Relacorilant and nab-paclitaxel in patients with platinum-resistant ovarian cancer (ROSELLA): an open-label, randomised, controlled, phase 3 trial

Alexander B Olawaiye, Laurence Gladieff, David M O'Malley, Jae-Weon Kim, Gabriel Garbaos, Vanda Salutari, Lucy Gilbert, Linda Mileshkin, Alix Devaux, Elizabeth Hopp, Yong Jae Lee, Ana Oaknin, Mariana Scaranti, Byoung-Gie Kim, Nicoletta Colombo, Michael E McCollum, Connie Diakos, Andrew Clamp, Aliza L Leiser, Boglárka Balázs, Bradley J Monk, Giuseppa Scandurra, Emily McClung, Emilie Kaczmarek, Brian Slomovitz, Helena De La Cueva, Aknar Freire de Carvalho Calabrich, Chiara Cassani, Benoit You, Toon Van Gorp, Cristina Churruca, Giuseppe Caruso, Shibani Nicum, Andrea Bagaméri, Grazia Artioli, Lubomir Bodnar, Sokbom Kang, Ignace Vergote, Amanda Kesner-Hays, Hristina I Pashova, Sachin G Pai, Iulia Cristina Tudor, Adrian M Jubb, Domenica Lorusso

Summary

Background Relacorilant, a first-in-class selective glucocorticoid receptor antagonist, increases a tumour's sensitivity to chemotherapy by reducing cortisol signalling. This study aimed to show whether the addition of relacorilant to nab-paclitaxel improves progression-free and overall survival in females with platinum-resistant ovarian cancer.

Methods This randomised, controlled, open-label phase 3 trial (ROSELLA [GOG-3073/ENGOT-ov72]) was done at 117 hospitals and community oncology treatment centres in 14 countries across Australia, Europe, Latin America, North America, and South Korea. Patients had to be aged 18 years or older and had to have a confirmed diagnosis of platinum-resistant, epithelial (ie, high-grade serous, endometrioid, or carcinosarcoma with a ≥30% epithelial component) ovarian, primary peritoneal, or fallopian tube cancer; up to three previous lines of anticancer therapy and previous bevacizumab and disease progression or intolerance to the most recent therapy; measurable disease according to the Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1); an Eastern Cooperative Oncology Group performance status of 0 or 1; and adequate organ function. Patients were assigned (1:1) to relacorilant (150 mg orally the day before, of, and after nab-paclitaxel infusion) plus nab-paclitaxel (80 mg/m² intravenously on days 1, 8, and 15 of each 28-day cycle) or nab-paclitaxel monotherapy (100 mg/m² intravenously on the aforementioned schedule). The dual primary endpoints were progression-free survival assessed by blinded independent central review per Response Evaluation Criteria in Solid Tumours (version 1.1) and overall survival, and were assessed in all randomly assigned patients by intention to treat. The safety population included all randomly assigned patients who received at least one dose of the assigned treatment. This trial was registered at ClinicalTrials.gov, NCT05257408, and is ongoing.

Findings Between Jan 5, 2023, and April 8, 2024, 381 patients were randomly assigned to the combination group (n=188) or to the nab-paclitaxel monotherapy group (n=193). Patients receiving relacorilant plus nab-paclitaxel had a statistically significant improvement in progression-free survival assessed by blinded independent central review compared with those receiving nab-paclitaxel monotherapy (hazard ratio 0·70 [95% CI 0·54–0·91]; median 6·54 months [95% CI 5·55–7·43] *vs* 5·52 months [3·94–5·88]; stratified log-rank p=0·0076). At the planned interim analysis, there was a clinically meaningful difference in overall survival with the addition of relacorilant to nab-paclitaxel (0·69 [95% CI 0·52–0·92]; 15·97 months [95% CI 13·47–not reached] *vs* 11·50 months [10·02–13·57]; log-rank p=0·0121). Adverse events were similar across study groups when adjusted for nab-paclitaxel exposure; no new safety signals were observed.

Interpretation The addition of relacorilant to nab-paclitaxel prolonged progression-free survival and interim results also showed an improvement in overall survival. Together, the results position the combination of relacorilant and nab-paclitaxel as a potential new standard treatment for patients with platinum-resistant ovarian cancer.

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University of Pittsburgh School of Medicine and UPMC Magee-Women's Hospital, Gynecologic Oncology Group, Pittsburgh, PA, USA (A B Olawaiye MD); **Oncopole Claudius Regaud IUCT-Oncopole, Toulouse, France** (L Gladieff MD); **GINECO, Paris, France** (L Gladieff); **James Comprehensive Cancer Center, The Ohio State University, Columbus, OH, USA** (D M O'Malley MD); **Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, South Korea** (Prof J-W Kim MD); **Instituto Médico de la Fundación Estudios Clínicos, Santa Fe, Argentina** (G Garbaos MD); **Department of Woman, Child, and Public Health, Fondazione Policlinico Universitario Agostino Gemelli, Rome, Italy** (V Salutari MD); **Division of Gynecologic Oncology, Research Institute, McGill University Health Centre, Gerald Bronfman Department of Oncology, McGill University, Montreal, QC, Canada** (L Gilbert MD); **Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia** (L Mileshkin MBBS); **Oncology Department of Grand Hôpital de Charleroi, Charleroi, Belgium** (Prof A Devaux MD); **Belgium and Luxembourg Gynaecological Oncology Group, Leuven, Belgium** (Prof A Devaux); **Department of Obstetrics and Gynecology, Medical College of Wisconsin, Milwaukee, WI, USA** (E Hopp MD); **Yonsei University**

Introduction

Epithelial ovarian cancer has a high morbidity and mortality; approximately 207 000 ovarian cancer-related deaths occurred worldwide in 2020.[1] Platinum-based chemotherapy is efficacious, yet approximately 70% of patients experience disease relapse,[2,3] which becomes platinum-resistant. Treatment options for patients with platinum-resistant ovarian cancer include non-platinum chemotherapy administered alone or with bevacizumab.[2] Weekly paclitaxel is considered the most active regimen

College of Medicine, Seoul, South Korea (Prof Y J Lee MD); Medical Oncology Service, Vall d'Hebron Institute of Oncology, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain (Prof A Oaknin MD); DASA Oncologia, Hospital 9 de Julho, São Paulo, Brazil (M Scaranti MD); Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea (Prof B-G Kim MD); Gynecologic Oncology Program, European Institute of Oncology, IRCCS, Milan, Italy (Prof N Colombo MD; Prof G Caruso MD); Department of Medicine and Surgery, University of Milan–Bicocca, Milan, Italy (Prof N Colombo); Virginia Oncology Associates, Norfolk, VA, USA (M E McCollum MD); Royal North Shore Hospital, St Leonards, NSW, Australia (C Diakos MBBS); The Christie NHS Foundation Trust, Manchester, UK (A Clamp BMBCh); University of Manchester, Manchester, UK (A Clamp); Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA (A L Leiser MD); Department of Gynecology, Hungarian National Institute of Oncology, Budapest, Hungary (B Balázs MD, A Bagaméri MD); Florida Cancer Specialists and Research Institute, West Palm Beach, FL, USA (Prof B J Monk MD); Medical Oncology Unit, Cannizzaro Hospital, Catania, Italy (G Scandurra MD); Faculty of Medicine, Kore University of Enna, Enna, Italy (G Scandurra); Stanford University, Palo Alto, CA, USA (E McClung MD); Centre Oscar Lambret, Lille, France (E Kaczmarek MD); GINECO, Paris, France (E Kaczmarek, Prof B You MD); Mount Sinai Comprehensive Cancer Center, Miami Beach, FL, USA (B Slomovitz MD); Hospital La Fe Valencia, Valencia, Spain (H De La Cueva MD); Ensino e Terapia de Inovação Clínica AMO-ETICA, Salvador, Brazil (A Freire de Carvalho Calabrich MD); Department of Clinical, Surgical, Diagnostic, and Pediatric Sciences, University of Pavia, Pavia, Italy (C Cassani MD); Unit of Obstetrics and Gynecology, IRCCS San Matteo Foundation, Pavia, Italy (C Cassani); Lyon University Hospital (HCL), Lyon, France (Prof B You); University

Research in context

Evidence before this study

In a search of PubMed for articles published up to April 15, 2025, using the search terms "selective" AND "glucocorticoid receptor" AND ("cancer" or "carcinoma") with no language restrictions, we found that data have been published on selective glucocorticoid receptor antagonism in ovarian cancer for only three clinical trials, two with the selective glucocorticoid receptor antagonist relacorilant and one with the less selective ORIC-101. The first trial (NCT03928314) was a phase 1 dose escalation and expansion study to determine the recommended phase 2 dose of ORIC-101 in combination with nab-paclitaxel in patients with advanced solid cancers. The second trial (NCT02762981) was a phase 1/2 study to determine the recommended phase 2 dose of relacorilant plus nab-paclitaxel in patients with advanced solid cancers. The third trial (NCT03776812) was a randomised, phase 2 study evaluating the combination of relacorilant plus nab-paclitaxel in patients with platinum-resistant ovarian cancer.

Added value of this study

The positive progression-free survival results with supportive interim overall survival data from ROSELLA (GOG-3073, ENGOT-ov72) confirm the findings from previous phase 1 and 2 studies of relacorilant in patients with solid tumours. A study of ORIC-101 concluded that it did not show meaningful clinical benefit in patients who previously progressed on taxanes when combined with nab-paclitaxel. These differences between ORIC-101 and relacorilant suggest that the properties of relacorilant and its selective glucocorticoid receptor antagonism could be a crucial pharmacological attribute that underpins its clinical efficacy.

Implications of all the available evidence

Combined with the evidence from previous studies, our study supports relacorilant plus nab-paclitaxel as a potential new standard of care for patients with platinum-resistant ovarian cancer, without the need for biomarker selection. This study is the first positive clinical trial conducted with registrational intent for a selective glucocorticoid receptor antagonist in patients with cancer. The data are expected to prompt the evaluation of relacorilant in other solid cancer indications and in combination with other classes of anti-cancer agents. The targeted agent bevacizumab also extends progression-free survival in combination with a weekly taxane in this setting. As relacorilant has an orthogonal mechanism of action to bevacizumab, our findings support further research to evaluate the triplet combination of relacorilant, nab-paclitaxel, and bevacizumab in patients with platinum-resistant ovarian cancer. Translational and mechanistic research might inform further rational clinical development and research on future generations of selective glucocorticoid receptor antagonists. The findings from ROSELLA might also prompt prospective clinical studies to evaluate the impact of glucocorticoid use on the efficacy of chemotherapy in ovarian cancer. Additional follow-up time will improve precision in the estimated overall survival benefit and further clarify the clinical benefit of the relacorilant combination tested herein.

in this setting, with a median progression-free survival of 3·9–5·5 months and an objective response rate of 26–32%;[4–8] the reported efficacy of nab-paclitaxel is similar,[9] and it has a National Comprehensive Cancer Network compendia listing[10] for the treatment of patients with platinum-resistant ovarian cancer.[9,11,12] Patients with folate receptor α-positive serous ovarian cancer also have the option of mirvetuximab soravtansine.[13,14] However, median overall survival for patients with platinum-resistant disease remains short at 10–16 months.[4–9,12–17]

Glucocorticoid receptor signalling in ovarian cancer[18,19] reduces tumour sensitivity to chemotherapy by increasing the expression of anti-apoptotic proteins.[19,20] In addition, expression of the glucocorticoid receptor or elevated cortisol concentrations are associated with poor prognosis in patients with ovarian cancer.[18,21,22] Relacorilant is a novel, selective glucocorticoid receptor antagonist[23] that shows synergy with paclitaxel in non-clinical tumour models.[20] Clinically, relacorilant was combined with nab-paclitaxel, a rational partner that does not require co-administration of corticosteroids. In a phase 2 trial, the addition of intermittently dosed relacorilant to nab-paclitaxel in patients with platinum-resistant ovarian cancer extended progression-free survival, with a trend towards improved overall survival.[12]

Here, we report the results of the confirmatory ROSELLA trial, which investigated the efficacy and safety of relacorilant plus nab-paclitaxel compared with nab-paclitaxel monotherapy in patients with platinum-resistant ovarian cancer.

Methods

Study design

ROSELLA (GOG-3073/ENGOT-ov72) is an open-label, randomised, controlled, phase 3 trial conducted at 117 sites across 14 countries. Clinical trial sites, including hospitals and community oncology treatment centres, were located across Australia, Europe, Latin America, North America, and South Korea. The study was conducted in accordance with ethical review committees, local regulations, ethical principles based on the Declaration of Helsinki, and Good Clinical Practice guidelines consistent with the International Council for Harmonization requirements. A full list of the ethics committees, approval numbers, and dates are provided in the appendix (pp 2–9).

Participants

ROSELLA enrolled adult females (eg, those ≥18 years) with a confirmed diagnosis of platinum-resistant, epithelial (ie, high-grade serous, endometrioid, or carcinosarcoma with a ≥30% epithelial component) ovarian, primary peritoneal, or fallopian tube cancer. Patients must have received one to three lines of previous systemic anticancer therapy and had disease progression or intolerance to the most recent therapy. At least one previous line of platinum-based therapy, platinum-resistant disease (defined as progression <6 months from their last dose of platinum), and previous treatment with bevacizumab were required. Patients must have had measurable disease according to the Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1), an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate organ function. Patients were excluded if they had not responded to their initial platinum-containing regimen, had disease progression within 1 month of their last dose of first-line platinum therapy, or had an ongoing requirement for chronic systemic corticosteroids. Full eligibility criteria are listed in the appendix (pp 20–152). Written informed consent was obtained from all patients.

Randomisation and masking

Patients were enrolled by the trial sites. Patients were randomly assigned (1:1) to receive relacorilant plus nab-paclitaxel (combination therapy) or nab-paclitaxel monotherapy. A permuted block randomisation with block size of four was used. The random allocation sequence was developed by an independent contract research organisation. Randomisation was centrally assigned using the Interactive Response Technology System. The sponsor study team, investigators, and site staff did not have access to the live randomisation schedule in the Interactive Response Technology System. Randomisation was stratified according to previous lines of therapy (one *vs* more than one) and region (North America *vs* Europe *vs* South Korea, Australia, and Latin America). Patients continued to receive treatment until disease progression, unmanageable toxicity, or death. All patients were followed up for disease progression and overall survival. Crossover was not permitted and could not occur outside the trial because relacorilant was not commercially available for any indication during the period that the trial was conducted.

Procedures

Patients in the combination group received relacorilant (150 mg administered orally the day before, the day of, and the day after receiving nab-paclitaxel) plus nab-paclitaxel (80 mg/m² intravenously on days 1, 8, and 15 of each 28-day cycle). Patients in the control group received nab-paclitaxel monotherapy (100 mg/m² intravenously on days 1, 8, and 15 of each 28-day cycle). In the combination group, the dose of nab-paclitaxel was reduced because relacorilant is an inhibitor of *CYP3A4*, which metabolises nab-paclitaxel. Pharmacokinetic data from the phase 2 trial showed that the lower dose of nab-paclitaxel in the combination group, when given with relacorilant, provides a comparable exposure to the monotherapy group.[12] Granulocyte colony-stimulating factor use was permitted per local institutional guidelines. There is not a uniform, single, global standard-of-care treatment for patients with platinum-resistant ovarian cancer.[2] The choice of nab-paclitaxel treatment for the control treatment was justified by published clinical trial data[9,12] showing similar or better outcomes when compared with other treatment options. In addition, using the same agent in the relacorilant combination and control groups allowed for the contribution of components to be clearly defined.

Outcomes

The dual primary endpoints were progression-free survival, defined as the time from randomisation until first documented progressive disease by RECIST (version 1.1) per blinded independent central review (BICR), or death, whichever occurred first, and

Hospital Leuven, Leuven Cancer Institute, Leuven, Belgium (Prof T Van Gorp MD); **Belgium and Luxembourg Gynaecological Oncology Group, Leuven, Belgium** (Prof T Van Gorp); **Hospital Donostia, San Sebastián, Spain** (C Churruca MD); **Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy** (Prof G Caruso); **University College Hospital, London, UK** (S Nicum MBChB); **Azienda ULSS2 Marca Trevigiana, Treviso, Italy** (G Artioli MD); **Institute of Health Sciences, University of Siedlce, Siedlce, Poland** (L Bodnar MD); **Department of Cancer Control and Population Health, National Cancer Center, Goyang, South Korea** (Prof S Kang MD); **Department of Gynecologic Oncology, University Hospital Leuven, Leuven, Belgium** (Prof I Vergote MD); **Corcept**

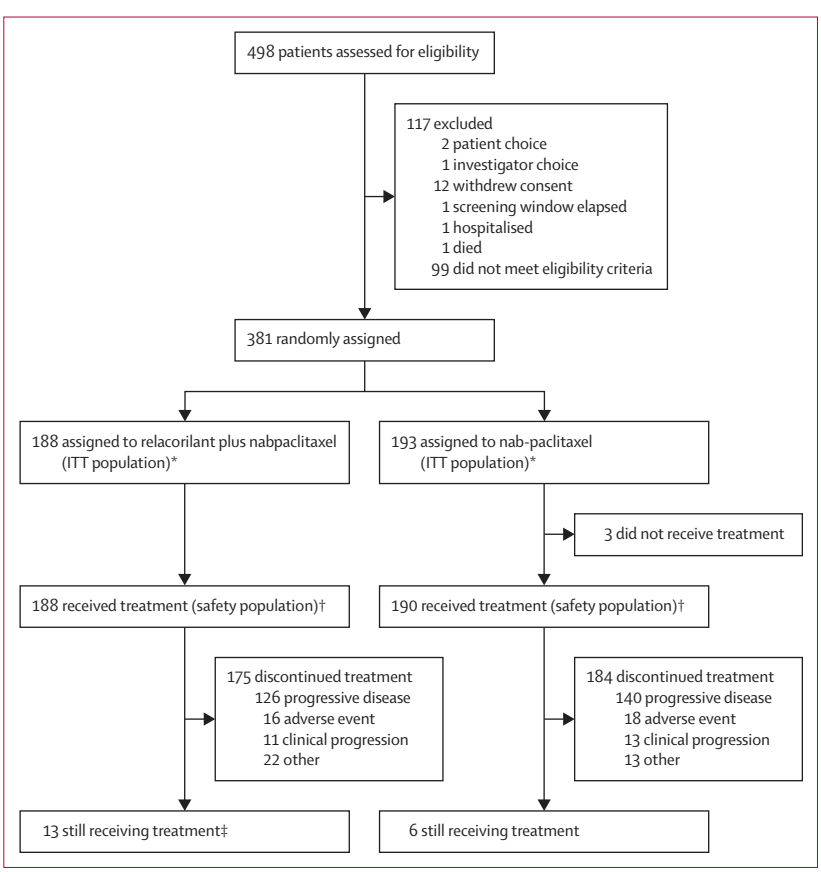

Figure 1: **Trial profile**
Three patients in the nab-paclitaxel monotherapy group withdrew consent and did not receive treatment. ITT=intent-to-treat. *All randomly assigned patients were analysed according to the randomised treatment group. †All randomly assigned patients who received at least one dose of study treatment (ie, relacorilant plus nab-paclitaxel or nab-paclitaxel monotherapy). ‡Refers to patients on nab-paclitaxel at the data cutoff.

Therapeutics, Redwood City, CA, USA (A Kesner-Hays PhD, H I Pashova PhD, S G Pai MD, I C Tudor PhD, A M Jubb FRCPath); **Department of Biomedical Science, Humanitas University, Pieve Emanuele, Italy** (Prof D Lorusso MD); **Humanitas San Pio X Hospital, Milan, Italy** (Prof D Lorusso)

Correspondence to: Dr Alexander B Olawaiye, University of Pittsburgh School of Medicine and UPMC Magee-Women's Hospital, Gynecologic Oncology Group, Pittsburgh, PA 15213, USA
olawaiyea@upmc.edu

overall survival, defined as the time from randomisation to death. These dual endpoints was changed from the original protocol's sole primary endpoint of progression-free survival assessed by BICR (with overall survival tested as a key secondary endpoint) to address regulatory authority feedback. Tumour assessment scans were performed every 8 weeks for the first 40 weeks, then every 12 weeks. Patients who discontinued treatment before disease progression were required to continue radiographical tumour assessments on the same schedule until unequivocal radiographical disease progression. When permissible by local regulations, public records for survival status were consulted if the patient was lost to follow-up. All efforts to reach the patient, including at least three documented attempts, had to be exhausted before a patient was deemed lost to follow-up. Secondary endpoints were investigator-assessed progression-free survival according to RECIST (version 1.1), objective response rate, best overall response, duration of response, clinical benefit rate (defined as the proportion of patients who attained complete response, partial response, or stable disease according to RECIST at 24 weeks), CA-125 response per Gynecologic Cancer Intergroup criteria, combined CA-125 and radiographical response according to Gynecologic Cancer Intergroup and RECIST criteria, and safety (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0).

	Relacorilant plus nab-paclitaxel (n=188)	Nab-paclitaxel monotherapy (n=193)
Age, years	61·0 (26–85)	62·0 (33–86)
≥65	72 (38%)	80 (41%)
Race		
White	136 (72%)	135 (70%)
Black or African American	3 (2%)	2 (1%)
Asian	22 (12%)	26 (13%)
Other or not reported	27 (14%)	30 (16%)
Ethnicity		
Hispanic or Latino	16 (9%)	17 (9%)
Non-Hispanic or Latino	145 (77%)	146 (76%)
Not reported or unknown	27 (14%)	30 (16%)
Geographical region		
North America	45 (24%)	45 (23%)
Europe	107 (57%)	109 (56%)
South Korea, Australia, and Latin America	36 (19%)	39 (20%)
Eastern Cooperative Oncology Group performance status score		
0	135 (72%)	127 (66%)
1	53 (28%)	62 (32%)
2	0	1 (1%)
Missing	0	3 (2%)
Stage at initial diagnosis*		
1–3	110 (59%)	114 (59%)
4	65 (35%)	66 (34%)
Missing data	13 (7%)	13 (7%)
BRCA mutation		
BRCA1 or *BRCA2* mutation	23 (12%)	24 (12%)
BRCA1 and *BRCA2* wildtype	133 (71%)	128 (66%)
Unknown	32 (17%)	41 (21%)
Previous lines of systemic therapy		
1	15 (8%)	18 (9%)
2	92 (49%)	89 (46%)
3	81 (43%)	86 (45%)
Previous lines of therapy in the platinum-resistant setting		
0	121 (64%)	111 (58%)
1	55 (29%)	68 (35%)
2	12 (6%)	14 (7%)

(Table continues on next page)

Statistical analysis

The intent-to-treat population, defined as all randomly assigned patients irrespective of whether they received treatment, analysed according to the randomised treatment group, was used for analysis of the primary endpoints, investigator-assessed progression-free survival, and clinical benefit rate. Objective response rate and duration of response were analysed among patients with baseline measurable disease (per RECIST) in the intent-to-treat population. The safety population included all randomly assigned patients who received at least one dose of the assigned treatment. A group sequential weighted Holm procedure was used for the dual primary endpoints, progression-free survival, and overall survival. The study was considered to have a positive outcome if either of the two primary endpoints reached statistical significance. For the primary endpoint of progression-free survival by BICR, the null hypothesis of no difference among the two study groups was tested at a two-sided α=0·04 level of significance using a stratified log-rank test with the same factors that were used to stratify the randomisation schedule. With 1:1 randomisation, 230 events ensured the study had an 86·4% power to detect a 50% increase in progression-free survival (hazard ratio [HR] 0·66) with a log-rank test at a two-sided α=0·04 significance level. Assuming an exponential distribution of progression-free survival, this corresponds to an increase in median progression-free survival from 3·8 months to 5·8 months, approximating the phase 2 results.[12] An enrolment target of 360 patients was set to achieve 230 events, allowing for a 10% dropout rate in the first 12 months of follow-up. The primary endpoint of overall survival was allocated a two-sided α=0·01 level of significance for the stratified log-rank test. If the null hypothesis for progression-free survival by BICR was rejected, then, per the Holm procedure, overall survival would be tested at α=0·05, using a stratified log-rank test. The Kaplan–Meier method was used for time-to-event endpoints and to estimate the medians for progression-free survival, overall survival, and duration of response. The HRs were estimated using a Cox regression model with treatment group as the main effect and stratification factors at randomisation as covariates. An interim analysis of overall survival was performed at

the time of the primary analysis of progression-free survival per the statistical analysis plan. At the time of the interim overall survival analysis, a two-sided stratified log-rank test was conducted at an α=0·0001 significance level (this constitutes the alpha spending function). The formal final analysis of overall survival will be conducted at an α=0·0499 significance level because progression-free survival assessed by BICR is significant. All other secondary efficacy endpoints were tested at a nominal two-sided α=0·05 level of significance, with no additional adjustment for multiplicity. A stratified Cochran–Mantel–Haenszel test was used to test differences in clinical benefit and objective response rates between treatment groups. Descriptive statistics are provided for safety endpoints; statistical methods for exposure-adjusted incidence rates are provided in the appendix (p 11).

Role of the funding source

The funding source supported trial conduct, patient enrolment, and drug supply. The analysis and interpretation of data, writing of the report, and the decision to submit for publication were the responsibility of the authors.

Results

Patients were enrolled from Jan 5, 2023, to April 8, 2024; the data cutoff date for the primary analysis was Feb 24, 2025. 381 patients were randomly assigned and included in the intent-to-treat population; 188 were assigned to the combination group and 193 to the nab-paclitaxel monotherapy group (figure 1). All patients in the combination group and 190 in the nab-paclitaxel monotherapy group received at least one dose of the assigned treatment and were included in the safety population. Important protocol deviations are listed in the appendix (p 14). The proportion of Black or African American and Hispanic participants was low (five [1%] and 33 [9%], respectively; table 1). However, there was a higher proportion of Asian participants (48 [13%]). Of note, 57 (15%) participants did not report their race or ethnicity.

Patients were heavily pre-treated: 149 (39%) had received at least one line of therapy in the platinum-resistant setting, 73 (19%) had received a taxane in their last line of therapy, and 15 (4%) had received a taxane for platinum-resistant disease (table 1). 234 (61%) patients had received a previous poly (ADP-ribose) polymerase inhibitor, and of these 183 (78%) had radiographic progression while receiving their inhibitor. Notably, 26 (7%) of patients progressed within 3 months of the last dose of front-line platinum therapy and met primary platinum-refractory definitions from pivotal trials.[14] Ascites reported at baseline was similar in the combination and monotherapy groups (eight [4%] *vs* seven [4%]).

In the safety population, the mean duration of nab-paclitaxel exposure was 5·34 months (SD 4·12) and the median duration was 4·52 months (IQR 1·91–7·18, range 0·0–20·8; mean number of cycles 6·3 [SD 4·46] and median number of cycles 5·5 [IQR 3·0–8·0, range 1–23]), in the combination group, and 4·28 months (3·23) and 3·48 months (1·48–5·75, 0·0–15·7; 5·2 [3·50] and 4·0 [2·0–7·0, 1–18]) in the

	Relacorilant plus nab-paclitaxel (n=188)	Nab-paclitaxel monotherapy (n=193)
(Continued from previous page)		
Previous taxane in the platinum-resistant setting	8 (4%)	7 (4%)
Previous exposure		
Bevacizumab	188 (100%)	193 (100%)
Taxane	187 (99%)	192 (99%)
Pegylated liposomal doxorubicin	121 (64%)	125 (65%)
Poly (ADP-ribose) polymerase inhibitor	114 (61%)	120 (62%)
Mirvetuximab soravtansine	3 (2%)	5 (3%)
Primary platinum-free interval		
1 to ≤3 months	13 (7%)	13 (7%)
>3 to ≤6 months	41 (22%)	45 (23%)
>6 months	134 (71%)	135 (70%)
Most recent taxane-free interval		
≤6 months	22 (12%)	33 (17%)
>6 to ≤12 months	37 (20%)	30 (16%)
>12 months	128 (68%)	129 (67%)
Ascites	8 (4%)	7 (4%)

Data are n (%) or median (range). Region (North America *vs* Europe *vs* South Korea, Australia, and Latin America) and previous lines of therapy (1 *vs* >1) per the Interactive Response Technology System data were stratification factors. Percentages might not add to 100 due to rounding. *BRCA*=Breast Cancer gene. *Based on the International Federation of Gynecology and Obstetrics cancer staging system.[24]

Table 1: **Baseline demographics and clinical characteristics (intent-to-treat population)**

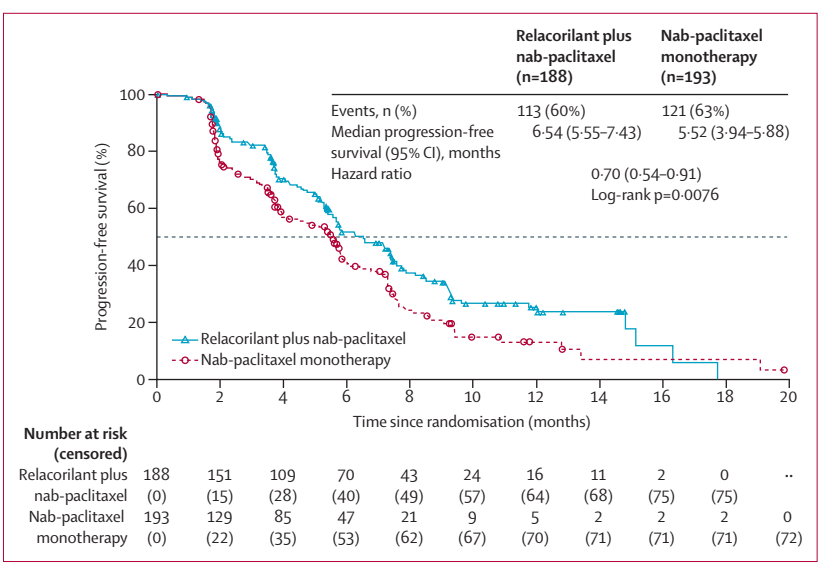

Figure 2: **Efficacy findings comparing relacorilant plus nab-paclitaxel with nab-paclitaxel monotherapy for progression-free survival**

Kaplan–Meier estimates of the dual primary endpoint progression-free survival assessed by blinded independent central review in the relacorilant plus nab-paclitaxel group and the nab-paclitaxel monotherapy group are shown. Analyses were performed in the intent-to-treat population.

See Online for appendix

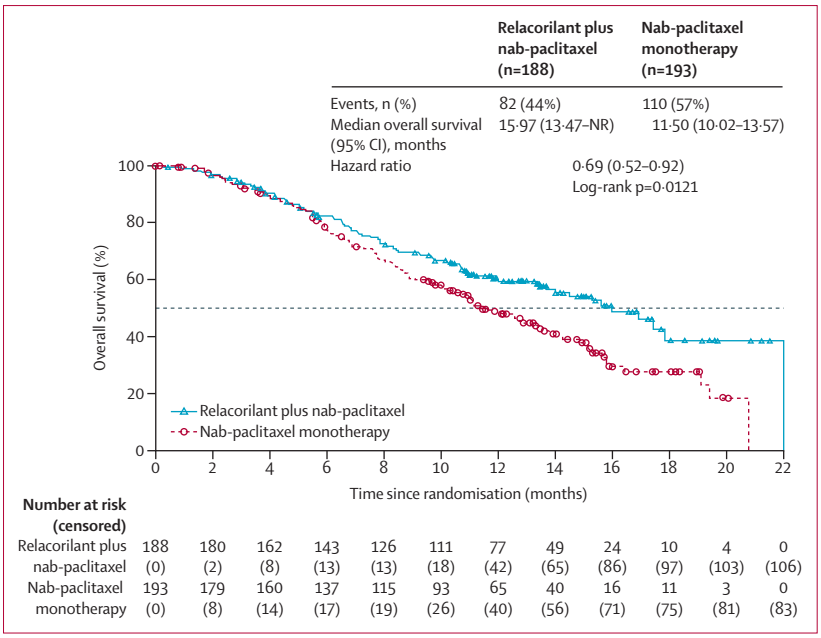

Figure 3: **Efficacy findings comparing relacorilant plus nab-paclitaxel with nab-paclitaxel monotherapy for the interim overall survival analysis**

Kaplan–Meier estimates of the dual primary endpoint of overall survival (at an interim analysis) in the relacorilant plus nab-paclitaxel group and the nab-paclitaxel monotherapy group are shown. Analyses were performed in the intent-to-treat population. 30 (8%) of 381 patients were censored in the first 6 months of the overall survival Kaplan–Meier curve, 13 in the combination group and 17 in the nab-paclitaxel monotherapy group; six patients were lost to follow-up and 24 withdrew consent.NR=not reached.

nab-paclitaxel monotherapy group. The mean duration of relacorilant exposure was 5·52 months (SD 4·10) and median duration was 4·73 months (IQR 2·12–7·47, range 0·2–20·7; mean number of cycles 6·5 [SD 4·48] and median number of cycles 5·5 [IQR 3·0–8·5, range 1–23]) in the combination group. Treatment compliance for relacorilant was high, with a mean dose intensity of 88·9% of the expected (SD 11·8; median 92·0% [IQR 83·6–98·2, range 37·5–100·0]). Nab-paclitaxel also achieved its planned dose intensity with similar means of 80·2% (SD 15·5; median 80·1% [IQR 68·1–94·9, range 33·3–100·0]) in the combination group and 86·0% (15·2; 89·5 [76·3–100·0, 20·0–100·0]) in the monotherapy group. 17 (9%) of 188 patients in the combination group remained on therapy for at least 12 months, with the longest ongoing treatment for 21 months at the time of the data cutoff, compared with seven (4%) of 190 patients in the nab-paclitaxel monotherapy group.

Progression-free survival assessed by BICR was longer in the relacorilant combination group (median 6·54 months [95% CI 5·55–7·43]) than in the nab-paclitaxel monotherapy group (5·52 months [3·94–5·88]; figure 2). The risk of progression assessed by BICR, or death, was significantly reduced in the relacorilant combination group, with an HR of 0·70 (95% CI 0·54–0·91; stratified log-rank p=0·0076; figure 2). Median follow-up for progression-free survival assessed by BICR was 9·0 months (95% CI 7·5–9·8). All sensitivity analyses for progression-free survival assessed by BICR were concordant with the primary efficacy analysis result, indicating that the results were robust to censoring rules implemented for the primary analysis (appendix p 15). The frequency and reasons for censoring were similar across the treatment groups (appendix p 16). The proportional hazard assumption was tested and was not violated (Kolmogorov-type supremum test p=0·3380; appendix pp 10–11).

At the time of the primary analysis, a planned interim analysis of overall survival was done. With a median follow-up of 13·9 months (95% CI 13·3–14·9), overall survival was longer in the relacorilant combination group (median 15·97 months [95% CI 13·47–not reached]) than in the nab-paclitaxel monotherapy group (11·50 months [10·02–13·57]; figure 3). The HR for overall survival was 0·69 (95% CI 0·52–0·92; stratified log-rank p=0·0121), favouring the relacorilant combination group (figure 3; p value for significance at the interim analysis <0·0001; per the prespecified alpha-spending function, 0·0499 is available for the next overall survival hypothesis test). At the 12-month landmark, 60·0% of patients were alive in the combination group, compared with 49·0% of patients in the nab-paclitaxel monotherapy group.

Investigator-assessed progression-free survival results (HR 0·71 [95% CI 0·57–0·89]; stratified log-rank p=0·0030) were consistent with progression-free survival assessed by BICR (appendix p 13). Progression-free survival assessed by BICR and interim overall survival consistently favoured the relacorilant combination group over the nab-paclitaxel monotherapy group in all clinically relevant subgroups (figure 4).

The objective response rate assessed by the investigator (36·9% *vs* 30·1%; stratified Cochran–Mantel–Haenszel test nominal p=0·17) was numerically higher in the relacorilant combination group compared with the nab-paclitaxel monotherapy group (appendix p 17). In addition, the clinical benefit rate at 24 weeks assessed by the investigator (51·1% *vs* 38·9%; p=0·016) was higher in the relacorilant combination group compared with the nab-paclitaxel monotherapy group (appendix p 17).

Frequent adverse events regardless of attribution are shown in table 2; the most common were neutropenia, anaemia, fatigue, and nausea. The overall frequencies of grade 3 or worse adverse events (140 [74%] *vs* 113 [59%]), all serious adverse events (66 [35%] *vs* 45 [24%]), and grade 3 or worse neutropenia (82 [44%] *vs* 48 [25%]), anaemia (34 [18%] *vs* 16 [8%]), and fatigue (17 [9%] *vs* three [2%]) were numerically higher in the combination group, which had a 30% longer median treatment duration with nab-paclitaxel compared with the nab-paclitaxel monotherapy group, respectively (4·52 months [IQR 1·91–7·18] *vs* 3·48 months [1·48–5·75]). The CIs for exposure-adjusted incidence rate differences between groups overlapped 0 for all

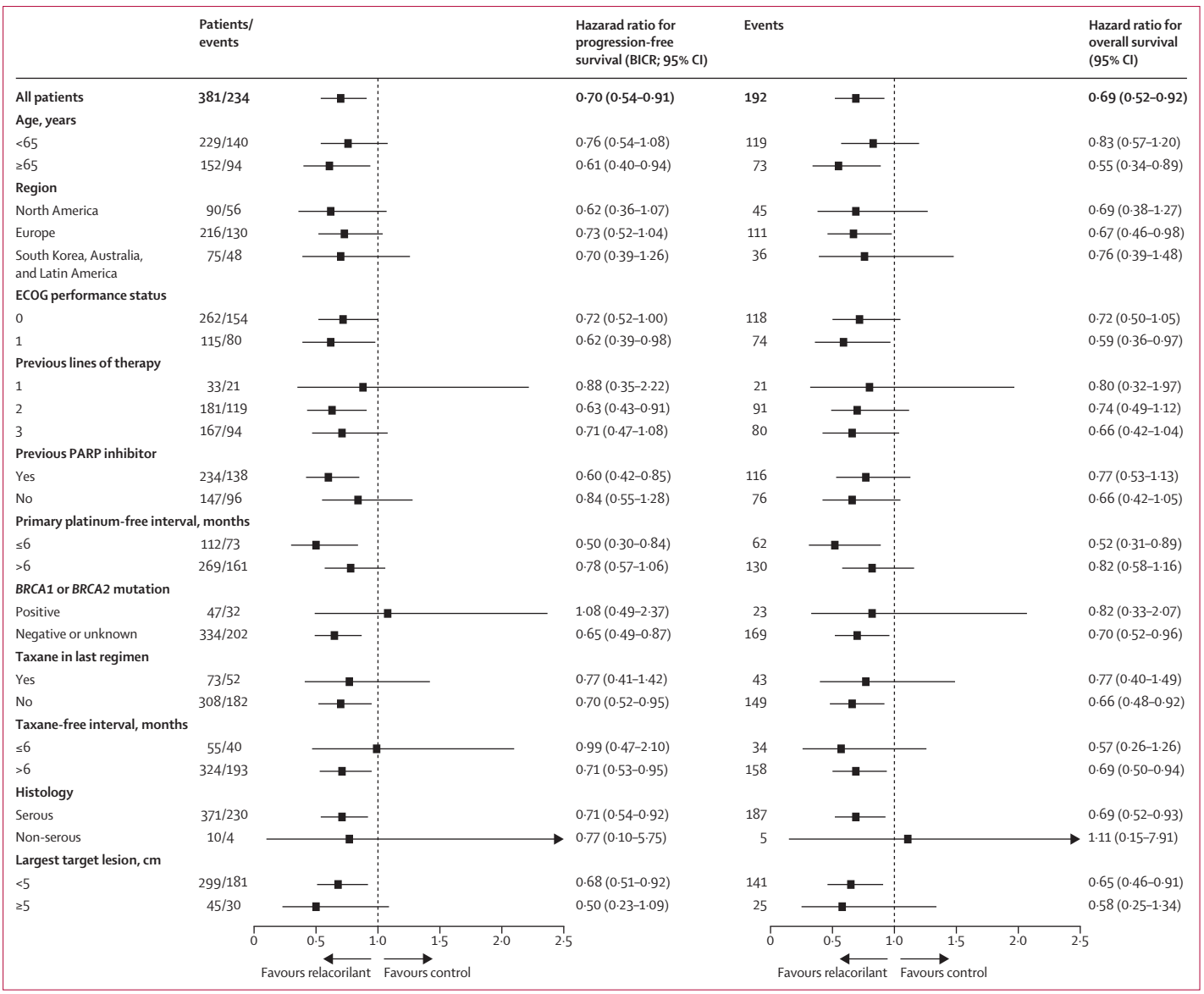

Figure 4: **Efficacy findings comparing relacorilant plus nab-paclitaxel with nab-paclitaxel monotherapy in subgroup analyses of progression-free survival and overall survival**
The results of exploratory subgroup analyses of progression-free survival assessed by blinded independent central review and overall survival in the intent-to-treat population are shown. The hazard ratios reported throughout this figure are based on a Cox proportional-hazards model, stratified according to the randomisation factors that were collected in the interactive response technology system, except when the randomisation factor is the subgroup under analysis; then, only a single stratification variable was used. Under the assumption of proportional hazards, a hazard ratio of less than 1 indicates a reduction in the hazard in favour of the combination group. BICR=blinded independent central review. *BRCA*=breast cancer gene. ECOG=Eastern Cooperative Oncology Group. PARP=poly (ADP-ribose) polymerase.

serious adverse events, including febrile neutropenia, and for the treatment-emergent adverse events of neutropenia and anaemia (table 3). Serious adverse events of febrile neutropenia (four [2%] in the combination group and one [1%] in the nab-paclitaxel monotherapy group), sepsis (three [2%] and two [1%]), and infections and infestations (system organ class; 16 [9%] and nine [5%]) were infrequent. Growth factor use was at the discretion of the investigator and was more frequent in the combination group (82 [44%] patients; 50 [27%] as prophylaxis and 50 [27%] for adverse events) than in the nab-paclitaxel monotherapy group (41 [22%] patients; 29 [15%] as prophylaxis and 31 [16%] for adverse events). A lower incidence of ascites was reported in the combination group compared with nab-paclitaxel monotherapy (5·3% *vs* 10·5%), even when adjusted for nab-paclitaxel exposure (table 3). Abdominal paracenteses during treatment were also lower in the combination group than the nab-paclitaxel monotherapy group (14 [7%] *vs* 25 [13%]).

	Relacorilant plus nab-paclitaxel (n=188)		Nab-paclitaxel monotherapy (n=190)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse events	188 (100%)	140 (74%)	189 (99%)	113 (59%)
Treatment-related adverse events*				
Related to relacorilant	146 (78%)	74 (39%)	..	..
Related to nab-paclitaxel	177 (94%)	113 (60%)	172 (91%)	78 (41%)
Related to both relacorilant and nab-paclitaxel	138 (73%)	69 (37%)	..	..
Serious adverse events	66 (35%)	60 (32%)	45 (24%)	39 (21%)
Treatment interruptions due to adverse events				
Nab-paclitaxel (plus relacorilant)†	137 (73%)	..	104 (55%)	..
Dose reductions due to adverse events				
Relacorilant‡	13 (7%)	..	..	..
Nab-paclitaxel	91 (48%)	..	60 (32%)	..
Discontinuations due to adverse events				
Relacorilant	18 (10%)	..	..	..
Nab-paclitaxel (plus relacorilant)†	17 (9%)	..	15 (8%)	..
Adverse events leading to death	4 (2%)	..	0	..
Most frequent adverse events occurring in ≥20% of study participants in either group (by preferred term)§				
Neutropenia¶	120 (64%)	82 (44%)	93 (49%)	48 (25%)
Anaemia‖	115 (61%)	34 (18%)	105 (55%)	16 (8%)
Fatigue**	99 (53%)	17 (9%)	85 (45%)	3 (2%)
Nausea	82 (44%)	7 (4%)	66 (35%)	6 (3%)
Diarrhoea	74 (39%)	7 (4%)	52 (27%)	3 (2%)
Alopecia	72 (38%)	1 (1%)	59 (31%)	0
Constipation	61 (32%)	1 (1%)	51 (27%)	0
Abdominal pain	55 (29%)	4 (2%)	54 (28%)	2 (1%)
Vomiting	48 (26%)	5 (3%)	43 (23%)	3 (2%)
Decreased appetite	41 (22%)	3 (2%)	22 (12%)	1 (1%)
Hypomagnesaemia	40 (21%)	3 (2%)	36 (19%)	2 (1%)

Data are n (%). Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). *The relatedness of adverse events to treatment was determined by the investigator. †Relacorilant was always interrupted or discontinued when nab-paclitaxel was interrupted. ‡Ten patients had one dose reduction and three patients had two dose reductions. §Adverse events were coded using the MedDRA dictionary (version 27.0) and sorted by descending incidence using the relacorilant plus nab-paclitaxel group. ¶Combined term including neutropenia, decreased neutrophil count, and febrile neutropenia. ‖Combined term including anaemia, decreased haemoglobin, and decreased red blood cell count. **Combined term including fatigue and asthenia.

Table 2: **Adverse events that occurred during the treatment period in the safety population**

	Relacorilant plus nab-paclitaxel (n=188)		Nab-paclitaxel monotherapy (n=190)		EAIR difference (95% CI)*
	EAIR (95% CI)†	Total PYE‡	EAIR (95% CI)†	Total PYE‡	
All treatment-emergent adverse events	4063·1 (3503·1 to 4687·3)	4·6	3850·1 (3320·7 to 4439·9)	4·9	213·0 (–585·5 to 1011·5)
Neutropenia§	284·3 (235·7 to 340·0)	42·2	230·5 (186·1 to 282·4)	40·3	53·8 (–15·5 to 123·1)
Anaemia¶	248·5 (205·2 to 298·3)	46·3	243·4 (199·1 to 294·6)	43·1	5·11 (–60·0 to 70·2)
Ascites	10·5 (5·0 to 19·3)	95·6	25·6 (15·7 to 39·6)	78·1	–15·2 (–27·6 to –2·7)
All serious adverse events	82·8 (64·1 to 105·4)	79·7	62·5 (45·6 to 83·6)	72·0	20·3 (–7·0 to 47·6)
Febrile neutropenia	4·1 (1·1 to 10·5)	97·2	1·2 (0·0 to 6·9)	80·9	2·9 (–2·1 to 7·8)
System organ class of infection and infestation (including sepsis)	16·8 (9·6 to 27·2)	95·4	11·5 (5·3 to 21·9)	78·0	5·2 (–6·1 to 16·6)

EAIR=exposure-adjusted incidence rates. PYE=patient-years exposure. *EAIR difference: ([relacorilant plus nab-paclitaxel] – nab-paclitaxel monotherapy). The exact CI for the EAIR difference between the two treatment groups is based on two independent Poisson distributions. †EAIR is defined as event incidence rate per 100 PYE: (total number of patients with an event / total PYE) × 100. The exact 95% CI is based on a Poisson distribution for EAIR. ‡The total PYE to a treatment is the sum of individual patient's PYE within the treatment exposure period. §Combined term including neutropenia, decreased neutrophil count, and febrile neutropenia. ¶Combined term including anaemia, decreased haemoglobin, and decreased red blood cell count.

Table 3: **EAIR of selected adverse events in the safety population**

Dose reductions and discontinuations of relacorilant due to adverse events were 13 (7%) and 18 (10%), (table 2; appendix p 18). Dose modifications of nab-paclitaxel due to adverse events were numerically higher in the combination group (table 2), whereas the dose intensities relative to the planned doses were comparable, and discontinuations due to adverse events were infrequent and comparable in the combination and monotherapy groups (17 [9%] and 15 [8%]). Adverse events leading to frequent dose modifications or discontinuations of nab-paclitaxel are shown in the appendix (p 18).

There were four deaths on study treatment (or within 30 days of the last dose of the study drug) due to adverse events, all in the combination group (one each due to cardiac arrest, intestinal perforation, ischaemic stroke, and septic shock). One death (due to septic shock, on study day 87 in a patient with febrile neutropenia) was considered related to nab-paclitaxel by the investigator, and none of the deaths were related to relacorilant. The cause of death for the other three patients was attributed to their advanced ovarian cancer.

Discussion

The ROSELLA trial met its primary objective: the addition of relacorilant to nab-paclitaxel for patients with platinum-resistant ovarian cancer showed a statistically significant improvement in progression-free survival assessed by BICR and a clinically meaningful difference in overall survival at an interim analysis. This population has a poor prognosis. All patients had cancer progression following bevacizumab and a taxane, a significant proportion of patients had received at least one line of therapy in the platinum-resistant setting and a previous poly (ADP-ribose) polymerase inhibitor. A progression-free survival benefit was seen consistently across all clinically relevant subgroups. Although an interim analysis, similar results were observed for overall survival in these subgroups. These consistent trends in subgroups of patients with poor prognosis (eg, older patients, more heavily pre-treated patients, patients with short primary platinum-free intervals, and patients with a large burden of disease), together with a reduction in reported ascites in patients receiving combination therapy, are clinically relevant. The results confirm positive findings from a previously reported phase 2 trial in patients with platinum-resistant ovarian cancer, which showed that the addition of intermittently dosed relacorilant improved progression-free survival compared with nab-paclitaxel monotherapy (HR 0·66 [95% CI 0·44–0·98]; p=0·038) with a median progression-free survival assessed by the investigator of 5·6 months versus 3·8 months.[12] Together, these compelling datasets support a role for relacorilant in enhancing the efficacy of taxane chemotherapy for patients with cancer.

The participants in this trial were enrolled globally across North America, Europe, Latin America, South Korea, and Australia. Consistent with reported distribution of ovarian cancer among ethnicities,[1] White people were the most highly represented group in the study. Therefore, although the outcomes of this global trial are applicable to a diverse population, there continue to be opportunities to improve representation.

The efficacy of relacorilant plus nab-paclitaxel shown in our study compares favourably with published benchmarks: weekly nab-paclitaxel,[9,12] weekly paclitaxel,[4–8] pegylated liposomal doxorubicin,[6] topotecan,[6] gemcitabine,[16,17] and (in patients with folate-receptor alpha positive serous tumours) mirvetuximab soravtansine.[13,14] Notably, while not directly compared in prospectively designed trials, published data for weekly paclitaxel and weekly nab-paclitaxel monotherapy show a three to four-fold higher objective response rate, and an approximately two-fold longer progression-free survival than other chemotherapy options.[4–9,14–17,25] Therefore, a weekly taxane could be considered a more rigorous control group in phase 3 clinical trials than investigator's choice chemotherapy listing all available agents in the resistant setting. Nab-paclitaxel is a rational combination partner for a selective glucocorticoid receptor antagonist such as relacorilant because of the lack of requirement for corticosteroid premedication. There are no published data directly comparing weekly nab-paclitaxel with weekly paclitaxel in patients with platinum-resistant ovarian cancer. Nevertheless, patients with platinum-resistant ovarian cancer who received nab-paclitaxel monotherapy in this study, the phase 2 trial,[12] and another phase 2 trial by Coleman and colleagues[9] showed median progression-free survival estimates (5·5 months, 3·8 months, and 4·5 months, respectively) that are comparable to weekly paclitaxel (range 3·9–5·5 months),[4–8] validating nab-paclitaxel as an appropriate comparator.

The most common adverse events due to relacorilant plus nab-paclitaxel (ie, neutropenia, anaemia, fatigue, and nausea) are well known adverse events for nab-paclitaxel, easy to monitor and manage, and reversible. When corrected for increased nab-paclitaxel exposure in the combination group, the safety profile of relacorilant plus nab-paclitaxel was comparable to nab-paclitaxel monotherapy. Published safety data for relacorilant monotherapy in healthy participants and participants with endogenous hypercortisolism show that it is well tolerated with no evidence of neutropenia.[23,26] Dose modifications and discontinuations of relacorilant were infrequent. There were no new safety signals, and the safety profile of relacorilant plus nab-paclitaxel was broadly consistent with the phase 2 trial.[12] Neutropenia was well managed without granulocyte colony-stimulating factor use in most patients, with few cases of febrile neutropenia or sepsis. The frequency and severity of adverse events in the nab-paclitaxel monotherapy group were similar to published phase 3 data reporting the safety profile of weekly paclitaxel in patients with platinum-resistant ovarian cancer.[5,7,14]

Study limitations include the open-label design and the applicability of these results to patients with greater than three lines of anticancer therapy. The risk of bias in the progression-free survival assessment for a study with an open-label design was mitigated by using an objective assessment method (BICR) and a dual primary endpoint of overall survival. The median duration of follow-up for overall survival is less than the estimated median overall survival in the relacorilant combination group at this interim analysis. Additional follow-up time will improve precision in the estimated overall survival benefit and allow for complete reporting of progression-free survival and subsequent therapies. Subgroup analyses of progression-free survival and overall survival showed a similar treatment effect in patients with one, two, or three previous lines of systemic therapy, suggesting that relacorilant could benefit heavily pre-treated patients. Only bevacizumab has previously shown a statistically significant additive progression-free survival benefit in combination with a weekly taxane, in the AURELIA trial;[6] there have been many phase 3 trials that have not found significant benefits for other novel agents.[25] The median progression-free survival and interim overall survival in the control group of AURELIA are similar to the ROSELLA study despite progress over the intervening 15 years. However, the ROSELLA population is a more heavily pre-treated group, with more lines of therapy and more previous bevacizumab use; ROSELLA was also done in an era when many patients progressed on treatment with a poly (ADP-ribose) polymerase inhibitor, which is associated with reduced chemo-sensitivity.[27] Although bevacizumab is often used in earlier lines of therapy, there is evidence in the platinum-sensitive setting that patients might benefit from rechallenge.[28] Relacorilant does not have overlapping toxicity with bevacizumab and does not increase the risk of bowel obstruction or perforations. Therefore, given the potential for additive benefit, the combination of bevacizumab with relacorilant plus nab-paclitaxel is being explored in an ongoing study (NCT06906341). Finally, trials to explore the comparative efficacy of relacorilant plus nab-paclitaxel and targeted therapies in biomarker-defined populations will be important to inform treatment choice and sequencing.

In summary, relacorilant plus nab-paclitaxel shows a progression-free survival benefit in patients with platinum-resistant ovarian cancer compared with a weekly taxane. This outcome, with a clinically meaningful median overall survival difference of 4·5 months at the interim analysis, positions relacorilant plus nab-paclitaxel as a potential new standard for patients without the need for biomarker selection. Overall, relacorilant plus nab-paclitaxel was well tolerated, and adverse events were manageable.

Contributors

All authors provided resources, critically reviewed and edited the manuscript, approved the final version, and agreed to be accountable for all aspects of the work. All authors were given the opportunity to access the data in the study, and agreed to submit for publication. ABO, DL, DMO, BJM, AK-H, HIP, SGP, ICT, and AMJ accessed and verified the data. ABO, LGl, J-WK, GG, VS, LGi, LM, AD, EH, YJL, AO, MS, B-GK, NC, MEM, CD, AC, ALL, BB, BJM, GS, EM, EK, BS, HDLC, AFdCC, CCa, BY, TVG, CCh, GC, SN, AB, GA, LB, AK-H, HIP, SGP, ICT, AMJ, and DL were involved with the investigation. ABO, DMO, NC, BJM, HIP, ICT, and DL conceived the study. HIP and ICT were involved in the data curation, data analysis, and validation. AK-H, HIP, SGP, ICT, and AMJ were involved in the formal analysis, method, and visualisation of data. ABO, DMO, ICT, AMJ, DL, HIP, SGP, J-WK, IV, LM, BJM, SK, and AK-H were involved with project administration. ABO, DMO, LGl, ICT, AMJ, DL, HIP, SGP, AO, AC, BJM, BY, and TVG were involved with writing the original draft. ABO, DMO, ICT, AMJ, DL, J-WK, IV, and LM were involved with supervision.

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AB reports consulting fees and support for attending meetings from MSD and AstraZeneca; payment or honoraria from MSD, AstraZeneca, and AbbVie; and participation on Data Safety Monitoring or Advisory Boards for MSD, GlaxoSmithKline (GSK), AstraZeneca, and AbbVie. AC reports support for the present manuscript from Corcept; grants or contracts from AstraZeneca, Advenchen, Eisai, Immunogen, MSD, and Mural Oncology; payment or honoraria from GSK; and participation on Data Safety Monitoring or Advisory Boards for GSK, and Immunogen. AD reports payment or honoraria from GSK and support for attending meetings from Gilead, Novartis, and AstraZeneca. AFdCC reports payment or honoraria from Roche, MSD, Daiichi, Adium, GSK, AstraZeneca, Pfizer, Amgen, and AbbVie; support for attending meetings from Roche, MSD, Daiichi, Adium, GSK, and AstraZeneca; and participation on Data Safety Monitoring or Advisory Boards for Roche, MSD, Daiichi, Adium, GSK, AstraZeneca, Pfizer, Amgen, and AbbVie. AK-H reports stock or stock options in Corcept and Exelixis. AMJ and SGP report support for the present manuscript, stock or stock options, and employment from Corcept. AO reports consulting fees from AbbVie, Agenus, AstraZeneca, Clovis, Corcept, Deciphera, Daiichi Sankyo, Debiopharm International, Eisai, Exelixis, F Hoffmann–La Roche, Genmab, GSK, ImmunoGen, Itheos, MSD, Mersana, Myriad Genetics, Novocure, OncoXerna, PharmaMar, Regeneron, Sattucklabs, Seagen–Pfizer, Stemline Therapeutics Sutro Biopharma, TORL Bio Therapeutics, Zentalis, and Zymeworks; payment or honoraria from the NSGO, Peerview, Peervoice, Medscape, Asociación Colombiada de Ginecológos Oncólogos, the ESO, AstraZeneca, GSK; support for attending meetings from AstraZeneca, PharmaMar, and Roche; and participation on a Data Safety Monitoring Board or Advisory Board for AbbVie, Agenus, AstraZeneca, Clovis Oncology, Corcept, Deciphera Pharmaceuticals, Daiichi Sankyo, Debiopharm International, Eisai, Exelixis, F Hoffmann–La Roche, Genmab, GSK, ImmunoGen, Itheos, MSD, Mersana, Myriad Genetics, Novocure, OncoXerna, PharmaMar, Regeneron, Sattucklabs, Seagen–Pfizer, Stemline Therapeutics Sutro Biopharma, TORL Bio Therapeutics, Zentalis, and Zymeworks. BJM reports consulting fees from AbbVie, Alkermes, AstraZeneca, BioNTech, Corcept, Daiichi Sankyo, Eisai, Genmab–Seagen–Pfizer, the Gynecologic Oncology Group Foundation, Gradalis, ImmunoGen–AbbVie, Incyte, Karyopharm, pharmaand, ProfoundBio, Regeneron, Roche–Genentech, Sutro Biopharma, Tubulis, Verastem Oncology, Zentalis, and Zymeworks; and payment or honoraria from AbbVie, AstraZeneca, BioNTech, Corcept, Daiichi Sankyo, Eisai, Genmab, Genmab–Seagen–Pfizer, the Gynecologic Oncology Group Foundation, GSK, ImmunoGen–AbbVie, Incyte, Karyopharm, Lilly, Mersana Therapeutics, MSD, Mural Oncology, Myriad Genetics, Natera, Novartis, Novocure, Onco4, Panavance, pharmaand, ProfoundBio, Regeneron, Roche–Genentech, Sutro Biopharma, Tubulis, Verastem, Zentalis, Zymeworks, AstraZeneca, Eisai, ImmunoGen–AbbVie, Lilly, MSD, and Tesaro–GSK. BS reports consulting fees from AbbVie, GSK, GenMab, Seagen, Pfizer, Novocure, Aadi, Gilead, Eisai, Merck, Incyte, and Regeneron. BY reports consulting fees from MSD, AstraZeneca, GSK–TESARO, Bayer, Roche–Genentech, ECS Progastrine, Novartis, LEK, Amgen, Clovis, Merck Serono, Bristol Myers Squibb, Seagen, Myriad, Menarini, Gilead, Eisai, pharmaand, and AbbVie; and stock or stock options in See2Cure. CCa reports payment or honoraria from GSK and AstraZeneca. CD reports payment or honoraria from Pierre Fabre and

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Data sharing

De-identified datasets for the results reported in this publication can be made available to qualified researchers following submission of a methodologically sound proposal to datarequests@corcept.com. Data will be made available for such requests following the online publication of this Article and for 1 year thereafter in compliance with applicable privacy laws, data protection, and requirements for consent and anonymisation. Data will be provided by Corcept Therapeutics.

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