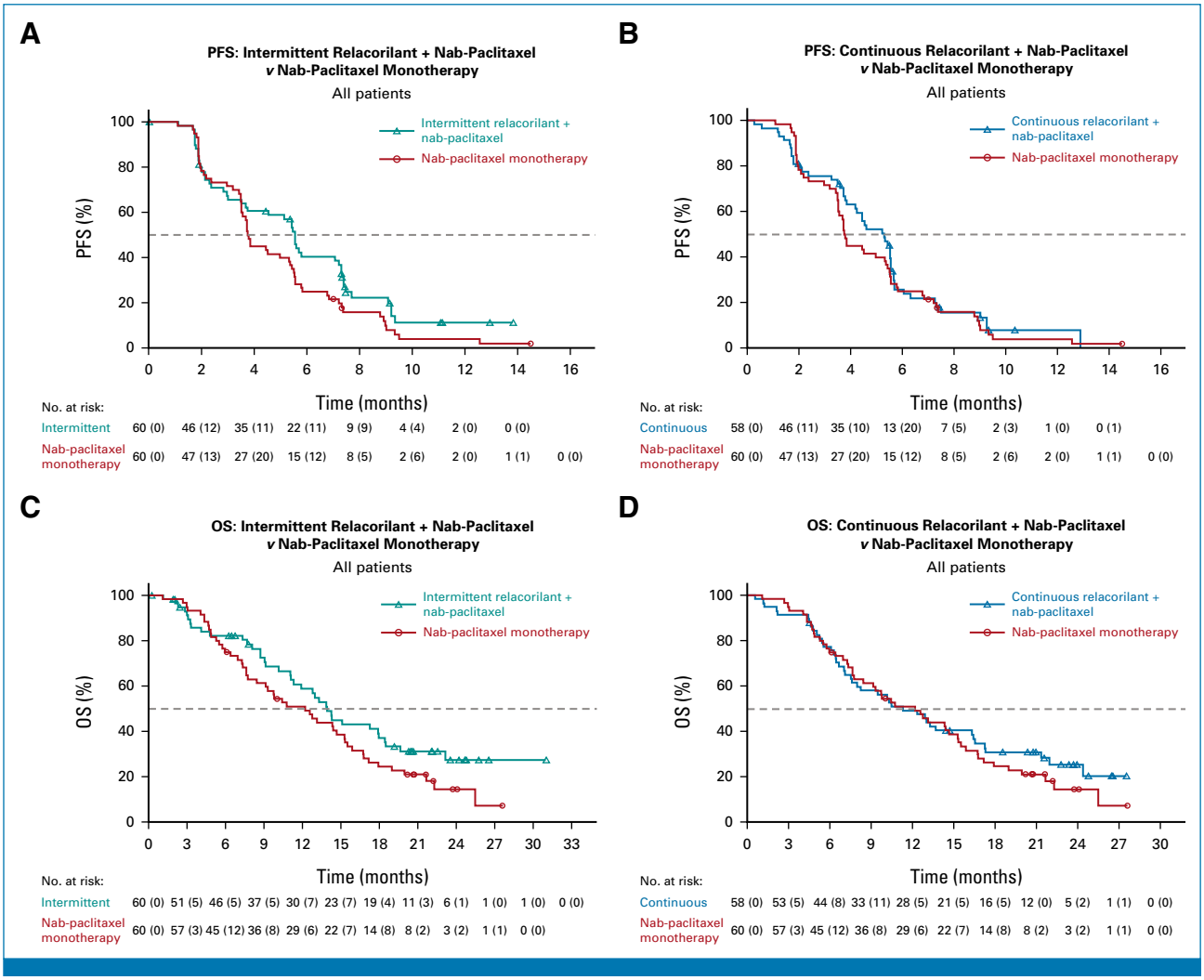

FIG 2. PFS and OS for intermittent relacorilant + nab-paclitaxel versus nab-paclitaxel monotherapy and continuous relacorilant + nab-paclitaxel versus nab-paclitaxel monotherapy. (A) and (B) PFS in all patients. At the primary analysis, 47 of 60 (78.3%, intermittent), 50 of 58 (86.2%, continuous), and 57 of 60 (95.0%, nab-paclitaxel monotherapy) patients had experienced a PFS event (PD by RECIST v1.1 or death). The median follow-up was 11.1 months. Intermittent relacorilant + nab-paclitaxel improved PFS compared with nab-paclitaxel monotherapy (log-rank, $P = .038$). (C) and (D) OS in all patients. At the OS analysis, 37 of 60 (61.7%, intermittent), 42 of 58 (72.4%, continuous), and 49 of 60 (81.7%, nab-paclitaxel monotherapy) OS events had occurred. The median follow-up was 22.5 months. A trend toward improved OS was observed in the intermittent arm (HR, 0.67; 95% CI, 0.43 to 1.03; $P = .066$). OS, overall survival; PD, progressive disease; PFS, progression-free survival.

PROs

Estimated mean decreases from baseline were reported in all arms and for all reported PRO instruments (Data Supplement [Table S2]). Changes in PROs in patients treated with intermittent relacorilant were in line with those observed with nab-paclitaxel monotherapy, while larger numerical decreases were observed with continuous relacorilant ($P < .05$).

Safety

Safety results are reported as of the final OS analysis. Overall, adverse events (AEs) were comparable across all study arms, with intermittent relacorilant + nab-paclitaxel being tolerated better than the continuous relacorilant regimen. Grade ≥3 fatigue was numerically higher in both relacorilant arms compared with nab-paclitaxel monotherapy, while other grade ≥3 AEs (such as neutropenia and peripheral neuropathy) were numerically lower in the intermittent relacorilant arm compared with nab-paclitaxel monotherapy. All relacorilant-treated patients (per protocol mandate) and 46.7% of patients in the nab-paclitaxel monotherapy arm received G-CSF. The most common AEs of any grade were fatigue/asthenia, nausea, anemia, abdominal discomfort, peripheral neuropathy, alopecia, constipation, neutropenia, and vomiting (Table 3). GI disorders were reported in 149 of 177 (84.2%) patients (41 of 177 [23.2%] grade ≥3). Rash incidence was comparable in the intermittent and nab-paclitaxel monotherapy arms but noted more frequently in the continuous arm, with one

TABLE 2. BOR and Objective Response in Patients With Measurable Disease at Baseline and DOR in the Intent-to-Treat Population

Response	Intermittent Relacorilant (150 mg) + Nab-Paclitaxel (80 mg/m^2; n = 56)	Continuous Relacorilant (100 mg) + Nab-Paclitaxel (80 mg/m^2; n = 54)	Nab-Paclitaxel Monotherapy (100 mg/m^2; n = 53)
BOR, No. (%)			
CR	1 (1.8)	4 (7.4)	2 (3.8)
PR	19 (33.9)	15 (27.8)	17 (32.1)
SD	20 (35.7)	23 (42.6)	21 (39.6)
PD	14 (25.0)	9 (16.7)	12 (22.6)
NE	2 (3.6)	3 (5.6)	1 (1.9)
ORR, No. (%)	20 (35.7)	19 (35.2)	19 (35.8)
Two-sided 95% CI	23.4 to 49.6	22.7 to 49.4	23.1 to 50.2
DOR, median (95% CI), months	5.55 (3.75 to 5.88)	3.79 (2.33 to 5.55)	3.65 (2.89 to 5.09)
Stratified HR (95% CI)	0.36 (0.16 to 0.77)	0.72 (0.33 to 1.58)	—
Log-rank *P* value *v* nab-paclitaxel monotherapy	.006	.423	—

NOTE. Intermittent relacorilant dosed once on the day before, once the day of, and once the day after nab-paclitaxel infusion. Continuous relacorilant dosed once daily. Nab-paclitaxel dosed once per day on days 1, 8, and 15 of each 28-day cycle.
Abbreviations: BOR, best overall response; CR, complete response; DOR, duration of response; HR, hazard ratio; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

event of grade ≥3. Serious AEs (SAEs) were reported in 16 of 60 (26.7%), 31 of 57 (54.4%), and 19 of 60 (31.7%) patients in the intermittent, continuous, and nab-paclitaxel monotherapy arms, respectively, and were most commonly related to the GI tract or infections/infestations. Fourteen SAEs occurring in 10 patients were considered related to one or both study drugs: three in the intermittent (anemia, pneumocystis jirovecii pneumonia, general physical health deterioration), six in the continuous (white blood cell count decreased, anemia, abdominal pain, back pain, constipation, melanocytic hyperplasia), and five in the nab-paclitaxel monotherapy arm (upper respiratory tract infection, hypocalcemia, hypomagnesemia, hypophosphatemia, syncope). Three AEs leading to death were reported (two in the intermittent arm [intestinal obstruction, general physical health deterioration] and one in the continuous arm [pneumonia]); no deaths were considered related to study drug.

PK

Large variability in relacorilant and nab-paclitaxel exposures was observed, consistent with the well-characterized PK profiles of both compounds. The overall range of nab-paclitaxel exposures was largely overlapping across all arms and consistent with those reported for nab-paclitaxel 100-125 mg/m^2 monotherapy[25] (Data Supplement [Table S3]).

No relationships in exposure-response (PFS, response by RECIST) were observed for relacorilant or nab-paclitaxel. Evaluation of relacorilant and nab-paclitaxel exposures versus safety end points (eg, peripheral neuropathy, neutropenia, and asthenia) showed overlapping exposures in the presence or absence of the AE (Data Supplement [Appendix]).

Pharmacodynamics and GR Expression

Suppression (average $\log_2$ FC < 0) was observed for 221 of 239 GR target genes after treatment with relacorilant + nab-paclitaxel (Fig 3A); nab-paclitaxel monotherapy exhibited less suppression of these genes (Mann-Whitney $P < .0001$). Greater suppression of serum and GC-regulated kinase (*SGK1*), one representative gene from the panel, was observed in relacorilant-treated patients compared with patients treated with nab-paclitaxel monotherapy (Mann-Whitney $P = .013$; Fig 3B).

Study arms were balanced for GR expression (IHC in 131 tumor samples; H-scores 0-300 observed). There was a trend toward higher H-scores in patients with BOR of complete or partial response in the relacorilant + nab-paclitaxel arms (Fig 3C), while high GR expression was associated with BOR of stable or progressive disease in the nab-paclitaxel monotherapy arm.

DISCUSSION

This phase II study was the first randomized, controlled trial of relacorilant, an SGRM, with nab-paclitaxel in patients with recurrent, platinum-resistant/refractory ovarian cancer. Effective treatment options for this patient population are sparse, and outcomes remain poor. This is especially true for women with primary platinum-refractory disease, who are generally excluded from trials but were randomly

TABLE 3. Most Frequent AEs (reported in >10% of study patients overall)

	Intermittent Relacorilant (150 mg) + Nab-Paclitaxel (80 mg/m^2; n = 60), No. (%)		Continuous Relacorilant (100 mg) + Nab-Paclitaxel (80 mg/m^2; n = 57), No. (%)		Nab-Paclitaxel Monotherapy (100 mg/m^2; n = 60), No. (%)	
Adverse Event	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatigue or asthenia	33 (55.0)	7 (11.7)	41 (71.9)	5 (8.8)	39 (65.0)	1 (1.7)
Anemia[a]	29 (48.3)	8 (13.3)	37 (64.9)	11 (19.3)	34 (56.7)	7 (11.7)
Nausea	31 (51.7)	1 (1.7)	43 (75.4)	2 (3.5)	27 (45.0)	1 (1.7)
Abdominal discomfort[b]	25 (41.7)	4 (6.7)	27 (47.4)	2 (3.5)	25 (41.7)	0
Alopecia	22 (36.7)	0	21 (36.8)	0	24 (40.0)	0
Neutropenia[c]	12 (20.0)	4 (6.7)	22 (38.6)	15 (26.3)	22 (36.7)	9 (15.0)
Febrile neutropenia	0	0	0	0	1 (1.7)	1 (1.7)
Peripheral neuropathy[d]	22 (36.7)	0	31 (54.4)	9 (15.8)	21 (35.0)	3 (5.0)
Constipation	18 (30.0)	1 (1.7)	25 (43.9)	4 (7.0)	17 (28.3)	0
Musculoskeletal pain[e]	11 (18.3)	0	19 (33.3)	0	16 (26.7)	0
Diarrhea	15 (25.0)	0	23 (40.4)	0	15 (25.0)	1 (1.7)
Dyspnea	5 (8.3)	1 (1.7)	12 (21.1)	2 (3.5)	15 (25.0)	0
Vomiting	17 (28.3)	1 (1.7)	27 (47.4)	5 (8.8)	15 (25.0)	0
Edema peripheral	10 (16.7)	0	8 (14.0)	0	12 (20.0)	1 (1.7)
Hypomagnesemia	5 (8.3)	0	8 (14.0)	0	11 (18.3)	1 (1.7)
Pyrexia	7 (11.7)	0	4 (7.0)	0	11 (18.3)	0
Cough	8 (13.3)	0	6 (10.5)	0	10 (16.7)	0
Decreased appetite	13 (21.7)	0	20 (35.1)	0	10 (16.7)	1 (1.7)
Back pain	7 (11.7)	0	10 (17.5)	0	9 (15.0)	0
Pain in extremity	10 (16.7)	0	7 (12.3)	0	8 (13.3)	0
Headache	7 (11.7)	0	7 (12.3)	0	7 (11.7)	0
Dysgeusia	7 (11.7)	0	7 (12.3)	0	5 (8.3)	0
Hypokalemia	3 (5.0)	1 (1.7)	13 (22.8)	2 (3.5)	5 (8.3)	0
Stomatitis	3 (5.0)	0	15 (26.3)	4 (7.0)	3 (5.0)	0
Rash	4 (6.7)	0	12 (21.1)	1 (1.8)	2 (3.3)	0

NOTE. Intermittent relacorilant dosed once on the day before, once the day of, and once the day after nab-paclitaxel infusion. Continuous relacorilant dosed once daily. Nab-paclitaxel dosed once per day on days 1, 8, and 15 of each 28-day cycle. Data cutoff date: March 7, 2022 (final OS analysis).

Abbreviations: AE, adverse event; G-CSF, growth-colony stimulating factor; OS, overall survival.

[a]Anemia, hemoglobin decreased.

[b]Abdominal pain, abdominal pain upper, abdominal distension.

[c]Neutropenia, neutrophil count decreased. All patients in the relacorilant-treated and 46.7% of those in the nab-paclitaxel monotherapy arm received prophylactic G-CSF.

[d]Hypoesthesia, neuropathy peripheral, neurotoxicity, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy.

[e]Arthralgia, myalgia.

overrepresented in the intermittent arm of this trial. Although the study did not meet its primary end point, intermittent relacorilant + nab-paclitaxel improved PFS, DOR, and OS compared with nab-paclitaxel monotherapy in this heavily pretreated population. These findings highlight the potential of GR modulation as a novel mechanism to restore chemosensitivity and enhance chemotherapy efficacy. A confirmatory phase III study evaluating intermittent relacorilant + nab-paclitaxel (ClinicalTrials.gov identifier: NCT05257408) is ongoing.

High GR expression was previously reported in ovarian tumors.[10,26,27] In a small study of patients who received dexamethasone or placebo before surgery, all ovarian tumors expressed GR by IHC.[28] Dexamethasone-treated patients experienced an average 6.1-fold and 8.2-fold increase in the expression of prosurvival GR target genes *SGK1* and *DUSP1*, respectively, whereas no significant changes were observed in placebo-treated patients. *In vitro* assays in GR-positive HeyA8 and SKOV3 cells showed that dexamethasone treatment upregulated *SGK1* and *DUSP1* and inhibited carboplatin/gemcitabine-induced cell death. Concurrent treatment with relacorilant reversed these effects.[18] A pharmacodynamic analysis performed as part of the current study confirmed that relacorilant + nab-paclitaxel can suppress GR target genes.

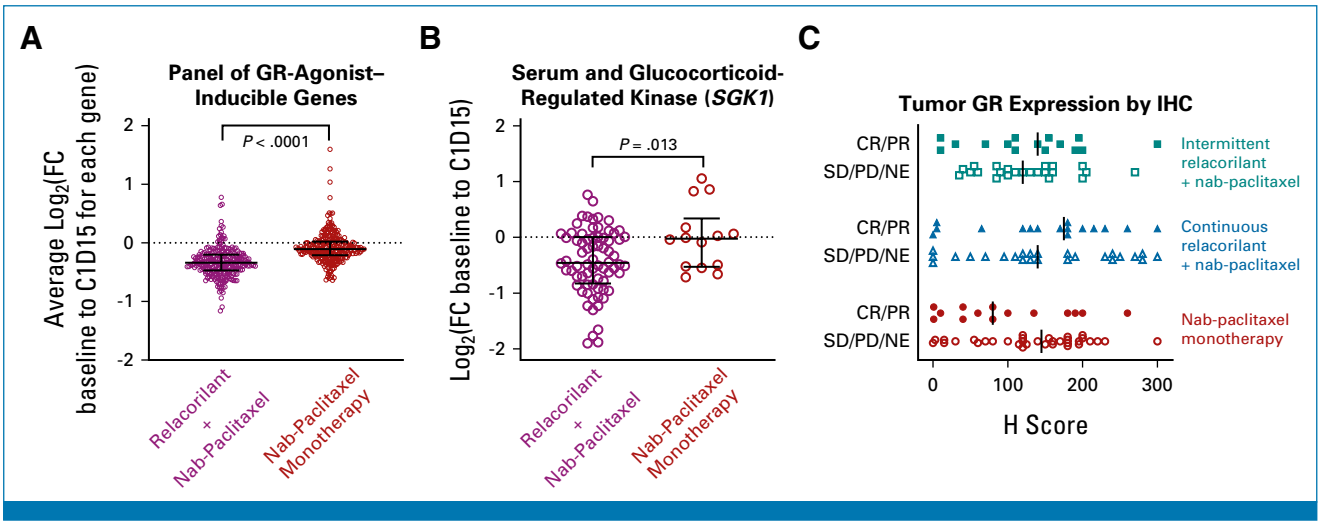

FIG 3. Pharmacodynamic and tumor GR expression analysis. (A) FC from cycle 1 day 1 to cycle 1 day 15 (predose) was assessed for 239 GR-agonist–inducible genes in whole blood. The FC for each gene was averaged across the relacorilant-treated (intermittent and continuous arm combined) or nab-paclitaxel monotherapy groups (total of 86 patients). 221 of the 239 GR-agonist–inducible genes were suppressed after treatment with relacorilant + nab-paclitaxel. Less suppression of these genes was observed in nab-paclitaxel monotherapy treated patients (Mann-Whitney $P < .0001$). (B) Serum and GC-regulated kinase (*SGK1*), an example from the panel of GR-agonist–inducible genes, was suppressed in the relacorilant + nab-paclitaxel treated patients (intermittent and continuous combined). In the nab-paclitaxel monotherapy arm, *SGK1* was less suppressed ($P = .013$). (C) Tumor GR expression was determined by IHC. High baseline tumor GR expression (H-score ≥100) was observed in 89 (67.9%) samples (26 of 38, 31 of 44, and 32 of 49 in the intermittent, continuous, or nab-paclitaxel monotherapy arms, respectively). High tumor GR expression was associated with BOR of PR/CR in the relacorilant + nab-paclitaxel arms and SD/PD/NE in the nab-paclitaxel monotherapy arm. Black vertical lines denote the median. Blood samples were drawn on day 1 and day 15 before relacorilant administration. ORR was higher in the relacorilant + nab-paclitaxel arms (40.4%, 23 of 57) as compared with the nab-paclitaxel monotherapy arm (18.8%, 6 of 32) for patients with high tumor GR expression (χ^2 $P = .0369$; Data Supplement [Table S4]). BOR, best overall response; CR, complete response; FC, fold change; GC, glucocorticoid; GR, glucocorticoid receptor; IHC, immunohistochemistry; NE, nonevaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

High GR expression was also an independent predictor of PFS[10] and associated with decreased OS in patients with ovarian cancer, independent of BRCA mutation status. BRCA wild-type high-grade serous ovarian cancers with high GR expression have shown particularly poor outcomes.[27] High tumor GR expression was associated with increased ORR in the relacorilant + nab-paclitaxel arms of the current study compared with nab-paclitaxel monotherapy, potentially emphasizing effects of relacorilant in tumors with high GR. However, similar correlations between GR expression and efficacy were not observed in other end points, and benefit was observed across the range of GR H-scores. These findings indicate that high GR expression is unlikely to be a prerequisite for treatment effect with relacorilant.

Overall, intermittent relacorilant + nab-paclitaxel was tolerated better than the continuous regimen and showed an AE profile comparable with nab-paclitaxel monotherapy. Some observed AEs, such as fatigue, may overlap with GR modulation and were numerically higher in the relacorilant-treated arms. However, interpretation of this finding is limited by the small number of patients who experienced these AEs. Prophylactic growth factor was used in all arms to address neutropenia risk, a known adverse drug reaction of nab-paclitaxel[29] that occurs more frequently in patients with multiple prior therapies.[30] Only one event of febrile neutropenia was reported in this study, occurring in the nab-paclitaxel monotherapy arm. Confirmation of the relacorilant safety profile is an objective of the ongoing phase III study.

The better efficacy observed with intermittent versus continuous relacorilant is not fully understood. Dose interruptions or adjustments, which could affect efficacy, occurred with similar frequency in both arms; dosing compliance was high (mean [range] relative dose intensity 85.4% [41.8-100.0] and 91.2% [32.0-100.0] for continuous and intermittent dosing, respectively). The higher dose of relacorilant administered in the intermittent arm around nab-paclitaxel infusion may facilitate relacorilant's ability to enhance antitubulin effects without increasing toxicity.

Study limitations include the open-label design and that baseline tumor GR IHC was determined from archival biopsies predominantly collected >1 year before study start.

In conclusion, the primary goal for treating recurrent, platinum-resistant ovarian cancer is to improve symptoms and prolong survival. An agent with a convenient dosing schedule that can be synergistically combined with existing

therapies, without cumulative toxicity or cross-resistance, is particularly desirable. The findings of the reported study suggest that relacorilant may be such an agent. The numerically favorable safety profile and better efficacy observed in the intermittent arm compared with the continuous arm support the use of intermittent relacorilant in ovarian cancer. Treatment with a higher relacorilant dose concurrent with the greatest nab-paclitaxel exposure resulted in clinically meaningful improvements in PFS, DOR, and OS without increased side effect burden. Greater improvement in OS was observed in an ad-hoc analysis in patients who received 1-3 prior lines of therapy, including bevacizumab and excluding patients with primary platinum-refractory disease. This patient population is being studied in a confirmatory phase III trial (ClinicalTrials.gov identifier: NCT05257408).

AFFILIATIONS

[1]Gynecologic Oncology Program, European Institute of Oncology, IRCCS, Milan, Italy
[2]Department of Medicine and Surgery, University Milan-Bicocca, Milan, Italy
[3]Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University Hospital Leuven, Leuven Cancer Institute, Leuven, Belgium
[4]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
[5]Gynaecologic Cancer Programme, Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain
[6]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical Center, New York, NY
[7]The University of Chicago, Chicago, IL
[8]Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, PA
[9]Corcept Therapeutics Inc, Menlo Park, CA
[10]Fondazione Policlinico Universitario Gemelli IRCCS, Catholic University of Sacred Heart, Rome, Italy

CORRESPONDING AUTHOR

Nicoletta Colombo, MD, European Institute of Oncology, IRCCS, University of Milan-Bicocca, Via Ripamonti 435, Milan 20141, Italy; e-mail: nicoletta.colombo@ieo.it.

PRIOR PRESENTATION

Presented in part at the European Society for Medical Oncology (ESMO) 2021 Virtual Congress, September 16-21, 2021; the ASCO 2022 Annual Meeting, Chicago, IL, June 3-7, 2022; the ESMO 2022 Congress, Paris, France, September 9-13, 2022; the International Gynecologic Cancer Society 2022 Annual Global Meeting, New York City, NY, September 29-October 1, 2022.

SUPPORT

Supported by Corcept Therapeutics Inc.

CLINICAL TRIAL INFORMATION

NCT03776812

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.22.02624.

AUTHOR CONTRIBUTIONS

Conception and design: Nicoletta Colombo, Gini F. Fleming, Andrew E. Greenstein, Joseph M. Custodio, Iulia C. Tudor
Provision of study materials or patients: Nicoletta Colombo, Toon Van Gorp, Ursula A. Matulonis, Ana Oaknin, Rachel N. Grisham, Gini F. Fleming, Alexander B. Olawaiye, Domenica Lorusso
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The authors thank the study participants and their families for their contributions to the study. The authors acknowledge Lyndah Dreiling, MD, of Corcept Therapeutics for her contributions to the study and to this manuscript. The authors also acknowledge medical writing support by Tina K. Schlafly, PhD, CMPP, an employee of Corcept Therapeutics. All authors reviewed and approved the final version.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Relacorilant + Nab-Paclitaxel in Patients With Recurrent, Platinum-Resistant Ovarian Cancer: A Three-Arm, Randomized, Controlled, Open-Label Phase II Study

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Nicoletta Colombo
Employment: Sarepta Therapeutics
Honoraria: Roche/Genentech, AstraZeneca, GlaxoSmithKline, MSD Oncology, Clovis Oncology, Pfizer, Amgen, Immunogen, Novartis, Mersana, Eisai, Advaxis, Nuvation Bio
Consulting or Advisory Role: Roche/Genentech, AstraZeneca, Clovis Oncology, Pfizer, MSD Oncology, GlaxoSmithKline, Immunogen, Mersana, Eisai, Advaxis, Nuvation Bio

Toon Van Gorp
Consulting or Advisory Role: AstraZeneca (Inst), Immunogen (Inst), Eisai Europe (Inst), OncXerna Therapeutics (Inst), GlaxoSmithKline (Inst), MSD/Merck (Inst), Seagen (Inst)
Research Funding: Amgen (Inst), Roche (Inst), AstraZeneca (Inst)
Travel, Accommodations, Expenses: MSD/Merck (Inst), Immunogen (Inst), GlaxoSmithKline (Inst), PharmaMar (Inst), AstraZeneca (Inst)

Ursula A. Matulonis
Honoraria: Advaxis, Alkermes, Symphogen
Consulting or Advisory Role: Merck, Novartis, NextCure, AstraZeneca, Blueprint Medicines, Trillium Therapeutics, GlaxoSmithKline, Agenus, 2X Oncology, Boehringer Ingelheim, Immunogen, Curelab Oncology
Speakers' Bureau: Med Learning Group
Research Funding: Merck, Novartis, Tesaro, Syndax, Immunogen, Mersana, Leap Therapeutics, Fujifilm, SQZ Biotech
Travel, Accommodations, Expenses: AstraZeneca, Immunogen

Ana Oaknin
Consulting or Advisory Role: AstraZeneca, PharmaMar, Clovis Oncology, Tesaro, Immunogen, Genmab, Mersana, GSK, Deciphera, Agenus, Corcept Therapeutics, Eisai, Roche, Merck Sharp & Dohme, Novocure, Shattuck Labs, Sutro Biopharma, ITeos Therapeutics, Seagen, OneXerna Therapeutics, Inc, Regeneron
Research Funding: AbbVie (Inst), Advaxis (Inst), Aeterna Zentaris (Inst), Aprea Therapeutics (Inst), Clovis Oncology Inc (Inst), Eisai (Inst), Roche (Inst), Regeneron (Inst), Bristol Myers Squibb International Corporation (BMS) (Inst), Immunogen (Inst), Medimmune (Inst), Merck Sharp & Dohme (Inst), Tesaro (Inst), Amgen (Inst), Millennium Pharmaceuticals Inc, (Inst), PharmaMar (Inst)
Travel, Accommodations, Expenses: AstraZeneca, Clovis Oncology, PharmaMar, Roche

Rachel N. Grisham
Consulting or Advisory Role: GlaxoSmithKline, AstraZeneca, Signatera, Corcept Therapeutics, Intellisphere, SpringWorks Therapeutics, Verastem, Myriad Genetics
Research Funding: Context Therapeutics (Inst), Verastem (Inst), SpringWorks Therapeutics (Inst), Bayer (Inst), Novartis (Inst)
Travel, Accommodations, Expenses: EMD Serono
Other Relationship: Prime Oncology, MCM Education, OncLive, Aptitude Health, Cardinal Health
Uncompensated Relationships: Verastem

Gini F. Fleming
This author is an Associate Editor for *Journal of Clinical Oncology*. Journal policy recused the author from having any role in the peer review of this manuscript.
Honoraria: Physicans' Education Resource
Research Funding: Corcept Therapeutics (Inst), AbbVie (Inst), Iovance Biotherapeutics (Inst), Syros Pharmaceuticals (Inst), Sermonix Pharmaceuticals (Inst), Compugen (Inst), Plexxikon (Inst), Roche (Inst), GlaxoSmithKline (Inst), Celldex (Inst), AstraZeneca (Inst), Molecular Templates (Inst), CytomX Therapeutics (Inst), Astellas Pharma (Inst), K-Group Beta (Inst), Pfizer (Inst), Merck (Inst), Incyte (Inst)
Other Relationship: DSI (Inst), Merck (Inst), Caris Life Sciences (Inst), Eisai (Inst), AstraZeneca (Inst)
Uncompensated Relationships: AbbVie

Alexander B. Olawaiye
Consulting or Advisory Role: Clovis Oncology, AstraZeneca, Tesaro, Genentech, GlaxoSmithKline, Novocure

Dorothy D. Nguyen
Employment: AmMax Bio, Corcept Therapeutics
Stock and Other Ownership Interests: AmMax Bio, Corcept Therapeutics
Travel, Accommodations, Expenses: AmMax Bio, Corcept Therapeutics

Andrew E. Greenstein
Employment: Corcept Therapeutics, Exelxis
Stock and Other Ownership Interests: Corcept Therapeutics, Exelixis

Joseph M. Custodio
Employment: Corcept Therapeutics
Stock and Other Ownership Interests: Corcept Therapeutics
Patents, Royalties, Other Intellectual Property: I'm an inventor of patents with Corcept
Travel, Accommodations, Expenses: Corcept Therapeutics

Hristina I. Pashova
Employment: Corcept Therapeutics
Stock and Other Ownership Interests: Corcept Therapeutics

Iulia C. Tudor
Employment: Medivation, Pfizer, Corcept Therapeutics
Stock and Other Ownership Interests: Medivation, Pfizer, Corcept Therapeutics, Inc, CytomX Therapeutics, BioNTech SE, Moderna Therapeutics
Patents, Royalties, Other Intellectual Property: In 2022, there are two original patent applications naming me as inventor: US Provisional Patent Application 63/403,478 Methods of Treating Prostate Cancer Using Exicorilant and Enzalutamide US Provisional Patent Application 63/420,409 treatments for amyotrophic lateral sclerosis using dazucorilant
Travel, Accommodations, Expenses: Medivation, Pfizer, Corcept Therapeutics, Inc

Domenica Lorusso
Consulting or Advisory Role: PharmaMar, AstraZeneca, Clovis Oncology, GlaxoSmithKline, MSD, Genmab, Seagen, Immunogen, Oncoinvest, Corcept Therapeutics, Sutro Biopharma, Novartis
Speakers' Bureau: AstraZeneca, Clovis Oncology, GlaxoSmithKline, MSD, PharmaMar, ImmunoGen, Seagen, Genmab
Research Funding: PharmaMar (Inst), Clovis Oncology (Inst), GlaxoSmithKline (Inst), MSD (Inst), AstraZeneca (Inst), Genmab (Inst), Seagen (Inst), Immunogen (Inst), Incyte (Inst), Novartis (Inst), Roche (Inst)
Travel, Accommodations, Expenses: AstraZeneca, Clovis Oncology, GlaxoSmithKline
Uncompensated Relationships: Gynecological Cancer InterGroup

No other potential conflicts of interest were reported.