AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00019
Edition Number	3
Date	31 July 2013

Phase II randomised, double blind, multicentre study to assess the efficacy of AZD2281 in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with two or more platinum containing regimens

Study dates: First subject enrolled: 28 August 2008
Last subject enrolled: 9 February 2010
58% interim overall survival data cut-off: 26 November 2012

Phase of development: Therapeutic exploratory (II)

International Co-ordinating Investigator:
Sponsor's Responsible Medical Officer:

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

This is an updated Clinical Study Report Synopsis and replaces the previous version dated 26 July 2011, which reported the primary progression free survival analysis (data cut-off 30 June 2010). This updated version includes an overall survival analysis at 58% data maturity, and extensive analyses of the subpopulation of patients with *BRCA* mutations, as this has been confirmed as the subpopulation of patients who receive the greatest benefit from treatment with olaparib.

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centre(s)

This was an international multicentre study conducted in 82 sites in 16 countries: Australia (7), Belgium (2), Czech Republic (1), Estonia (1), Germany (8), Israel (7), Canada (3), France (5), Netherlands (1), Poland (7), Romania (3), Russia (6), Spain (5), Ukraine (7), UK (8), USA (11).

Publications

Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer. N Engl J Med 2012;366:1382-92.

Objectives and criteria for evaluation

The study objectives and criteria for evaluation reported in this synopsis are summarised in Table S1.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To determine the efficacy (assessed by PFS) of olaparib (capsule formulation) compared to placebo in the overall population.	PFS	Efficacy
Secondary	**Secondary**	
To determine the efficacy of olaparib (capsule formulation) compared to placebo by assessment of OS, best overall response and response rate (RECIST, CA-125, RECIST or CA-125), disease control rate, duration of response, change in tumour size, time to progression by CA-125 or RECIST.	OS, best overall response, response rate (RECIST, CA-125 [GCIG criteria], RECIST or CA-125), disease control rate[a], duration of response, change in tumour size at Weeks 12 and 24, time to progression by CA-125 or RECIST.	Efficacy
To determine the safety and tolerability of olaparib (capsule formulation) compared to placebo.	AEs, physical examination, vital signs including BP and pulse, ECG and laboratory findings including clinical chemistry, haematology and urinalysis.	Safety
To determine the effects of olaparib (capsule formulation) compared to placebo on disease related symptoms.	Disease-related symptoms: time to worsening and improvement/no change/worsening rates measured by FOSI, defined as the sum of 8 FACT-O items.	HRQL
To determine the quality of life of patients treated with olaparib (capsule formulation) compared to placebo.	Health-related quality of life: time to worsening and improvement/no change/worsening rates measured by TOI (primary HRQL endpoint; derived from FACT-O) and total FACT-O.	HRQL

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Intermediate clinical endpoints to evaluate whether PFS benefits are maintained with longer follow up, and to determine whether the PFS benefit is maintained beyond first progression. (These analyses were added at the time of the 58% interim OS analysis in response to the request from European regulatory agencies because PFS and PFS2 data were not collected after the primary PFS analysis.)	**Time to discontinuation of olaparib/placebo treatment (TDT):** the time from randomisation to discontinuation of olaparib/placebo treatment or death. **Time to first subsequent therapy or death (TFST):** the time from randomisation to the start date of the first cancer therapy received following the discontinuation of olaparib/placebo treatment or death. **Time to second subsequent therapy or death (TSST; an approximation of PFS2):** the time from randomisation to the start of a patient's second cancer therapy subsequent to the discontinuation of olaparib/placebo treatment or death.	Efficacy

[a] Defined as the percentage of patients who had at least 1 confirmed visit response of CR or PR or demonstrated SD or NED for at least 23 weeks (i.e. 24 weeks ± 1 week) prior to any evidence of progression.

AE Adverse event; BP Blood pressure; *BRCA* Breast Cancer Susceptibility Gene; DNA Deoxyribonucleic acid; ECG Electrocardiogram; CA-125 Cancer Antigen (CA)-125; CSR Clinical Study Report; GCIG Gynaecologic Cancer InterGroup; HRQL Health related quality of life; FACT-O Functional Analysis of Cancer Therapy – Ovarian; FOSI FACT/NCCN Ovarian Symptom Index; HRQL Health-related quality of life; NCCN National Comprehensive Cancer Network; OS Overall survival; PFS Progression free survival; RECIST Response Evaluation Criteria in Solid Tumours; TOI Trial outcome index.

Study design

The study was a randomised, double blind, multi-centre study in platinum sensitive high grade serous ovarian cancer patients who had received 2 or more previous platinum-containing regimens. Platinum-sensitivity was defined as disease progression greater than 6 months after completion of their penultimate platinum regimen (from last dose) prior to enrolling on this study. In the last platinum regimen prior to enrolling on this study, patients had to demonstrate an objective stable maintained response (complete response [CR], or partial response [PR] by Gynaecologic Cancer InterGroup [GCIG] and/or Response Evaluation Criteria in Solid Tumours [RECIST]) and this response had to be maintained to allow entry to the study. Patients had to be treated on the study within 8 weeks of completion of their final dose of the platinum-containing regimen. Patients were randomised in a 1:1 ratio (olaparib:matching placebo) to receive either olaparib 400 mg twice daily (bd) capsules or olaparib matching placebo bd capsules.

Target subject population and sample size

It was intended to randomise a total of 250 patients (125 in each group) with advanced platinum-sensitive serous ovarian cancer who had received 2 or more previous platinum-containing regimens and demonstrated an objective stable maintained response in the last platinum regimen prior to enrolment on the study, with an estimated life expectancy of at least 16 weeks and an Eastern Co-operative Oncology Group (ECOG) performance status (PS) of 0 to 2.

The primary analysis was to be performed when a total of 137 progression free survival (PFS) events had been observed in the overall population: this was reported in the synopsis dated 26 July 2011 with 153 progression events. If the true hazard ratio (HR) was 0.75 (likely to correspond to a 33% increase in median PFS from 9 to 12 months) and the overall type I error rate was 20% (1-sided), there would be approximately 80% power to demonstrate a promising difference in favour of olaparib (ie, $p<0.2$, 1-sided).

The eligible population for this study (platinum sensitive high-grade serous ovarian cancer patients in response to a platinum-containing therapy) was chosen based on olaparib clinical and nonclinical data and supportive literature evidence available at the time the study commenced. Knowledge of *BRCA* mutation status prior to study entry was not mandated, as it was considered that the study population would already be suitably enriched by patients with tumours with homologous recombination deficiencies likely to benefit from polyadenosine 5' diphosphoribose polymerase (PARP) inhibition with olaparib. Initial subgroup analyses of the primary variable for this study, PFS, indicated promising results in the small number of patients (97/265) for whom locally assessed germline *BRCA* (g*BRCA*) status was recorded on their case report form (CRF) (as reported in the synopsis dated 26 July 2011). In order to investigate this effect further in a larger sample size of patients with known *BRCA* mutation status, further *BRCA* status testing was performed in patients who had consented to i) Pharmacogenetic (PGx) testing and had provided blood and/or ii) tumour biomarker analysis and had provided an archival tumour biopsy samples at study entry.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

AstraZeneca Pharmaceuticals Investigational Products supplied olaparib or olaparib matching placebo as an oral 50 mg capsule, with Gelucire 44/14 (Lauroyl macroglycerides) as an excipient (solubiliser). Olaparib and olaparib matching placebo capsules were dosed at 400 mg bd orally. The following batch numbers of olaparib and olaparib matching placebo were used:

- Olaparib: 60227E08, 3075510R, 3070200R, 3071641R, 3072918R, 3065254R, 3065255R, 3070199R, 3080106R, 3080721R, 3084949R, 3086689R, 3086691R, 3090870R, 3091601R, 3094511R, 3094512R

- Placebo to match olaparib: 60099C08, 3065253R, 3070197R, 3071643R, 3091600R

Duration of treatment

Patients started treatment with olaparib or matching placebo capsules within 8 weeks of their last dose of platinum-containing regimen. Patients were administered study treatment continuously throughout a 28-day cycle. Patients continued taking olaparib or matching placebo capsules until objective disease progression (determined by RECIST) provided that, in the Investigator's opinion, they were benefiting from treatment and they did not meet any other discontinuation criteria.

Statistical methods

The primary PFS analysis was performed with a data cut-off (DCO) of 30 June 2010. An interim analysis of OS was performed at 38% OS maturity, and a further full interim OS analysis at 58%. The final survival analysis is planned to be performed at approximately 85% maturity.

The analyses used a Cox PH adjusting for the following factors (using source-verified CRF data):

- Time to disease progression from completion of penultimate platinum-containing therapy (last dose) prior to enrolment on the study (>6 to ≤12 months versus >12 months).
- Objective response to last platinum-containing regimen prior to enrolment on the study (CR versus PR).
- Ethnic descent (Jewish versus Non-Jewish).

The effect of treatment was estimated by the adjusted HR together with its corresponding 80% and 95% confidence intervals (CIs). Kaplan-Meier plots of PFS were presented by treatment group. If the observed p-value for the treatment difference was <0.025 (1 sided) then the result was regarded as statistically significant. A global interaction test was performed to test for consistency over all subgroups defined by the stratification factors plus *BRCA* status.

The primary analysis used PFS programmatically derived from the target lesion measurements and non-target lesion and new lesion assessments recorded by the investigators (DCO 30 June 2010).

Based on feedback received from European regulatory agencies and in line with the recently revised European Medicines Agency 'Guideline on the evaluation of anticancer medicinal products in man', exploratory analyses were conducted to evaluate whether PFS benefits were maintained with longer follow up, and to assess the impact of olaparib on the activity of next-line anti-cancer therapies. As specified in the protocol, formal PFS follow up with routine scanning did not continue after the primary PFS analysis. Therefore, 3 additional exploratory analyses were conducted at the time of the 58% interim OS analysis (DCO 26 November 2012): these were time to discontinuation of olaparib/placebo treatment or death (TDT), time to first subsequent therapy or death (TFST), and time to second subsequent therapy or death (TSST; an approximation for PFS2).

A re-analysis of the PFS data (30 June 2010 DCO) was performed including 2 additional scans received after the original PFS database lock and 1 data correction. The corrected data are used in the intermediate clinical endpoints analyses (TDT, TFST and TSST), OS analyses, and all analyses by *BRCA* mutation.

The interim analysis of OS presented in this synopsis was performed at 58% maturity (154 deaths out of 265 patients) (DCO 26 November 2012). The analysis of OS used the same methodology and model as the primary analysis of PFS.

Other secondary efficacy endpoints were analysed as of the primary analysis DCO (30 June 2010). The objective response rate (ORR) was compared between olaparib and placebo using logistic regression, adjusting for the same set of factors as for PFS. The effect of treatment (olaparib relative to placebo) was estimated using the adjusted odds ratio and its corresponding 80% and 95% CIs. Best overall response and disease control rate were summarised (number of patients [%] by treatment group).

Summary statistics by treatment group for the duration of objective response were presented, including the Kaplan-Meier estimate of the median duration for those patients who responded.

Time to cancer antigen (CA)-125 or RECIST progression was analysed in the same way as the primary analysis of PFS, adjusting for the same set of covariates. Logistic regression of CA-125 response (olaparib versus placebo) and CA-125 and/or RECIST response was carried out.

For tumour size, a comparison of the 2 treatment groups was performed using an analysis of covariance (ANCOVA) analysis of the % change in tumour size at 12 weeks and 24 weeks with covariates as per the primary analysis of PFS along with baseline sum of target lesions. For the analysis at each timepoint (12 weeks and 24 weeks), the least squares mean difference in percentage change in tumour size were presented along with corresponding 80% and 95% CIs.

No adjustments were made for multiplicity introduced by analysing multiple endpoints (excluding OS), or analyses within the *BRCA* subgroups. Control of type I error for the exploratory endpoints was not defined in this Phase II study. As such, where p-values <0.05 are observed for these endpoints (meeting nominal significance), statistical significance is stated. The multiplicity adjustment for OS has been detailed in the original protocol and SAP (and amended when there were insufficient OS events at the time of the PFS analyses and an interim at 100 deaths [~40% maturity] added). In October 2012, the protocol was further amended and the OS analyses at 60% maturity were classed as a subsequent interim analysis with a final analysis planned to occur at approximately 85% maturity. This amendment detailed the change to the multiplicity adjustment in order to continue controlling the overall alpha at 2.5% (1-sided); the significance level at the 40% interim analyses was as specified in Nov 2011 (p-value < 0.0005 1-sided), the significance level at the 60% analyses would be $p<0.015$ (1-sided) and at each subsequent analysis half the remaining alpha will be spent, unless it is the final analysis where all the remaining alpha will be spent.

Safety and tolerability were assessed using adverse events (AEs)/serious adverse events (SAEs), physical examination, laboratory data/vital signs and electrocardiograms (ECGs) that were collected for all patients. Appropriate summaries of laboratory data/vital signs and AEs/SAEs were produced for all patients in the safety analysis set. These data are presented as of the interim analysis of OS (DCO 26 November 2012). On-treatment AEs and SAEs

were defined as having an onset date between the date of first dose and 30 days following the date of last dose of study medication.

For each of the trial outcome index (TOI; the primary endpoint for health related quality of life [HRQL]), FACT/NCCN ovarian symptom index (FOSI) and total functional analysis of cancer therapy - ovarian (FACT-O) endpoints, the proportion of patients with best responses of 'Improved', 'No Change' and "Worsened" were compared between treatments using logistic regression with factors as for the analysis of PFS. The time to worsening was compared between treatments for each of the TOI, FOSI and total FACT-O, using a Cox proportional hazards model using the same factors as for the analysis of PFS. The association between HRQL/symptom response (TOI, FACT-O, FOSI) and RECIST response were assessed through cross tabulation of the 2 response categories. These data are presented as of the DCO of 30 June 2010.

This synopsis includes data for the overall study population and in the population of patients with *BRCA* mutation status.

Subject population: overall population

Of the 326 patients enrolled into the study, 61 patients were not randomised as they were screening failures. Of the 265 patients randomised into the study, all olaparib patients (136) and 128/129 placebo patients received study treatment. One patient (Patient E1805004) was randomised to the placebo group but voluntarily withdrew her consent (and completely withdrew from the study) without receiving treatment. At DCO (26 November 2012), 23 (16.9%) and 3 (2.3%) patients in the olaparib and placebo groups, respectively, were still receiving study treatment. A total of 113 (83.1%) and 125 (97.7%) patients in the olaparib and placebo groups, respectively, discontinued treatment. The majority of patients (197/238 patients [87 and 110 patients in the olaparib and placebo groups, respectively]) who discontinued study treatment did so due to worsening of the condition under investigation. Eight patients discontinued study treatment due to AEs (6 and 2 patients in the olaparib and placebo groups, respectively). A total of 19 patients (11 and 8 patients in the olaparib and placebo groups, respectively) voluntarily discontinued treatment. The remaining patients discontinued for other reasons (10 patients), severe non-compliance (3 patients) and loss to follow-up (1 patient).

The majority (97%) of patients were White with a mean age of 59 years (range 21 to 89 years). Approximately 11% of the study population were Ashkenazi Jewish and 3% were of other Jewish descent. Demographic and baseline characteristics were generally well balanced between the 2 treatment groups.

Demographic and baseline characteristics were generally well balanced between treatment groups. Very few patients entered the study with an ECOG PS of 2 (1.1%). The stratification factors of time to disease progression from the penultimate platinum-containing therapy prior to study enrolment, ethnic descent of the patient, and objective response to the last platinum-containing regimen prior to study enrolment were generally balanced, although a

slightly lower percentage of patients had CR in the olaparib group compared with the placebo group.

Summary of efficacy results: overall population

Primary efficacy variable: Progression free survival

At the time of the primary PFS analysis (30 June 2010), PFS was significantly longer in the olaparib group compared with the placebo group. The HR was 0.35 (95% CI: 0.25, 0.49; p<0.00001). Median PFS was 8.4 months in the olaparib group compared with 4.8 months in the placebo group; a 3.6 month longer median PFS in the olaparib group compared with placebo (Table S2). The overall analysis updated with additional scan data and data corrections gave the same HR as the original PFS analyses.

Table S2 Primary, supportive and sensitivity analyses of PFS: FAS

Analysis	Events:Patients	Median[a], months	HR	95% CI
Overall	Olaparib: 60:136 (44.1%) Placebo: 93:129 (72.1%)	8.4 4.8	0.35	0.25, 0.49
Supportive analysis: Stratified log rank test	Olaparib: 60:136 (44.1%) Placebo: 93:129 (72.1%)	NC	0.37	0.26, 0.51
Sensitivity analysis: Evaluation time bias	Olaparib: 60:136 (44.1%) Placebo: 93:129 (72.1%)	NC	0.39	0.28, 0.55
Sensitivity analysis: Attrition bias	Olaparib: 60:136 (44.1%) Placebo: 92:129 (71.3%)	NC	0.36	0.25, 0.50
Overall updated with additional scan data and data corrections	Olaparib: 60:136 (44.1) Placebo: 94:129 (72.9)	8.4 4.8	0.35	0.25, 0.49
Sensitivity analysis: independent central review	Olaparib: 54:133 (40.6) Placebo: 81:127 (63.8)	8.5 5.1	0.39	0.28, 0.56

CI Confidence interval; FAS Full analysis set; HR Hazard ratio; NC Not calculated; PFS Progression free survival.

[a] Calculated using the Kaplan-Meier technique.

The analysis was performed using a Cox proportional hazards model with factors for treatment (olaparib versus placebo), time to disease progression (>6-12 months and >12 months, in the penultimate platinum therapy prior to enrolment), objective response (complete response [CR] or partial response [PR], in the last platinum therapy prior to enrolment), and Jewish descent (yes or no).

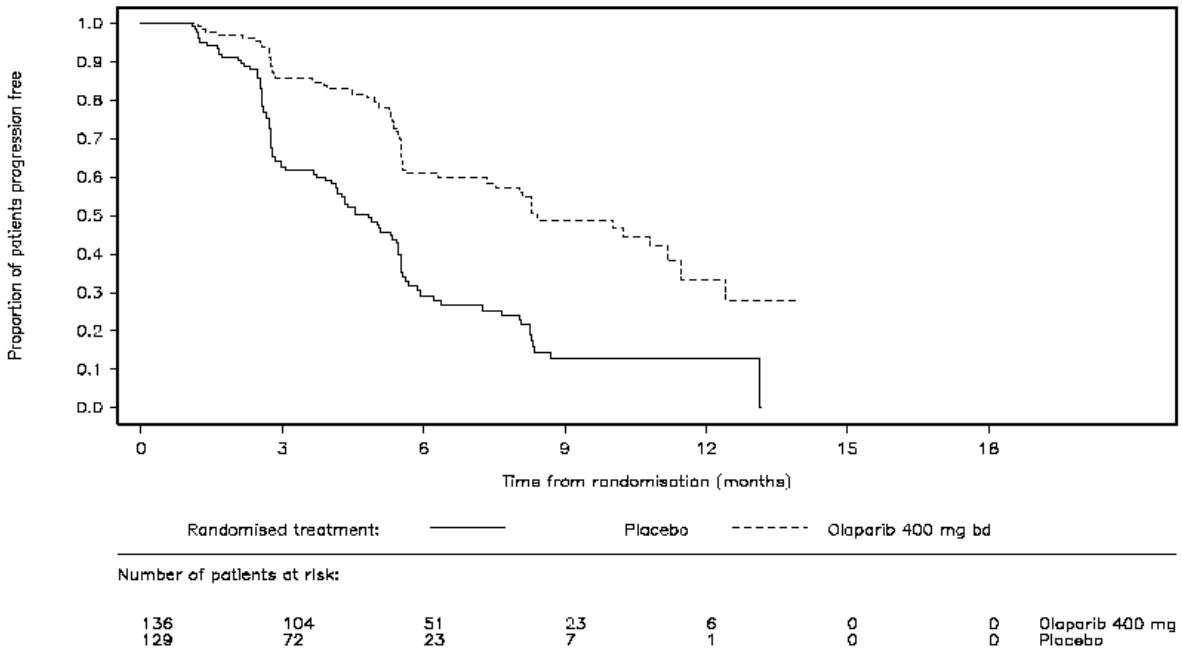
A hazard ratio < 1 favours olaparib.

Data cut-off: 30 June 2010.

Sensitivity analyses of PFS, including supportive analysis of PFS by blinded independent central review, were consistent with the primary analysis.

The Kaplan-Meier plot of progression-free survival for the olaparib and placebo groups is presented in Figure S1.

Figure S1 Kaplan-Meier plot of progression-free survival for the olaparib 400 mg bd and placebo groups: FAS



bd Twice daily; FAS Full analysis set.
Data cut-off: 30 June 2010.

Subgroup analyses of PFS were performed, including subgroups by *BRCA* status which at the time of the original analyses was known for only 97 patients (CRF data only). These analyses indicated that the subgroup of patients with *BRCA* mutation showed a differential benefit to the overall population.

Exploratory analyses of time to discontinuation of olaparib/ placebo treatment or death and time to first subsequent therapy: overall population

Results of the exploratory analyses of time to discontinuation of olaparib/ placebo treatment or death (TDT) and time to first subsequent therapy or death (TFST) performed at the interim OS DCO (26 November 2012) were consistent with the primary PFS analysis. There was a statistically significant improvement in the olaparib arm compared with the placebo arm: TDT HR was 0.39 (95% CI: 0.30, 0.51; p<0.00001); and TFST HR was 0.41 (95% CI: 0.31, 0.54; p<0.00001). The median time to discontinuation of olaparib/placebo was 8.6 months in the olaparib group and 4.6 months in the placebo group. The median time to first subsequent therapy was 13.4 months in the olaparib group and 6.7 months in the placebo group.

Exploratory analysis of time to second subsequent therapy or death (TSST): overall population

The exploratory analysis of time to second subsequent therapy or death performed at the interim OS DCO was an approximation for time to second progression. There was a statistically significant delay in TSST in the olaparib group compared with the placebo group (HR 0.54; 95% CI 0.41, 0.72; p=0.00002). The median time to second subsequent therapy was 19.1 months in the olaparib group and 14.8 months in the placebo group.

Secondary efficacy variables: Overall survival, Best objective response (RECIST), Objective response rate, Disease control rate, Tumour size, CA-125 (GCIG criteria) and RECIST response time to progression by CA-125 (GCIG criteria) or RECIST, and HRQL in the overall population

The interim analysis of OS was performed at 58% maturity (154 deaths out of 265 patients). The results showed a non-statistically significant numerical advantage overall: the HR was 0.88 (95% CI: 0.64, 1.21; p=0.438). Results of the key secondary efficacy variables are presented in Table S3.

Table S3 Summary of key secondary efficacy variables

Variable (Population)	Olaparib 400 mg bd	Placebo
OS (58% maturity), N	136	129
n (%) of deaths	77 (56.6%)	77 (59.7%)
Median overall survival, months[a]	29.8	27.8
95% CI for median	27.2, 35.7	24.4, 34.0
Treatment effect, hazard ratio (80% CI)[b]	0.88 (0.72, 1.09)	
2-sided p-value	0.438	
ORR[c] (Evaluable for response set), N	57	48
n (%) of events	7 (12.3)	2 (4.2)
Treatment effect, odds ratio (95% CI)	3.36 (0.75, 23.72)	
2-sided p-value	0.11687	
Disease control rate (FAS)[d], N	136	129
n (%) of patients	72 (52.9)	32 (24.8)
Percentage change in tumour size at 24 weeks[e] (Evaluable for response set)		
N	57	48
Number of patients contributing to analysis	56	47
Unadjusted mean	9.1	40.8
LS Mean	0.0	33.5
Treatment effect, difference in LS Mean (95% CI)	-33.4 (-59.4, -7.4)	
2-sided p-value	0.01221	

Table S3 Summary of key secondary efficacy variables

Variable (Population)	Olaparib 400 mg bd	Placebo
TOI improvement rate (Evaluable for TOI set), N	115	111
N		
n (%) improved	23 (20.0)	20 (18.0)
Treatment effect, odds ratio (95% CI)	1.14 (0.58, 2.24)	
2-sided p-value	0.69902	
TOI time to worsening (Evaluable for TOI set), N	115	111
n (%) of events	64 (55.7)	56 (50.5)
Median time to worsening, months (95% CI)[k]	3.8 (2.8, 7.4)	4.6 (3.7, 7.4)
Treatment effect, hazard ratio (95% CI)[j]	1.08 (0.75, 1.55)	
2-sided p-value	0.68126	

bd Twice daily; CI Confidence interval; CR Complete response; FAS Full analysis set; LS Least square; ORR Objective response rate; OS Overall survival; PFS Progression free survival; TOI Trial outcome index.

[a] Calculated using the Kaplan-Meier technique.

[b] Analysis was performed using a Cox proportional hazards model with factors for treatment, ethnic descent, platinum sensitivity and response to final platinum therapy.

[c] The analysis was performed using logistic regression with factors for treatment, ethnic descent, platinum sensitivity, and response to final platinum therapy. An odds ratio >1 favoured olaparib.

[d] Defined as the percentage of patients who had at least 1 confirmed visit response of CR or PR or demonstrated SD or NED for at least 23 weeks (i.e. 24 weeks ± 1 week) prior to any evidence of progression.

[e] The analysis was performed using analysis of covariance with factors for treatment, ethnic descent, platinum sensitivity, response to final platinum therapy and a covariate accounting for sum of target lesion diameters at baseline.

Data cut-off: 26 November 2012 for overall survival and 30 June 2010 for other variables.

The direction of the treatment effect was consistent in the secondary endpoint of time to RECIST or CA 125 progression.

As for TOI, analyses of FOSI and total FACT-O did not detect any statistically significant differences between treatment groups as measured by improvement or worsening rates and time to worsening.

Summary of safety results: overall population

The overall median exposure to study treatment was 263.5 days (approximately 9 months) and 141.0 days (approximately 5 months) in the olaparib and placebo groups, respectively. The mean daily dose was 681.6 mg (range: 164.4 mg to 800.0 mg) and 784.2 mg (range: 400.0 mg to 800.0 mg). The mean dose adherence was lower in the olaparib group (84.0%) compared with the placebo group (96.2%).

A total of 132 (97.1%) patients in the olaparib 400 mg bd group and 119 (93.0%) patients in the placebo group reported AEs. The most common AEs were: nausea (70.6% and 35.9% in

the olaparib 400 mg bd and placebo groups, respectively), fatigue (52.2% versus 39.1%), vomiting (33.8% versus 14.1%) and anaemia (21.3% versus 5.5%). These were reported at a 5% greater frequency in the olaparib 400 mg bd group compared with the placebo group. Other common AEs also reported at a 5% greater frequency in the olaparib 400 mg bd group compared with the placebo group included: constipation (20.6% versus 10.9%), decreased appetite (20.6% versus 13.3%), headache (20.6% versus 12.5%), abdominal pain upper (17.6% versus 7.8%), cough (17.6% versus 10.2%), dyspepsia (17.6% versus 8.6%), back pain (16.2% versus 10.9%), dysgeusia (16.2% versus 6.3%), dizziness (13.2% versus 7.0%), dyspnoea (11.8% versus 6.3%) and upper respiratory tract infection (11.8% versus 6.3%). AEs reported at an incidence of between a 10% and 5% greater frequency in the olaparib 400 mg bd group compared with the placebo group included: muscle spasm (9.6% versus 3.9%), pyrexia (9.6% versus 3.1%), neuropathy peripheral (8.8% versus 2.3%) and stomatitis (8.8% versus 3.1%).

Hot flush was reported at a 5% greater frequency in the placebo group compared with the olaparib 400 mg bd group.

Most AEs were Common Toxicity Criteria for Adverse Events (CTCAE) Grade 1 or 2. A higher percentage of patients had AEs of CTCAE Grade ≥3 in the olaparib group (40.4%) compared with the placebo group (21.9%). Fatigue and anaemia (reported in 10 and 7 patients, respectively) were the most frequently reported CTCAE ≥3 AEs in the olaparib group; abdominal pain and fatigue were the most frequently reported CTCAE ≥3 AEs in the placebo group (both reported in 4 patients).

Of the 264 patients who received study medication, 154 patients died during the study; 77 (56.6%) and 77 (60.2%) in the olaparib and placebo groups, respectively. In the investigator's opinion, the majority of patients in both treatment groups (50.0% in olaparib group and 55.5% in placebo group) died due to progression of their ovarian cancer.

One patient (olaparib group) had the reason for death recorded as AE only: she died as a result of haemorrhagic stroke during the 30 day follow-up period. The patient had a germline and tumour *BRCA* mutation.

Two patients (both olaparib group) had the reason for death recorded as disease under study and AE. One patient (tumour *BRCA* mutation, unknown germline status) died in the post follow-up period on Day 1062 (48 days after stopping treatment) due to progressive ovarian cancer; this patient also had jaundice cholestatic that was considered by the investigator to be the secondary cause of death, and not related to study treatment. The other patient (g*BRCA* wildtype) died in the post follow-up period on Day 430 (117 days after stopping treatment) due to progressive ovarian cancer; this patient also had myelodysplastic syndrome that was considered by the investigator to be the secondary cause of death.

Six patients in each group had deaths in the category "other". These were deaths reported outside of the 30-day follow-up period after study treatment discontinuation and not reported as due to disease under study. In the olaparib group, the 'other' causes of death were euthanasia, septic shock, cerebrovascular disorder, cerebral haemorrhage and cause unknown

(n=2); all occurred in the post follow up period, many months after olaparib treatment had been discontinued and after patients had received subsequent anti-cancer therapy. In the placebo group, the 'other' causes of death were renal failure acute, pulmonary embolism, cardiopulmonary failure, septic shock, and cause unknown (n=2); all occurred in the post follow up period, and 5/6 patients had received subsequent anti cancer therapy.

SAEs were reported by 25 (18.4%) patients in the olaparib group and 11 (8.6%) patients in the placebo group. The only SAEs reported in more than 1 patient were small intestinal obstruction (2 patients in the olaparib group and 3 patients in the placebo group), anaemia (3 patients in the olaparib group), intestinal obstruction (1 patient in each treatment group), pneumonia (1 patient in each treatment group) gastritis (2 patients in the placebo group) and UTI (1 patient in each treatment group).

Nine patients had study treatment discontinued due to an AE: 7 (5.1%) patients in the olaparib group and 2 (1.6%) patients in the placebo group. In the olaparib group, 3 AEs that led to permanent discontinuation of study treatment were considered by the investigator to be serious: CTCAE Grade 5 jaundice cholestatic (the AE was a secondary cause of death); CTCAE Grade 4 small intestinal obstruction; and CTCAE Grade 5 haemorrhagic stroke (the patient died as a result of the AE). None of the other AEs leading to permanent discontinuation of study treatment were considered by the investigator to be serious. Apart from the SAEs mentioned above, all the AEs leading to permanent discontinuation of study treatment were CTCAE Grade 2. The majority of AEs leading to discontinuation of study treatment resolved after treatment was stopped.

It was necessary to temporarily interrupt or reduce the dose of olaparib due to toxicity for 47 (34.6%) and 28 (20.6%) patients, respectively; vomiting, nausea and fatigue were the most common AEs leading to olaparib dose interruption, and nausea, fatigue, anaemia /haemoglobin decreased, and vomiting were the most common AEs leading olaparib dose reduction. It was necessary to temporarily interrupt or reduce the dose of placebo during the study due to toxicity for 12 (9.4%) and 3 (2.3%) patients, respectively. Abdominal pain, fatigue and small intestinal obstruction were the most common AEs leading to placebo dose interruption; no events led to dose reduction in more than 1 patient in the placebo group.

One event of myelodysplastic syndrome was reported during study treatment or within the 30-day follow up period. The non-serious AE of CTCAE Grade 3 myelodysplastic syndrome was reported on-treatment, 422 days after the start of placebo treatment, in a patient carrying a tumour *BRCA* mutation (unknown germline *BRCA* mutation status). No action was taken with respect to the study treatment and the AE was ongoing at DCO. One patient in the olaparib group (g*BRCA* wildtype) had myelodysplastic syndrome recorded as the secondary cause of death in the post follow-up period (46 days after discontinuation of olaparib): the primary cause of death was progressive ovarian cancer and the patient died on Day 430 (117 days after stopping treatment).

Anaemia, neutropenia and thrombocytopenia are known to be associated with olaparib treatment. Laboratory changes seen for these parameters were consistent with data from previously reported monotherapy studies; the majority of changes were grade 1 or 2. More

olaparib treated patients than placebo treated patients had a decrease in lymphocyte values; however, the majority of changes were grade 1 or 2. In the olaparib group, a trend towards elevated mean corpuscular volume (MCV) was observed, with no apparent clinical sequelae. There was a small increase in serum creatinine within the normal range (mean and median) relative to baseline at Day 8 for olaparib treated patients, which remained consistent throughout the treatment period and returned to baseline levels at follow up. There were no unexpected changes noted in vital signs or physical examination safety parameters in the olaparib or placebo groups, and no individual abnormalities raised any new safety concerns.

Subject population: patients with a *BRCA* mutation

At the time of writing the primary CSR dated 26 July 2011 g*BRCA* mutation status was known for only 97/265 patients (37%) whose mutation status had been captured at screening on the CRF. In order to increase the sample size for the g*BRCA* subgroup analyses g*BRCA* status was retrospectively determined using the Myriad Genetic Laboratories Inc diagnostic assay (Integrated BRAC*Analysis*®). Combining the CRF and Myriad data, the g*BRCA* mutation status is known for 210/265 patients (79% of the study population). To further increase knowledge of patients' *BRCA* status, an analysis of tumour *BRCA* (t*BRCA*) status was undertaken at Foundation Medicine; the sequence variants were classified according to the Breast Cancer Information Care database. Tumour *BRCA* mutation status was determined for 209/265 (79%) of the study population. When the assessment of t*BRCA* mutation status was combined with the assessment of *gBRCA* mutation status based on the information captured on CRFs and from the Myriad diagnostic assay, the *BRCA* mutation status was known for 254/265 patients (96% of the study population). The *BRCA* data were classified as *BRCA* mutated (variants that are linked to increased risk of breast and ovarian cancer when inherited); *BRCA* wildtype/ *BRCA* unknown (variant of unknown significance); and *BRCA* missing. In total, 136 patients had a *BRCA* mutation (either germline and/or tumour) and 118 were *BRCA*wt/variant of unknown significance (108 patients identified as wt and 10 patients with a variant of unknown significance). A further 11 patients had no data on *BRCA* mutation status (*BRCA* missing).

All 136 patients with a *BRCA* mutation received treatment: 74 patients received olaparib and 62 patients received placebo. At DCO (26 November 2012), 15 (20.3%) and 3 (4.8%) patients in the olaparib and placebo groups, respectively, were still receiving study treatment. A total of 59 patients in each treatment group (79.7% and 95.2% in the olaparib and placebo groups, respectively) discontinued treatment. The majority of patients (94/118 patients [42 and 52 patients in the olaparib and placebo groups, respectively]) who discontinued study treatment did so due to worsening of the condition under investigation. Five patients discontinued study treatment due to AEs, all of whom received olaparib. A total of 13 patients (9 and 4 patients in the olaparib and placebo groups, respectively) voluntarily discontinued treatment. The remaining patients discontinued for other reasons (5 patients), and severe non-compliance (1 patient).

Ninety-six patients carried a g*BRCA* mutation and all received treatment: 53 patients received olaparib and 43 patients received placebo. At data cut off (26 November 2012), 10 (18.9%)

and 2 (4.7%) patients with a g*BRCA* mutation in the olaparib and placebo groups, respectively, were still receiving study treatment.

As in the overall study population, demographic and baseline characteristics were generally well balanced between the 2 treatment groups for patients with a *BRCA* mutation (germline or tumour) and patients with a g*BRCA* mutation. The age distribution of the *BRCA* population was younger than the overall population (age <50 years: 25.7% versus 18.9%, *BRCA*m versus overall population, respectively and age ≥65 years, 20.6% versus 30.2%, *BRCA*m versus overall population, respectively). This is consistent with the hereditary nature of g*BRCA* mutation.

Summary of efficacy results: analysis by *BRCA* status

Primary efficacy variable: Progression free survival

In patients with *BRCA* mutation, based on the PFS DCO (30 June 2010), there were 72/136 progression events (26 events in the olaparib group and 46 events in the placebo group), indicating the data were relatively mature. A clinically meaningful and statistically significant PFS benefit (HR: 0.18; 95% CI: 0.11, 0.31; p<0.00001), corresponding to an 82% reduction in the risk of disease progression or death, was demonstrated for patients with *BRCA*-mutated ovarian cancer treated with olaparib versus placebo. Median PFS was 11.2 months in the olaparib group compared with 4.3 months in the placebo group; demonstrating a clinically relevant 6.9-month improvement in median PFS for patients treated with olaparib compared with placebo (Table S4).

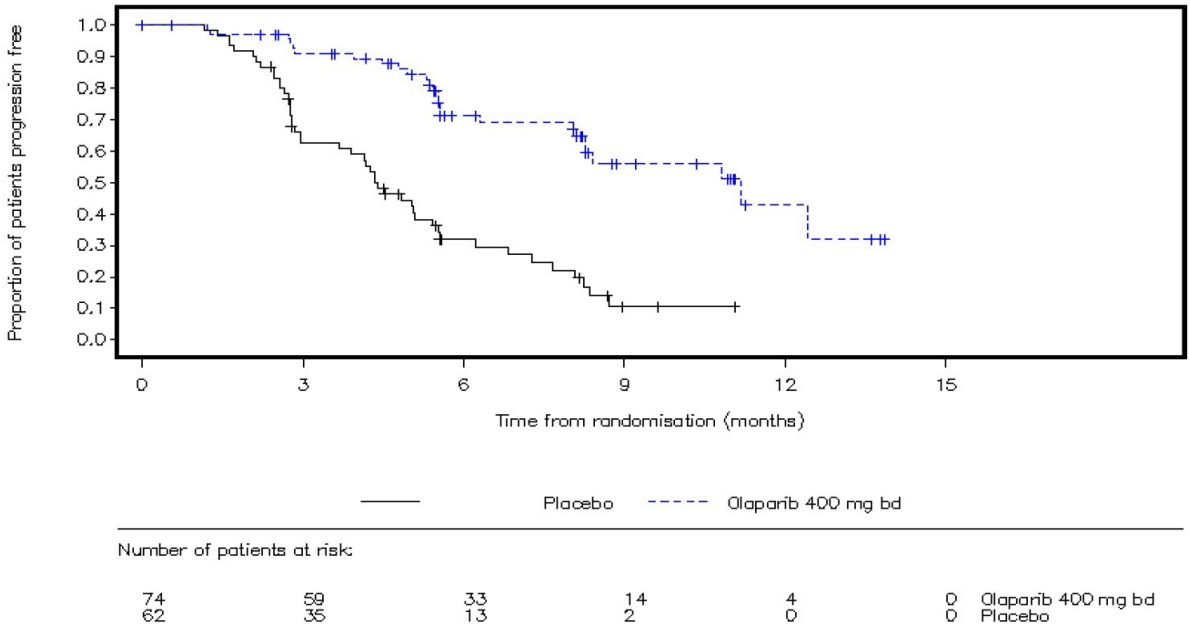
Table S4 Summary of primary analysis of PFS: patients with *BRCA* mutation

	Olaparib 400 mg bd n=74	**Placebo n=62**
n (%) of events	26 (35.1)	46 (74.2)
Median PFS, months[a]	11.2	4.3
Treatment effect, hazard ratio (95% CI)	0.18 (0.11, 0.31)	
2-sided p-value	<0.00001	

bd Twice daily; *BRCA* Breast cancer susceptibility gene; CI Confidence interval; PFS Progression free survival.
[a] Calculated using the Kaplan-Meier technique.
The analysis was performed using a Cox proportional hazards model with factors for treatment (olaparib versus placebo), time to disease progression (>6-12 months and >12 months, in the penultimate platinum therapy prior to enrolment), objective response (CR or PR, in the last platinum therapy prior to enrolment), and Jewish descent (yes or no).
A hazard ratio < 1 favours olaparib.
Data cut-off: 30 June 2010.

The Kaplan-Meier plot of PFS for patients with *BRCA* mutation is presented in Figure S2. There was clear separation of the curves in favour of olaparib; this separation was observed at 3 months (first scan). There was no evidence of a lack of proportional hazards.

Figure S2 **Kaplan-Meier plot of progression free survival for the olaparib 400 mg bd and placebo groups: patients with *BRCA* mutation**

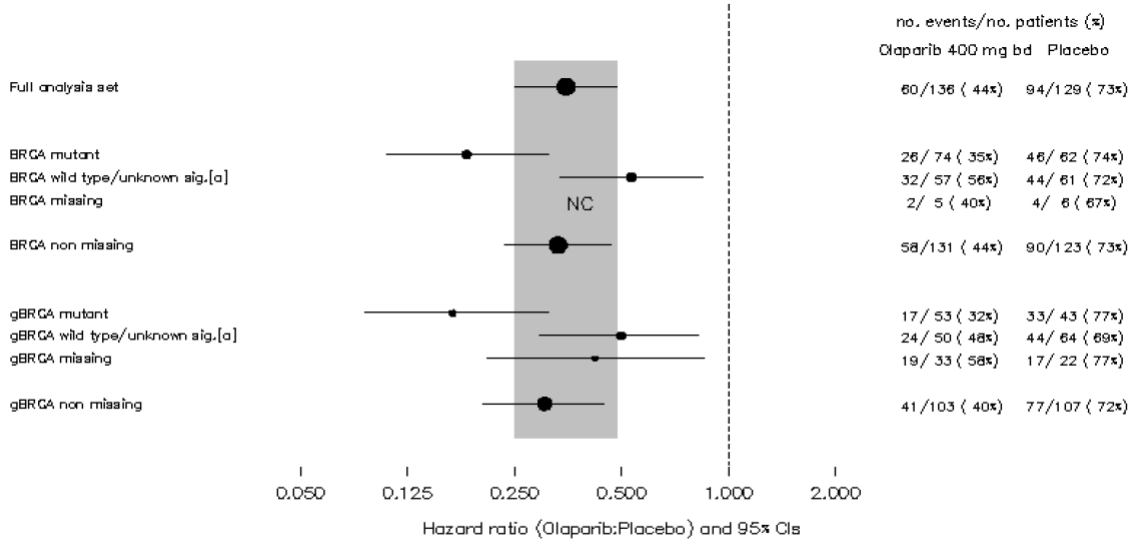


bd Twice daily; *BRCA* Breast cancer susceptibility gene.
Data cut-off: 30 June 2010.

The investigator-assessed PFS benefit in patients with *BRCA* mutation status was confirmed by independent central radiological review (HR 0.22; 95% CI 0.12-0.40; p<0.00001; median not reached versus 4.8 months).

Consistent with the biological rationale for PARP inhibition in *BRCA*-deficient tumours, PFS outcomes in patients with *BRCA* mutations (HR 0.18; 95% CI 0.11-0.31; p<0.00001) were consistent with those observed in the smaller subgroup of patients with g*BRCA* mutations (HR 0.17; 95% CI 0.09-0.31; p<0.00001; Figure S3). Both *BRCA* mutated subgroups (patients with *BRCA* mutations and patients with g*BRCA* mutations) demonstrated a greater differential benefit for PFS than the overall population or the *BRCA* wild type/ variant of unknown significance population (PFS HR 0.53, 95% CI 0.33-0.84, p=0.007).

Figure S3 Forest plot of analysis of PFS by *BRCA* subgroup (FAS Population)



NC – Not calculated. A hazard ratio of <1 favours olaparib. Dot size is proportional to the number of events in the group.
[a] BRCA wild type or BRCA mutation of unknown significance.
Analysis incorporates the most accurate data known at the time of analysis.

bd Twice daily; *BRCA* Breast cancer susceptibility gene; FAS Full analysis set; PFS Progression free survival.
a = *BRCA* wild type or *BRCA* variant of unknown significance.
Data cut-off: 30 June 2010.

Exploratory analyses of time to discontinuation of olaparib/placebo treatment (TDT) and time to first subsequent therapy or death (TFST): patients with *BRCA* mutation

Exploratory analyses for the time to discontinuation of olaparib/placebo treatment or death (TDT) and time to first subsequent therapy (TFST) were performed at the interim OS DCO for patients with *BRCA* mutation. For both analyses, there was a statistically significant delay in the olaparib group compared with the placebo group (HR of 0.36 [95% CI 0.24, 0.53]; p<0.00001 and 0.35 [95% CI 0.23, 0.52]; p<0.00001 for TDT and TFST, respectively). The median time to discontinuation of olaparib/placebo was 11.0 months in the olaparib group and 4.6 months in the placebo group. The median time to subsequent therapy was 15.6 months in the olaparib group and 6.2 months in the placebo group.

Exploratory analysis of time to second subsequent therapy or death (TSST): patients with *BRCA* mutation

Exploratory analyses for the time to second subsequent therapy or death (TSST; an approximation for time to second progression) were performed at the interim OS DCO for patients with *BRCA* mutation. There was a statistically significant delay in the olaparib group compared with the placebo group (HR 0.46; 95% CI 0.30, 0.70; p=0.00027). Median time to second subsequent therapy was 23.8 months in the olaparib group and 15.3 months in the placebo group.

Secondary efficacy variables: Overall survival and HRQL in patients with *BRCA* mutation

Key results of the interim OS analysis and HRQL data for patients with *BRCA* mutation are presented in Table S5. Other secondary efficacy variables were not analysed by *BRCA* status.

The interim OS analysis was performed at 52% maturity in patients with *BRCA*m (71 deaths out of 136 patients). The results showed a non-statistically significant numerical advantage overall: the HR was 0.74 (95% CI: 0.46, 1.19; p=0.20813).

Table S5 Summary of key secondary efficacy variables: patients with *BRCA* mutation

Variable (Population)	Olaparib 400 mg bd	Placebo
OS in patients with a *BRCA* mutation (52% maturity)		
N	74	62
n (%) of deaths	37 (50.0)	34 (54.8)
Median overall survival, months[a]	34.9	31.9
Treatment effect, hazard ratio (95% CI)[b]	0.74 (0.46, 1.19)	
2-sided p-value	0.20813	
TOI improvement rate (Evaluable for TOI set in patients with a *BRCA* mutation)		
N	64	53
n (%) improved[c]	16 (25.0)	10 (18.9)
Treatment effect, odds ratio (95% CI)	1.37 (0.56, 3.46)	
2-sided p-value	0.49155	
TOI time to worsening (Evaluable for TOI set in patients with a *BRCA* mutation)		
N	64	53
n (%) of events	33 (51.6)	29 (54.7)
Median time to worsening, months[a]	5.7	3.7
Treatment effect, hazard ratio (95% CI)[b]	0.80 (0.48, 1.34)	
2-sided p-value	0.39521	

bd Twice daily; *BRCA* Breast cancer susceptibility gene; CI Confidence interval; FACT-O Functional Analysis of Cancer Therapy – Ovarian; FOSI FACT/NCCN Ovarian Symptom Index; OS Overall survival; TOI Trial outcome index.

[a] Calculated using the Kaplan-Meier technique.

[b] Analysis was performed using a Cox proportional hazards model with factors for treatment, ethnic descent, platinum sensitivity and response to final platinum therapy. A hazard ratio < 1 favours olaparib.

[c] Data cut-off: 26 November 2012 for overall survival and 30 June 2010 for other variables.

The HR for OS was numerically more favourable in the *BRCA* mutated subgroup compared with the g*BRCA* mutated subgroup. In patients with *BRCA* mutated ovarian cancer, there was a non-statistically significant numerical advantage for olaparib-treated patients compared with

placebo-treated patients, but there was no OS advantage in patients who did not have a *BRCA* mutation (HR 0.98; 95% CI 0.62, 1.55; p=0.94626). In contrast, in the g*BRCA* subgroups, the observed point estimates for OS HR were similar for patients with g*BRCA* mutations (HR 0.85; 95% CI 0.48, 1.53; p=0.59316) and patients who were g*BRCA* wild-type/ variant of unknown significance (HR 0.85; 95% CI 0.52, 1.38; p=0.51904).

A total of 16 patients in the placebo group and none in the olaparib group went on to receive a PARP inhibitor after study treatment. Of these 16 patients, 11 were g*BRCA*m by CRF which means that their *BRCA* status was known by the investigator. Approximately a quarter of patients in the *BRCA* mutated subgroup (14/62; 22.6%) went on to receive a PARP inhibitor. A higher proportion in the g*BRCA* mutated subgroup, approximately a third of patients (13/43; 30.2%), went on to receive a PARP inhibitor.

As for TOI, analyses of FOSI and total FACT-O in patients with *BRCA* mutated ovarian cancer did not detect any statistically significant differences between treatment groups as measured by improvement or worsening rates and time to worsening.

Summary of safety results: analysis by *BRCA* status

In patients with a *BRCA* mutation, the overall median exposure to study treatment was longer in the olaparib group compared with the placebo group: 337.0 days (approximately 11 months) and 139.5 days (approximately 4.5 months) in the olaparib and placebo groups, respectively. This represented a longer duration of treatment in the olaparib group compared with the overall population olaparib group (which was 263 days). The median exposure to placebo was similar in patients with *BRCA* mutation and the overall placebo group (141 days).

The number of patients with *BRCA* mutation who had at least 1 AE in any category during the course of the study is presented in Table S6.

Table S6 Summary of number (%) of patients who had at least one AE in any category: Safety analysis set (*BRCA* mutation)

	Number (%) of patients[a]	
	Olaparib 400 mg bd n=74	**Placebo n=62**
Any AE	72 (97.3)	58 (93.5)
Any AE of CTCAE Grade 3 or higher	28 (37.8)	11 (17.7)
Any AE with outcome = death	2 (2.7)	0
Any SAE (including events with outcome = death)	16 (21.6)	6 (9.7)
Any AE leading to discontinuation of study treatment	6 (8.1)	0

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

Includes adverse events with an onset date between the date of first dose and 30 days following the date of last dose of study medication.

AE Adverse event; bd Twice daily; CTCAE Common Toxicity Criteria for Adverse Events; SAE Serious adverse event.

Data cut-off: 26 November 2012.

Of the 136 patients with *BRCA* mutation who received study medication, 71 patients died during the study; 37 (50.0%) and 34 (54.8%) in the olaparib and placebo groups, respectively. Consistent with the overall population, in the investigator's opinion the majority of patients in both treatment groups (41.9% in olaparib group and 48.4% in placebo group) died due to progression of their ovarian cancer.

The safety and tolerability profiles observed in patients with *BRCA* mutation and g*BRCA* mutation were similar to that of the overall population for both the olaparib and placebo groups.