STUDY REPORT SYNOPSIS

Study Title	Real-World Treatment Patterns, BRCA Testing Practices, Outcomes, and Health Care Utilization in Platinum-Sensitive Recurrent Serous Ovarian Cancer: A Multi-Country Retrospective Study
AstraZeneca Study Number	D0816R00004
Medicinal Products	Not applicable; this is a retrospective, non-interventional study
Background	Platinum-based chemotherapy is considered standard treatment for platinum-sensitive recurrent ovarian cancer (PS-ROC). Standard treatments and new targeted agents continue to be evaluated on survival and other clinical endpoints in trial settings. However, data on PS-ROC treatment patterns and survival in real-world settings (i.e., routine practice) are limited. Such data are needed to inform health-health technology and reimbursement assessments of standard and new treatments.
Objectives	**Primary Objective** 1. To describe in a multinational, real-world population, treatment patterns for women with PS-ROC. **Secondary Objectives** 1. Estimate the proportion of women with PS-ROC who were tested for BRCA mutations. 2. Among women who were tested for BRCA mutations, document the testing method used (e.g., direct DNA sequencing, single-strand conformation polymorphism, etc.), estimate the distribution of BRCA mutation status (BRCAm or BRCA wild type) among those tested, and among those with BRCAm, the distribution of mutation type (BRCA1m vs. BRCA2m). 3. Describe demographic and clinical characteristics of women diagnosed with PS-ROC, stratified by whether BRCA mutation testing was done and, among women who were tested, by BRCA mutation status (BRCA1m, BRCA2m, BRCA wild type, or BRCA inconclusive, or BRCA result unavailable). 4. Estimate overall survival (OS) for women diagnosed with PS-ROC from initial ovarian cancer diagnosis and from start of treatment for platinum-sensitive recurrence until death or end of available follow-up, stratified by BRCA mutation status. 5. Describe overall cancer-related health care utilization patterns (percentage of patients with and number of hospitalizations, emergency room visits, physician follow-up visits, treatments) from first date of platinum-sensitive recurrence until death or end of available follow-up, stratified by BRCA mutation status. 6. Document the background prevalence (within 12 months preceding the date of platinum-sensitive recurrence) of selected medical conditions and comorbidities of interest, stratified by BRCA mutation status. 7. Estimate rates of selected treatment- and/or disease-related side effects (febrile neutropenia, neutropenia requiring hospitalization, nephrotoxicity, new or worsening neuropathy, platinum hypersensitivity, myelodysplastic syndrome, acute myeloid leukemia (AML), other new primary malignancies

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	excluding non-melanoma skin cancers) from first date of platinum-sensitive recurrence until death or end of available follow-up, stratified by BRCA mutation status.
Study Design	This study was a retrospective, non-interventional observational review of medical records for patients in multiple countries diagnosed with PS-ROC. We retrospectively reviewed a sample of anonymized medical records from 13 countries to assess PS-ROC treatment patterns, survival, and other clinical outcomes. Countries included in the study were: United Kingdom [UK]; Canada [CAN]; Netherlands [NL]; Germany [GER]; Spain [SP]; Italy [IT]; South Korea [SK]; Belgium [BE]; Switzerland [SW]; Portugal [PO]; Australia [AU]; France [FR]; and Israel [IS].
Inclusion Criteria and Statistical Methods	Women determined to have serous PS-ROC (with a progression-free interval of ≥6 months after first-line platinum completion) during 2009-2013 were selected, with the study index date defined as PS-ROC diagnosis date. Background patient and disease characteristics, as well as first-line treatments were evaluated as pre-index history. Second- or later-line treatments and other downstream endpoints (including survival) and were assessed from index until death or last medical record. Analyses were descriptive and exploratory in nature. Event time endpoints were analyzed using the Kaplan-Meier method.
Data Collection Procedures	Study recruitment was physician-based, whereby physicians (primarily oncologists) were recruited for study participation from national provider directories in each country. Through these physicians, patients' medical records were screened on the basis of specific inclusion criteria (described above) in order to obtain the analysis population of interest. The participating physicians directly entered anonymized patient data into an electronic case report form (eCRF) via a secure Web-based data collection portal.
Results	**Patient Characteristics** Country-specific results are presented in the main body of this report. In total, 2,113 patients were analyzed (mean [standard deviation (SD)] and median age at index: 60 [11] and 60 years, respectively). The majority of patients (59%) were still alive at the time of the medical record abstraction (41% were deceased). Median total follow-up duration, from the study index date until the earlier of death (for deceased patients) or last medical record (for patients still alive) was 20 months. **BRCA Testing** A total of 456 patients (22%) were recorded as having received a BRCA test at any point in their medical history. Of those, 430 patients had a conclusive result available. Among the patients with a test performed and a conclusive result available, 126 (29%) were recorded as BRCA-positive (1m or 2m), with the remaining 304 patients (71%) recorded as BRCA-negative (wild-type). In the entire study sample (n = 2,113), including patients with and without BRCA testing, approximately 6% were recorded as BRCA-positive. **Initial Therapy Course** IV carboplatin + IV paclitaxel was, by far, the most commonly reported first-line chemotherapy regimen (75% of patients), as expected based on current guidelines. The next most common regimens were IV carboplatin + IV paclitaxel + bevacizumab (7%) and IV carboplatin monotherapy (7%). The distribution of first-line therapy regimens did not differ appreciably by BRCA testing or result status.

Mean (SD) and median duration of first line IV carboplatin + IV paclitaxel therapy was 5 (2) and 5 months, respectively; over this duration, mean (SD) and median number of cycles administered was 6 (1) and 6 cycles, respectively.

One hundred eighty-one patients (9% of the study sample) received maintenance therapy after first-line completion; bevacizumab was the maintenance agent used in 150 (83%) of these patients. Among the 150 patients receiving bevacizumab, mean (SD) and median duration of the maintenance regimen was 6 (4) and 6 months, respectively; over this duration, mean (SD) and median number of bevacizumab cycles administered was 10 (6) and 9 cycles, respectively.

Second-Line Treatment (Relapse Setting)

Following the study index date (first determination of PS-ROC), approximately three-quarters of patients (74%) initiated a second-line systemic therapy. While second-line therapy involved retreatment with a platinum-based regimen in nearly all cases, the distribution of specific regimens initiated in the second-line setting was more varied as compared with first-line. Among patients receiving second-line therapy, IV carboplatin + IV paclitaxel was the most common regimen initiated (28% of second-line initiators), followed by IV carboplatin + gemcitabine (15%), IV carboplatin monotherapy (9%), and IV carboplatin + bevacizumab + gemcitabine (8%). Patients initiating second-line therapy generally did so quickly after determination of having PS-ROC: mean [SD] and median time to second-line initiation from the index date was 2 [4] and 0 months, respectively. (Note: 0 months indicates initiation of second-line treatment within the *same* month as the study index date). For the common second-line regimens, therapy duration was generally between 5 and 6 months at the median.

Best Response to Second-Line Therapy

Among patients initiating second-line therapy (n = 1,568), for all second-line regimens combined, 74% of patients had an objective response to therapy (33% complete response, 41% partial response). Stable disease was recorded as best response to second-line therapy in 14% of patients, while progressive disease was recorded as best response in 10%; best clinical response was unknown for 2% of second-line initiators. Median time to best response, for all second-line regimens combined, was 4 months.

Progression-Free Survival

Among patients initiating a second-line therapy, 63% were observed to have a clinical progression event or death during the available follow-up time. Without adjustment for censoring, examining only patients with a progression event, median time to progression (among those observed to progress) was 10 months (mean [SD] = 11 [9] months). Assessed via Kaplan-Meier (including adjustment for censoring), median (95% confidence interval [CI]) PFS was 15 (14, 16) months; first quartile (95% CI) PFS was 8 (7, 8) months. Examining the two most common second-line regimens (IV carboplatin + IV paclitaxel and IV carboplatin + gemcitabine), crude median PFS (among only patients with a progression event) was 11 and 9 months, respectively. Median (95% CI) PFS for these regimens from Kaplan-Meier estimation was 15 (14, 18) and 15 (12, 17) months, respectively.

Overall Survival

In total, 866 patients (41%) died before the medical record abstraction date. Based on Kaplan-Meier estimation, median (95% CI) OS from initial ovarian cancer diagnosis was 69 (63, 72) months. Median (95% CI) OS from the study index date

was 36 (34, 40) months. Second-line therapy initiators had a median (95% CI) OS from second-line initiation of 37 (34, 41) months, as compared with 30 (24, 36) months among patients who did not receive second-line therapy. For the most common second-line regimen observed, IV carboplatin + IV paclitaxel, first quartile (95% CI) OS and median (95% CI) OS were 25 (20, 30) and — (46, —) months, respectively (median not reached). Examining the Kaplan-Meier survival curves in Figures ALL1a-2c, there appeared to be no statistically significant difference by BRCA status in OS from either initial ovarian cancer diagnosis or from initiation of second-line systemic therapy.

Disease-Related Resource Utilization

In the recurrence setting, during all available follow-up from the study index date (median 20 months), more than half (54%) of patients had at least one ovarian cancer-related hospitalization. Mean (SD) and median number of disease-related hospital admissions per patient were 3 (7) and 1, respectively, with a range of 0 to 101. Thirty-seven percent of patients had at least one disease-related emergency room encounter during follow-up (mean [SD] and median number of encounters: 1 [2] and 0, respectively). Office visits/consults and hospital outpatient/day visits were both prevalent (72% and 57%, respectively) and frequent (mean [SD] number of encounters: 12 [16] and 7 [10] per patient, respectively). Key cancer-related supportive therapies were also prevalent in the post-index follow-up period; among the most prevalent were antiemetics (72%), pain medications (54%), antibiotics (39%), red blood cell transfusions (34%), and granulocyte-colony stimulating factors (30%).