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A SPECIAL MEETING REVIEW EDITION

Highlights in Ovarian Cancer From the 2016 ESMO Congress

A Review of Selected Presentations From the 2016 European Society for Medical Oncology Congress
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Special Reporting on:

- A Randomized, Double-Blind Phase 3 Trial of Maintenance Therapy With Niraparib vs Placebo in Patients With Platinum-Sensitive Recurrent Ovarian Cancer (ENGOT-OV16/NOVA Trial)
- A Phase II Study of the Cell Cycle Checkpoint Kinases 1 and 2 Inhibitor (LY2606368; Prexasertib Monomesylate Monohydrate) in Sporadic High-Grade Serous Ovarian Cancer (HGSOC) and Germline *BRCA* Mutation-Associated Ovarian Cancer (g*BRCA*m+ OvCa)
- Results of a Phase 2 Trial of Selinexor, an Oral Selective Inhibitor of Nuclear Export (SINE) in 114 Patients With Gynaecological Cancers
- Clinical Activity of the Poly(ADP-ribose) Polymerase (PARP) Inhibitor Rucaparib in Patients (pts) With High-Grade Ovarian Carcinoma (HGOC) and a *BRCA* Mutation (*BRCAmut*): Analysis of Pooled Data From Study 10 (Parts 1, 2a, and 3) and ARIEL2 (Parts 1 and 2)
- PiSARRO: A EUTROC Phase 1b Study of APR-246 With Carboplatin (C) and Pegylated Liposomal Doxorubicin (PLD) in Relapsed Platinum-Sensitive High-Grade Serous Ovarian Cancer (HGSOC)
- Use of Bevacizumab (Bev) in Real Life for First-Line (fl) Treatment of Ovarian Cancer (OC). Part 1: The ENCOURAGE Cohort of 1158 Patients (pts) by GINECO

PLUS Meeting Abstract Summaries

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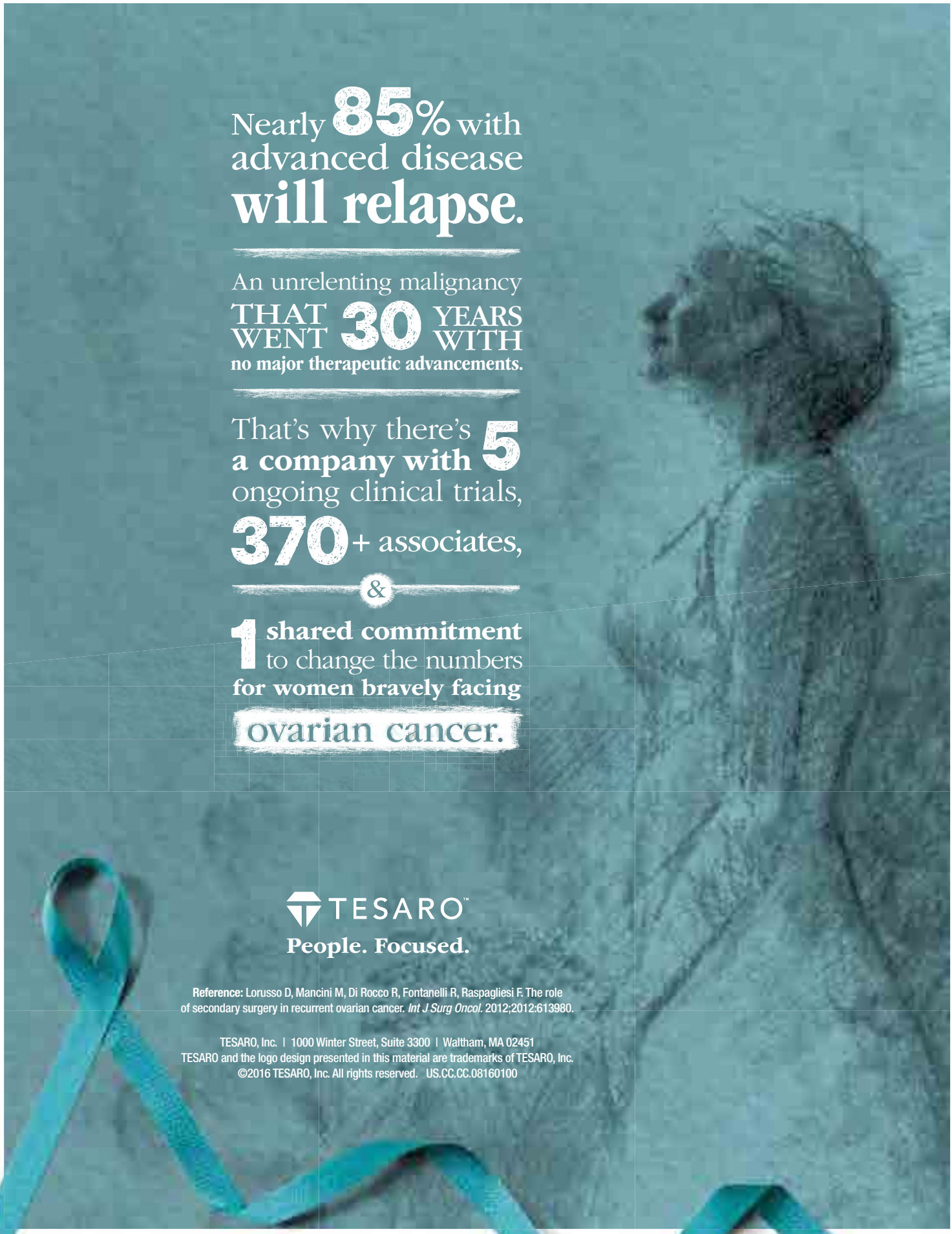

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A Randomized, Double-Blind Phase 3 Trial of Maintenance Therapy With Niraparib vs Placebo in Patients With Platinum-Sensitive Recurrent Ovarian Cancer (ENGOT-OV16/NOVA Trial)

Patients with recurrent ovarian cancer represent an important unmet medical need. Despite a high initial response rate to platinum and taxane treatments, most patients with advanced cancer relapse repeatedly, with ever-shortening intervals between relapses.[1] Patients who relapse are typically treated with combination chemotherapy, but the use of this treatment is limited by cumulative toxicities. Germline *BRCA1* and *BRCA2* mutations play a key role in hereditary disease and lead to homologous recombination repair-deficient disease (HRD). However, HRD is also present in approximately half of patients with sporadic ovarian cancer who do not have *BRCA* mutations.

Poly(ADP-ribose) polymerase (PARP) binds to DNA single-stranded breaks, activating the base excision repair pathway.[2,3] Niraparib is an orally available drug that inhibits PARP1 and PARP2.[4] Drugs in this class are predicated on the concept that inhibition of the PARP repair pathway combined with the inherent DNA repair defects of ovarian cancer cells will lead to cell death.[5,6] Cells with mutated copies of both *BRCA1* or *BRCA2* genes are 100- to 1000-fold more sensitive to PARP inhibitors than cells with wild-type copies of these genes.[7,8] Platinum-sensitive tumors are also more responsive to PARP inhibitors than platinum-resistant tumors.[2,9]

The phase 3 NOVA trial (A Maintenance Study With Niraparib Versus Placebo in Patients With Platinum Sensitive Ovarian Cancer) was designed to test the hypothesis that maintenance treatment with niraparib would provide a clinical benefit to patients with recurrent, platinum-sensitive ovarian cancer, regardless of germline *BRCA1/2* mutation status.[10,11] This randomized, placebo-controlled trial was conducted in collaboration with the European Network of Gynaecological Oncological Trial groups; the lead group was the Nordic Society of Gynecological Oncology. Eligible patients were adults with histologically diagnosed ovarian, fallopian tube, or primary peritoneal cancer with high-grade serous histologic features. Prior to enrollment, patients received platinum-based chemotherapy, and patients with platinum-sensitive disease were invited to participate in the trial. Platinum-sensitive disease was defined as a complete response (CR) or partial response (PR) and disease progression occurring more than 6 months after the final round of platinum therapy. Patients were enrolled within 8 weeks of receiving their final dose of platinum-based therapy.

Two cohorts of patients were enrolled based on the presence or absence of the germline *BRCA* mutation. Of the 533 enrolled patients, 203 had a germline *BRCA* mutation and 350 did not. Prior to randomization within each cohort, patients were stratified

ABSTRACT SUMMARY The CHIVA Study: a GINECO Randomized Double Blind Phase II Trial of Nintedanib Versus Placebo With the Neo-Adjuvant Chemotherapy (NACT) Strategy for Patients (pts) With Advanced Unresectable Ovarian Cancer (OC). Report of the Interval Debulking Surgery (IDS) Safety Outcome

Improving the response rate to neoadjuvant chemotherapy by adding antiangiogenic therapy could increase the rate of complete resection at interval debulking surgery. However, the use of bevacizumab raises concerns regarding wound healing. The phase 2 CHIVA study (Vargatef in Addition to First Line Chemotherapy With Interval Debulking Surgery in Patients With Ovarian Cancer) evaluated the safety and efficacy of nintedanib, an oral antiangiogenic tyrosine kinase inhibitor with a short half-life (Abstract 859PD). The trial enrolled patients with International Federation of Gynecology and Obstetrics stage IIIC to IV cancer of the ovary, fallopian tube, or primary peritoneum. Patients were randomized 2:1 to receive nintedanib or placebo in addition to chemotherapy before and after interval debulking surgery. All patients received 3 cycles of neoadjuvant chemotherapy before interval debulking surgery and 3 cycles of chemotherapy after. There were 72 patients in the nintedanib arm and 49 in the placebo arm. The majority of patients had serous/papillary disease of histologic grade 3. The rates of complications during surgery were 13% in patients receiving nintedanib vs 18% in those receiving placebo. The addition of nintedanib to neoadjuvant chemotherapy did not increase the rate of postoperative complications. In the placebo vs nintedanib cohorts, rates of grade 1/2 AEs were 52% vs 54%, respectively, and rates of grade 3/4 AEs were 18% vs 13%.

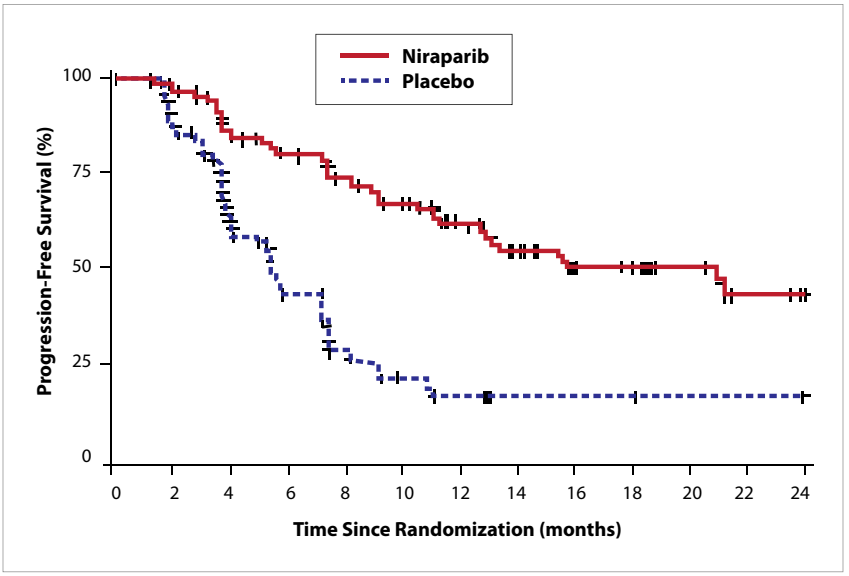

Figure 1. In the cohort of patients with the germline *BRCA* mutation in the phase 3 NOVA trial, progression-free survival was significantly improved with niraparib vs placebo. NOVA, A Maintenance Study With Niraparib Versus Placebo in Patients With Platinum Sensitive Ovarian Cancer. Adapted from Mirza MR et al. ESMO abstract LBA3_PR.[10]

based on the time to progression after completion of the penultimate round of chemotherapy, use of bevacizumab, and the best response during the last platinum regimen. Patients in each cohort were randomized 2:1 to receive either niraparib (300 mg once daily) or placebo. For the patients without germline *BRCA* mutations, a DNA-based test was performed on archived tissue samples to identify tumors with HRD. Patients in the placebo group who progressed were not allowed to cross over into the niraparib arm. The primary endpoint was progression-free survival (PFS) based on blinded, central review. Health-related quality of life was assessed at baseline and at intervals throughout the study.

The germline *BRCA* mutation cohort included 138 patients in the niraparib arm and 65 in the placebo arm. The non–germline *BRCA* mutation cohort included 234 patients receiving niraparib and 116 patients receiving placebo. The median age was 57 years in the germline *BRCA* cohort and 62 years in the non–germline *BRCA* cohort. In the 4 cohorts based on germline *BRCA* mutation and treatment, between 46% and 66% of patients had received 2 previous lines of chemotherapy, and between 33% and 54% of patients had received 3 or more previous lines of chemotherapy. Among the patients receiving niraparib, treatment continued in 47 patients with the germline *BRCA* mutation and in 46 without the mutation. Approximately 51% of patients had achieved a CR, and the remainder achieved a PR. Across the entire study group, approximately 39% of patients had relapsed between 6 and 12 months after the penultimate platinum therapy, and 61% had relapsed at 12 months or later. Approximately one-fourth of the enrolled patients had received prior bevacizumab.

At the time of data cutoff, patients had a median follow-up of 16.9 months. In the cohort of patients with the germline *BRCA* mutation, median PFS was 21.0 months with niraparib vs 5.5 months with placebo (hazard ratio [HR], 0.27; 95% CI, 0.173-0.410; *P*<.0001; Figure 1). Responses were durable. At 18 months after the end of treatment, 50% of patients who received niraparib vs 16% who received placebo remained alive without progression. Kaplan-Meier analysis revealed early separation of the 2 treatment arms, and separation was maintained throughout the observation period. In the patients with a non–germline *BRCA* mutation, median PFS was 9.3 months with niraparib vs 3.9 months with placebo (HR, 0.45; 95% CI, 0.338-0.607; *P*<.0001; Figure 2). The 18-month PFS rate was 30% for niraparib vs 12% for placebo. In the subgroup of patients without the germline *BRCA* mutation who were HRD-positive, the median PFS was also significantly improved by treatment with niraparib (12.9 vs 3.8 months; HR, 0.38; 95% CI, 0.254-0.586; *P*<.0001). For this subgroup, the 18-month PFS rate was 37% for those receiving niraparib vs 9% for those receiving placebo. Kaplan-Meier analysis for both of these cohorts showed clear separation of the curves, consistent with durable responses. A benefit was observed across all subgroups, regardless of patient characteristics, region, prior time to progression, prior treatment, and germline mutation in *BRCA1* or *BRCA2*.

Exploratory analyses were conducted in subgroups of patients from the non–germline *BRCA* mutation cohort. Among patients who were HRD-positive, those with a somatic *BRCA* mutation had a median PFS of 20.9 months with niraparib vs 11.0 months with placebo (HR, 0.27; 95% CI, 0.081-0.903; *P*=.0248). In those with the wild-type *BRCA* mutation, the median PFS was 9.3 months with niraparib vs 3.7 months with placebo (HR, 0.38; 95% CI, 0.231-0.628; *P*=.0001). Niraparib yielded a significant improvement in median PFS for the HRD-negative patients (6.9 vs 3.8 months; HR, 0.58; 95% CI, 0.361-0.922; *P*=.0226). Rates of PFS at 18

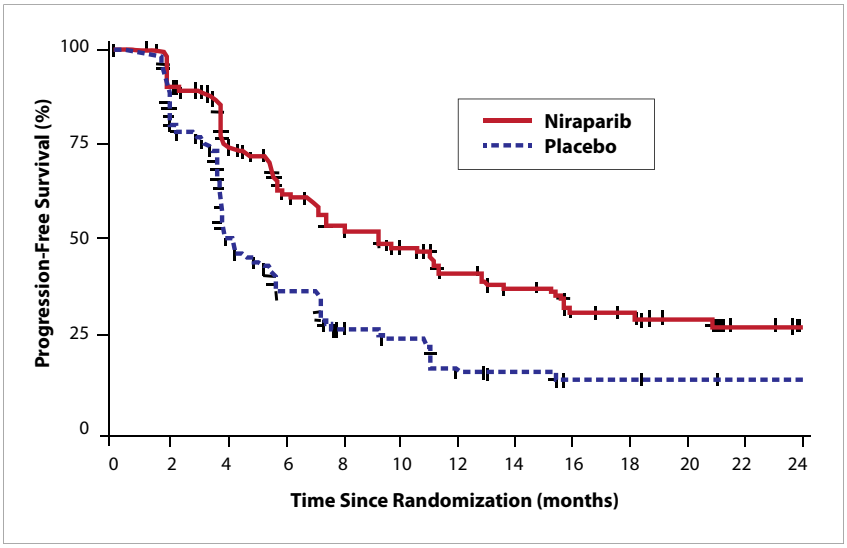

Figure 2. In the cohort of patients with the non–germline *BRCA* mutation in the phase 3 NOVA trial, progression-free survival was significantly improved with niraparib vs placebo. NOVA, A Maintenance Study With Niraparib Versus Placebo in Patients With Platinum Sensitive Ovarian Cancer. Adapted from Mirza MR et al. ESMO abstract LBA3_PR.[10]

Table 1. Rates of PFS at 18 Months Among Patients From the Non–Germline *BRCA* Mutation Arm of the NOVA Trial

	HRD-Positive Somatic *BRCA* Mutation	HRD-Positive *BRCA* Wild-Type	HRD-Negative
Niraparib	52%	27%	19%
Placebo	19%	6%	7%

HRD, homologous recombination repair-deficient disease; NOVA, A Maintenance Study With Niraparib Versus Placebo in Patients With Platinum Sensitive Ovarian Cancer; PFS, progression-free survival.

Adapted from Mirza MR et al. ESMO abstract LBA3_PR.[10]

months were also superior for patients treated with niraparib (Table 1).

In patients with the germline *BRCA* mutation, niraparib conferred a longer chemotherapy-free interval (22.8 vs 9.4 months; HR, 0.26; 95% CI, 0.169-0.414; *P*<.0001) and longer time to first subsequent treatment (21.0 vs 8.4 months; HR, 0.31; 95% CI, 0.205-0.481; *P*<.0001). In the non–germline *BRCA* mutation arm, niraparib also conferred a longer chemotherapy-free interval (12.7 vs 8.6 months; HR, 0.50; 95% CI, 0.370-0.666; *P*<.0001) and longer time to first subsequent treatment (11.8 vs 7.2 months; HR, 0.55; 95% CI, 0.412-0.721; *P*<.0001). Overall survival (OS) data were immature, with fewer than 20% of patient deaths in either treatment arm (HR, 0.73).

The most common grade 3/4 treatment-emergent adverse events (AEs) in the patients who received niraparib were thrombocytopenia (28.3%), anemia (24.8%), and neutropenia (11.2%). Most hematologic AEs were successfully managed with dose adjustments and/or treatment delay. Treatment discontinuations occurred in 14.7% of patients receiving niraparib vs 2.2% of those receiving placebo. Rates of myelodysplastic syndrome/acute myeloid leukemia were 1.4% with niraparib vs 1.1% with placebo. The patient-reported outcomes were similar for the niraparib and placebo cohorts. In both arms, the adherence rates were high.

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A Phase II Study of the Cell Cycle Checkpoint Kinases 1 and 2 Inhibitor (LY2606368; Prexasertib Monomesylate Monohydrate) in Sporadic High-Grade Serous Ovarian Cancer (HGSOC) and Germline *BRCA* Mutation-Associated Ovarian Cancer (g*BRCA*m+ OvCa)

In normal cells, DNA damage activates checkpoints that pause the cell cycle to allow DNA repair or apoptosis.[1] In an effort to improve the efficacy of DNA-damaging chemotherapy, checkpoint inhibitors are being investigated as a means to inhibit DNA repair by preventing activation of checkpoints. Checkpoint kinase (Chk) 1 is a protein kinase that responds to DNA damage by blocking progression through the S phase and preventing the cell from prematurely entering mitosis. In cells without DNA damage, inhibition of Chk1 can lead to the generation of double-stranded DNA breaks, unscheduled DNA replication, and the accumulation of stalled replication forks. Chk2 is a serine/threonine kinase that also responds to DNA damage by altering cellular activities, inducing cell cycle checkpoint activation, cell death, DNA repair, and tolerance of DNA damage.[2] The loss of checkpoint activation during the S phase allows the cell to enter mitosis with fragmented chromosomes, ultimately leading to cell death. Chk1 and Chk2 play an important role in cell cycle regulation in tumors with p53 mutations, such as high-grade serous ovarian cancer.

Prexasertib (LY2606368) is a second-generation Chk1 and Chk2 inhibitor that induces double-stranded DNA breaks, abolishes critical DNA damage checkpoints, and interferes with repair by homologous recombination, leading to death in various cancer cell lines.[3] In mice bearing Calu-6 tumor xenografts, treatment with prexasertib led to DNA damage and growth inhibition. A phase 1 study of patients with advanced solid tumors established the recommended phase 2 dose of prexasertib as 105 mg/m^2 once every 14 days.[4] The most common grade 3/4 treatment-emergent AEs were neutropenia, leukopenia, anemia, thrombocytopenia, and fatigue. Grade 4 neutropenia occurred in 73.3% of patients and was generally transient, and febrile neutropenia occurred in 7% of patients.

A single-arm, phase 2 study evaluated the efficacy and safety of prexasertib in 2 cohorts of patients with ovarian cancer.[5] Cohort 1 included patients with the germline *BRCA* mutation. Cohort 2 included patients with high-grade serous ovarian cancer without the *BRCA* mutation. Patients received prexasertib (105 mg/m^2 intravenously) every 14 days. The primary endpoint consisted of the overall response rate (ORR) and rates of CR and PR based on Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria.[6] Because transient grade 3/4 neutropenia occurred in a large proportion of patients in the phase 1 study, complete blood counts were taken on day 8 of cycle 1, and growth factor was administered in patients with sustained grade 3/4 neutropenia or febrile neutropenia. Prophylactic antibiotics or prophylactic growth

ABSTRACT SUMMARY ICON8 Stage 1A and 1B Analysis: Safety and Feasibility of Weekly Carboplatin and Paclitaxel Regimens in First-Line Ovarian Cancer

The JGOG 3016 study investigated a first-line regimen of dose-dense paclitaxel and carboplatin vs standard paclitaxel and carboplatin in patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (Katsumata N et al. *Lancet Oncol*. 2013;14[10]:1020-1026). The dose-dense regimen increased median PFS by 11 months and median OS by 3 years. Rates of toxicity were higher in the dose-dense arm, and the proportion of patients who completed 6 cycles of treatment were 61.5% in the dose-dense arm vs 72% in the standard-chemotherapy arm. The ICON8 study was designed to investigate results of the same regimen in non-Japanese patients, with the first stage evaluating feasibility (Abstract 861P). More than 75% of patients received 6 cycles of platinum-based chemotherapy. Although toxicity rates were acceptable and febrile neutropenia was rare, the protocol treatment completion rate was low, ranging from 50% to 78%. The independent data monitoring committee recommended that treatment continue with no changes, except for the early use of granulocyte-colony stimulating factor. PFS results from the study are anticipated in 2017, with OS results expected in 2018.

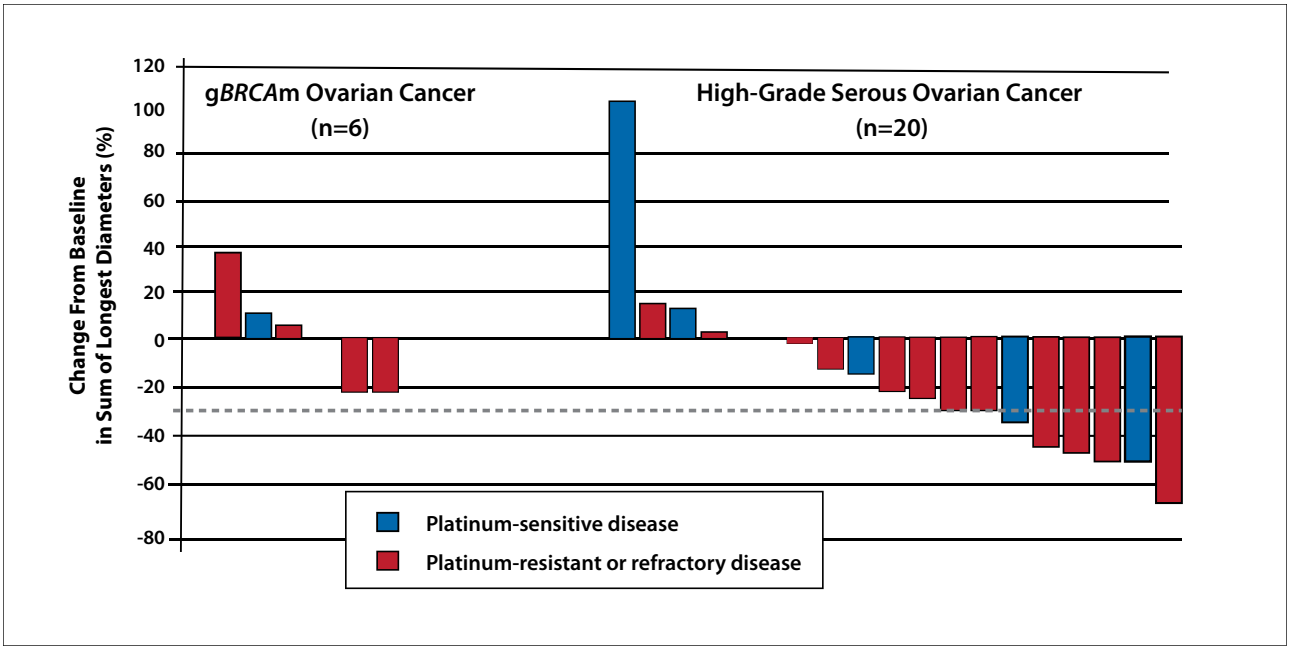

Figure 3. Best response for target lesions among patients treated with prexasertib in a phase 2 trial. g*BRCA*m, germline *BRCA* mutated. Adapted from Lee J et al. ESMO abstract 855O.[5]

factor support was not administered with the first treatment. Dose reductions to 80 mg/m^2 were mandated in patients who experienced prolonged neutropenia, grade 3/4 neutropenia, or febrile neutropenia despite growth factor support. The study included patients with refractory or recurrent ovarian cancer with measurable disease and a lesion amenable to biopsy. Patients in cohort 1 provided documentation of their *BRCA1* or *BRCA2* mutation status. Patients in cohort 2 had a negative *BRCA* mutation test or negative family history of hereditary breast or ovarian cancer syndrome. Enrolled patients had a good performance status, and there was no limit to the number of prior therapies. The trial has a planned enrollment of 24 patients per cohort.

In the cohort of 7 patients with the germline *BRCA* mutation, the median number of prior treatments was 7. One patient had clear cell ovarian cancer that was platinum-sensitive, and the remaining patients had platinum-resistant or -refractory disease. All of the patients in this cohort had received treatment with a PARP inhibitor, and all but 1 had received treatment with bevacizumab prior to study entry. The 25 patients in cohort 2 had received a median of 5 prior therapies, and the majority of patients had platinum-resistant or -refractory disease. Approximately 25% had received prior treatment with a PARP inhibitor, and two-thirds had received prior treatment with bevacizumab.

Of the 6 evaluable patients with the germline *BRCA* mutation, none achieved a CR or PR. Four patients (67%) achieved stable disease lasting at least 4 months. The median response duration was 4 months (range, 4-5 months). Of the 20 evaluable patients with high-grade serous ovarian cancer, none achieved a CR, 7 (35%) achieved a PR, and 5 (25%) achieved stable disease lasting at least 4 months, yielding a disease control rate of 60%. In the 5 patients with stable disease, the median duration was 5 months (range, 4 to 7+ months). The disease control rate was 67% in cohort 1 and 60% in cohort 2. In the 6 patients with the germline *BRCA* mutation, 2 patients showed a reduction in tumor size by approximately 20%, and tumor size remained stable or increased in the remaining patients (Figure 3). In cohort 2, a PR was observed in 2 of the 5 patients with platinum-sensitive disease and in 5 of the 15 patients with platinum-resistant or platinum-refractory disease.

Treatment-related hematologic AEs were common. Grade 3/4 neutropenia was observed in 86% to 88% of patients in the 2 cohorts. Neutropenia was generally transient, resolving to grade 2 or lower within 8 days. Two patients (8%) with high-grade serous ovarian cancer had febrile neutropenia, including 1 who required a dose reduction despite growth factor support. Grade 3 lymphocytopenia occurred in 3 patients (43%) with the germline *BRCA* mutation, and grade 3/4 lymphocytopenia occurred in 19 patients (76%) with high-grade serous ovarian cancer. A grade 3/4 reduction in platelets occurred in 1 patient (14%) in cohort 1 and 6 patients (24%) in

cohort 2. Nonhematologic AEs were generally mild. One patient experienced grade 3 diarrhea and vomiting during the prexasertib infusion.

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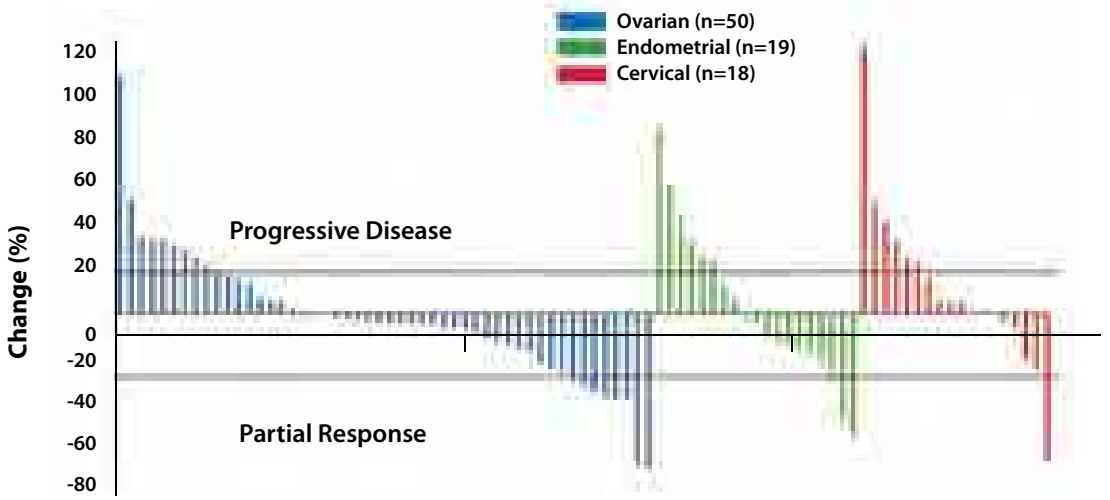
Results of a Phase 2 Trial of Selinexor, an Oral Selective Inhibitor of Nuclear Export (SINE) in 114 Patients With Gynaecological Cancers

Exportin 1 (XPO1/CRM1) is the only nuclear exporter for many cell growth regulators and the major tumor suppressor proteins, including p53, p73, BRCA1, and pRB.[1] XPO1 is upregulated in many cancers, leading to cytoplasmic localization and degradation of p53 and other tumor suppressors. Selinexor is a small molecule inhibitor of nuclear export (SINE), a class of drugs in development aimed at restoring normal cellular export functions, including nuclear retention and accumulation of tumor suppressors, as well as induction of apoptosis.[2] A phase 1 study of selinexor in patients with advanced solid tumors demonstrated acceptable safety. The most common treatment-related AEs were fatigue (70%), nausea (70%), and anorexia (66%) and were mostly grade 1 or 2. The most common grade 3/4 toxicities were thrombocytopenia (16%), fatigue (15%), and hyponatremia (13%). Selinexor elicited 1 CR and 6 PRs among 157 evaluable patients. The study established the maximum tolerated dose at 65 mg/m^2 administered twice weekly.

Selinexor has also demonstrated efficacy in a mouse model and in patients with ovarian cancer.[3] Overexpression of XPO1 RNA and nuclear localization of XPO1 correlated with platinum resistance and decreased survival. Inhibition of XPO1 decreased cell viability while restoring platinum sensitivity in both immortalized ovarian cancer cells and patient-derived ovarian cancer cell lines. Selinexor treatment with or without platinum decreased tumor growth and prolonged survival in a platinum-resistant mouse model. Also in this study, 5 patients with late-stage, recurrent, heavily pretreated ovarian cancer received treatment with selinexor.[3] The drug

ABSTRACT SUMMARY Non Pegylated Liposomal Doxorubicin (NPLD, Myocet™) + Carboplatin (cb) in Patients (pts) With Ovarian Cancer in Late Relapse (OCLR): a Phase 2 GINECO Study

Pegylated liposomal doxorubicin is part of standard treatment for ovarian cancer patients, but shortages of the drug occurred from 2011 to 2013. In the interest of having an alternative to the pegylated formulation, the Groupe d'Investigateurs Nationaux pour l'Etude des Cancers de l'Ovaire et du Sein group evaluated the efficacy and safety of nonpegylated liposomal doxorubicin plus carboplatin in patients with recurrent platinum-sensitive ovarian cancer (Abstract 863P). Enrolled patients had ovarian, fallopian tube, or extraovarian papillary serous cancer in first or second relapse with greater than 6 months' time to progression after the last platinum administration. The 87 patients had a median age of 67 years, and 56% had a platinum-free interval exceeding 12 months. Eighty percent of patients received 6 cycles of nonpegylated liposomal doxorubicin plus carboplatin, and 9% received up to 9 cycles. Nearly all patients (96%) received granulocyte-colony stimulating factor support. The study yielded a disease control rate of 40% (95% CI, 29%-50%) at 12 months and a median PFS of 11.4 months (95% CI, 10.2-13.1 months). The ORR was 58% (95% CI, 47%-68%) and included 21% CRs. The most common grade 3/4 AEs were neutropenia (16.7%), fatigue (13.1%), and anemia (12.8%). Febrile neutropenia was noted in 6.0% of patients.



Percent Change in Target Lesions

Cancer Type	Dose	n	PR (%)	SD ≥12 Weeks (%)	SD <12 Weeks (%)	PD (%)
Ovarian	All doses	59	8 (14%)	21 (36%)	4 (7%)	26 (44%)
Endometrial	50 mg/m^2 (BIW)	20	3 (15%)	6 (30%)	3 (15%)	8 (40%)
Cervical	50 mg/m^2 (BIW)	23	1 (4%)	5 (22%)	2 (9%)	15 (65%)

Figure 4. Tumor response in the phase 2 SIGN study, which evaluated selinexor. BIW, twice weekly; PD, progressive disease; PR, partial response; SD, stable disease; SIGN, Selinexor in Gynecological Neoplasms. Adapted from Vergote I et al. ESMO abstract 854O.[4]

demonstrated acceptable tolerability. One patient experienced a PR, and 3 experienced the cessation of tumor growth.

The SIGN study (Selinexor in Gynecological Neoplasms) evaluated selinexor in 3 cohorts of patients with ovarian, endometrial, or cervical cancer.[4] This phase 2 trial enrolled adult patients with an Eastern Cooperative Oncology Group performance status of 0 or 1 and a life expectancy of at least 12 weeks. Patients with ovarian cancer had platinum-resistant or platinum-refractory disease and had received at least 1 prior chemotherapy treatment, with no upper limit on the number of prior treatments. Ovarian cancer patients originally received selinexor at 50 mg/m^2 twice weekly and were later randomized to receive either 35 mg/m^2 twice weekly or 50 mg/m^2 once weekly. Patients with endometrial or cervical cancer received selinexor at 50 mg/m^2 twice weekly. The primary endpoint was the disease control rate, defined as patients who achieved a CR, PR, or stable disease for at least 12 weeks.

The 66 patients with ovarian cancer had a median age of 62 years (range, 31-80 years) and had received a median of 6 prior treatments (range, 1-11). Prior treatments included platinum-based agents (100%), taxanes (100%), and anthracyclines (83%). Nausea, vomiting, fatigue, and anorexia are known AEs associated with selinexor. The twice-weekly selinexor dosage of 50 mg/m^2 was associated with grade 3 nausea, vomiting, and anorexia in 9 patients with ovarian cancer (12%), 6 patients with endometrial cancer (8%), and 4 patients with cervical cancer (6%). These frequencies were reduced in ovarian cancer patients who received the lower doses. The twice-weekly selinexor dosage of 35 mg/m^2 was associated with 1 event each of grade 3 vomiting or anorexia. The once-weekly dosage of 50 mg/m^2 was associated with 1 event each of grade 3 nausea or vomiting. In the cohorts of patients treated with 50 mg/m^2 twice weekly, 35 mg/m^2 twice weekly, and 50 mg/m^2 once weekly, grade 3 fatigue was observed in 11 (15%), 5 (24%), and 1 (5%), respectively. Grade 3 weight loss was observed in 0 (0%), 1 (5%), and 1 (5%), respectively. Grade 3 anemia was observed in 8 (11%), 2 (10%), and 1 (5%). There was no grade 4 fatigue, weight loss, or anemia.

One patient (1%) in the cohort receiving selinexor at 50 mg/m^2 twice weekly experienced grade 4 thrombocytopenia, and 17 (23%) experienced grade 3 thrombocytopenia. In contrast, with the reduced drug dosages, there was only 1 report (5%) of grade 3 thrombocytopenia, which occurred

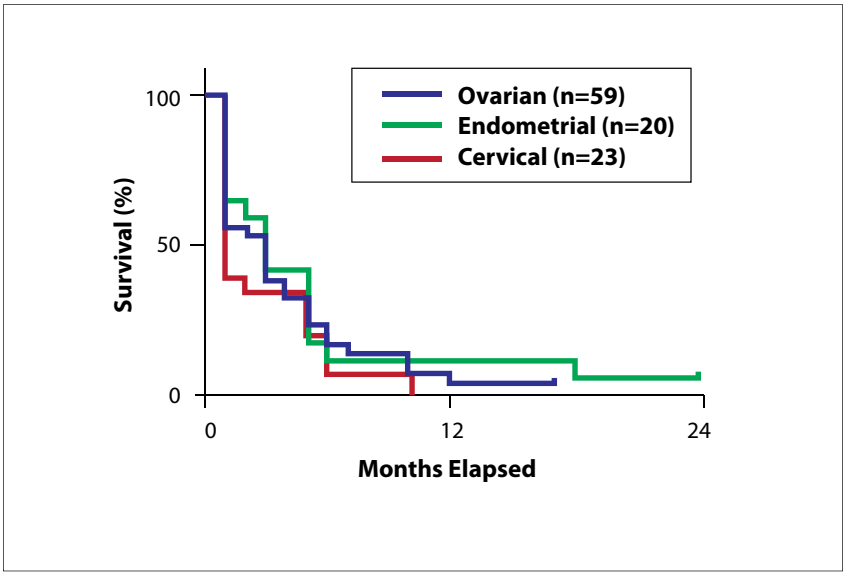


Figure 5. Progression-free survival in the phase 2 SIGN study, which evaluated selinexor. SIGN, Selinexor in Gynecological Neoplasms. Adapted from Vergote I et al. ESMO abstract 854O.[4]

ABSTRACT SUMMARY A Phase 1b Study of the Nanoparticle-Drug Conjugate (NDC) CRLX101 in Combination With Weekly Paclitaxel in Patients (pts) With Platinum-Resistant Ovarian Cancer (OC)

CRLX101 is a novel targeted nanoparticle conjugated to camptothecin, a potent topoisomerase inhibitor (Abstract 864). CRLX101 has been designed to deliver camptothecin directly to tumor cells, thus avoiding the toxicity associated with unmodified camptothecin. A phase 1b/2 study enrolled patients with persistent or recurrent platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer. Using a 3+3 dose-escalation design, the study found no dose-limiting toxicities with CRLX101 administered at 12 mg/m^2 or 15 mg/m^2 every 2 weeks combined with paclitaxel (80 mg/m^2) administered weekly for 3 out of 4 weeks. The higher dose was chosen for the phase 2 study. Of the 9 patients evaluated in the dose-escalation study, 5 patients (56%) achieved a PR and 4 patients (44%) had a reduction in the CA-125 level of at least 50% from baseline. Among the 5 patients who had received prior treatment with bevacizumab, 3 (60%) achieved a PR. The median duration of treatment was 106 days (range, 49-230 days). Preliminary data from the first 9 patients enrolled in the phase 2 study demonstrated a CA-125 reduction of 50% or greater from baseline in 4 (44%) and a measurable reduction in tumor dimensions in 7 (77%). The median duration of therapy was 119 days. The majority of AEs were of mild to moderate severity. Enrollment of 26 patients is planned for the phase 2 portion of the study, and a pivotal registration study is being planned. Based on the phase 1b data, the US Food and Drug Administration (FDA) granted Fast Track status to CRLX101 in combination with paclitaxel for patients with platinum-resistant ovarian cancer.

within the 35 mg/m^2 twice weekly group. No grade 4 platelet reductions were observed.

Tumor response varied among the patient groups (Figure 4). In the 59 evaluable patients with ovarian cancer who received selinexor in any of the 3 dose cohorts, the disease control rate was 49%, reflecting 8 patients with a PR and 21 with a CR. The disease control rates were 45% and 42% in patients who received selinexor at 50 mg/m^2 twice weekly or once weekly, respectively, and 61% in patients who received selinexor at 35 mg/m^2 once weekly. The disease control rate was 45% in the 20 patients with endometrial cancer and 26% in the 23 patients with cervical cancer. In the entire study group, 44 patients met the conditions for disease control. Despite being heavily pretreated, these patients spent a median of 20 weeks on the study. Four patients had received treatment for longer than 1 year and were continuing treatment at the time the data were reported. For the cohorts of patients with ovarian, endometrial, or cervical cancer, median PFS was 3 months, 3 months, and 1 month, respectively (Figure 5). Median OS was 7 months, 8 months, and 5 months. Selinexor is being studied in combination with other agents, and phase 3 trials in ovarian and endometrial cancer are being planned.

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Clinical Activity of the Poly(ADP-ribose) Polymerase (PARP) Inhibitor Rucaparib in Patients (pts) With High-Grade Ovarian Carcinoma (HGOC) and a *BRCA* Mutation (*BRCA*mut): Analysis of Pooled Data From Study 10 (Parts 1, 2a, and 3) and ARIEL2 (Parts 1 and 2)

Approximately 14% to 18% of epithelial ovarian cancers harbor a germline mutation in *BRCA1* or *BRCA2*, and 5% to 7% have a somatic *BRCA* mutation.[1-3] Rucaparib is a PARP inhibitor that has demonstrated clinical activity in 2 phase 2 studies of patients with high-grade ovarian carcinoma harboring a *BRCA* mutation.[4,5] Data from these 2 studies were pooled to evaluate the clinical safety and efficacy of the PARP inhibitor.[6] Study 10 and ARIEL2 (A Study of Rucaparib in Patients With Platinum-Sensitive, Relapsed, High-Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer) included patients who had received 2 or more prior chemotherapy regimens and had platinum-resistant or platinum-sensitive disease. Part 1 of Study 10 applied dose escalation to determine the maximum tolerated dose and optimal phase 2 dose of rucaparib in patients with solid tumors. Part 2a of the study evaluated rucaparib at the recommended phase 2 dose in patients with ovarian cancer harboring the germline *BRCA* mutation who had received 2 to 4 prior lines of chemotherapy. Part 3 of the study was a phase 2 extension that evaluated the pharmacokinetics of a higher-dose tablet in patients with solid tumors harboring a *BRCA* mutation. ARIEL2 was an open-label study of rucaparib in patients with platinum-sensitive, relapsed, high-grade ovarian cancer. Part 1 evaluated PFS as the primary endpoint and enrolled patients who had received at least 2 prior lines of chemotherapy. Part 2 evaluated ORR as the primary endpoint and enrolled patients who had received 3 to 4 prior lines of chemotherapy.

For the pooled data analysis, the safety population included 377 patients with ovarian cancer, including primary peritoneal and fallopian tube cancer. Sixty-two patients were from Study 10, and 315 were from ARIEL2. The efficacy population included 106 patients who had received 2 or more prior chemotherapy regimens, including at least 2 platinum-based regimens, and these patients had a deleterious germline *BRCA* mutation or somatic *BRCA* mutation. The analysis included 42 patients from Study 10 and 64 from ARIEL2. Patients in the safety and efficacy populations were scheduled to receive rucaparib at 600 mg twice daily, and had received at least 1 dose of the study drug. Patients had a median age of approximately 61 years (range, 31-86 years), and 61% had a performance status of 0. More than 80% of patients in both the efficacy and safety populations had epithelial ovarian cancer. In the efficacy population, 83.0% of patients had the germline *BRCA* mutation, 12.3% had the somatic *BRCA* mutation, and the origin was uncertain in 4.7%. In the safety population, 62.1% of patients carried the wild-type *BRCA* mutation, 28.6% of patients had the germline *BRCA* mutation, 6.1% had the somatic *BRCA* mutation, and the origin was uncertain in 3.2%.

In the efficacy population, 61.3% of patients had received 3 or more prior therapies of any type, and 43.4% had received 3 or more prior platinum-based therapies. The platinum-free interval was less than 6 months in 25.5% of patients, 6 to 12 months in 52.8%, and longer than 12 months in 21.7%. One-fourth of the patients had platinum-resistant or -refractory disease.

In this heavily pretreated population, rucaparib was associated with a median PFS of 10.0 months (95% CI, 7.3-12.5 months; range, 0.0 to 22.1+ months). The 6-month PFS rate was 79%, and the 12-month PFS rate was 41%. The ORR in the efficacy population was 53.8% (range, 43.8%-63.5%) and included 9 CRs, 48 PRs, and 36 patients with stable disease. Subgroup analysis showed lower response rates in patients with more prior lines of treatment and in those with platinum-resistant or -refractory disease. Similar outcomes were observed in patients with the germline vs somatic *BRCA* mutation and in patients with a mutation in *BRCA1* vs *BRCA2*. In the 57 patients who achieved a CR or PR, the median duration of response was 9.3 months (95% CI, 6.6-11.7 months; range, 1.7 to 19.8+ months).

The safety population included 377 patients. These patients had received a median of 2 prior chemotherapies (range, 1-7), and a median of 2 prior platinum-based chemotherapies (range, 1-5). The platinum-free interval was less than 6 months in 23.9% of patients, 6 to 12 months in 40.3%, and longer than 12 months in 34.2%. Grade 3/4 treatment-related AEs were

ABSTRACT SUMMARY Impact of Age on the Safety and Efficacy of Bevacizumab (Bev)-Containing Therapy in Patients (pts) With Primary Ovarian Cancer (OC): Analyses of the OTILIA German Non-Interventional Study on Behalf of the North-Eastern German Society of Gynaecological Oncology Ovarian Cancer Working Group

The OTILIA study (Ovarian Cancer Treatment First-Line With Avastin) is evaluating the real-world efficacy and safety of bevacizumab-containing regimens as first-line treatment for stage IIIB to IV ovarian cancer (Abstract 867P). The second interim analysis compared outcomes in patients younger than 70 years (n=429) vs those 70 years or older (n=284). In the younger vs the older cohort, median duration of bevacizumab exposure was 13.8 months vs 13.1 months, respectively. However, many patients were still receiving bevacizumab therapy at the time the study was reported. There were 363 patients who discontinued treatment. Discontinuation of bevacizumab owing to an AE of any grade occurred in 13% of the younger patients vs 18% of the older patients. Grade 3/4 AEs led to discontinuation in 7% and 9% of patients, respectively. Other common reasons for discontinuation included disease progression, completion of 15 months' documentation, and patient request. With 278 recorded PFS events, the median PFS was 21.7 months (95% CI, 20.7-22.8 months). For the younger vs the older cohort, median PFS was 22.6 months (95% CI, 21.3-23.9 months) vs 20.2 months (95% CI, 17.2-21.3 months). Based on Cox regression modeling, age did not influence PFS (HR, 1.11; 95% CI, 0.86-1.44; *P*=.43). Tolerability was similar for the 2 patient cohorts, based on similar rates of AEs of any grade, AEs of grade 3 or higher, types of AEs, and AEs leading to discontinuation of bevacizumab. Final analysis of the OTILIA trial will be performed in 2019.

observed in 46.9% of patients. Dose interruption owing to an AE occurred in 58.6% of patients, and dose reduction owing to a treatment-related AE occurred in 44.3% of patients. Discontinuation owing to a treatment-related AE occurred in 8.0% of patients. An AE leading to death occurred in 2.4% of patients. The most common AEs of any grade were nausea (76.9%), asthenia/fatigue (76.7%), and vomiting (46.2%). The most common grade 3/4 AEs were anemia (24.9%), increased alanine transaminase or aspartate transaminase (10.9%), and asthenia/fatigue (10.9%). Increases in levels of transaminase normalized over time as treatment continued. Myelodysplastic syndrome/acute myeloid leukemia was reported in less than 1% of patients.

Rucaparib is being evaluated in 2 ongoing phase 3 trials. The ARIEL3 study (A Study of Rucaparib as Switch Maintenance Following Platinum-Based Chemotherapy in Patients With Platinum-Sensitive, High-Grade Serous or Endometrioid Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer) is evaluating rucaparib as maintenance therapy, and ARIEL4 (A Study of Rucaparib Versus Chemotherapy *BRCA* Mutant Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Patients) is comparing rucaparib vs chemotherapy in patients with ovarian cancer that is resistant or partially sensitive to platinum therapy.[7,8]

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PiSARRO: A EUTROC Phase 1b Study of APR-246 With Carboplatin (C) and Pegylated Liposomal Doxorubicin (PLD) in Relapsed Platinum-Sensitive High-Grade Serous Ovarian Cancer (HGSOC)

The p53 protein is a key tumor suppressor and is encoded by the *TP53* gene.[1] In the presence of DNA damage or other cellular abnormalities, p53 induces activities such as cell cycle arrest, DNA repair, and apoptosis. Driver mutations in *TP53* have been observed in 96% of patients with high-grade serous ovarian cancer.[2] Although patients with high-grade serous ovarian cancer show a high response rate to first-line platinum therapy, most patients relapse and develop platinum resistance. Therapies that restore p53 activities, such as apoptosis, present a novel approach to treating patients with platinum-refractory or -resistant disease. APR-246 (PRIMA-1^{MET}) is a small molecule prodrug that covalently modifies mutated p53, forcing it into the wild-type conformation and restoring its ability to induce apoptosis and other activities.[3,4] In vitro studies have demonstrated the ability of APR-246 to increase tumor cell chemosensitivity by inhibiting thioredoxin reductase and other mechanisms. The prodrug has been used successfully to resensitize ovarian cancer cell lines to platinum drugs and doxorubicin. PiSARRO (p53 Suppressor Activation in Recurrent High Grade Serous Ovarian Cancer, a Phase Ib/II Study of Systemic Carboplatin Combination Chemotherapy With or Without APR-246) is a first-in-human study of APR-246 monotherapy. The study demonstrated cell cycle arrest, increased apoptosis, and increased transcription of p53 target genes in tumor cells from treated patients.[5] APR-246 achieved preliminary efficacy in 2 patients with hematologic malignancies. Treatment was generally well-tolerated.

The ongoing phase 1b/2 portion of the study is evaluating a 3+3 dose escalation of APR-246 to determine the recommended phase 2 dose in combination with pegylated liposomal doxorubicin and carboplatin.[6] APR-246 was administered intravenously at 35 mg/kg, 50 mg/kg, and 67.5 mg/kg over 6 hours on days 1 to 4; carboplatin (area under the curve [AUC] 5) and pegylated liposomal doxorubicin (30 mg/m^2) were administered on day 4. Treatment was administered in 28-day cycles for a maximum of 6 cycles. Eligible patients had relapsed high-grade serous ovarian cancer that was partially or fully platinum sensitive. (Partial sensitivity was defined as a platinum-free interval of 6 to 12 months. Full sensitivity was defined as a platinum-free interval from >12 months to 24 months.) Patients were required to have archival tumor specimens with positive nuclear staining for p53. Response was assessed by RECIST 1.1.[7] Following recruitment into the 3

ABSTRACT SUMMARY Principal Results of the Cancer of the Ovary Abiraterone Trial (CORAL): A Phase II Study of Abiraterone in Patients With Recurrent Epithelial Ovarian Cancer (CRUKE/12/052)

The prospective, multicenter, open-label, single-arm, phase 2 CORAL study (Cancer of the Ovary Abiraterone Trial) evaluated abiraterone in patients with recurrent ovarian cancer (Abstract LBA33_PR). Abiraterone is a CYP17 inhibitor of androgen biosynthesis that has been approved by the FDA for the treatment of prostate cancer. Enrolled patients were postmenopausal and had confirmed epithelial, ovarian, fallopian tube, or primary peritoneal cancer with evidence of disease progression within 12 months of the last systemic treatment. Patients received abiraterone (1000 mg) once daily plus prednisone/prednisolone (5 mg) twice daily in continuous 28-day cycles until progression. The 42 patients had a median age of 65 years, 88% had high-grade serous histology, and 47% had received 3 or more prior lines of therapy. At baseline, hormone receptor status was positive for the estrogen receptor, progesterone receptor, or androgen receptor in 92.1%, 59.5%, and 69.0% of cases, respectively. One patient with low-grade serous histology and positive androgen receptor expression achieved a response that lasted 47 weeks. Eleven patients (26%) achieved a clinical benefit from abiraterone treatment. Abiraterone therapy was delayed or interrupted in 10 patients (23.8%). The most common grade 3/4 AEs were hypertension (29%), abdominal pain (14%), and hypokalemia (10%). The trial was closed early based on a lack of adequate benefit. Detailed characterization of the patients who did achieve a clinical benefit is underway.

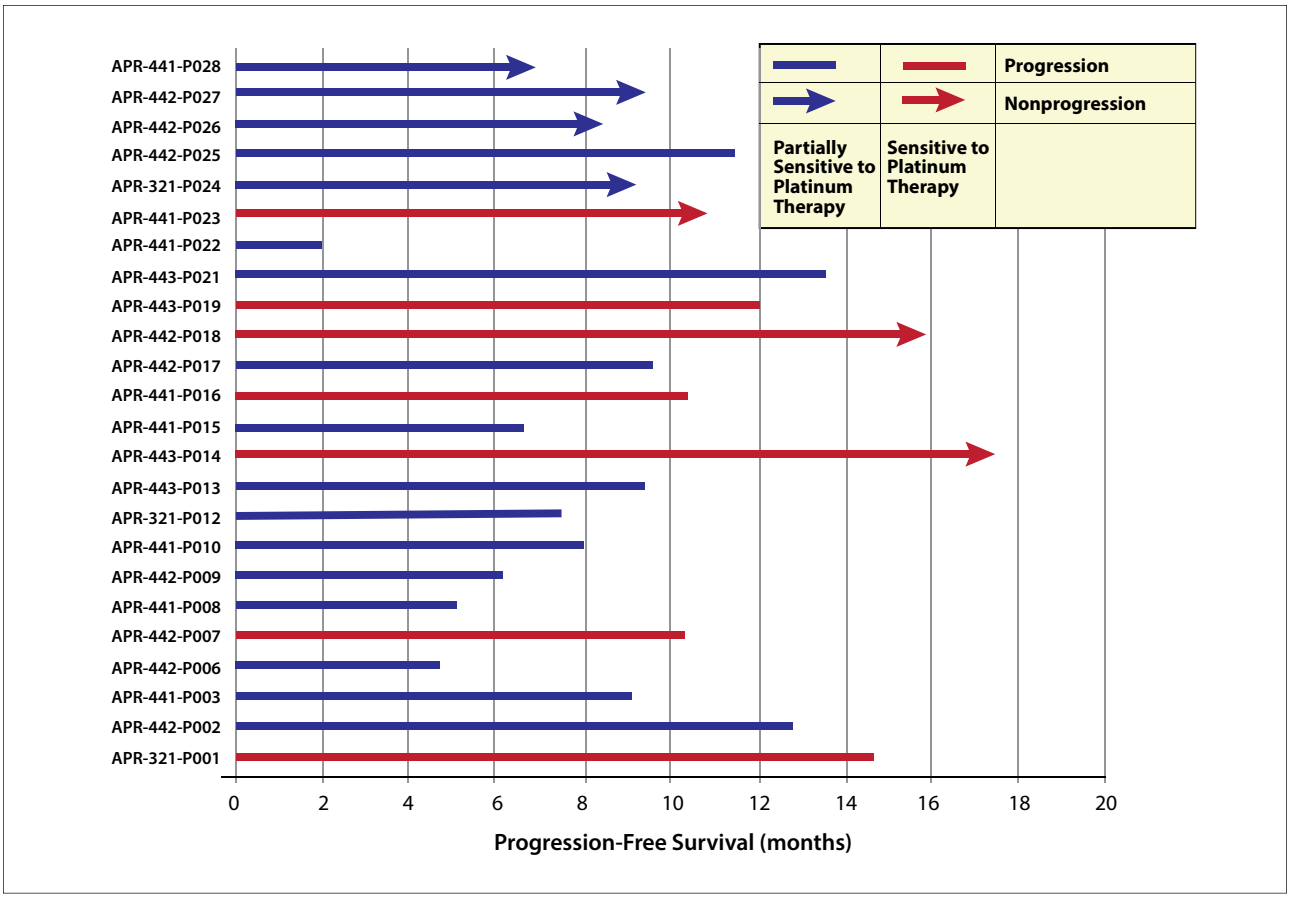

Figure 6. Progression-free survival in a phase 1b/2 study of APR-246. Adapted from Basu B et al. ESMO abstract 386P.[6]

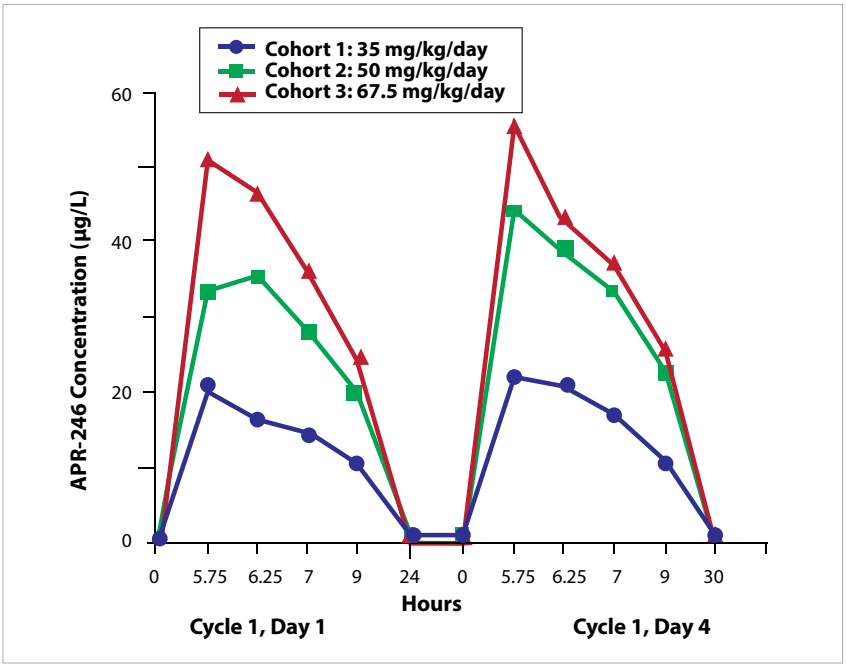

Figure 7. The pharmacokinetic profile of APR-246 in a phase 1b/2 study. The samples were taken on day 1 and day 4 of cycle 1. Adapted from Basu B et al. ESMO abstract 386P.[6]

dose cohorts, patients were enrolled into level 1 and level 3 dose cohorts for further evaluation of safety and efficacy. Exploratory studies included *TP53* gene sequencing, assessment of circulating tumor DNA, and analysis of mRNA and protein expression.

Recruitment goals were met for the 3 dose cohorts. Eighteen patients had partially platinum-sensitive disease, 10 had fully platinum-sensitive disease, and 26 had received more than 1 cycle of treatment. A dose-limiting toxicity, ruptured diverticulum, led to an expansion of the dose level 2 cohort to include 6 patients. The most common treatment-emergent AEs of any grade were nausea (68%), fatigue (64%), and neutropenia (61%). Reversible AEs related to the central nervous system were also among the most common, and included dizziness (64%), dysgeusia (32%), and headache

(29%). Across the dose level cohorts 1, 2, and 3, the proportions of patients with a grade 3/4 treatment-emergent AE were 77.8%, 83.3%, and 69.2%, respectively, consistent with a lack of dose-dependency. APR-246 showed low interpatient and intrapatient variability, with linear pharmacokinetics and no accumulation.

Of the 21 evaluable patients with radiologically measurable lesions, 3 had a confirmed CR, 10 had a confirmed PR, and 8 had stable disease. Of 2 patients with nonmeasurable disease, 1 had a CR and 1 had progressive disease. The median PFS for 22 evaluable patients was 316 days (95% CI, 280-414 days). PFS was similar for patients with fully or partially platinum-sensitive disease and was independent of the dose cohort (Figure 6). Sequencing of tumor DNA from 22 patients revealed *TP53* mutations in 100% of samples. The highest dose level of APR-246, 67.5 mg/kg, was chosen as the recommended phase 2 dose for use in combination with carboplatin and pegylated liposomal doxorubicin (Figure 7). Patients with recurrent high-grade serous ovarian cancer are now being recruited to the randomized phase 2 portion of the study to evaluate carboplatin plus pegylated liposomal doxorubicin with or without APR-246.

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Use of Bevacizumab (bev) in Real Life for First-Line (fl) Treatment of Ovarian Cancer (OC). Part 1: The ENCOURAGE Cohort of 1158 Patients (pts) by GINECO

Two phase 3 trials, GOG-0218 (Gynecologic Oncology Group study 0218) and ICON7 (Carboplatin and Paclitaxel With or Without Bevacizumab in Treating Patients With Newly Diagnosed Ovarian Epithelial Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cavity Cancer), investigated first-line bevacizumab plus chemotherapy in patients with ovarian cancer.[1,2] Together, the trials evaluated 3401 women. The studies met their primary endpoints, showing that PFS was increased by adding bevacizumab to chemotherapy and using bevacizumab maintenance. In trial GOG-0218, median PFS was increased to 14.1 months with bevacizumab vs 10.3 months for the control arm (P<.001).[2] In ICON7, the addition of bevacizumab to chemotherapy yielded a median PFS of 24.1 months vs 22.4 months for chemotherapy alone (P=.004) at 42 months.[1] In the subgroup of patients at high risk of progression, PFS was 18.1 months with bevacizumab vs 14.5 months without (P=.002).[1] In December 2011, bevacizumab gained approval in the European Union for first-line treatment of ovarian cancer in combination with carboplatin and paclitaxel in newly diagnosed ovarian cancer.

The ENCOURAGE trial (First Line Ovarian Cancer Treatment - Cohort Study) was conducted to assess the safety of first-line bevacizumab in ovarian cancer patients treated in a real-world setting.[3] Enrolled patients were adults with ovarian, fallopian tube, or primary peritoneal cancer whose first-line treatment included bevacizumab. The primary endpoint was to evaluate the cardiovascular, renal, and digestive toxicities of bevacizumab in this setting. The study included consecutive patients from 102 treatment centers in France, including academic hospitals, private hospitals, private clinics, and oncology centers.

Of 1158 evaluable patients, 557 (48%) had received first-line bevacizumab and 601 (52%) had not. Among the latter group, reasons provided for not administering first-line bevacizumab included age or comorbidity (29%), International Federation of Gynecology and Obstetrics stage and residue (27%), neoadjuvant strategy (22%), inclusion in another

Table 2. Adverse Events in Patients Who Did or Did Not Receive Bevacizumab in a Real-World Analysis

Comorbidity	Bevacizumab	
	Not Received (n=601)	Received (n=557)
Alteration of general status	19	0
Digestive trouble (eg, subocclusive disease, Crohn's disease)	7	0
Venous thrombosis	33	36
Renal/liver insufficiency	5	0
Wound healing issue (eg, bedsores, colostomy, fistula, peritonitis)	27	5
Bleeding	4	10
Cardiovascular disorders (eg, stroke, cardiac rhythm disorder, cardiac failure)	21	33
Other comorbidities (eg, meningioma, lupus neuropathy)	6	0

Adapted from Berton-Rigaud D et al. ESMO abstract 895P.[3]

trial (13%), progressive disease or death (3%), and patient refusal (2%). Among patients who received the angiogenesis inhibitor, bevacizumab was administered with carboplatin in 99% of cases and with paclitaxel in 98%, and the bevacizumab dose was 15 mg/kg in 80.2% of cases. Characteristics associated with the use of bevacizumab included age older than 70 years (used in 71%), use of neoadjuvant therapy (used in 65%), and stage IIIb to IV disease with no residue after initial surgery (used in 60%). Factors associated with not using bevacizumab included stage I to IIIa disease (not used in 87%) and comorbidities (not used in 57%). Bleeding, cardiovascular disorders, and venous thrombosis were more common among the patients who received bevacizumab (Table 2).

ABSTRACT SUMMARY Phase I Dose of Oral Quisinostat, in Combination With Gemcitabine (G) and Cisplatin (Cis) or Paclitaxel (P) and Carboplatin (Carbo) in Patients (pts) With Non-Small Cell Lung Cancer or Ovarian Cancer (OC)

A phase 1 study was conducted to determine the maximum tolerated dose of quisinostat, an oral histone deacetylase inhibitor, in patients with ovarian cancer or non–small cell lung cancer (Abstract 387P). Quisinostat has been shown to halt the proliferation of paclitaxel-resistant cells. Patients with ovarian cancer received paclitaxel (175 mg/m^2) and carboplatin (AUC 5) on day 7 of each cycle plus escalated doses of quisinostat (8 mg, 10 mg, and 12 mg) on days 1, 3, 5, 7, 9, and 11 of a 3-week cycle. Ovarian cancer patients were required to have received no more than 3 prior modes of anticancer drug therapy and had no resistance to paclitaxel. The study included 18 patients with ovarian cancer. No dose-limiting toxicities were observed in any of the cohorts; thus the maximum tolerated dose was not established. The 12-mg dose of quisinostat was chosen as the recommended phase 2 dose in combination with paclitaxel and carboplatin. Of 16 evaluable patients with ovarian cancer, 6 (37.5%) achieved a response, most of whom had platinum-resistant disease. The median time to progression for the patients with ovarian cancer had not been reached at the time the study was reported.

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Highlights in Ovarian Cancer From the 2016 ESMO Congress: Commentary

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The 2016 Congress of the European Society for Medical Oncology (ESMO) provided data of immense scientific value. The presentation of numerous abstracts was accompanied by simultaneous publication in the *New England Journal of Medicine* and other journals. In ovarian cancer, results from the NOVA trial (A Maintenance Study with Niraparib Versus Placebo in Patients with Platinum Sensitive Ovarian Cancer) provided the strongest data in 30 years.[1,2] Other studies in ovarian cancer evaluated promising therapies with novel mechanisms of action, and provided analyses of the real-world use of bevacizumab.

The NOVA Trial

Until now, the introduction of cisplatin in the 1980s represented the last major advance in the management of ovarian cancer.[3] The subsequent addition of paclitaxel and bevacizumab to the treatment armamentarium provided minimal improvement.[4,5] I presented results of the phase 3 NOVA trial, which evaluated the selective poly(ADP-ribose) polymerase 1/2 (PARP1/2) inhibitor niraparib as maintenance therapy in patients with platinum-sensitive ovarian cancer.[1] The median progression-free survival (PFS) was 21.0 months with niraparib vs 5.5 months with placebo in the cohort of patients with the germline *BRCA* mutation. At 18 months after the end of treatment, PFS was 50% in patients who received niraparib vs 16% in patients who received placebo. In patients with the non–germline *BRCA* mutation, the median PFS was 9.3 months with niraparib vs 3.9 months with placebo. At 18 months, PFS was 30% for niraparib vs 12% for placebo.

The NOVA trial is the first phase 3 trial of a PARP inhibitor in ovarian cancer. PARP inhibitors are a strong class of drugs for ovarian cancer. The results of the NOVA trial have set a high bar for the approval of new therapies in this setting.

An interesting aspect of the NOVA trial is that it enrolled platinum-sensitive patients with high-grade serous or high-grade endometrial cancer, which includes 70% of the population. There was clinically meaningful efficacy in the whole population. The trial also assessed efficacy according to 2 cohorts. The cohort of patients with the germline *BRCA* mutation, which is approximately 15% of the entire population, had a hazard ratio of 0.27. Among the remaining patients—those with a non–germline *BRCA* mutation—the hazard ratio was 0.45, which is extremely positive. Assessment of another primary endpoint involved testing for homologous recombination deficiency (HRD) in the non–germline *BRCA* population. Among the HRD-positive population, the hazard ratio was 0.38, which is remarkable.

During the data analysis, the positive results raised a few questions. The non–germline *BRCA* population, which is a heterogeneous group, was divided into HRD-positive and HRD-negative patients. Within the HRD-positive group, there was a small somatic *BRCA*-mutation population, and the rest were so-called *BRCA* wild-type. Although the numbers were small, an exploratory analysis was performed on both these groups. For the somatic *BRCA* patients, the hazard ratio was 0.27, which is similar to the patients with the germline *BRCA* mutation. For the remaining patients—those with the *BRCA* wild-type mutation who were HRD-positive—the hazard ratio was 0.38, which was similar to the entire group. This analysis suggests that the strong results seen among patients with HRD-positive disease were not driven by the subset with the somatic *BRCA* mutation, but by the entire group.

HRD testing was included in the NOVA trial to identify likely responders and nonresponders, and to see whether this test could be used as a companion diagnostic tool. It ended up that the patients expected to be nonresponders did achieve a clinically meaningful response. Among HRD-negative patients, median PFS was 6.9 months with niraparib vs 3.8 months with placebo, for a hazard ratio of 0.58. We found that the median was less relevant than the separation between the Kaplan-Meier curves, which continued throughout the follow-up period, thus indicating long-term response.

One-fifth of patients did not relapse and were still receiving niraparib at 18 months. This finding is clinically meaningful.

The question is: What is the role of the HRD test? It cannot be used as a companion diagnostic tool. Patients with HRD-positive disease have a better chance for response. The test does not indicate, however, which HRD-negative patients will or will not respond to treatment. The HRD test might be used as a supplementary test, but a better tool is still needed for these patients. In a study from The Cancer Genome Atlas, HRD testing captured 95% of mutations and scarring.[6] It is not known, however, whether there are other mechanisms that are responsible for PARP efficacy. It is necessary to find a better test to distinguish between responders and nonresponders. Until that time, it seems likely that niraparib should be administered to all patients in this setting.

Another important question concerns the long-term responders. Quite a few patients remained on treatment and responded for a long time. We need to find a way to identify those patients likely to achieve a long-term response.

Other Novel Therapies

A phase 2 study by Dr Jung-Min Lee trial provided compelling data on prexasertib monomesylate monohydrate, the first checkpoint kinase 1 and 2 inhibitor tested in ovarian cancer.[7] Among the 6 evaluable patients with a germline *BRCA* mutation, 4 patients (67%) achieved stable disease lasting at least 4 months. The median response duration was 4 months (range, 4-5 months). None of these patients achieved a complete or partial response. Among the 20 evaluable patients with high-grade serous ovarian cancer, 7 (35%) achieved a partial response, and 5 (25%) achieved stable disease. There were no complete responses in this subgroup. Development of prexasertib monomesylate monohydrate is in an early stage, and randomized phase 3 trials are forthcoming.

Dr Ignace Vergote presented the results from a study evaluating selinexor, a first-in-class selective inhibitor of exportin 1, a nuclear exporter.[8] Selinexor retains the good molecules, such as p53 and IκB, within the nucleus. This fairly large, phase 2 trial enrolled patients with ovarian, endometrial, or cervical cancer. The trial provided compelling results for patients with ovarian and endometrial cancer. Among these patients, nearly half had disease control for more than 12 weeks. A phase 3 trial is being planned for patients with endometrial cancer.

Dr Rebecca Kristeleit provided data from Study 10 and ARIEL2 (A Study of Rucaparib in Patients With Platinum-Sensitive, Relapsed, High-Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer), which evaluated the PARP inhibitor rucaparib in patients with ovarian cancer and a *BRCA* mutation.[9] The patients had active disease and were not receiving maintenance therapy. The study showed very strong responses to rucaparib. Like all PARP inhibitors, rucaparib was well-tolerated. There were some specific toxicities, but nothing compared to what is seen with chemotherapy. Most patients remained on treatment, which implies that the drug is well-tolerated. A weakness to the data is that they were drawn from a combined analysis of subgroups of patients from 2 nonrandomized studies. Assessment of rucaparib will require results from a randomized study. Data from the randomized, phase 3 ARIEL3 trial will be available by the end of 2017.[10]

The ICON8 trial (Weekly Chemotherapy in Ovarian Cancer) evaluated weekly carboplatin and paclitaxel in the first-line management of ovarian cancer.[11] The results showed that this regimen is feasible and safe. We await the efficacy results, which should be available in 2017. This important trial was difficult to run because it lacked support from industry. If the results are positive, the use of bevacizumab will drastically decrease.

The nanoparticle–drug conjugate CRLX101 was studied in combination with weekly paclitaxel in a phase 1b/2 study of patients with platinum-resistant ovarian cancer.[12] This therapy

ABSTRACT SUMMARY An Investigator Initiated Phase I Study Combining the Dual mTORC1/2 Inhibitor AZD 2014 in Combination With Weekly Paclitaxel in High-Grade Serous Ovarian Cancer

The phase 1 TAX-TORC study is examining vistusertib (AZD2014) plus weekly paclitaxel in patients with high-grade serous ovarian cancer (Abstract 362PD). Vistusertib is a dual inhibitor of the mTORC1 and mTORC2 serine/threonine kinases, members of a pathway involved in resistance to taxane treatment. The investigator-initiated study included 25 patients with high-grade serous ovarian cancer and a median 3 (range, 1-10) prior lines of treatment. All patients had received prior paclitaxel. Ninety-six percent of patients had relapsed within a year of the most recent treatment. Treatment was generally well-tolerated. The most common grade 1/2 AEs were fatigue (68%), skin rash (48%), diarrhea (44%), and neuropathy (44%). The most common grade 3/4 AEs were neutropenia (16%), vomiting (12%), and skin rash (8%). The CA-125 response rate was 56%, and the RECIST 1.1 response rate was 48%. The preliminary median PFS was 6.7 months, and 9 patients remained on-study when the data were reported. The recommended phase 2 dose and schedule is paclitaxel at 80 mg/m^2 weekly plus vistusertib at 50 mg twice daily, 3 days per week, administered for 6 of 7 weeks.

delivers camptothecin directly to the tumor tissue, and provides a new mechanism of action for the treatment of ovarian cancer. CRLX101 showed signs of antitumor activity, with very few adverse events. The phase 2 portion of the study has been expanded. A phase 3 trial is being planned for 2017. It will be interesting to see more data for this therapy.

The phase 1 TAX-TORC study evaluated the dual mammalian target of rapamycin complex (mTORC) inhibitor vistusertib (AZD2014) in combination with weekly paclitaxel in patients with high-grade serous ovarian cancer.[13] The regimen was well-tolerated, and was associated with a RECIST response rate of 48%. Phase 2 and 3 trials of this combination are accruing and should provide more information about whether it is effective.

Dr Bristi Basu presented results from the phase 1b PiSARRO trial (p53 Suppressor Activation in Recurrent High Grade Serous Ovarian Cancer, a Phase Ib/II Study of Systemic Carboplatin Combination Chemotherapy With or Without APR-246) of APR-246, a small molecule prodrug, with carboplatin and pegylated liposomal doxorubicin.[14] APR-246 is an interesting drug with a novel mechanism; it stabilizes mutant p53 into a wild-type conformation. The study showed promising efficacy, with high response rates. A phase 2 trial is underway.

Bevacizumab

Dr Alexander Mustea presented results from a study assessing the impact of age on the safety and efficacy of bevacizumab among patients in Germany.[15] It found that age did not influence outcome. Although the results are interesting, they are unlikely to change clinical practice. Management practices are culture-based, so findings from this German study may not be applicable to other countries. Results from this trial support my use of bevacizumab in older patients.

The ENCOURAGE trial (First Line Ovarian Cancer Treatment - Cohort Study) evaluated the real-life use of bevacizumab as first-line treatment for ovarian cancer in France.[16] It showed that most patients received bevacizumab according to the labeled indication, but there was some variability among patients with comorbidities and those older than 70 years. This is a phase 4 trial, and although the results are important, they are specific to France, where the trial was conducted.

Disclosure

Dr Mirza serves on the Board of Directors of Karyopharm, the manufacturer of selinexor.

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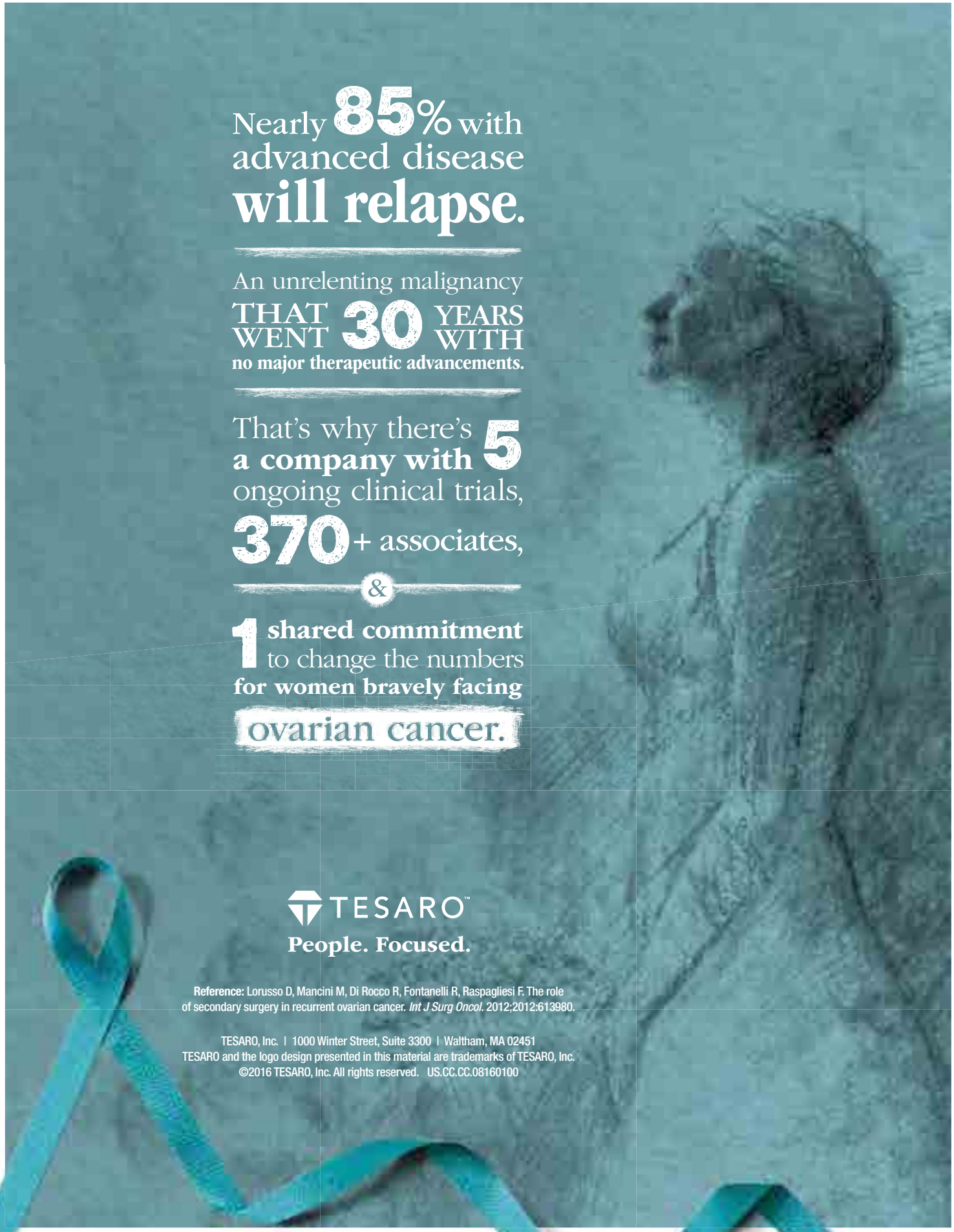

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