



THE UNIVERSITY *of* EDINBURGH

## Edinburgh Research Explorer

# Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial

### Citation for published version:

Banerjee, S, Moore, KN, Colombo, N, Scambia, G, Kim, B, Oaknin, A, Friedlander, M, Lisyanskaya, A, Floquet, A, Leary, A, Sonke, GS, Gourley, C, Oza, A, González-martín, A, Aghajanian, C, Bradley, WH, Holmes, E, Lowe, ES & Disilvestro, P 2021, 'Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial', *The Lancet Oncology*. [https://doi.org/10.1016/S1470-2045\(21\)00531-3](https://doi.org/10.1016/S1470-2045(21)00531-3)

### Digital Object Identifier (DOI):

[10.1016/S1470-2045\(21\)00531-3](https://doi.org/10.1016/S1470-2045(21)00531-3)

### Link:

[Link to publication record in Edinburgh Research Explorer](#)

### Document Version:

Peer reviewed version

### Published In:

The Lancet Oncology

### Publisher Rights Statement:

This is a pre-copyedited, author-produced version of an article accepted for publication in *The Lancet Oncology* following peer review.

The version of record "Banerjee S, Moore KN, Colombo N, et al. Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial". *Lancet Oncol* 2021;Epub ahead of print: Oct 26 is available online at: DOI: [10.1016/S1470-2045\(21\)00531-3](https://doi.org/10.1016/S1470-2045(21)00531-3)  
<https://www.thelancet.com/journals/lanonc/home>

### General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

### Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact [openaccess@ed.ac.uk](mailto:openaccess@ed.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.



1 **Maintenance olaparib for patients with newly diagnosed advanced**  
2 **ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year**  
3 **follow-up from a randomised, placebo-controlled, double-blind,**  
4 **phase 3 trial**

5 Susana Banerjee, Kathleen Moore, Nicoletta Colombo, Giovanni Scambia, Byoung-Gie  
6 Kim, Ana Oaknin, Michael Friedlander, Alla Lisyanskaya, Anne Floquet, Alexandra Leary,  
7 Gabe S Sonke, Charlie Gourley, Amit Oza, Antonio González-Martín, Carol Aghajanian,  
8 William Bradley, Eileen Holmes, Elizabeth S Lowe, Paul DiSilvestro

9 **The Royal Marsden NHS Foundation Trust and Institute of Cancer Research,**  
10 **London, UK (S Banerjee PhD); Stephenson Cancer Center, Oklahoma City, OK, USA**  
11 **(Prof KN Moore MD); University of Milan-Bicocca and Istituto Europeo di Oncologia**  
12 **IRCCS, Milan, Italy (Prof N Colombo PhD); Università Cattolica del Sacro Cuore-**  
13 **Fondazione Policlinico A. Gemelli, IRCCS, Rome, Italy (Prof G Scambia MD);**  
14 **Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul,**  
15 **Korea (Prof B-G Kim MD); Vall d'Hebron Institute of Oncology (VHIO), Hospital**  
16 **Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona,**  
17 **Spain (Prof A Oaknin MD); University of New South Wales Clinical School, Prince of**  
18 **Wales Hospital, Randwick, Australia (Prof M Friedlander MD); St Petersburg City**  
19 **Oncology Dispensary, St Petersburg, Russia (A Lisyanskaya MD); Institut Bergonié,**  
20 **Comprehensive Cancer Centre, Bordeaux, and Groupe d'Investigateurs Nationaux**  
21 **pour l'Etude des Cancers Ovariens, France (A Floquet MD); Institut Gustave-Roussy,**  
22 **Villejuif, and Groupe d'Investigateurs Nationaux pour l'Etude des Cancers**  
23 **Ovariens, France (A Leary MD); The Netherlands Cancer Institute, Amsterdam, The**  
24 **Netherlands (Prof GS Sonke MD); Cancer Research UK Edinburgh Centre, University**  
25 **of Edinburgh, Edinburgh, UK (Prof C Gourley PhD); Princess Margaret Cancer**

26 **Centre, Toronto, ON, Canada** (Prof A Oza MD); **Clínica Universidad de Navarra,**  
27 **Madrid, and Program in Solid Tumors, Center for Applied Medical Research (CIMA),**  
28 **Spain** (A González-Martín MD); **Memorial Sloan Kettering Cancer Center, New York,**  
29 **NY, USA** (Prof C Aghajanian MD), **Froedtert and the Medical College of Wisconsin,**  
30 **Milwaukee, WI, USA** (WH Bradley MD); **AstraZeneca, Cambridge, UK** (E Holmes, PhD);  
31 **AstraZeneca, Gaithersburg, MD, USA** (ES Lowe MD); **Women & Infants Hospital,**  
32 **Providence, RI, USA** (Prof P DiSilvestro MD)

33 **Correspondence to:** Dr Susana Banerjee, The Royal Marsden NHS Foundation Trust  
34 and Institute of Cancer Research, 203 Fulham Road, London SW3 6JJ, UK. Tel: +44-208-  
35 661-3563 E-mail: [susana.banerjee@rmh.nhs.uk](mailto:susana.banerjee@rmh.nhs.uk)

36 **Figures/tables:** 3 figures/3 tables [2 supplementary figures/1 supplementary table]

37 **Key words:** olaparib, PARP inhibitor, newly diagnosed ovarian cancer, BRCA mutation,  
38 SOLO1

39 **Word count (including Research in context):** 4618 (max 4500)

40

41

## 42 **Summary**

### 43 **Background**

44 There is a high unmet need for treatment regimens that increase the chance of a cure for  
45 women with newly diagnosed advanced ovarian cancer. In SOLO1/GOG 3004, the PARP  
46 inhibitor, olaparib, significantly improved progression-free survival (PFS) versus placebo  
47 in BRCA-mutated patients; median PFS was not reached at the primary analysis. We  
48 report here on an updated analysis of progression-free survival from SOLO1 that took  
49 place after 5 years' follow-up.

### 50 **Methods**

51 This randomised, double-blind trial (NCT01844986), performed across 118 centres (15  
52 countries), enrolled patients aged  $\geq 18$  years who were Eastern Cooperative Oncology  
53 Group performance status 0–1 and had BRCA-mutated newly diagnosed advanced high-  
54 grade serous or endometrioid OC with complete/partial clinical response after platinum-  
55 based chemotherapy. Patients were randomised 2:1 to maintenance olaparib tablets  
56 (300 mg twice daily) or placebo for up to 2 years via web or voice-response system with  
57 stratification according to clinical response after platinum-based chemotherapy. Masking  
58 occurred in patients, treatment providers and data assessors. Efficacy is reported in the  
59 intention-to-treat population (primary endpoint PFS) and safety in patients with  $\geq 1$   
60 treatment dose. Updated post-hoc analyses are presented after 5 years' follow-up (data  
61 cutoff: March 5, 2020).

### 62 **Findings**

63 Between September 3, 2013 and March 6, 2015, 260 patients were randomised to  
64 olaparib and 131 to placebo. Median treatment duration was 24.6 months (IQR 11.2–  
65 24.9) with olaparib and 13.9 months (IQR 8.0–24.8) with placebo; median follow-up was

66 4·8 (IQR 2·8–5·3) and 5·0 years (IQR 2·6–5·3), respectively. In this post-hoc analysis,  
67 median PFS was 56·0 (95% CI 41·9–not reached) versus 13·8 months (95% CI 11·1–  
68 18·2), respectively (HR 0·33; 95% CI 0·25–0·43). The most common grade 3–4 adverse  
69 events (AEs) were anaemia (57 of 260 [22%] olaparib patients versus 2 of 130 [2%]  
70 placebo patients) and neutropenia (22 [8%] olaparib patients and 6 [5%] placebo patients),  
71 and serious adverse events occurred in 55 (21%) olaparib patients and 17 (13%) placebo  
72 patients. No treatment-related AEs occurring during study treatment or up to 30 days after  
73 discontinuation were reported as leading to death. No additional cases of myelodysplastic  
74 syndrome or acute myeloid leukaemia (MDS/AML) were reported, including after the 30-  
75 day safety follow-up period.

## 76 **Interpretation**

77 For patients with newly diagnosed advanced OC and a BRCA mutation, after, to our  
78 knowledge, the longest follow-up for any PARP inhibitor trial in this setting, the benefit  
79 derived from 2 years' maintenance olaparib was sustained beyond the end of treatment,  
80 extending median PFS past 4·5 years. No new safety signals were observed, and  
81 incidence of MDS/AML was low.

82 **Funding** AstraZeneca and Merck Sharpe & Dohme Corp, a subsidiary of Merck & Co.,  
83 Inc, Kenilworth, NJ, USA.

84 **Word count:** 417 [word limit: 300 words]

85

## 86 **Research in context**

### 87 **Evidence before this study**

88 We searched PubMed and the databases of the American Society of Clinical Oncology,  
89 European Cancer Organisation, European Society of Gynaecological Oncology,  
90 European Society for Medical Oncology, and Society of Gynaecological Oncology for  
91 articles and conference abstracts published between Jan 1, 2018 and Jan 1, 2021,  
92 including the search terms “poly(ADP-ribose) polymerase inhibitor” or “PARP inhibitor”  
93 and “ovarian cancer”, using no language restrictions. PARP inhibitors as maintenance  
94 therapy have been reported in the newly diagnosed advanced ovarian cancer setting in  
95 four phase 3 trials SOLO1 (olaparib), PAOLA-1 (olaparib in combination with  
96 bevacizumab), PRIMA (niraparib) and VELIA (veliparib). No studies have reported efficacy  
97 benefits of PARP inhibitors as maintenance monotherapy extending beyond completion  
98 of treatment.

### 99 **Added value of this study**

100 To our knowledge, we report here the longest follow-up period for a PARP inhibitor in the  
101 newly diagnosed advanced ovarian cancer setting and the first demonstration of a  
102 progression-free survival benefit with PARP inhibitor maintenance monotherapy that  
103 extends beyond completion of treatment. The current analysis demonstrates a  
104 progression-free survival benefit that is sustained for years following completion of 2 years  
105 of maintenance olaparib.. The progression-free survival benefit was consistent  
106 irrespective of whether patients were defined as higher or lower clinical risk or if they had  
107 a *BRCA1* or *BRCA2* mutation. To our knowledge, SOLO1 is the first study reporting  
108 longer-term follow-up for safety in patients with newly diagnosed ovarian cancer receiving  
109 PARP inhibitor maintenance therapy. The safety profile for patients in the maintenance  
110 olaparib arm remained consistent with that reported at the primary data cutoff with no new

111 safety signals. Importantly, no additional cases of myelodysplastic syndrome or acute  
112 myeloid leukaemia were reported.

113 **Implications of all the available evidence**

114 While overall survival data are not yet available, results of SOLO1 support the use of  
115 maintenance olaparib as a standard of care for women with newly diagnosed ovarian  
116 cancer and a BRCA mutation and suggest that maintenance olaparib can provide long-  
117 term remission, and potentially cure, for some patients.

118

## 119 **Introduction**

120 Patients with newly diagnosed advanced ovarian cancer are at high risk of relapse –  
121 approximately 70% of patients will relapse within the first 3 years – and 5-year survival is  
122 30–50%.<sup>1-3</sup> Once relapse occurs, advanced ovarian cancer is typically incurable;  
123 therefore, there is a high unmet need for first-line treatment regimens that can substantially  
124 delay recurrence, prolong survival, and ultimately increase the possibility of cure. Although  
125 evidence suggests that patients harbouring a *BRCA1* or *BRCA2* (BRCA) mutation may  
126 experience longer initial progression-free survival, presence of a BRCA mutation has not  
127 been shown to be predictive of long-term survival,<sup>4,5</sup> and at 5 years' survival is still only  
128 approximately 50%.<sup>2</sup>

129 Olaparib is a first-in-class oral poly(ADP-ribose) polymerase (PARP) inhibitor. Sensitivity  
130 to PARP inhibitors occurs by a variety of mechanisms including trapping of PARP on to  
131 DNA single-strand breaks, preventing their repair and leading to the generation of double-  
132 strand breaks. These double-strand breaks cannot be repaired accurately in tumour cells  
133 that have defects in the homologous recombination repair pathway, such as those  
134 harbouring loss of function mutations in *BRCA1* and/or *BRCA2*.<sup>6</sup> The accumulation of DNA  
135 damage caused by PARP inhibition leads to synthetic lethality and tumour-cell death.<sup>7,8</sup>

136 The landmark SOLO1/GOG 3004 study was the first to assess the efficacy and safety of  
137 a PARP inhibitor as maintenance therapy for patients with newly diagnosed advanced  
138 ovarian cancer.<sup>9</sup> At the data cutoff for the primary analysis (May 17, 2018) median duration  
139 of follow-up was 3·4 years, and results showed that olaparib reduced the risk of disease  
140 progression or death by 70%<sup>9</sup> compared with placebo (hazard ratio [HR] 0·30; 95%  
141 confidence interval [CI] 0·23–0·41,  $p < 0·001$ ; 51% data maturity). Median progression-free  
142 survival was not reached in the olaparib arm and was 13·8 months in the placebo arm.



143 Data from SOLO1 led to approval of olaparib as maintenance treatment for patients with  
144 BRCA-mutated advanced ovarian cancer who are in complete or partial response to first-  
145 line platinum-based chemotherapy in the USA, EU, Japan and other countries and PARP  
146 inhibitor maintenance therapy now represents a new standard of care in the management  
147 of newly diagnosed ovarian cancer. More recently, results from other phase 3 studies with  
148 PARP inhibitors in the newly diagnosed setting have demonstrated efficacy benefits in  
149 populations with and without biomarker-selection.<sup>10-12</sup> However, there are limited data  
150 regarding the long-term benefits and safety of PARP inhibitors extending beyond therapy  
151 completion in newly diagnosed patients.

152 We report here on an updated analysis of progression-free survival from SOLO1  
153 performed after 5 years' follow-up, which to our knowledge is the longest period of follow-  
154 up for a PARP inhibitor in the first-line setting.

155

## 156 **Methods**

### 157 **Study design and participants**

158 The SOLO1 (NCT01844986; GOG-3004) study design has been reported previously.<sup>9</sup> In  
159 short, this was a randomised, double-blind, placebo-controlled, phase 3 study conducted  
160 in 118 centres in 15 countries (Supplementary Appendix).<sup>9</sup> Patients were eligible if they  
161 were  $\geq 18$  years of age, had an Eastern Cooperative Oncology Group performance status  
162 0–1 and had newly diagnosed, histologically confirmed advanced (stage III or IV, as  
163 determined by International Federation of Gynaecology and Obstetrics staging) high-  
164 grade serous or high-grade endometrioid ovarian cancer, including primary peritoneal or  
165 fallopian tube cancer. Patients with stage III disease must have had an attempt at optimal  
166 cytoreductive surgery (upfront or interval), and those with stage IV disease must have had  
167 a biopsy or upfront or interval cytoreductive surgery. Patients had a deleterious or

168 suspected deleterious germline or somatic *BRCA1* and/or *BRCA2* mutation, as  
169 determined by local or central testing, with the use of BRACAnalysis CDx® (Myriad  
170 Genetic Laboratories, Inc., Salt Lake City, Utah, USA) or, in China, a *BRCA1/2* genetic  
171 testing assay (BGI, Shenzhen, China). Patients were required to have completed first-line  
172 platinum-based chemotherapy without bevacizumab and to be in complete clinical  
173 response (no evidence of disease on imaging after chemotherapy and a normal CA-125  
174 level) or partial clinical response (a  $\geq 30\%$  decrease in tumour volume from the start to the  
175 end of chemotherapy, or no evidence of disease on imaging after chemotherapy but a CA-  
176 125 level above the upper limit of the normal range). Patients had to have a life expectancy  
177 of  $\geq 16$  weeks and normal organ and bone marrow function within 28 days of study drug  
178 administration. Patients who had received prior PARP inhibitor therapy or who had a  
179 history of myelodysplastic syndrome, or acute myeloid leukaemia criteria were ineligible. Full  
180 eligibility criteria are in the appendix (pp5–7).

181 All patients provided written, informed consent. The study protocol was approved by the  
182 ethics committees at each participating institution and is available alongside the published  
183 primary analysis.<sup>9</sup> This study was performed in accordance with the Declaration of  
184 Helsinki, Good Clinical Practice guidelines and the AstraZeneca policy on bioethics.

### 185 **Randomisation and masking**

186 Patients were randomly assigned (2:1) to receive olaparib or placebo within 8 weeks  
187 following completion of their last dose of chemotherapy. Randomisation was performed  
188 centrally with a block design, with stratification according to clinical response after  
189 platinum-based chemotherapy (complete or partial). The investigator who enrolled  
190 patients contacted an interactive voice-response system/web-based system for allocation  
191 of randomised treatment.

192 Treatment assignment was masked from patients and from anyone administering  
193 interventions, assessing outcomes, or analysing data, by the use of unique identifiers  
194 generated during randomisation. Olaparib and placebo tablets were identical in  
195 appearance and packaging.

## 196 **Procedures**

197 Patients received either olaparib tablets (300 mg twice daily) or matching placebo, orally  
198 as maintenance monotherapy. Patients received treatment for up to 2 years or until  
199 investigator-assessed objective disease progression on imaging (according to modified  
200 Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1), whichever occurred  
201 first, or was stopped if other discontinuation criteria were met (appendix p7). Patients  
202 without evidence of disease at 2 years stopped receiving trial interventions but patients  
203 with evidence of disease at 2 years could continue to receive study treatment in a blinded  
204 manner if, in the opinion of the investigator, this was in the patient's best interest. Dose  
205 modifications and discontinuation were permitted to manage adverse events (appendix  
206 p7). After discontinuation of the trial intervention, patients could receive treatments at the  
207 investigators' discretion. Crossover between treatment groups within the study was not  
208 permitted, and routine unblinding will not take place until after the prespecified final overall  
209 survival analysis.

210 Patients' tumours were assessed by computed tomography or magnetic resonance  
211 imaging, according to RECIST criteria, at baseline and every 12 weeks ( $\pm 1$  week) up to  
212 3 years, and then every 24 weeks ( $\pm 1$  week) relative to the date of randomisation until  
213 objective radiological disease progression. Central review of scans was not required after  
214 the primary progression-free survival analysis. Following initial disease progression,  
215 patients were followed for second disease progression or death every 12 weeks, with  
216 tumour assessments carried out according to local clinical practice. Adverse events were

217 monitored throughout the treatment period (including at routine clinic visits occurring on  
218 days 8, 15, 22, and 29, then every 4 weeks until week 156, and then every 12 weeks  
219 thereafter) using the National Cancer Institute's Common Terminology Criteria for Adverse  
220 Events (v4.0), and for 30 days after discontinuation of study treatment. Additionally,  
221 patients were proactively followed for myelodysplastic syndrome (MDS), acute myeloid  
222 leukaemia (AML) and new primary malignancy events beyond the 30-day post-treatment  
223 safety assessment; investigators were required to report all instances of these events.  
224 Any case of MDS/AML or new primary malignancy occurring after the 30-day safety follow-  
225 up period was reported as a serious adverse event even after discontinuation of treatment  
226 and regardless of investigator's assessment of causality or knowledge of the treatment  
227 arm.

## 228 **Outcomes**

229 We report here on a post-hoc descriptive updated analysis performed 5 years after the  
230 last patient was randomised (data cutoff: March 5, 2020). The primary endpoint was  
231 investigator-assessed progression-free survival, defined as the time from randomisation  
232 to objective disease progression on imaging according to RECIST v1.1, or death from any  
233 cause; results of the prespecified primary analysis at 51% maturity (data cutoff May 17,  
234 2018) have been previously reported.<sup>9</sup>

235 Secondary efficacy endpoints included in this updated analysis are safety and tolerability,  
236 time from randomisation to second disease progression or death, times from  
237 randomisation to first and second subsequent therapy or death and time from  
238 randomisation to discontinuation of study treatment or death. Additional endpoints have  
239 been described previously.<sup>9,13,14</sup>

240 A final overall survival analysis is planned to be carried out at 60% data maturity as  
241 prespecified in the study protocol.

242 **Statistical analysis**

243 For SOLO1, it was determined that 206 primary endpoint events (disease progression or  
244 death) would provide the trial with 90% power, at a two-sided significance level of 0·05, to  
245 show a significant difference in progression-free survival between the olaparib group and  
246 the placebo group, with a corresponding HR for disease progression or death of 0·62  
247 (assuming a median progression-free survival of 13 months in the placebo group).  
248 Because the rate of primary endpoint events was lower than projected, the protocol was  
249 amended so that the primary analysis of progression-free survival was performed when  
250 approximately 196 events had occurred (data maturity, approximately 50%) or when the  
251 last patient to undergo randomisation had done so at least 3 years earlier, whichever came  
252 first. Our updated progression-free survival analysis was performed 5 years after the last  
253 patient was randomised. Progression-free survival was analysed using a log-rank test  
254 stratified by response to first-line platinum-based chemotherapy, with HRs and CIs  
255 estimated using a Cox proportional hazards model. The proportional hazards assumption  
256 was met for progression-free survival, as assessed by visual inspection.

257 Exploratory post-hoc analyses of progression-free survival were performed in patient  
258 subgroups based on clinical risk (higher-risk and lower risk) and on BRCA mutation status  
259 (*BRCA1* and *BRCA2*). Higher-risk patients were defined as those with stage IV disease  
260 or those with stage III disease that had either residual disease following primary debulking  
261 surgery or had undergone interval surgery. Lower-risk patients were defined as those with  
262 stage III disease who did not have residual disease following primary debulking surgery.  
263 HRs and 95% CIs for exploratory subgroup analyses were estimated from Cox  
264 proportional hazards models including treatment, subgroup of interest and subgroup of  
265 interest by treatment interaction terms.

266 A post-hoc analysis of recurrence-free survival, defined post hoc as time from  
267 randomisation to disease recurrence (new lesions by imaging according to RECIST v1·1)

268 or death for the subgroup of patients in complete clinical response to platinum-based  
269 chemotherapy at baseline (according to electronic case report form data), was performed  
270 using the same methods and model as the exploratory subgroup progression-free survival  
271 analyses.

272 Analyses of time to second disease progression or death, times to first and second  
273 subsequent therapy or death and time to discontinuation of study treatment or death were  
274 performed using a method similar to that used for the analysis of progression-free survival.

275 Efficacy data were analysed in the intent-to-treat population, which included all  
276 randomised patients (full analysis set), and safety was analysed in all patients who  
277 received at least one dose of randomised treatment. All calculations were performed with  
278 SAS® software version 9·04·01·M5 (SAS Institute, Inc, Cary, North Carolina). The study  
279 was overseen by a data monitoring committee. This study is registered with  
280 ClinicalTrials.gov number NCT01844986.

### 281 **Role of the funding source**

282 The trial was designed in collaboration between Drs Moore and DiSilvestro, AstraZeneca,  
283 and the Gynecologic Oncology Group. AstraZeneca was responsible for overseeing the  
284 collection, analysis, and interpretation of the data. All authors had full access to the raw  
285 data (SB, KM, NC, GS, BGK, AOaknin, MF, ALisyanskaya, AF, ALeary, GSS, CG, AOza,  
286 AGM, CA, WB, EH, ESL, PDS). The manuscript was written by the authors with medical  
287 writing support, which was funded by AstraZeneca and Merck Sharp & Dohme Corp., a  
288 subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, who are co-developing olaparib and  
289 provided input into data interpretation. The authors attest to the accuracy and  
290 completeness of the data, and to adherence to the study protocol. The corresponding  
291 author had full access to all the data and the final responsibility to submit for publication.

292

## 293 Results

294 Between September 3, 2013 and March 6, 2015, 391 patients underwent randomisation.  
295 All 260 patients assigned to olaparib and 130 of the 131 patients assigned to placebo  
296 received the trial intervention (one patient in the placebo group decided to withdraw before  
297 receiving the intervention) (**figure 1**). Baseline characteristics were well balanced between  
298 the trial arms (**table 1**). Most patients (72%) had mutations in *BRCA1*; 27% of patients had  
299 mutations in *BRCA2* and three patients (1%), all in the olaparib group, had mutations in  
300 both.

301 For the updated progression-free survival analysis, data cutoff (March 5, 2020) took place  
302 5 years after the last patient was randomised corresponding to a median follow-up for  
303 progression-free survival of 4·8 years (interquartile range [IQR] 2·8–5·3) in the olaparib  
304 group and 5·0 years (IQR 2·6–5·3) in the placebo group. Maintenance treatment duration  
305 was capped at 2 years for patients who had a complete response or no evidence of  
306 disease. Median treatment duration in the safety analysis set was 24·6 months (range 0–  
307 73·6) in the olaparib arm, consistent with the treatment cap, and 13·9 months (range 0·2–  
308 60·9) in the placebo arm. One hundred and twenty-three olaparib patients (47%) and 35  
309 placebo patients (27%) completed their trial intervention at 2 years, per the study protocol  
310 (**figure 1**); 111 patients (43%) and 92 patients (71%), respectively, discontinued study  
311 treatment prior to 2 years, and 26 patients (10%) and 3 patients (2%), respectively  
312 continued their trial intervention beyond 2 years. All 13 patients who were receiving  
313 olaparib at the primary data cutoff (May 17, 2018)<sup>9</sup> were still receiving olaparib at the  
314 current data cutoff. A Kaplan–Meier curve illustrating the time to discontinuation of study  
315 treatment or death is shown in appendix p11.

316 At the updated progression-free survival analysis, 218 of 391 patients had a progression-  
317 free survival event (data maturity 56%). Results showed that the benefit of maintenance

318 olaparib was sustained beyond the end of treatment with a median progression-free  
319 survival of 56·0 months (95% CI 41·9–not reached) in the olaparib arm compared with  
320 13·8 months (95% CI 11·1–18·2) in the placebo arm (HR 0·33; 95% CI 0·25–0·43) (**figure**  
321 **2a**). Based on Kaplan–Meier estimates, 48% of olaparib patients and 21% of placebo  
322 patients were free from progression 5 years after randomisation (**figure 2a**).

323 Results of the secondary efficacy outcomes of time to second disease progression or  
324 death and times to first and second subsequent therapy or death support the observed  
325 progression-free survival benefit (**figure 2b; table 2**). The Kaplan–Meier estimate of the  
326 rate of freedom from second disease progression or death at 5 years in the overall  
327 population was 64% in the olaparib group compared with 41% in the placebo group (HR  
328 0·46; 95% CI 0·33–0·65). The Kaplan–Meier estimate of the rate of freedom from the use  
329 of a first subsequent therapy or death at 5 years was 52% in the olaparib group compared  
330 with 23% in the placebo group (HR 0·33; 95% CI 0·25–0·44). The Kaplan–Meier estimate  
331 of the rate of freedom from the use of a second subsequent therapy or death at 5 years  
332 was 62% in the olaparib group compared with 36% in the placebo group (HR 0·46; 95%  
333 CI 0·34–0·63). At the data cutoff, 104 olaparib patients and 94 placebo patients had  
334 received a first subsequent therapy (appendix p8).

335 The post-hoc endpoint of recurrence-free survival was analysed in the subgroup of  
336 patients who were in clinical complete response to platinum-based chemotherapy at  
337 baseline (73% and 77% of olaparib- and placebo-arm patients, respectively). Results  
338 showed that the risk of disease recurrence or death was reduced by 63% for women in  
339 the olaparib arm compared with those in the placebo arm (HR 0·37; 95% CI 0·27–0·52)  
340 (**figure 2c**). The Kaplan–Meier estimate of the rate of freedom from relapse or death for  
341 women treated with olaparib who had a complete response to chemotherapy at baseline  
342 was 52% at 5 years.



343 Of the 391 patients, 219 (56%) were defined as having higher clinical risk and 172 (44%)  
344 as lower clinical risk. Results of the exploratory subgroup analysis showed that  
345 maintenance olaparib resulted in a consistent progression-free survival benefit over  
346 placebo in both higher- and lower-risk groups (**figure 3**). Median progression-free survival  
347 in the higher-risk group was 40·6 months (95% CI 27·9–not reached) in the olaparib arm  
348 compared with 11·1 months (95% CI 8·3–13·8) in the placebo arm, representing a 29·5-  
349 month improvement (HR 0·34; 95% CI 0·24–0·49). Median progression-free survival in  
350 the lower-risk group was not reached in the olaparib arm and 21·9 months (95% CI 13·7–  
351 33·4) in the placebo arm (HR 0·38; 95% CI 0·25–0·59). Based on Kaplan–Meier  
352 estimates, in the higher-risk subgroup, 42% of olaparib patients were free from  
353 progression at 5 years compared with 17% of placebo patients. In the lower-risk subgroup  
354 56% of olaparib patients were free from progression at 5 years compared with 25% of  
355 placebo patients (**figure 3**). The progression-free survival benefit of maintenance olaparib  
356 compared with placebo was also consistent in patients regardless of whether their tumours  
357 harboured a *BRCA1* or *BRCA2* mutation (appendix p12).

358 The safety profile of maintenance olaparib remained consistent with that seen at the  
359 primary data cutoff.<sup>9</sup> Adverse events of any grade were reported in 256 of 260 (98%)  
360 olaparib patients and 120 of 130 (92%) placebo patients, and grade  $\geq 3$  adverse events  
361 were reported in 103 (40%) and 25 (19%) patients, respectively (**table 3**). Serious adverse  
362 events occurred in 55 (21%) olaparib patients and 17 (13%) placebo patients in the  
363 placebo group, and treatment-related serious adverse event occurred in 27 (10%) and two  
364 (2%) patients, respectively. The most commonly occurring treatment-related serious  
365 adverse event was anaemia, which occurred in 17 of 260 (7%) olaparib patients and no  
366 placebo patients. Adverse events were usually managed by dose interruption (occurring  
367 in 136 [52%] olaparib patients and 22 [17%] placebo patients) or dose reduction (75 [29%]

368 olaparib patients and 4 [3%] placebo patients) rather than discontinuation (30 [12%]  
369 olaparib patients and 4 [3%] placebo patients) .

370 At the time of this analysis, 69 (27%) of 260 patients in the olaparib group and 52 (40%)  
371 of 131 patients in the placebo group had died; deaths related to the disease under  
372 investigation occurred in 65 (25%) of the 260 patients in the olaparib group and 50 (38%)  
373 of the 131 patients in the placebo group. In the olaparib group no adverse events that  
374 occurred during study treatment or up to 30 days after discontinuation resulted in death;  
375 one patient (1%) in the placebo group had an adverse event that occurred during this  
376 follow-up period and resulted in death. No treatment-related adverse events that occurred  
377 during study treatment or up to 30 days after discontinuation were reported as leading to  
378 death in either treatment group. Adverse events that occurred after the 30-day follow-up  
379 period had an outcome of death in two (1%) of 260 patients in the olaparib group, both  
380 due to AML, and no patients in the placebo group. Two deaths (1% of patients) in the  
381 olaparib group and one death (1%) in the placebo group, that were unrelated to adverse  
382 events or the disease under investigation, occurred after the end of the safety follow-up  
383 period.

384 No new cases of MDS or AML were reported since the primary data cutoff (AML was  
385 reported in three of 260 [1%] olaparib patients and no placebo patients at the primary data  
386 cutoff), even with proactive follow-up for MDS, AML and new primary malignancies after  
387 discontinuation of study treatment. Incidence of new primary malignancies remained  
388 balanced between arms with long-term follow-up. New primary malignancies occurred in  
389 eight (3%) olaparib patients (breast cancer [n=6], lip and/or oral cavity cancer [n=1], and  
390 thyroid cancer [n=1]) and five (4%) placebo patients (breast cancer [n=3], lung  
391 adenocarcinoma [n=1] and squamous cell carcinoma of the tongue [n=1]);three (1%) and  
392 two (2%) events, respectively, occurred since the primary data cutoff.

393

## 394 **Discussion**

395 In the current analysis, we report on an updated assessment of progression-free survival,  
396 which took place after 5 years' follow-up. To our knowledge, this is the longest duration of  
397 follow-up for treatment with any PARP inhibitor in a newly diagnosed cancer setting. While  
398 a minority of patients continued to receive olaparib for longer than 2 years, results show  
399 that the benefit derived from maintenance olaparib was sustained substantially beyond  
400 the end of treatment. Median progression-free survival for patients with a BRCA mutation  
401 who received maintenance olaparib (which had not been reached at the primary analysis)<sup>9</sup>  
402 was 56 months, 3·5 years longer than in the placebo arm. In a setting where median  
403 overall survival from initiation of chemotherapy is around 5 years, our findings show that  
404 almost half of patients who received maintenance olaparib remained progression-free 5  
405 years after randomisation, following chemotherapy.<sup>2</sup> It is worth noting that this benefit was  
406 achieved without any detriment to quality of life and maintenance olaparib was associated  
407 with patient-centred benefits including improved quality-adjusted progression-free survival  
408 and longer time without significant symptoms of toxicity, compared with placebo.<sup>14</sup>

409 The absolute improvement in progression-free survival in the SOLO1 study was  
410 substantially greater than that reported with maintenance olaparib in patients with a BRCA  
411 mutation in the relapsed setting (13·6 month improvement in median progression-free  
412 survival in SOLO2),<sup>15</sup> highlighting the importance of early use of maintenance olaparib  
413 therapy. Furthermore, given that ovarian cancer is typically incurable once relapse occurs,  
414 our findings suggest an increased possibility of cure for newly diagnosed patients with a  
415 BRCA mutation; however, longer follow-up is needed for evaluation of survival. Twelve-  
416 year survival has been suggested to be a reasonable surrogate of statistical cure in  
417 patients with ovarian cancer.<sup>16,17</sup> Most events of disease recurrence and subsequent  
418 ovarian cancer deaths occur within 5–10 years of diagnosis, after which time, death rates

419 approach that of women in the general population.<sup>2,18</sup> There is the possibility that the best  
420 chance of cure for the broadest population of women with ovarian cancer (BRCA-mutated  
421 and beyond) may lie with the use of combination treatments. The combination of olaparib  
422 and bevacizumab as maintenance therapy has been shown to improve progression-free  
423 survival compared with bevacizumab and placebo in patients who tested positive for  
424 homologous recombination deficiency.<sup>12</sup> A number of ongoing phase 3 trials (including  
425 NCT03737643, NCT03602859, NCT03740165 and NCT03522246) are assessing  
426 combination treatments in the newly diagnosed advanced ovarian cancer setting and it is  
427 hoped that with use of predictive biomarkers and data from long-term follow-up, treatment  
428 decisions can be optimised to improve outcomes for all patients.

429 A strength of the SOLO1 study is that it included eligible patients irrespective of surgical  
430 status and outcome. While recognising that all patients with advanced ovarian cancer are  
431 potentially at high risk for relapse, we performed exploratory analyses on patients based  
432 on their clinical risk and found the progression-free survival benefit provided by  
433 maintenance olaparib to be consistent. Selection of the optimal first-line treatment regimen  
434 is crucial for all patients, whether they are considered higher or lower risk, as this remains  
435 the only chance of cure for these women. Our findings show that in the lower-risk subgroup,  
436 patients in the maintenance olaparib arm were more than twice as likely to be progression  
437 free at 5 years compared with those in the placebo arm. Previous results from this trial  
438 have also shown there to be no difference in efficacy of maintenance olaparib between  
439 patients who received upfront or interval debulking surgery, and in patients who had  
440 upfront surgery no difference was observed between those with or without residual  
441 disease.<sup>13</sup> Together, these findings highlight that all eligible patients should be offered a  
442 first-line maintenance regimen containing a PARP inhibitor, irrespective of the estimated  
443 risk of relapse.

444 Median progression-free survival was consistent in the placebo arm between patients who  
445 had a *BRCA1* or *BRCA2* mutation, and while progression-free survival in the olaparib arm  
446 appeared to be longer for patients with a *BRCA2* mutation fewer patients were included  
447 in the *BRCA2* mutation subgroup, which may impact the observations. PARP inhibitors  
448 have been shown to provide a consistent efficacy benefit in ovarian cancer patients with  
449 a *BRCA1* or *BRCA2* mutation.<sup>19,20</sup> While only a small number of patients in SOLO1 had a  
450 somatic BRCA mutation, studies in the relapsed ovarian cancer setting have shown  
451 olaparib to have similar efficacy irrespective of whether mutations are germline or somatic  
452 in origin.<sup>21,22</sup> SOLO1 has established BRCA mutations as predictive biomarkers for  
453 olaparib in the newly diagnosed ovarian cancer setting. Results from randomised phase  
454 3 trials have also shown this to be the case in breast, prostate and pancreatic cancers,<sup>23-</sup>  
455 <sup>26</sup> raising the possibility that the presence of a BRCA mutation may be predictive of  
456 response to olaparib, irrespective of tumour type, and research assessing a tumour  
457 agnostic, biomarker-driven approach to treatment is warranted.

458 Recurrence-free survival was analysed in patients who were in clinical complete response  
459 to platinum-based chemotherapy at baseline – around three-quarters of the SOLO1  
460 population. Consistent with other subgroups, the benefit of maintenance olaparib in this  
461 population continued beyond the end of treatment.

462 Maintenance olaparib also increased the time to second disease progression compared  
463 with placebo, suggesting that patients' ability to receive and benefit from subsequent  
464 therapy was not diminished. This finding was observed despite the use of PARP inhibitors  
465 as a first subsequent therapy by over a quarter of patients in the placebo group, which  
466 may explain why in the placebo arm the median time to second disease progression or  
467 death appears long in comparison with median progression-free survival. Overall survival  
468 data were immature at the time of this analysis.

469 The safety profile of maintenance olaparib remained consistent with that seen at the  
470 primary data cutoff<sup>9</sup> and in trials involving patients with relapsed disease.<sup>15,27</sup> It is  
471 reassuring that with active follow-up for these events, no new cases of MDS/AML were  
472 reported and the incidence of new primary malignancies remained balanced between  
473 arms.

474 A limitation of our study is the lack of an active comparator arm. The placebo comparator  
475 arm in SOLO1 was based on standard of care in many countries when the trial was  
476 designed. Bevacizumab is approved in this setting in combination with platinum-based  
477 chemotherapy and continued as maintenance monotherapy, based on a improvement in  
478 median progression-free survival of 3·8 months compared with chemotherapy and  
479 placebo;<sup>28</sup> however, no progression-free survival benefit was observed in a retrospective  
480 analysis of patients with a homologous recombination repair gene mutation  
481 (predominantly in *BRCA1* or *BRCA2*).<sup>29</sup>

482 Results from SOLO1 represent, to our knowledge, the longest follow-up for any PARP  
483 inhibitor in the newly diagnosed advanced ovarian cancer setting. A sustained  
484 progression-free survival benefit was observed following 2 years of treatment with  
485 maintenance olaparib, which is the only PARP inhibitor for which efficacy has been  
486 demonstrated beyond completion of therapy. In a disease setting where only half of  
487 women survive for 5 years from diagnosis, our findings suggest that maintenance olaparib  
488 can provide long-term remission, and potentially cure, for some women.

489

## 490 **Contributors**

491 KM, ESL and PDS contributed to the design of the study. ESL contributed to the conduct  
492 of the study. SB, KM, NC, GS, BGK, AOaknin, MF, ALisyanskaya, AF, ALeary, GSS, CG,

493 AOza, AGM, CA, WB, and PDS contributed to the acquisition of data. KM and EH  
494 accessed and verified the raw data. EH and ESL contributed to data analysis. All authors  
495 contributed to data interpretation. SB led the writing, review and revision of the manuscript.  
496 KM, NC, GS, BGK, AOaknin, MF, ALisyanskaya, AF, ALeary, GSS, CG, AOza, AGM, CA,  
497 WB, EH, ESL and PDS contributed to writing, review and/or revision of the manuscript.

## 498 **Declaration of interests**

499 SB reports grants to her institution from AstraZeneca for this study; grants to her institution  
500 from AstraZeneca, GlaxoSmithKline and Tesaro; personal consulting fees from Amgen,  
501 AstraZeneca, Epsilogen, Genmab, GSK, Immunogen, Mersana, MSD, Merck Serono,  
502 Oncxerna, Pfizer, and Roche; personal fees from Amgen, AstraZeneca, Clovis Oncology,  
503 GSK, Pfizer, Takeda and Tesaro; support for attending a meeting/travel from Nucana;  
504 unpaid participation on a Epsilogen Advisory Board; and role as Director of Membership  
505 for the European Society of Medical Oncology (unpaid). KM reports clinical trial support  
506 paid to her institution for this study; contracts from Genentech/Roche, Lilly  
507 Pharmaceuticals and PTC Therapeutics, for ovarian cancer investigator-initiated trials;  
508 consulting fees from IMab; payment to her institution for educational content in  
509 gynaecological cancers from Onc Live, Physician Education Resource (PER), PRIME  
510 Oncology and Research to Practice; payment to her institution for advisory boards for use  
511 of assets in gynaecological cancers from Alkermes, Aravive, Blueprint Pharmaceuticals,  
512 Eisai, Genentech/Roche, Immunogen, Mersana, Mereo and VBL Therapeutics;  
513 participation on a data safety monitoring board for Incyte; payments to her institution for  
514 being an Associate Director of GOG partners and committee chair for NRG Ovarian  
515 Cancer. NC reports grants from AstraZeneca, PharmaMar and Roche; personal  
516 consulting fees from AstraZeneca, BIOCAD, Clovis Oncology, Eisai, GlaxoSmithKline,  
517 Immunogen, Merck Sharp & Dohme, Mersana, Oncxerna, Pfizer, PharmaMar, Roche and

518 Tesaro; and personal fees from AstraZeneca, Clovis Oncology, Eisai, GlaxoSmithKline,  
519 Merck Sharp & Dohme, Novartis and Tesaro. GS reports grant/research support from  
520 MSD Italia S.r.l.; consulting fees from Johnson & Johnson and Tesaro Bio Italy S.r.l.; and  
521 speakers bureau fees/honoraria from Clovis Oncology Italy S.r.l. AOaknin reports grants  
522 to her institution from AbbVie Deutschland, Ability Pharmaceuticals, Advaxis Inc., Aeterna  
523 Zentaris, Amgen SA, Aprea Therapeutics AB, Bristol Myers Squibb, Clovis Oncology Inc,  
524 Eisai Ltd, F. Hoffmann-La Roche Ltd, Immunogen Inc., Merck, Sharp & Dohme de España  
525 SA, Millennium Pharmaceuticals Inc., Pharmamar SA, Regeneron Pharmaceuticals and  
526 Tesaro Inc.; personal fees from AstraZeneca, Clovis Oncology, Deciphera Pharmarceutia,  
527 Genmab, GlaxoSmithKline, Immunogen, Mersana Therapeutic, PharmaMar, Roche,  
528 Sutro and Tesaro; and support for attending meetings and/or travel from AstraZeneca,  
529 Pharmamar and Roche. MF reports personal advisory board and lecture fees, support to  
530 travel to a meeting and a grant to his institution from AstraZeneca; personal advisory board  
531 fees and a grant to his institution from Novartis; personal advisory board fees from  
532 GlaxoSmithKline, Lilly, MSD and Takeda; personal lecture fees from Act Genomics and  
533 GlaxoSmithKline; research support to his institution from BeiGene; consulting for AbbVie  
534 (not remunerated); and participation on the AGITG IDMSC. AF reports support for  
535 attending a medical congress from AstraZeneca. ALeary reports grants from AstraZeneca  
536 and Sanofi; consulting fees from Seattle Genetics; honoraria/reimbursement and advisory  
537 board fees from AstraZeneca; advisory board fees or CME from Ability Pharma, Biocad,  
538 Clovis Oncology, GSK, Medscape, Merck Serono, MSD, TouchCongress and Zentalis;  
539 and support for attending meetings and/or travel from AstraZeneca, Clovis Oncology, GSK  
540 and Roche; and participation on a data safety monitoring board or advisory board for  
541 ARIEL4 and TROPHIMMUNE. GSS reports instiitutional research support from  
542 AstraZeneca/Merck for this study; institutional research support from Novartis and Roche;  
543 and consulting fees paid to his institution from Biovica and Seagen. CG reports clinical



544 trial funding for this study to his institution from AstraZeneca; clinical research grants to  
545 his institution from Aprea, AstraZeneca, BergenBio, Clovis, GlaxoSmithKline, Medannexin,  
546 MSD, Novartis, Nucana and Tesaro; personal consulting fees from AstraZeneca,  
547 GlaxoSmithKline, MSD and Tesaro; honoraria for lectures/presentations from  
548 AstraZeneca, Chugai, Clovis Oncology, GlaxoSmithKline, MSD, Nucana, Roche, Takeda  
549 and Tesaro; honoraria for lectures/presentations/preparing educational materials from  
550 Cor2Ed; advisory board attendance for AstraZeneca, Chugai, GlaxoSmithKline, MSD,  
551 Nucana, Roche and Tesaro; and being a committee member on the Scottish Medicines  
552 Consortium. AOza reports a grant from AstraZeneca to his institution outside the  
553 submitted work. AGM reports clinical trial funding from GlaxoSmithKline and Roche;  
554 consulting fees from Alkermes, Amgen, AstraZeneca, Clovis, Genmab, GlaxoSmithKline,  
555 Immunogen, Mersana, MSD, Oncoinvent, Pharmamar, Roche, Sotio and Takeda;  
556 personal fees from AstraZeneca, Clovis, GSK, MSD and Roche; support for attending  
557 meetings and/or travel from AstraZeneca, GSK, MSD, Pharmamar and Roche; and being  
558 the current chairman of GEICO and the chairman from 2018 to 2020 of ENGOT. CA  
559 reports receiving advisory board fees from AbbVie, AstraZeneca/Merck, Eisai/Merck,  
560 Mersana Therapeutics, Repare Therapeutics and Roche/Genentech; participation on an  
561 advisory board for Blueprint Medicine; participation on the board of directors for GOG  
562 Foundation and NRG Oncology; clinical trial funding to her institution from , AstraZeneca  
563 for this study; and clinical trial funding to her institution from AbbVie, AstraZeneca, Clovis,  
564 and Genentech. ESL reports full-time employment with AstraZeneca during the conduct  
565 of the study and AstraZeneca stock ownership. EH reports full-time employment with  
566 AstraZeneca, contracted by PHASTAR, during the conduct of the study. BGK,  
567 ALisyanskaya, WB and PDS declared no competing interests.

568 **Data sharing**

569 Data underlying the findings described in this manuscript may be obtained in accordance  
570 with AstraZeneca's data sharing policy described at  
571 <https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure>.

572 **Acknowledgements**

573 This study was funded by AstraZeneca and is part of an alliance between AstraZeneca  
574 and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA  
575 (MSD).

576 We thank all the women who participated in this study, their families, and the investigators.

577 Medical writing assistance was provided by Elin Pyke, MChem, of Mudskipper Business  
578 Ltd, funded by AstraZeneca and MSD.

579

580

581 **References**

- 582 1. Ledermann JA, Raja FA, Fotopoulou C, et al. Newly diagnosed and relapsed epithelial  
583 ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.  
584 *Ann Oncol* 2013; **24 Suppl 6**: vi24-32.
- 585 2. Tewari KS, Burger RA, Enserro D, et al. Final overall survival of a randomized trial of  
586 bevacizumab for primary treatment of ovarian cancer. *J Clin Oncol* 2019; **37**(26): 2317-28.
- 587 3. De Angelis R, Sant M, Coleman MP, et al. Cancer survival in Europe 1999-2007 by  
588 country and age: results of EURO CARE--5-a population-based study. *Lancet Oncol* 2014;  
589 **15**(1): 23-34.
- 590 4. Kim SI, Lee M, Kim HS, et al. Effect of BRCA mutational status on survival outcome in  
591 advanced-stage high-grade serous ovarian cancer. *J Ovarian Res* 2019; **12**(1): 40.
- 592 5. Kotsopoulos J, Rosen B, Fan I, et al. Ten-year survival after epithelial ovarian cancer  
593 is not associated with BRCA mutation status. *Gynecol Oncol* 2016; **140**(1): 42-7.
- 594 6. Walsh CS. Two decades beyond BRCA1/2: Homologous recombination, hereditary  
595 cancer risk and a target for ovarian cancer therapy. *Gynecol Oncol* 2015; **137**(2): 343-50.
- 596 7. Bryant HE, Schultz N, Thomas HD, et al. Specific killing of BRCA2-deficient tumours  
597 with inhibitors of poly(ADP-ribose) polymerase. *Nature* 2005; **434**(7035): 913-7.
- 598 8. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant  
599 cells as a therapeutic strategy. *Nature* 2005; **434**(7035): 917-21.
- 600 9. Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly  
601 diagnosed advanced ovarian cancer. *N Engl J Med* 2018; **379**(26): 2495-505.
- 602 10. Coleman RL, Fleming GF, Brady MF, et al. Veliparib with first-line chemotherapy and  
603 as maintenance therapy in ovarian cancer. *N Engl J Med* 2019; **381**(25): 2403-15.

- 604 11. Gonzalez-Martin A, Pothuri B, Vergote I, et al. Niraparib in patients with newly  
605 diagnosed advanced ovarian cancer. *N Engl J Med* 2019; **381**(25): 2391-402.
- 606 12. Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus bevacizumab as first-line  
607 maintenance in ovarian cancer. *N Engl J Med* 2019; **381**(25): 2416-28.
- 608 13. DiSilvestro P, Colombo N, Scambia G, et al. Efficacy of maintenance olaparib for  
609 patients with newly diagnosed advanced ovarian cancer with a brca mutation: Subgroup  
610 analysis findings from the solo1 trial. *J Clin Oncol* 2020; **38**(30): 3528-37.
- 611 14. Friedlander M, Moore KN, Colombo N, et al. Patient-centred outcomes and effect of  
612 disease progression on health status in patients with newly diagnosed advanced ovarian  
613 cancer and a BRCA mutation receiving maintenance olaparib or placebo (SOLO1): a  
614 randomised, phase 3 trial. *Lancet Oncol* 2021; **22**(5): 632-42.
- 615 15. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance  
616 therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation  
617 (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet*  
618 *Oncol* 2017; **18**(9): 1274-84.
- 619 16. McLaughlin JR, Rosen B, Moody J, et al. Long-term ovarian cancer survival associated  
620 with mutation in BRCA1 or BRCA2. *J Natl Cancer Inst* 2013; **105**(2): 141-8.
- 621 17. Sopik V, Iqbal J, Rosen B, Narod SA. Why have ovarian cancer mortality rates  
622 declined? Part I. Incidence. *Gynecol Oncol* 2015; **138**(3): 741-9.
- 623 18. Harter P, Hilpert F, Mahner S, Heitz F, Pfisterer J, du Bois A. Systemic therapy in  
624 recurrent ovarian cancer: current treatment options and new drugs. *Expert Rev Anticancer*  
625 *Ther* 2010; **10**(1): 81-8.
- 626 19. Lorusso D, Lotz J-P, Harter P, et al. Maintenance olaparib plus bevacizumab (bev)  
627 after platinum-based chemotherapy plus bev in patients (pts) with newly diagnosed advanced

628 high-grade ovarian cancer (HGOC): Efficacy by BRCA1 or BRCA2 mutation in the Phase III  
629 PAOLA-1 trial. *J Clin Oncol* 2020; **38 (suppl 15)**: Abstr 6039.

630 20. Gonzalez Martin A, Matulonis UA, Korach J, et al. Niraparib efficacy and safety in  
631 patients with BRCA mutated (BRCAm) ovarian cancer: Results from three phase 3 niraparib  
632 trials. *J Clin Oncol* 2021; **39 (15\_suppl)**: 5518-.

633 21. Dougherty BA, Lai Z, Hodgson DR, et al. Biological and clinical evidence for somatic  
634 mutations in BRCA1 and BRCA2 as predictive markers for olaparib response in high-grade  
635 serous ovarian cancers in the maintenance setting. *Oncotarget* 2017; **8(27)**: 43653-61.

636 22. Pignata S, Oza AM, Hall G, et al. ORZORA: Maintenance olaparib for patients with  
637 platinum-sensitive relapsed ovarian cancer: outcomes by somatic and germline BRCA and  
638 other homologous recombination repair gene mutation status. *Gynecol Oncol* 2021: Abstr  
639 10503.

640 23. Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline BRCA-Mutated  
641 Metastatic Pancreatic Cancer. *N Engl J Med* 2019; **381(4)**: 317-27.

642 24. de Bono J, Mateo J, Fizazi K, et al. Olaparib for Metastatic Castration-Resistant  
643 Prostate Cancer. *N Engl J Med* 2020; **382(22)**: 2091-102.

644 25. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients  
645 with a Germline BRCA Mutation. *N Engl J Med* 2017; **377(6)**: 523-33.

646 26. Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant Olaparib for Patients with BRCA1- or  
647 BRCA2-Mutated Breast Cancer. *N Engl J Med* 2021; **384(25)**: 2394-405.

648 27. Ledermann JA, Harter P, Gourley C, et al. Overall survival in patients with platinum-  
649 sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an  
650 updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. *Lancet*  
651 *Oncol* 2016; **17(11)**: 1579-89.

652 28. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary  
653 treatment of ovarian cancer. *N Engl J Med* 2011; **365**(26): 2473-83.

654 29. Norquist BM, Brady MF, Harrell MI, et al. Mutations in Homologous Recombination  
655 Genes and Outcomes in Ovarian Carcinoma Patients in GOG 218: An NRG  
656 Oncology/Gynecologic Oncology Group Study. *Clin Cancer Res* 2018; **24**(4): 777-83.

657

658

659 **Table 1: Baseline characteristics\***

Characteristic	Olaparib group (n=260)	Placebo group (n=131)
Clinical response after platinum-based chemotherapy <sup>†</sup> , n (%)		
Complete response	213 (82)	107 (82)
Partial response	47 (18)	24 (18)
Number of cycles of platinum-based chemotherapy, n (%)		
4	2 (1)	0
5	2 (1)	1 (1)
6	198 (76)	106 (81)
7	17 (7)	10 (8)
8	18 (7)	7 (5)
9	23 (9)	7 (5)
Chemotherapy administration		
Only intravenous	225 (87)	107 (82)
Intraperitoneal <sup>‡</sup>	35 (13)	24 (18)
Debulking surgery <sup>§</sup> , n (%)		
Upfront	161 (62)	85 (65)
Interval	94 (36)	43 (33)
None	4 (2)	3 (2)
ECOG performance status, n (%)		
0	200 (77)	105 (80)
1	60 (23)	25 (19)
Missing	0	1 (1)
Primary tumour location, n (%)		
Ovary	220 (85)	113 (86)
Fallopian tubes	22 (8)	11 (8)
Primary peritoneal	15 (6)	7 (5)
Other <sup>  </sup>	3 (1)	0
FIGO stage**, n (%)		
III	220 (85)	105 (80)
IV	40 (15)	26 (20)

Characteristic	Olaparib group (n=260)	Placebo group (n=131)
CA-125 level, n (%)		
≤ULN	247 (95)	123 (94)
>ULN	13 (5)	7 (5)
Missing	0	1 (1)
Histology, n (%)		
Serous	246 (95)	130 (99)
Endometrioid	9 (3)	0
Mixed serous/endometrioid	5 (2)	1 (1)
BRCA mutation <sup>††</sup> , n (%)		
<i>BRCA1</i>	191 (73)	91 (69)
<i>BRCA2</i>	66 (25)	40 (31)
Both <i>BRCA1</i> and <i>BRCA2</i>	3 (1)	0
Germline	258 (99) <sup>‡‡</sup>	131 (100)
Somatic	2 (1)	0

660 \*Percentages may not total 100 because of rounding. ECOG denotes Eastern Cooperative Oncology Group.

661 †Complete response was defined as no evidence of disease on imaging (according to modified Response  
662 Evaluation Criteria in Solid Tumors, version 1.1) after chemotherapy and a normal CA-125 level. Partial response  
663 was defined as a decrease of at least 30% in tumour volume from the start to the end of chemotherapy or no  
664 evidence of disease on imaging after chemotherapy but a CA-125 level above the upper limit of the normal range  
665 (ULN).

666 ‡Patients are included in this category if any first-line chemotherapy was given by intraperitoneal administration.

667 §One patient had surgery on completion of chemotherapy and was not included in analyses of surgery timing.

668 ¶Other tumour locations included a combination of the ovary, fallopian tube, peritoneum, and omentum (in one  
669 patient), a combination of the ovary and peritoneum (one patient), and a combination of the ovary and fallopian  
670 tube (one patient).

671 \*\*International Federation of Gynecology and Obstetrics (FIGO) stage III indicates involvement of one or both  
672 ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis or metastasis to  
673 the retroperitoneal lymph nodes (or both), and stage IV indicates distant metastasis excluding peritoneal  
674 metastasis.



675 ††BRCA mutation status was determined centrally (at Myriad or BGI) or locally. For the five patients from China,  
676 germline BRCA mutation status was determined in China with the use of the BGI test.

677 ‡Includes one patient with a variant of uncertain significance.

678

679 **Table 2: Secondary efficacy outcomes of times to first (TFST) and second (TSST)**  
 680 **subsequent therapy or death in the overall population**

	Olaparib (n=260)	Placebo (n=131)
<b>TFST</b>		
Events, n (%)	118 (45)	97 (74)
Event free at 5 years, %*	52	23
Median, months (95% CI)	NR	15·1 (12·7–20·5)
	HR 0·33 (95% CI 0·25–0·44)	
<b>TSST</b>		
Events, n (%)	95 (37)	77 (59)
Event free at 5 years, %*	62	36
Median, months (95% CI)	NR	40·7 (32·9–55·3)
	HR 0·46 (95% CI 0·34–0·63)	

681 \*By Kaplan-Meier estimates

682

683

684 **Table 3: Summary of adverse events\***

n (%)	Olaparib (n=260)			Placebo (n=130)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Nausea	200 (77)	2 (1)	0	49 (38)	0	0
Fatigue or asthenia	156 (60)	10 (4)	0	52 (40)	2 (2)	0
Vomiting	103 (40)	1 (<1)	0	18 (14)	1 (1)	0
Diarrhoea	82 (32)	8 (3)	0	32 (25)	0	0
Constipation	72 (28)	0	0	25 (19)	0	0
Arthralgia	65 (25)	0	0	35 (27)	0	0
Abdominal pain	62 (24)	4 (2)	0	24 (9)	1 (1)	0
Headache	59 (23)	1 (<1)	0	28 (22)	3 (2)	0
Dysgeusia	56 (22)	0	0	5 (4)	0	0
Dizziness	53 (20)	0	0	19 (15)	1 (1)	0
Decreased appetite	53 (20)	0	0	13 (10)	0	0
Anaemia <sup>†</sup>	47 (18)	51 (20)	6 (2)	11 (8)	2 (2)	0
Upper abdominal pain	45 (17)	0	0	17 (13)	0	0

Cough	44 (17)	0	0	28 (22)	0	0
Dyspepsia	43 (17)	0	0	16 (12)	0	0
Back pain	42 (16)	0	0	16 (12)	0	0
Dyspnoea	40 (15)	0	0	7 (5)	0	0
Neutropenia <sup>‡</sup>	38 (15)	21 (8)	1 (<1)	9 (7)	5 (4)	1 (1)
Pyrexia	31 (12)	0	0	12 (9)	0	0
Upper respiratory tract infection	30 (12)	0	0	12 (9)	0	0
Pain in extremity	30 (12)	0	0	11 (8)	0	0
Urinary tract infection	29 (11)	2 (1)	0	8 (6)	0	0
Nasopharyngitis	28 (11)	0	0	17 (13)	0	0
Thrombocytopenia <sup>¶</sup>	27 (10)	1 (<1)	1 (<1)	3 (2)	0	2 (2)
Insomnia	27 (10)	0	0	16 (12)	0	0
Myalgia	25 (10)	0	0	13 (10)	0	0
Peripheral oedema	25 (10)	0	0	9 (7)	0	0
Cystitis	13 (5)	1 (<1)	0	0	5 (4)	0
Hypertension	8 (3)	1 (<1)	0	10 (8)	2 (2)	0

Syncope	2 (1)	1 (<1)	0	1 (1)	2 (2)	0
Breast cancer	0	1 (<1)	0	0	2 (2)	1 (1)

685 \*Data are shown for treatment-emergent adverse events that occurred in at least 10% of patients in either treatment group and all grade 3 and 4 events occurring  
686 in at least 2% of patients in either treatment arm during study treatment or up to 30 days after discontinuation of the intervention. All grade 3 and 4 events are  
687 shown in the appendix pp8–11. The only grade 5 adverse event to occur was a death in the placebo group. †Includes patients with anaemia, decreased  
688 haemoglobin level, decreased haematocrit, decreased red-cell count, erythropenia, macrocytic anaemia, normochromic anaemia, normochromic normocytic  
689 anaemia, or normocytic anaemia. ‡Includes patients with neutropenia, febrile neutropenia, neutropenic sepsis, neutropenic infection, decreased neutrophil  
690 count, idiopathic neutropenia, granulocytopenia, decreased granulocyte count, or agranulocytosis. ¶Thrombocytopenia is included to complete the profile of  
691 haematologic toxic effects; includes patients with thrombocytopenia, decreased platelet production, decreased platelet count, or decreased plateletcrit.

692

693

694

695 **Figure legends**

696 ***Figure 1: Trial profile at data cutoff March 5, 2020***

697

698 ***Figure 2: Kaplan–Meier estimates of (A) long-term progression-free survival, (B)***  
699 ***time to second progression or death and (C) long-term recurrence-free survival\****

700 \*Patients in complete response at baseline based on electronic case report form data

701

702 ***Figure 3: Kaplan–Meier estimates of long-term progression-free survival in patients***  
703 ***with (A) higher and (B) lower clinical risk***

704

## Table of contents

<b>SOLO1 investigators</b> .....	<b>1</b>
<b>Methods</b> .....	<b>5</b>
<b>Full eligibility criteria</b> .....	<b>5</b>
<b>Discontinuation criteria</b> .....	<b>7</b>
<b>Dose modification and discontinuation for adverse events</b> .....	<b>7</b>
<b>Results</b> .....	<b>8</b>
<b>Supplementary table 1: First subsequent anticancer therapies</b> .....	<b>8</b>
<b>Supplementary table 2: Summary of adverse events*</b> .....	<b>8</b>
<b>Supplementary figure 1: Kaplan–Meier estimate of time to discontinuation of study treatment or death (full analysis set)</b> .....	<b>11</b>
<b>Supplementary figure 2: Kaplan–Meier estimate of long-term progression-free survival in patients with (A) a <i>BRCA1</i> or (B) a <i>BRCA2</i> mutation</b> .....	<b>12</b>

## SOLO1 investigators

The table below lists the principal investigator for each site that randomised patients in the study.

<b>Site no.</b>	<b>Principal Investigator</b>	<b>No. of patients randomised</b>	<b>Country</b>
4102	Nicoletta Colombo	20	Italy
4106	Giovanni Scambia	18	Italy
6003	Byoung-Gie Kim	11	South Korea
7001	Ana Oaknin	11	Spain
0305	Michael Friedlander	10	Australia
6203	Alla Lisyanskaya	10	Russia
2804/2805	Susana Banerjee	9	UK
2302	Anne Floquet	9	France
2307	Catherine Lhomme*/Alexandra Leary	9	France
5001	Gabe Sonke	9	The Netherlands
2801	Charlie Gourley	9	UK
1001	Amit Oza	8	Canada
7002	Antonio González-Martín	8	Spain
7907	Carol Aghajanian	7	USA
4107	Francesco Raspagliesi	6	Italy
6002	Jae-Weon Kim	6	South Korea
7849	William Bradley	6	USA
7803/7804/7805	Joyce Liu	5	USA
1005	Lucy Gilbert	5	Canada

<b>Site no.</b>	<b>Principal Investigator</b>	<b>No. of patients randomised</b>	<b>Country</b>
1004	Diane Provencher	5	Canada
4105	Francesco Cognetti	5	Italy
6001	Joo-Hyun Nam	5	South Korea
5706	Magdalena Sikorska	5	Poland
6205	Sergey Tjulandin	5	Russia
7861	Daniel Anderson	5	USA
7801	Cara Mathews	5	USA
0304	Clare Scott	4	Australia
1007	Allan Covens	4	Canada
1002	Hal Hirte	4	Canada
2309	Frédéric Selle*/Jean-Pierre Lotz	4	France
4003	Amnon Amit	4	Israel
4001	Roni Shapira Frommer	4	Israel
6006	Sang-Yoon Park	4	South Korea
7004	Andrés Poveda	4	Spain
7873	Robert Burger	4	USA
7855	Guilherme Cantuaria	4	USA
1003	Stephen Welch	3	Canada
2306	Alain Lortholary	3	France
4005	Ram Eitan	3	Israel
4309	Koji Matsumoto	3	Japan
4312	Kazuhiro Takehara	3	Japan
5705	Mariusz Bidzinski	3	Poland
5702	Tomasz Byrski	3	Poland
6204	Olga Mikheeva	3	Russia
7007	Beatriz Pardo Búrdalo	3	Spain
7829	Michael Callahan	3	USA
7927	Michael Carney	3	USA
7816	Robin Farias-Eisner	3	USA
7850	Joanie Hope	3	USA
7826	Daniel Kredentser	3	USA
7846	David O'Malley	3	USA
7823	Jeanne Schilder	3	USA
0306	Linda Mileshkin	2	Australia
1306	Rutie Yin	2	China
1307	Jianqing Zhu	2	China
4108	PierFranco Conte	2	Italy
4101	Sandro Pignata	2	Italy
4301	Keiichi Fujiwara	2	Japan
4313	Yasuyuki Hirashima	2	Japan
4305	Toshiaki Saito	2	Japan



<b>Site no.</b>	<b>Principal Investigator</b>	<b>No. of patients randomised</b>	<b>Country</b>
6005	Sang-Young Ryu	2	South Korea
6210	Galina Statsenko	2	Russia
7006	Andrés Redondo	2	Spain
7005	María Jesús Rubio Pérez	2	Spain
2808	James Brenton	2	UK
7890	Sarah Adams	2	USA
7872	Deborah Armstrong	2	USA
7879	Michael Carney	2	USA
7802	Oliver Dorigo	2	USA
7892	John Farley	2	USA
7919/7926	Lou Fehrenbacher	2	USA
7864	James Kendrick	2	USA
7895	Joseph Lucci	2	USA
7888	Donna McNamara	2	USA
7807	Kathleen Moore	2	USA
7874	Heather Pulaski	2	USA
7840	Luis Rojas-Espailat	2	USA
7825	Peter Rose	2	USA
7865	Mark Shahin	2	USA
7830	Nicholas Taylor	2	USA
7819	Timothy Vanderkwaak	2	USA
7847	Robert Wenham	2	USA
0701	Roberto Hegg	1	Brazil
1006	Marie Plante	1	Canada
1317	Qi Zhou	1	China
2305	Florence Joly	1	France
2310	Béatrice Weber*/Marie-Christine Kaminsky	1	France
4002	Yfat Kadan	1	Israel
4304	Kenji Tamura	1	Japan
4310	Hidemichi Watari	1	Japan
6004	Jae Hoon Kim	1	South Korea
5704	Pawel Rózanowski	1	Poland
7003	Andrés Cervantes Ruipérez	1	Spain
2802	Jonathan Ledermann	1	UK
2806	Christopher Poole	1	UK
7914	Jamie Bakkum-Gamez	1	USA
7815	Kian Behbakht	1	USA
7843	Christopher Darus	1	USA
7841	Babak Edraki	1	USA
7901	David Engle	1	USA
7878	Charles Harrison	1	USA

<b>Site no.</b>	<b>Principal Investigator</b>	<b>No. of patients randomised</b>	<b>Country</b>
7917	Monica Hayes	1	USA
7860	Robert Higgins	1	USA
7903	Timothy Lestingi	1	USA
7806	Nathalie McKenzie	1	USA
7867	Peter Morris	1	USA
7828	David Mutch	1	USA
7883	Janet Osborne	1	USA
7876	Elena Ratner	1	USA
7899	Bobbie Jo Rimel	1	USA
7814	Shohreh Shahabi	1	USA
7886	Gamini Soori	1	USA
7851	Nicola Spirtos	1	USA
7908	Diane Yamada	1	USA

\*Former principal investigator

## Methods

### Full eligibility criteria

#### *Inclusion criteria*

1. Patients must be aged  $\geq 18$  years
2. Female patients with newly diagnosed, histologically confirmed, advanced (International Federation of Gynecology and Obstetrics [FIGO] stage III–IV) *BRCA1* or *BRCA2* (BRCA)-mutated high-grade serous or high-grade endometrioid (based on local histopathological findings) ovarian cancer, primary peritoneal cancer, and/or fallopian tube cancer who have completed first-line, platinum-based chemotherapy (intravenous or intraperitoneal)
3. Stage III patients must have had one attempt at optimal debulking surgery (upfront or interval debulking). Stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery
4. Documented mutation in *BRCA1* or *BRCA2* that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function)
5. Patients who have completed first-line platinum- (eg, carboplatin or cisplatin) containing therapy (intravenous or intraperitoneal) prior to randomisation
  - Patients must have, in the opinion of the investigator, clinical complete response or partial response and have no clinical evidence of disease progression on the post-treatment scan or a rising CA-125 level following completion of this chemotherapy course. Patients with stable disease on the post-treatment scan at completion of first-line, platinum-containing therapy are not eligible for the study
  - ‘Response’ refers to patients being, in the opinion of the investigator, in clinical complete response or partial response on the post-treatment scan. Clinical complete response is defined as no evidence of Response Evaluation Criteria in Solid Tumours (RECIST) measurable or non-measurable disease on the post-treatment scan and a normal CA-125 level. Partial response is defined as  $\geq 30\%$  reduction in tumour volume demonstrated from the start to finish of chemotherapy OR no evidence of RECIST measurable disease on the post-treatment scan with a CA-125 level that has not decreased to within the normal range
  - Platinum-based chemotherapy course must have consisted of a minimum of six and a maximum of nine treatment cycles; however, if platinum-based therapy must be discontinued early as a result of toxicities specifically related to the platinum regimen, patients must have received a minimum of four cycles of the platinum regimen
  - Patients must not have received bevacizumab during their first-line course of treatment, either in combination or as maintenance therapy following combination therapy
  - Patients must not have received an investigational agent during their first-line course of chemotherapy
  - Patients must be randomised within 8 weeks after their last dose of chemotherapy (last dose is the day of the last infusion)
6. Pre-treatment CA-125 measurements must meet a criterion specified below:
  - If the first value is less than or equal to the upper limit of normal (ULN), the patient is eligible to be randomised and a second sample is not required
  - If the first value is greater than ULN, a second assessment must be performed at least 7 days after the first. If the second assessment is  $\geq 15\%$  more than the first, the patient is not eligible
7. Patients must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:
  - Haemoglobin  $\geq 10.0$  g/dL with no blood transfusion in the past 28 days
  - Absolute neutrophil count  $\geq 1.5 \times 10^9/L$
  - Platelet count  $\geq 100 \times 10^9/L$
  - Total bilirubin  $\leq 1.5 \times$  institutional ULN
  - Aspartate aminotransferase/alanine aminotransferase  $\leq 2.5 \times$  institutional ULN unless liver metastases are present, in which case they must be  $\leq 5 \times$  ULN
  - Serum creatinine  $\leq 1.5 \times$  institutional ULN
8. Eastern Cooperative Oncology Group performance status 0–1
9. Patients must have a life expectancy  $\geq 16$  weeks
10. Postmenopausal or evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test prior to Myriad BRCA test during screening part 1, within 28 days of study treatment and confirmed prior to treatment on day 1

11. Patient is willing and able to comply with the protocol for the duration of the study, including undergoing treatment and scheduled visits and examinations
12. Formalin-fixed, paraffin-embedded tumour sample from the primary cancer must be available for central testing. If there is not written confirmation of the availability of an archived tumour sample prior to enrolment, the patient is not eligible for the study

#### *Exclusion criteria*

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
2. *BRCA1* and/or *BRCA2* mutations that are considered to be non-detrimental
3. Patients with early stage disease (FIGO Stage I, IIA, IIB, or IIC)
4. Stable disease or progressive disease on the post-treatment scan, or clinical evidence of progression at the end of the patient's first-line chemotherapy treatment
5. Patients where more than one debulking surgery has been performed before randomisation to the study. Eligible patients are those who, at the time of diagnosis, are deemed to be unresectable and undergo only a biopsy or oophorectomy but then go on to receive chemotherapy and interval debulking surgery
6. Patients who have previously been diagnosed and treated for earlier-stage ovarian, fallopian tube, or primary peritoneal cancer
7. Patients who have previously received chemotherapy for any abdominal or pelvic tumour, including treatment for prior diagnosis at an earlier stage for their ovarian, fallopian tube, or primary peritoneal cancer. Patients who have received prior adjuvant chemotherapy for localised breast cancer may be eligible, provided that it was completed more than 3 years prior to registration, and that the patient remains free of recurrent or metastatic disease
8. Patients with synchronous primary endometrial cancer unless both of the following criteria are met:
  - Stage <2
  - Less than 60 years old at the time of diagnosis of endometrial cancer with stage IA or IB grade 1 or 2, or stage IA grade 3 endometrioid adenocarcinoma OR ≥60 years old at the time of diagnosis of endometrial cancer with stage IA grade 1 or 2 endometrioid adenocarcinoma. Patients with serous or clear cell adenocarcinoma or carcinosarcoma of the endometrium are not eligible
9. Patients who have had drainage of their ascites during the final two cycles of their last chemotherapy regimen prior to enrolment on the study
10. Previous randomisation in the present study
11. Participation in another clinical study with an investigational product during their chemotherapy course immediately prior to randomisation
12. Any previous treatment with a poly(ADP-ribose) polymerase inhibitor (PARP) inhibitor, including olaparib
13. Other malignancy within the last 5 years, except adequately treated non-melanoma skin cancer; curatively treated in-situ cancer of the cervix; ductal carcinoma in-situ; Stage I grade 1 endometrial carcinoma; or other solid tumours, including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years. Patients with a history of localised breast cancer may be eligible, provided they completed their adjuvant chemotherapy more than 3 years prior to registration and that the patient remains free of recurrent or metastatic disease
14. Resting electrocardiogram with a corrected QT interval >470 msec on two or more time points within a 24-hour period or family history of long QT syndrome
15. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment (or a longer period depending on the defined characteristics of the agents used)
16. Concomitant use of known potent cytochrome P450 3A4 inhibitors, such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin, and nelfinavir
17. Persistent toxicities (Common Terminology Criteria for Adverse Events grade ≥2) caused by previous cancer therapy, excluding alopecia
18. Patients with myelodysplastic syndrome/acute myeloid leukaemia
19. Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study, as long as these were started at least 4 weeks prior to treatment. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days

20. Major surgery within 2 weeks of starting study treatment, and patients must have recovered from any effects of any major surgery
21. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on high-resolution computed tomography scan or any psychiatric disorder that prohibits obtaining informed consent
22. Patients unable to swallow orally administered medication, and patients with gastrointestinal disorders likely to interfere with absorption of the study medication
23. Breastfeeding women
24. Immunocompromised patients (eg, patients who are known to be serologically positive for HIV)
25. Patients with a known hypersensitivity to olaparib or any of the excipients of the product
26. Patients with known active hepatitis (ie, hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids
27. Previous allogeneic bone marrow transplant
28. Whole-blood transfusions in the last 120 days prior to entry to the study

#### **Discontinuation criteria**

Study treatment continued until investigator-assessed objective radiological disease progression (modified RECIST version 1.1 criteria), was stopped at 2 years in patients with complete response or no evidence of disease, could continue beyond 2 years in patients with ongoing partial response or was stopped if the following discontinuation criteria were met:

- Patient decision
- Adverse event
- Severe non-compliance with study protocol
- Bone marrow findings consistent with MDS/AML

#### **Dose modification and discontinuation for adverse events**

Any toxicity observed during study treatment could be managed by study treatment interruption if deemed appropriate by the investigator. Repeat dose interruptions were allowed as required for a maximum of 14 days on each occasion (or up to 28 days after discussion with the study physician). Study treatment was interrupted until the patient recovered completely or the toxicity reverted to CTCAE grade 1 or less. Where toxicity reoccurred following rechallenge with study treatment, and where further dose interruptions were considered inadequate for the management of toxicity, then the patient was considered for dose reduction or had to permanently discontinue study treatment. Once the study treatment dose was reduced it could not be re-escalated, even if the adverse event resolved. Treatment must be interrupted if any CTCAE grade 3 or 4 adverse event occurred that the investigator considered to be related to administration of study treatment.

## Results

**Supplementary table 1: First subsequent anticancer therapies**

First subsequent therapy, n (%)	Olaparib (n=260)	Placebo (n=131)
Any	104 (40)	94 (72)
Platinum containing regimen	55 (21)	31 (24)
Platinum in combination with bevacizumab	22 (8)	15 (11)
Other bevacizumab containing regimen	5 (2)	0
Other chemotherapy regimen*	6 (2)	11 (8)
PARP inhibitor	16 (6)	36 (27)
Hormonal agent	1 (<1)	2 (2)
Other investigational agent	1 (<1)	0

Patients may be counted under more than one subsequent treatment type

\*Excludes regimens containing platinum or bevacizumab

**Supplementary table 2: Summary of adverse events\***

n (%)	Olaparib (n=260)			Placebo (n=130)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Nausea	200 (77)	2 (1)	0	49 (38)	0	0
Fatigue or asthenia	156 (60)	10 (4)	0	52 (40)	2 (2)	0
Vomiting	103 (40)	1 (<1)	0	18 (14)	1 (1)	0
Diarrhoea	82 (32)	8 (3)	0	32 (25)	0	0
Constipation	72 (28)	0	0	25 (19)	0	0
Arthralgia	65 (25)	0	0	35 (27)	0	0
Abdominal pain	62 (24)	4 (2)	0	24 (9)	1 (1)	0
Headache	59 (23)	1 (<1)	0	28 (22)	3 (2)	0
Dysgeusia	56 (22)	0	0	5 (4)	0	0
Dizziness	53 (20)	0	0	19 (15)	1 (1)	0
Decreased appetite	53 (20)	0	0	13 (10)	0	0
Anaemia <sup>†</sup>	47 (18)	51 (20)	6 (2)	11 (8)	2 (2)	0
Upper abdominal pain	45 (17)	0	0	17 (13)	0	0
Cough	44 (17)	0	0	28 (22)	0	0

Dyspepsia	43 (17)	0	0	16 (12)	0	0
Back pain	42 (16)	0	0	16 (12)	0	0
Dyspnoea	40 (15)	0	0	7 (5)	0	0
Neutropenia <sup>‡</sup>	38 (15)	21 (8)	1 (<1)	9 (7)	5 (4)	1 (1)
Pyrexia	31 (12)	0	0	12 (9)	0	0
Upper respiratory tract infection	30 (12)	0	0	12 (9)	0	0
Pain in extremity	30 (12)	0	0	11 (8)	0	0
Urinary tract infection	29 (11)	2 (1)	0	8 (6)	0	0
Nasopharyngitis	28 (11)	0	0	17 (13)	0	0
Thrombocytopenia <sup>¶</sup>	27 (10)	1 (<1)	1 (<1)	3 (2)	0	2 (2)
Insomnia	27 (10)	0	0	16 (12)	0	0
Myalgia	25 (10)	0	0	13 (10)	0	0
Peripheral oedema	25 (10)	0	0	9 (7)	0	0
Anxiety	17 (7)	0	0	11 (8)	0	0
Peripheral neuropathy	14 (5)	1 (<1)	0	7 (5)	0	0
Leukopenia	13 (5)	4 (2)	0	5 (4)	0	0
Depression	13 (5)	1 (<1)	0	12 (9)	1 (1)	0
Cystitis	13 (5)	1 (<1)	0	0	5 (4)	0
Increased alanine aminotransferase	11 (4)	0	0	8 (6)	1 (1)	0
Lymphopenia	10 (4)	2 (1)	0	1 (1)	1 (1)	0
Hypertension	8 (3)	1 (<1)	0	10 (8)	2 (2)	0
Pneumonia	6 (2)	0	0	4 (3)	1 (1)	0
Urticaria	5 (2)	0	0	1 (1)	1 (1)	0
Urinary incontinence	4 (2)	2 (1)	0	0	0	0
Cellulitis	4 (2)	1 (<1)	0	0	1 (1)	0
Cataract	4 (2)	1 (<1)	0	1 (1)	0	0
Decreased lymphocyte count	3 (1)	2 (1)	0	0	0	0
Pneumonitis	3 (1)	1 (<1)	0	0	0	0
Pulmonary embolism	2 (1)	2 (1)	0	1 (1)	0	0
Rotator cuff syndrome	2 (1)	2 (1)	0	0	0	0

Hypotension	2 (1)	1 (<1)	0	0	0	0
Syncope	2 (1)	1 (<1)	0	1 (1)	2 (2)	0
Small intestinal obstruction	0	2 (1)	0	0	0	1 (1)
Wound infection	0	3 (1)	0	1 (1)	1 (1)	0
Breast cancer	0	1 (<1)	0	0	2 (2)	1 (1)
Wound complication	0	1 (<1)	0	1 (1)	0	0
Acute cholecystitis	0	1 (<1)	0	0	0	0
Ataxia	0	1 (<1)	0	0	0	0
Bone marrow failure	0	1 (<1)	0	0	0	0
Incarcerated hernia	0	1 (<1)	0	0	0	0
Infected lymphocele	0	1 (<1)	0	0	0	0
Intraductal proliferative breast lesion	0	1 (<1)	0	0	0	0
Intestinal obstruction	0	1 (<1)	0	0	0	0
Invasive ductal breast carcinoma	0	1 (<1)	0	0	0	0
Lip and/or oral cavity cancer	0	1 (<1)	0	0	0	0
Lung disorder	0	1 (<1)	0	0	0	0
Medical device site cellulitis	0	1 (<1)	0	0	0	0
Pleurisy	0	1 (<1)	0	0	0	0
Post-procedural complication	0	1 (<1)	0	0	0	0
Splenic cyst	0	1 (<1)	0	0	0	0
Stab wound	0	1 (<1)	0	0	0	0
Thyroid cancer	0	1 (<1)	0	0	0	0
Urosepsis	0	1 (<1)	0	0	0	0
Sepsis	0	0	1 (<1)	0	0	0
Incarcerated umbilical hernia	0	0	0	0	1 (1)	0
Leukocytosis	0	0	0	0	1 (1)	0
Myocardial infarction	0	0	0	0	1 (1)	0
Recurrent thyroid cancer	0	0	0	0	1 (1)	0

\*Data are shown for treatment-emergent adverse events that occurred in at least 10% of patients in either treatment group and all grade 3 and 4 events occurring during study treatment or up to 30 days after discontinuation of the intervention. The only grade 5 adverse event to occur was a death in the placebo group.

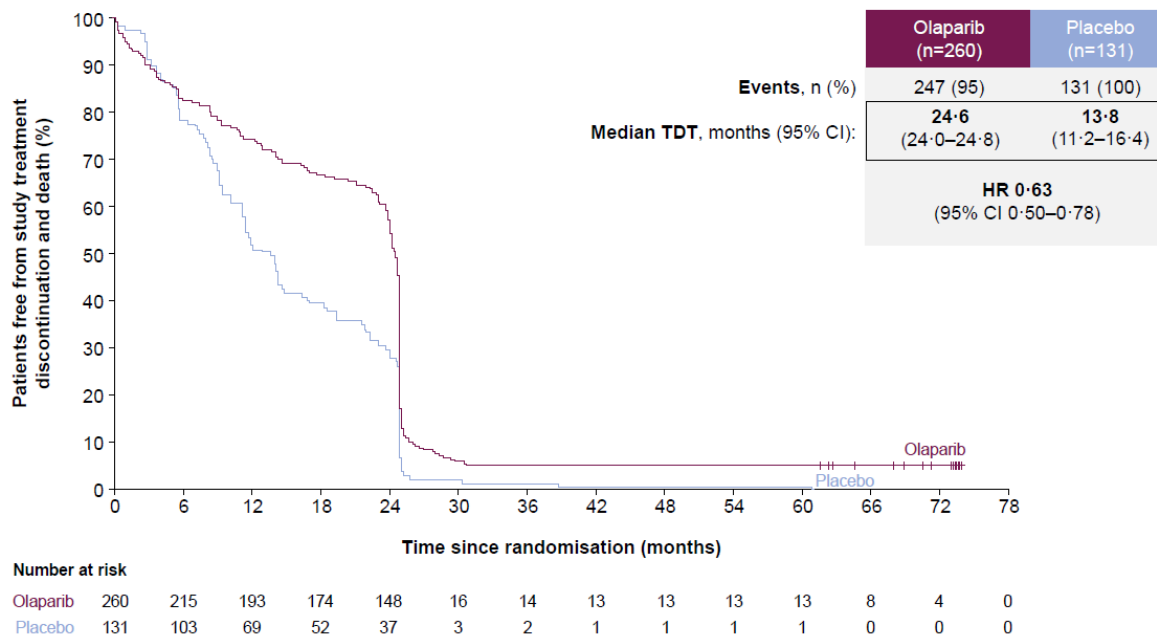


<sup>†</sup>Includes patients with anaemia, decreased haemoglobin level, decreased haematocrit, decreased red-cell count, erythropenia, macrocytic anaemia, normochromic anaemia, normochromic normocytic anaemia, or normocytic anaemia.

<sup>‡</sup>Includes patients with neutropenia, febrile neutropenia, neutropenic sepsis, neutropenic infection, decreased neutrophil count, idiopathic neutropenia, granulocytopenia, decreased granulocyte count, or agranulocytosis.

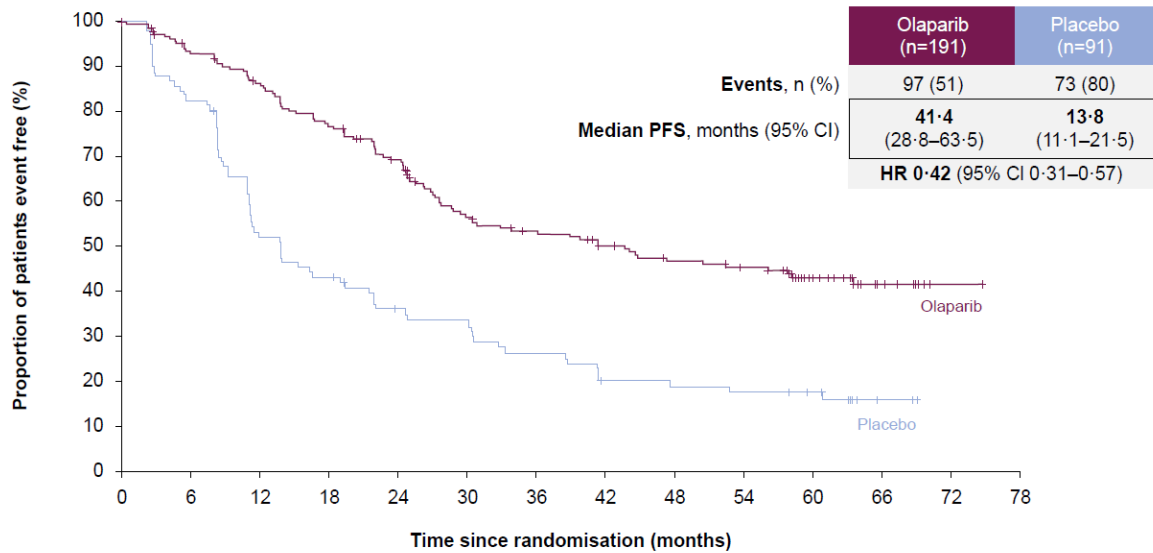
<sup>††</sup>Thrombocytopenia is included to complete the profile of haematologic toxic effects; includes patients with thrombocytopenia, decreased platelet production, decreased platelet count, or decreased plateletcrit, AE, adverse event.

**Supplementary figure 1: Kaplan–Meier estimate of time to discontinuation of study treatment or death (full analysis set)**



**Supplementary figure 2: Kaplan–Meier estimate of long-term progression-free survival in patients with (A) a *BRCA1* or (B) a *BRCA2* mutation**

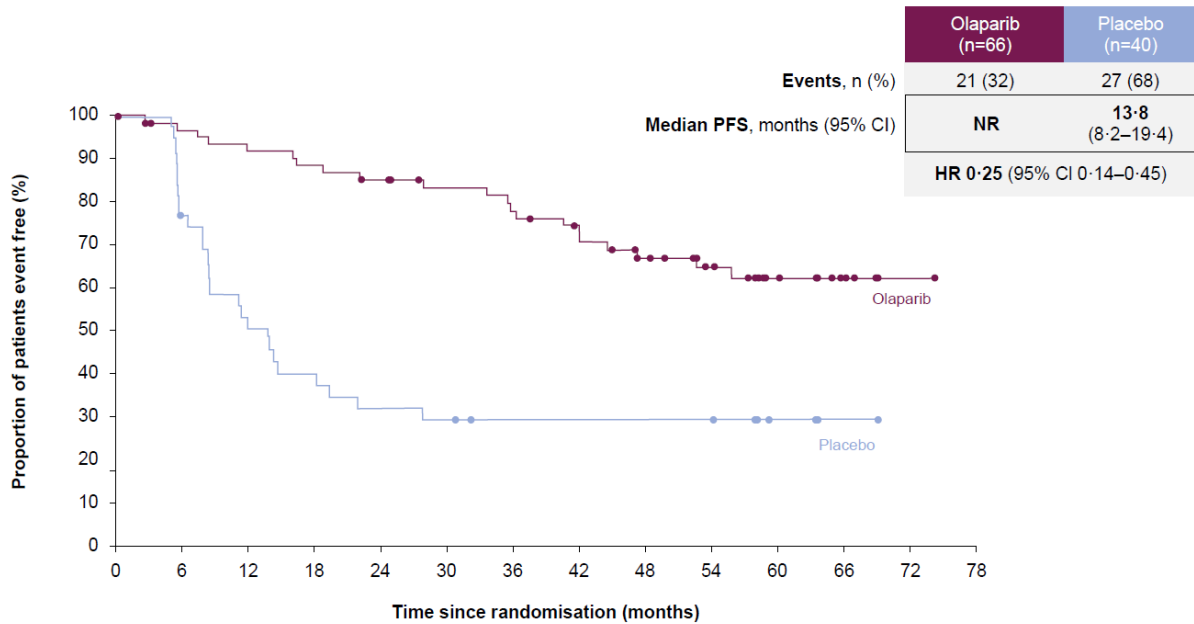
**A**



**Number at risk (number censored)**

	0	6	12	18	24	30	36	42	48	54	60	66	72	78
<b>Olaparib</b>	191 (0)	167 (11)	153 (13)	137 (13)	119 (17)	90 (25)	82 (28)	74 (31)	66 (34)	62 (36)	39 (56)	20 (74)	1 (93)	0 (94)
<b>Placebo</b>	91 (0)	74 (1)	46 (2)	38 (2)	29 (5)	27 (5)	21 (5)	15 (6)	14 (6)	13 (6)	11 (8)	2 (16)	0 (18)	0 (18)

**B**



**Number at risk (number censored)**

	0	6	12	18	24	30	36	42	48	54	60	66	72	78
<b>Olaparib</b>	66 (0)	59 (5)	56 (5)	54 (5)	51 (6)	47 (9)	44 (9)	38 (11)	33 (14)	27 (19)	17 (28)	9 (36)	1 (44)	0 (45)
<b>Placebo</b>	40 (0)	29 (2)	19 (2)	15 (2)	12 (2)	11 (2)	9 (4)	9 (4)	9 (4)	9 (4)	5 (8)	1 (12)	0 (13)	0 (13)

CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival



---

**Revised Clinical Study Protocol**

Drug Substance	AZD2281
Study Code	D0818C00001
GOG Code	GOG-3004

---

---

**A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients with BRCA Mutated Advanced (FIGO Stage III-IV) Ovarian Cancer following First Line Platinum Based Chemotherapy**

---

**Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden**

**This study is conducted by AstraZeneca in partnership with the Gynecologic Oncology Group (GOG) who are an expert in the disease area and will review and contribute to study specific documents such as the protocol, consent, statistical analysis plan and the clinical study report. GOG network sites in the US, Canada, Japan and Korea will be invited to participate in the study, GOG will also be involved in the review of site contracts and administer payments for US and Canada sites.**

**AstraZeneca Research and Development  
site representative**

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.

**The following Amendment(s) and Administrative Changes are included in this revised protocol:**

<b>Amendment No.</b>	<b>Date of Amendment</b>	<b>Local Amendment No.</b>	<b>Date of local Amendment</b>
_____	_____	_____	_____
_____	_____	_____	_____
<b>Administrative change No.</b>	<b>Date of Administrative Change</b>	<b>Local Administrative change No.</b>	<b>Date of local Administrative Change</b>
_____	_____	_____	_____
_____	_____	_____	_____

## PROTOCOL SYNOPSIS

---

**A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients with BRCA Mutated Advanced (FIGO Stage III-IV) Ovarian Cancer following First Line Platinum Based Chemotherapy.**

---

**International Co-ordinating Investigators:**

### **Study centre(s) and number of patients planned**

The study will be conducted in approximately 18 countries world-wide. Approximately 200 centres will be initiated to randomise approximately 344 patients.

<b>Study period</b>		<b>Phase of development</b>
Estimated date of first patient enrolled	Q3 2013	III
Estimated date of last patient completed	Q1 2023	III

## Objectives

### Primary:

To determine the efficacy by progression free survival (PFS) using investigator assessment according to modified Response Evaluation Criteria in Solid Tumours (RECIST 1.1) of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy.

### Secondary:

1. To determine the efficacy of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy by assessment of overall survival (OS), time to earliest progression by RECIST or Cancer Antigen-125 (CA-125), or death, and time from randomisation to second progression (PFS2)
2. To compare the effects of olaparib maintenance monotherapy compared to placebo on Health-related Quality of Life (HRQoL) as assessed by the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy
3. To assess efficacy of olaparib in patients identified as having a deleterious or suspected deleterious variant in either of the BRCA genes using variants identified with current and potential future *BRCA* mutation assays (gene sequencing and large rearrangement analysis)
4. To determine the efficacy of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy by assessment of time from randomisation to first subsequent therapy or death (TFST), time from randomisation to second subsequent therapy or death (TSST) and time from randomisation to study treatment discontinuation or death (TDT).

### Safety:

1. To assess the safety and tolerability of olaparib maintenance monotherapy in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy

## **Exploratory:**

- 1.
2. To explore the impact of treatment and disease state on health state utility by EuroQoL five dimensions, five level (EQ-5D-5L)
3. To explore the impact of treatment and disease on resource use
4. To explore the effects of olaparib maintenance monotherapy as assessed by the individual domains of the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O)
5. To explore the efficacy of olaparib by assessment of overall survival (OS) adjusting for the impact of spontaneous switching [outside of study design] to Polyadenosine 5' diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitors or other potentially active investigational agents
- 6.
7. Future exploratory research into factors that may influence development of cancer and/or response to study treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumor samples that were mandatory for entry onto the study or on optional tumor biopsy samples collected during the course of the study
8. To collect and store DNA (according to each country's local and ethical procedures) for future exploratory research into genes/genetic variation that may influence response (i.e., distribution, safety, tolerability and efficacy) to study treatments and or susceptibility to disease (optional)

The exploratory analyses may not be reported in the clinical study report (CSR), if not, they will be reported separately.

## **Study design**

This is a phase III, randomised, double-blind, placebo-controlled, multi-centre study to assess the efficacy of olaparib maintenance monotherapy in high risk advanced ovarian cancer patients (including patients with primary peritoneal and / or fallopian tube cancer) with BRCA mutations [documented mutation in BRCA1 or BRCA2] that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) who have responded following first line platinum based chemotherapy.

Patients will be randomised in a 2:1 ratio to the treatments as specified below:

- olaparib tablets *p.o.* 300mg twice daily.
- placebo tablets *p.o.* twice daily.

Randomisation will be stratified by:

- response to first line platinum chemotherapy (clinical complete response or partial response)

Patients will be randomised within 8 weeks after their last dose of chemotherapy (last dose is the day of the last infusion).

Patients in both treatment arms will have tumour assessments according to RECIST at baseline and every 12 weeks ( $\pm 1$  week) up to 3 years (156 weeks) and then every 24 weeks ( $\pm 1$  week) relative to date of randomisation, until objective radiological disease progression according to RECIST. All CT/MRI scans will be sent to an AstraZeneca appointed Clinical Research Organisation (CRO) for blinded independent central review. After the primary Progression Free Survival (PFS) analysis, central review of scans will no longer be required.

Patients should continue to receive study treatment for up to two years or until objective radiological disease progression as per RECIST as assessed by the investigator, whichever is earlier, and as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria. Patients who continue to have evidence of disease that remains stable (i.e., no evidence of disease progression) at two years or those who have progressed may continue to receive study treatment if, in the opinion of the investigator, it is in the patient's best interest. However, if at two years the patient has no evidence of disease, study treatment should be discontinued. A decision about continuing treatment with the investigational product beyond two years should be made after assessing the patient's disease status according to RECIST guidelines at week 108, and/or by assessing the patient's clinical condition. Continuation of treatment beyond week 108, based solely on clinical progression, is permissible only after case-by-case discussion with the AZ study physician.

All patients will continue to be assessed for radiological tumour assessments according to the study schedule (Table 1, Table 2, Table 3 and Table 4), until objective radiological disease progression, irrespective of their continuation on study treatment.

If a patient progresses and remains on treatment they will continue to be assessed and will be followed for second progression and then survival according to the study schedule (Table 3). Once a patient has progressed and discontinued treatment the patient will be followed as per local clinical practice, but assessment should be made every 12 weeks for second progression and then survival until the final analysis (Table 4).

### **Target patient population**

Eligible patients will be those patients with newly diagnosed, histologically confirmed, high risk advanced (International Federation of Gynecology and Obstetrics (FIGO) stage III-IV)

BRCA mutated high grade serous or high grade endometrioid (based on local histopathological findings) ovarian cancer, primary peritoneal cancer and / or fallopian-tube cancer who are in clinical complete response or partial response following completion of first line platinum-based chemotherapy. Patients who re-present following prior diagnosis at an earlier stage of disease are not eligible. Stage III patients should have had one attempt at optimal debulking surgery (upfront or interval debulking). Stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery.

Patients must have completed a minimum of six treatment and a maximum of nine treatment cycles of first line platinum-based therapy (e.g., carboplatin or cisplatin) before randomisation to the study and should have a clinical complete response or a partial response. However, if platinum based therapy must be discontinued early as a result of toxicities specifically related to the platinum regimen, patients must have received a minimum of four cycles of the platinum regimen.

Patients must not have received bevacizumab (either in combination or as maintenance therapy following combination therapy) or any investigational agent during their first line course of treatment.

Patients known to have germline BRCA mutation/s (gBRCAm i.e., blood) prior to randomisation can enter the study based on this result. The result must be made available to AstraZeneca. In addition the patients must consent to provide 2 blood samples. One sample will be used for a confirmatory Myriad gBRCA test post randomisation using the current commercial Myriad BRCA*Analysis*<sup>®</sup> (gene sequencing and large rearrangement analysis), which will be paid for by AstraZeneca.

Patients with unknown BRCA status must consent to provide 2 blood samples for germline BRCA testing, which will be paid for by AstraZeneca, and follow all local ethical procedures for genetic testing. One sample will be used to test for BRCA mutations using the current commercial Myriad BRCA*Analysis*<sup>®</sup> test prior to study entry. When the result from the Myriad test indicates the patient does have a deleterious or suspected deleterious BRCA mutation, the patient can be randomised into the study (providing they have fulfilled all other screening requirements).

These samples will be required for the study even if the patients are found not to have a BRCA mutation.

Patients that have a BRCA mutation identified via assessment of tumour may also be enrolled on the trial provided that all such testing has been undertaken in appropriately accredited laboratories (i.e., testing done for research use only will not be acceptable). These patients still



need a Myriad test, regardless of the result, they are eligible for randomisation as long as they fulfil all other screening criteria.

### **Investigational product, dosage and mode of administration**

Olaparib is available as a green film-coated tablet containing 150 mg or 100 mg of olaparib. Patients will be administered study treatment orally at a dose of 300 mg twice daily (twice daily). The planned dose of 300 mg twice daily will be made up of two x 150 mg tablets twice daily with 100 mg tablets used to manage dose reductions.

### **Comparator, dosage and mode of administration**

Placebo will be available as green film-coated tablets matching the olaparib tablets. These should be taken as per instructions for olaparib tablets.

### **Duration of treatment**

Patients should continue to receive study treatment for up to two years or until objective radiological disease progression as per RECIST as assessed by the investigator, whichever is earlier, and as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria as outlined in Section 5.8. Patients should continue with study treatment to RECIST progression as described above despite rises in CA-125. Patients who continue to have evidence of disease that remains stable (i.e., no evidence of disease progression) at two years or those who have progressed may continue to receive study treatment if, in the opinion of the investigator, it is in the patient's best interest. However, if at two years the patient has no evidence of disease, study treatment should be discontinued. A decision about continuing treatment with the investigational product beyond two years should be made after assessing the patient's disease status according to RECIST guidelines at week 108, and/or by assessing the patient's clinical condition. Continuation of treatment beyond week 108, based solely on clinical progression, is permissible only after case-by-case discussion with the AZ study physician.

Once patients have been discontinued from study treatment, other treatment options will be at the discretion of the investigator. Patients and investigators will not be routinely unblinded to study treatment prior to the final OS analysis. Within this study patients are not permitted to switch over to the opposite arm from which they were randomised.

### **Outcome variable(s):**

- **Primary outcome variable**
  - Progression Free Survival (PFS) by review of investigator-reported RECIST data
- **Secondary outcome variables**
  - Overall Survival

- Time to earliest Progression by RECIST or CA-125 or death
- Time from randomisation to second progression (PFS2)
- Time from randomisation to first subsequent therapy or death (TFST)
- Time from randomisation to second subsequent therapy or death (TSST).
- Time from randomisation to study treatment discontinuation or death (TDT)
- The Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy - Ovarian Cancer (FACT-O) will be used to determine:
  - Change from baseline in TOI score
  - Proportion improved
- 
- **Safety outcome variables**
  - Adverse event (AE), physical examination, vital signs including blood pressure (BP), pulse, electrocardiogram (ECG) and laboratory findings including clinical chemistry and haematology.
- **Exploratory outcome variables**
  - 
  - EuroQoL five dimensions, five level (EQ-5D-5L) health state utility index.
  - Patient-reported outcomes based on the Functional Assessment of Cancer Therapy - Ovarian (FACT-O).
  - Resource use as captured including inpatient admissions, intensive care unit (ICU) and length of stay in hospital
  - Overall survival adjusted for impact of subsequent PARP inhibitor trial or treatment
  - Potential retrospective biomarker & pharmacogenetic research (optional).
  - The individual domains of the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy –Ovarian Cancer (FACT-O) will be used to determine:

- Change from baseline in TOI domain score
- Proportion improved

### Statistical methods

In total 206 PFS events in the study would have 90% power to show statistically significant PFS at the 2-sided 5% level if the assumed true treatment effect were hazard ratio (HR) 0.62; this translates to a 8 month benefit in median PFS over 13 months on placebo (estimated from data reported by [Alsop et al 2012](#)) if PFS is exponentially distributed. Approximately 344 patients will be recruited (2:1 ratio) so that data maturity for the PFS analysis is approximately 60%. Assuming 18 months non-linear recruitment, 206 investigator-assessed PFS events are expected to occur approximately 36 months after first subject in is enrolled in the study (FSI). This will be the primary analysis of PFS.

The global recruitment to the study will close when approximately 344 patients are randomised. The primary statistical analysis of the efficacy of olaparib will include all patients who are randomised as part of the global enrolment.

The primary analysis will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised as part of the global enrolment but did not subsequently go on to receive study treatment are included in the Full Analysis Set (FAS). Therefore, all efficacy and health-related quality of life (HRQoL) data will be summarised and analysed using the FAS on an intention-to-treat (ITT) basis.

When assessing safety and tolerability, summaries will be produced based on the Safety Analysis Set. This will include all patients who receive at least one dose of randomised treatment (olaparib or placebo). The safety data will be summarised descriptively and will not be formally analysed.

PFS will be analysed using a log rank test stratified by response to first line platinum chemotherapy (clinical complete response or partial response). The HR together with its 95% confidence interval and p-value will be presented (a HR less than 1 will favour olaparib). This analysis will be performed when approximately 196 events have occurred or after the last patient randomised has had the opportunity to have been on the study for at least 36 months, whichever comes first. The primary analysis will be based on investigator-recorded assessment of disease progression by RECIST; however, sensitivity analyses will be performed including using the blinded independent central review (BICR) of disease progression.

Subgroup analyses will be conducted to assess consistency of treatment effect across potential or expected prognostic factors (see Section 12.2.2 for all predefined subgroups). Included will be a subgroup analysis by Myriad gBRCA mutation status (gBRCAm status confirmed by Myriad test vs gBRCA wildtype (wt) or missing by Myriad gBRCA test). An analysis will not

Date 21 February 2018

be performed if there are too few events available for a meaningful analysis of a particular subgroup (i.e., if there are less than 20 events in a subgroup). An initial OS and PFS2 analysis will be performed at the same time as the primary analysis of PFS and will use the same methodology and model.

Analyses of time to first subsequent therapy (TFST) and time to second subsequent therapy (TSST) will be conducted, using the same methodology as specified for the primary analyses of PFS.

Supportive analyses of time to earliest progression by RECIST or CA-125 or death and TDT will be provided, using the same methodology as specified for the primary analyses of PFS, however no multiple adjustment will be applied as these are viewed as supportive endpoints.

In order to describe the nature of the benefits of olaparib maintenance treatment, PFS, PFS2, TFST, TSST, change from baseline in TOI score and OS will be tested at a 2-sided significance level of 5%. However, in order to strongly control the type I error, a multiple testing procedure will also be employed where PFS is tested first using the full test mass, PFS2 will be tested if the null hypothesis for PFS is rejected, and OS will only be tested if statistical significance is shown for PFS and PFS2.

An interim analysis for OS and PFS2 will be performed at the time of the PFS analysis (approximately 100 OS events).

A further analysis of OS and PFS2 will be performed when the OS data are approximately 60% mature (approximately 206 events); this is anticipated to occur approximately 80 months after FSI.

Exploratory analyses of OS adjusting for impact of subsequent PARP inhibitor trial or treatment (or other potentially active investigational agents) may be performed if a sufficient proportion of patients switch. Methods such as Rank Preserving Structural Failure Time (RPSFT) ([Robins et al 1991](#)), Inverse Probability of Censoring Weighting (IPCW) ([Robins 1993](#)) and other methods in development will be explored. The decision to adjust and final choice of methods will be based on a blinded review of the data and the plausibility of the underlying assumptions. Details will be pre-specified in the statistical analysis plan (SAP) and Payer analysis plan.

#### **Analysis of Patient Reported Outcomes (PRO) endpoints:**

The analysis population for HRQoL data will be the FAS (ITT) set. Change from baseline in TOI score will be regarded as the primary analysis of the FACT-O questionnaire and will be analysed using a mixed model repeated measures (MMRM) analysis of the change from baseline TOI score.

## **Analysis of Exploratory endpoints:**

### **EQ-5D-5L**

Descriptive statistics, graphs and listings will be reported for health state utility values and visual analogue scale by visits as well as change in these scores from baseline. To support future economic evaluations of olaparib, additional appropriate analyses may be undertaken, for example, mean health state utility pre and post treatment, and pre and post progression.

### **FACT-O**

Descriptive statistics, graphs and listings will be reported to explore the impact of olaparib on symptoms and HRQoL. The relationship between patient-reported outcomes and progression and AEs will be assessed using descriptive summaries.

Further details of the exploratory analysis based on the FACT-O will be outlined in the SAP.

### **Resource Use**

Appropriate analyses of resource use, including hospitalisations and reasons thereof, will be undertaken to examine the impact of disease and treatment on resource use to primarily support the economic evaluation of olaparib.

### **Biomarkers**

Appropriate summaries of exploratory outcome variables and data listings will be produced and compared across the two treatment arms. Graphical methods will be widely used in exploring the characteristics and relationships of outcome variables.

<b>TABLE OF CONTENTS</b>	<b>PAGE</b>
TITLE PAGE.....	1
PROTOCOL SYNOPSIS.....	2
TABLE OF CONTENTS.....	12
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS.....	19
1. INTRODUCTION .....	25
1.1 Background.....	25
1.1.1 Ovarian cancer and its treatment .....	25
1.1.2 BRCA mutation positive ovarian cancer.....	25
1.1.3 PARP inhibition as a target for BRCA mutation positive ovarian cancer .....	26
1.1.4 Pre-clinical experience .....	26
1.1.5 Toxicology and safety pharmacology summary .....	26
1.1.6 Clinical experience.....	27
1.2 Research hypothesis.....	27
1.3 Rationale for conducting this study .....	27
1.3.1 Rationale for Study Design .....	28
1.3.2 .....	29
1.4 Benefit/risk and ethical assessment .....	30
2. STUDY OBJECTIVES.....	32
2.1 Primary objective.....	32
2.2 Secondary objectives.....	32
2.3 Safety objective.....	33
2.4 Exploratory objectives .....	33
3. STUDY PLAN AND PROCEDURES .....	34
3.1 Overall study design and flow chart .....	34
3.2 Rationale for study design, doses and control groups.....	54
4. PATIENT SELECTION CRITERIA.....	55
4.1 Inclusion criteria .....	55
4.2 Exclusion criteria .....	58
5. STUDY CONDUCT .....	61
5.1 Restrictions during the study .....	61
5.1.1 Olaparib and CYP3A4 .....	61

5.1.2	Contraception.....	61
5.2	Patient enrolment and randomisation and initiation of investigational product.....	61
5.2.1	Procedures for randomisation.....	62
5.3	Procedures for handling patients incorrectly enrolled or randomised or initiated on investigational product.....	63
5.4	Blinding and procedures for unblinding the study.....	63
5.4.1	Methods for ensuring blinding .....	63
5.4.2	Methods for unblinding the study.....	63
5.5	Treatments .....	64
5.5.1	Identity of investigational product(s).....	64
5.5.2	Doses and treatment regimens .....	64
5.5.2.1	Olaparib and matching placebo (study treatment).....	64
5.5.3	Labelling.....	65
5.5.4	Storage.....	65
5.5.5	Management of toxicity of study treatment .....	65
5.6	Concomitant and post-study treatment(s) .....	69
5.6.1	Medications that may NOT be administered.....	69
5.6.2	CYP3A4 .....	69
5.6.3	Anticoagulant Therapy.....	70
5.6.4	Anti-emetics/Anti-diarrhoeals .....	70
5.6.5	Palliative radiotherapy .....	70
5.6.6	Administration of other anti-cancer agents .....	71
5.6.7	Subsequent therapies for cancer .....	71
5.7	Treatment compliance.....	71
5.7.1	Accountability.....	71
5.8	Discontinuation of investigational product .....	71
5.8.1	Procedures for discontinuation of a patient from investigational product.....	72
5.9	Withdrawal from study.....	73
6.	COLLECTION OF STUDY VARIABLES .....	74
6.1	Recording of data.....	74
6.2	Data collection at enrolment and follow-up.....	74
6.2.1	Enrolment/Screening procedures.....	74
6.2.2	On study assessments.....	76
6.2.3	Follow-up procedures.....	78
6.2.3.1	Treatment Discontinuation Visit.....	78
6.2.3.2	Treatment discontinuation due to objective radiological disease progression or any other discontinuation criteria .....	78
6.2.4	Follow-up 30 day after last dose of study medication (follow-up visit).....	78
6.2.5	Survival .....	79

6.2.6	Second Progression .....	79
6.2.7	Patient management post primary analysis .....	80
6.2.8	Patient management post final analysis .....	80
6.3	Efficacy .....	81
6.3.1	CT and MRI scans Tumour assessments (modified RECIST 1.1) .....	81
6.3.2	Tumour Evaluation .....	81
6.3.3	Central reading of scans .....	83
6.4	Safety.....	83
6.4.1	Definition of adverse events .....	83
6.4.2	Definitions of serious adverse event .....	83
6.4.3	Recording of adverse events.....	84
6.4.4	Reporting of serious adverse events .....	88
6.4.5	Laboratory safety assessment .....	89
6.4.5.1	Full haematology assessments for safety; .....	89
6.4.5.2	Coagulation.....	90
6.4.5.3	Biochemistry assessments for safety.....	90
6.4.5.4	Disease specific tumour marker samples (CA-125) .....	91
6.4.5.5	Urinalysis.....	91
6.4.5.6	Bone marrow or blood cytogenetic samples .....	91
6.4.6	Physical examination .....	91
6.4.7	ECG.....	92
6.4.7.1	Resting 12-lead ECG .....	92
6.4.8	Vital signs.....	92
6.4.8.1	Pulse and blood pressure .....	92
6.4.8.2	Body temperature.....	92
6.4.9	Other safety assessments.....	92
6.4.10	Serum or urine pregnancy test .....	92
6.5	Patient reported outcomes (PRO): FACT-O and EQ-5D-5L .....	93
6.5.1	Administration of PRO questionnaires .....	93
6.5.2	FACT-O .....	94
6.5.3	PRO method or questionnaire for other purposes.....	94
6.5.4	EQ-5D-5L.....	94
6.6	Pharmacokinetics – Not Applicable.....	94
6.7	Biomarkers .....	94
6.7.1	Biomarker samples.....	94
6.7.2	Exploratory Biomarker Research on Archival Tumour Samples (Mandatory) .....	96
6.7.3	Exploratory Biomarker Research on Tumour Biopsy Samples (Optional).....	96
6.8	Pharmacogenetics .....	96
6.8.1	Collection of blood sample for Myriad germline BRCA1 and BRCA2 testing .....	96
6.8.1.1	Guidance for BRCA testing of patients with known BRCA status .....	97



6.8.1.2	Guidance for BRCA testing of patients with unknown BRCA status .....	97
6.8.2	.....	98
6.8.3	Exploratory blood sample for biomarker analysis (e.g. cfDNA) (Optional).....	99
6.8.4	Collection of pharmacogenetic samples (optional) .....	99
6.9	Health economics.....	99
6.9.1	Resource Use .....	99
7.	<b>BIOLOGICAL SAMPLING PROCEDURES</b> .....	99
7.1	Volume of blood .....	99
7.2	Handling, storage and destruction of biological samples.....	102
7.2.1	Pharmacogenetic (optional exploratory) samples.....	102
7.3	Labelling and shipment of biohazard samples .....	102
7.4	Chain of custody of biological samples .....	103
7.5	Withdrawal of informed consent for donated biological samples .....	103
8.	<b>ETHICAL AND REGULATORY REQUIREMENTS</b> .....	104
8.1	Ethical conduct of the study .....	104
8.2	Patient data protection.....	104
8.3	Ethics and regulatory review .....	104
8.4	Informed consent .....	105
8.5	Changes to the protocol and informed consent form .....	106
8.6	Audits and inspections .....	106
9.	<b>STUDY MANAGEMENT BY ASTRAZENECA</b> .....	107
9.1	Pre-study activities.....	107
9.2	Training of study site personnel .....	107
9.3	Monitoring of the study.....	107
9.3.1	Source data .....	108
9.4	Study agreements.....	108
9.4.1	Archiving of study documents.....	108
9.5	Study timetable and end of study.....	108
10.	<b>DATA MANAGEMENT BY ASTRAZENECA</b> .....	108
11.	<b>EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA</b> .....	109
11.1	Calculation or derivation of efficacy variable(s) .....	109
11.1.1	Progression Free Survival (PFS) .....	110
11.1.2	Secondary endpoints .....	110
11.1.2.1	Overall Survival.....	110

11.1.2.2	Time to earliest progression by RECIST 1.1 or CA-125 or death.....	111
11.1.2.3	Time from randomisation to second progression (PFS2).....	111
11.1.2.4	Time to first subsequent therapy or death (TFST).....	112
11.1.2.5	Time to second subsequent therapy or death (TSST) .....	112
11.1.2.6	Time to study treatment discontinuation or death (TDT) .....	112
11.1.2.7	Best Overall RECIST Response (BoR).....	112
11.2	Calculation or derivation of safety variable(s) .....	113
11.2.1	Other significant adverse events (OAE).....	113
11.3	Calculation or derivation of patient reported outcome variables.....	113
11.3.1	EQ-5D-5L (exploratory analysis) .....	116
11.4	Calculation or derivation of pharmacokinetic variables – Not Applicable .....	116
11.5	Calculation or derivation of pharmacodynamic variables – Not Applicable .....	116
11.6	Calculation or derivation of pharmacogenetic variables.....	116
11.7	Calculation or derivation of resource use.....	116
12.	STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA .....	117
12.1	Description of analysis sets .....	117
12.1.1	Full analysis set.....	117
12.1.2	Safety analysis set .....	117
12.2	Methods of statistical analyses .....	118
12.2.1	Multiplicity strategy for primary and key secondary endpoints.....	119
12.2.2	Analysis of primary endpoint .....	121
12.2.2.1	Sensitivity Analyses for Primary Endpoint.....	123
12.2.3	Analysis of secondary endpoints .....	124
12.2.3.1	Analysis of PFS2 endpoint .....	124
12.2.3.2	Analysis of OS endpoint .....	125
12.2.3.3	Analysis of TFST, TSST, TDT endpoints.....	125
12.2.3.4	Analysis of time to earliest progression by RECIST 1.1 or CA-125 or death.....	125
12.2.3.5	Summary of Best overall RECIST Response (BoR) .....	126
12.2.3.6	Analysis of PRO endpoints .....	126
12.2.3.7	Health State Utility – EQ-5D-5L .....	127
12.2.3.8	Impact of Switching to PARP inhibitors (or other potentially active investigational agents) on Overall Survival Analyses .....	127
12.2.4	Exploratory endpoints .....	127
12.2.5	Interim analyses .....	127
12.2.6	China Cohort.....	127
12.3	Determination of sample size .....	129
12.4	Data monitoring committee.....	129
13.	MEDICAL EMERGENCIES AND ASTRAZENECA CONTACTS.....	130

13.1	Overdose.....	131
13.2	Pregnancy .....	131
13.2.1	Maternal exposure.....	131
14.	LIST OF REFERENCES .....	132

## LIST OF TABLES

Table 1	Screening (Visit 1) Study Schedule For Patients with Unknown BRCA Mutation Status at Presentation – Complete Parts 1, 2 and 3: .....	42
Table 2	Screening (Visit 1) Study Schedule For Patients with Known BRCA Mutation Status at Presentation – complete Parts 2 and 3:.....	45
Table 3	Study Schedule – On Study Treatment and Discontinuation .....	47
Table 4	Study Schedule: Follow-up post discontinuation of study treatment .....	51
Table 5	Dose reductions for study treatment .....	68
Table 6	Samples for Biomarker Research.....	94
Table 7	Estimated maximum volume of blood to be drawn from each patient .....	100
Table 8	Health Related Quality of Life .....	115
Table 9	Health Related Quality of Life : Change rates - overall score.....	115
Table 10	Summary of Outcome Variables and Analysis Populations.....	117
Table 11	Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses .....	118

## LIST OF FIGURES

Figure 1	Overall Study Design Flow Chart.....	37
Figure 2	Screening Plan .....	39
Figure 3	Study Flow Chart Up to 108 Weeks on Treatment.....	40
Figure 4	Study Flow Chart At 108 Weeks on Treatment.....	41
Figure 5	Flow diagram for patients with known or unknown BRCA mutation status .....	98
Figure 6	Multiple Testing Procedure .....	120

## **LIST OF APPENDICES**

Appendix A	Signatures – not applicable
Appendix B	Additional Safety Information
Appendix C	IATA 6.2 Guidance Document
Appendix D	Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy’s Law
Appendix E	Acceptable Birth Control Methods
Appendix F	Guidance of Evaluation of objective tumour response using Modified RECIST v1.1 criteria
Appendix G	ECOG Performance status
Appendix H	Patient Reporting Outcomes – FACT-O and EQ-5D-5L
Appendix I	FIGO Staging
Appendix J	Guidance on grading of serous ovarian carcinomas

## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
Baseline	Refers to the most recent assessment of any variable prior to dosing with study treatment
BD	Twice daily
BICR	Blinded Independent Central Review
BoR	Best Overall RECIST Response
BP	Blood pressure
BRCA	Breast Cancer susceptibility gene
BRCA <i>Analysis</i> <sup>®</sup>	Gene sequencing and large rearrangement analysis for Hereditary Breast and Ovarian Cancer, registered trademark of Myriad Genetics, Inc
BRCA mutation or BRCAm	Breast Cancer susceptibility gene mutation (see gBRCA mutation or gBRCAm)
BUN	Blood urea nitrogen
CA-125	Cancer Antigen - 125
cfDNA	Circulating free DNA
CHO	Chinese hamster ovary
CI	Confidence Interval

<b>Abbreviation or special term</b>	<b>Explanation</b>
CCR	Clinical Complete Response. ‘Response’ is used throughout the protocol and refers to patients being, in the opinion of the investigator, in clinical complete response or partial response on the post-treatment scan. Clinical complete response is defined as no evidence of RECIST measurable or non-measurable disease on the post-treatment scan and a normal CA-125. Partial response is defined as $\geq 30\%$ reduction in tumor volume demonstrated from the start to finish of chemotherapy OR no evidence of RECIST measurable disease on the post-treatment scan with a CA-125 which has not decreased to within the normal range.
CR	Complete response
CRF	Case Report Form (electronic/paper)
CRO	Clinical Research Organisation
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed tomography
CTC / CTCAE	Common Terminology Criteria for Adverse Event
CYP450	Cytochrome P450 (enzyme)
DAE	Discontinuation of Investigational Product due to Adverse Event
DCIS	Ductal Carcinoma in Situ
DCO	Data Cut Off
DNA	Deoxyribonucleic acid
DSB	Double strand break
DUS	Disease under Study
ECG	Electrocardiogram
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
E-code	Enrolment code (allocated by IVRS/IWRS)
ECOG	Eastern Cooperative Oncology Group: A performance status using scales and criteria to assess how a patients disease is progressing
EMA	European Medicines Agency
EQ-5D-5L / EQ-5D	EuroQoL five dimensions, five level (EQ-5D-5L) health state utility index
EWB	Emotional well being
FACIT	Functional Assessment of Chronic Illness Therapy
FACT-O	Functional Assessment of Cancer Therapy – Ovarian: A multidimensional questionnaire for patients with ovarian cancer

<b>Abbreviation or special term</b>	<b>Explanation</b>
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
FIGO	International Federation of Gynecology and Obstetrics
FSH	Follicle stimulating hormone
FSI	First Subject In
FWB	Functional well being
gBRCA mutation or gBRCAm	The term "gBRCA mutation" is used to refer to a germline BRCA1 or BRCA2 mutation classified as "deleterious" or "suspected deleterious" in accordance with the American College of Medical Genetics and Genomics recommendations for standards for interpretation and reporting of sequence variants ( <a href="#">Richards et al 2008</a> ).
GBRCA wt	gBRCA wildtype
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma glutamyl transferase
GMP	Good Manufacturing Practice
GOG	Gynecologic Oncology Group
Grand	AZ Global Randomisation system
Hb	Haemoglobin
HCT	Haematocrit
HDPE	High-density polyethylene
HGSOC	High-grade serous ovarian cancer
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HR	Homologous recombination repair
HRCT	High Resolution Computed Tomography
HRD	Homologous recombination repair deficiencies
HRT	Hormone replacement therapy
HRQoL	Health-related Quality of Life
IATA	International Air Transport Association
IB	Investigator's brochure

<b>Abbreviation or special term</b>	<b>Explanation</b>
ICH	International Conference on Harmonisation
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the Investigators and/or activities internationally.
ICR	Independent Central Review
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
INR	International Normalised Ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intentions to Treat
IPCW	Inverse Probability of Censoring Weighting
IVR System	Interactive Voice Response System
IWR System	Interactive Web Response System
KM	Kaplan Meier
LDH	Lactic dehydrogenase
LH	Luteinizing hormone
LIMS	Laboratory Information Management System
LPLV	Last Patient Last Visit
MCH	Mean cell haemoglobin
MCHC	Mean cell haemoglobin concentration
MCV	Mean cell volume
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milli-gram
MMRM	Mixed Model for Repeated Measures
MRI	Magnetic resonance imaging
MTP	Multiple Testing Procedure
NCI	National Cancer Institute
NE	Not evaluable
NED	No Evidence of Disease
NTL	Non-target lesions



<b>Abbreviation or special term</b>	<b>Explanation</b>
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
ORR	Objective response rates
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation
PD	Progressive disease
PFS / PFS1	Progression Free Survival
PFS2	Time from randomisation to second progression
PGx	Pharmacogenetic research
PI	Principal Investigator
PK	Pharmacokinetics
p.o.	Per os (by mouth, orally)
PR	Partial response. 'Response' is used throughout the protocol and refers to patients being, in the opinion of the investigator, in clinical complete response or partial response on the post-treatment scan. Clinical complete response is defined as no evidence of RECIST measurable disease on the post-treatment scan and a normal CA-125. Partial response is defined as $\geq 30\%$ reduction in tumor volume demonstrated from the start to finish of chemotherapy OR no evidence of RECIST measurable disease on the post-treatment scan with a CA-125 which has not decreased to within the normal range.
PRO	Patient Reported Outcomes
PWB	Physical well being
QoL	Quality of Life
R&D	Research and Development
RBC	Red blood cell
RECIST	Response Evaluation Criteria In Solid Tumours. This study will use modified RECIST version 1.1
RI	Reticulocyte index
RPSFT	Rank Preserving Structural Failure Time
SAE	Serious adverse event (see definition in Section 6.4.2).
SAP	Statistical Analysis Plan
SD	Stable disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvate Transaminase

<b>Abbreviation or special term</b>	<b>Explanation</b>
SSB	Single strand break
SUSARs	Suspected Unexpected Serious Adverse Reactions
SWB	Social well being
Study treatment	Olaparib or matching placebo
tBRCA mutation or tBRCAm	The term "tBRCA mutation" is used to refer to a somatic tumour BRCA1 or BRCA2 mutation classified as "deleterious" or "suspected deleterious" in accordance with the American College of Medical Genetics and Genomics recommendations for standards for interpretation and reporting of sequence variants ( <a href="#">Richards et al 2008</a> ).
TDT	Time from randomisation to study treatment discontinuation or death
TFST	Time from randomisation to first subsequent therapy or death
TL	Target lesions
TOI	Trial Outcome Index
TSST	Time from randomisation to second subsequent therapy or death
UCL	Upper Confidence Limit
ULN	Upper limit of normal
WBC	White blood cells
WBDC	Web Based Data Capture
wt	Wildtype (patients without evidence of BRCA1 or BRCA2 deleterious or suspected deleterious mutations)

## **1. INTRODUCTION**

### **1.1 Background**

#### **1.1.1 Ovarian cancer and its treatment**

Ovarian cancer is the fifth most common cause of death from cancer in women ([Colombo et al 2010](#); [NCCN Clinical Practice Guidelines in Oncology](#)). In the United States there are about 21,550 new cases and 14,600 deaths estimated annually. In the European Community, approximately 28,000 new cases of ovarian cancer and approximately 17,000 deaths are reported annually, ranking ovarian cancer as the leading cause of death from gynaecological cancer. The incidence of ovarian cancer increases with age and is most prevalent in the eighth decade of life. More than 70% of the patients are diagnosed with advanced disease and less than 40% of women with ovarian cancer are cured ([Fleming et al 2009](#); [Jemal et al 2010](#)).

The standard therapy for advanced ovarian cancer consists of radical debulking surgery followed by post-operative platinum-based first-line chemotherapy. Since 1996, platinum and paclitaxel combination therapy has become the standard-of-care first-line chemotherapy regimen ([McGuire et al 1996](#)). Worldwide, the use of carboplatin has replaced that of cisplatin because of carboplatin's superior tolerability profile together with equal effectiveness. However, the success of this approach is limited and approximately 70% of patients fail to achieve complete responses, or eventually relapse, after a varying disease-free interval.

#### **1.1.2 BRCA mutation positive ovarian cancer**

An important risk factor for ovarian cancer is genetic predisposition with BRCA1 or BRCA2 mutations (ie, gBRCAm) which account for the majority of hereditary ovarian cancer. If a lifetime risk for ovarian cancers among women in the general population is estimated to be 1.4 percent (14 out of 1,000), a woman with BRCA1 or BRCA2 deleterious mutation has a lifetime risk of 15 to 40 percent (150–400 out of 1,000). BRCA mutated ovarian cancer patients can also develop ovarian cancer earlier in their life than those without the mutation. Deficiency in BRCA ultimately leads to the accumulation of genetic alterations as a result of the failure of cells to arrest and repair DNA damage or to undergo apoptosis, resulting in tumorigenesis. If all ovarian cancer patients underwent gBRCA testing, current estimates indicate that 13% to 14% of the overall ovarian cancer population would have gBRCA1/2 mutations, and the proportion of patients with gBRCA mutations may be as high as 22% in patients with high-grade serous ovarian cancer (HGSOC). In addition, a population of ovarian cancer patients whose tumours harbour BRCA1 and BRCA2 mutations that are not detected in the germline (~7%) also exist and are defined as somatic BRCA mutations (tBRCAm).

Patients with BRCA-mutated ovarian cancer currently have identical treatment options as sporadic ovarian cancer patients. They seem to have a better prognosis compared with the overall relapsed ovarian cancer patient population but the pattern of disease is similar, with patients eventually dying from their disease. Ovarian cancer patients with BRCA mutation

represent a small, well defined and medically recognised subpopulation for whom, despite the potential for personalised healthcare, no targeted treatment currently exists.

### **1.1.3 PARP inhibition as a target for BRCA mutation positive ovarian cancer**

Investigators should be familiar with the current olaparib (AZD2281) Investigator Brochure (IB).

Olaparib (AZD2281, KU-0059436) is a potent Polyadenosine 5' diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents.

PARP inhibition is a novel approach to targeting tumours with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HR). Tumours with HR deficiencies (HRD), such as ovarian cancers in patients with BRCA1/2 mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumour types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

BRCA1 and BRCA2 defective tumours are intrinsically sensitive to PARP inhibitors, both in tumour models *in vivo* ([Rottenberg et al 2008](#), [Hay et al 2009](#)) and in the clinic ([Fong et al 2009](#)). The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair ([Helleday 2011](#); [Murai et al 2012](#)). Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by HR repair. Olaparib has been shown to inhibit selected tumour cell lines *in vitro* and in xenograft and primary explant models as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies.

### **1.1.4 Pre-clinical experience**

The pre-clinical experience is fully described in the current version of the olaparib IB.

### **1.1.5 Toxicology and safety pharmacology summary**

Olaparib has been tested in a standard range of safety pharmacology studies e.g., dog cardiovascular and respiratory function tests, and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anaesthetised dog or any behavioural, autonomic or motor effects in the rat at the doses studied.

Rodent and dog toxicology studies have indicated that the primary target organ of toxicity is the bone marrow with recovery seen following withdrawal of olaparib. Ex vivo studies have confirmed that olaparib is cytotoxic to human bone marrow cells.

Olaparib was not mutagenic in the Ames test but was clastogenic in the Chinese hamster ovary (CHO) chromosome aberration test in vitro. When dosed orally, olaparib also induced micronuclei in the bone marrow of rats. This profile is consistent with the potential for genotoxicity in man.

Reproductive toxicology data indicate that olaparib can have adverse effects on embryofoetal survival and development at dose levels that do not induce significant maternal toxicity.

Further information can be found in the current version of the olaparib IB.

### **1.1.6 Clinical experience**

Clinical experience with olaparib is fully described in the current version of the olaparib IB.

## **1.2 Research hypothesis**

Olaparib administered as monotherapy in the maintenance setting improves progression free survival compared to placebo in patients with newly diagnosed BRCA mutated high risk advanced ovarian cancer who are in clinical complete response or partial response following first line platinum-based chemotherapy.

## **1.3 Rationale for conducting this study**

Based on the results of a pivotal phase II trial (D0810C00019), investigating olaparib maintenance therapy in relapsed ovarian cancer patients AstraZeneca is planning to conduct the current phase III trial to investigate the benefit of olaparib as maintenance monotherapy in the first line setting in patients with newly diagnosed high risk advanced BRCA mutation positive ovarian cancer. The phase II study was conducted with the capsule formulation of olaparib. The phase III trial will be conducted with the more patient friendly tablet formulation.

Study D0810C00019 is a randomised, double-blind, placebo-controlled study to evaluate maintenance treatment with olaparib (capsule formulation) in patients with platinum-sensitive relapsed HGSOV who had received  $\geq 2$  previous platinum regimens and were in partial or complete response following their last platinum-containing regimen. The primary endpoint was investigator-assessed PFS. In total, 265 patients were randomised to olaparib 400 mg twice daily (136) or placebo (129). The primary analysis was carried out following 153 PFS events and demonstrated that maintenance treatment with olaparib led to a significant PFS improvement vs placebo [HR 0.35 (95% confidence interval (CI) 0.25 -0.49);  $p < 0.00001$ ] ([Ledermann et al 2012](#)). A subgroup analysis (pre-specified in the SAP) suggested that olaparib may lead to a greater clinical benefit in patients with a known germline BRCAm. gBRCAm status was determined retrospectively for all consenting patients (n=166) using blood samples taken before randomisation. tBRCAm status was determined from archival

tumor samples of 196 patients. Since gBRCA wild-type patients may develop somatic tumor BRCA mutations, efficacy analyses were performed by known gBRCA mutation status and known total BRCA mutation status. gBRCAm patients had the greatest PFS benefit with olaparib maintenance vs placebo (HR, 0.17; 95% CI 0.09-0.31; median: 11.2 vs 4.1 months;  $P<0.001$ ). The PFS benefit was consistent when tBRCAm patients were included (HR, 0.18; 95% CI 0.11-0.31; median: 11.2 vs 4.3 months;  $P<0.0001$ ). In an interim analysis of OS (58% maturity), OS HRs from the gBRCAm and gBRCAwt subgroups were similar (0.85 and 0.84, respectively), however 30% gBRCAm placebo patients received a subsequent PARP inhibitor, confounding the OS data in this subgroup. The analysis of all BRCAm patients was less confounded and resulted in an OS HR of 0.74 (95% CI 0.46-1.19; median: 34.9 vs 31.9 m). Olaparib tolerability was similar in BRCAm patients and the overall population.

The phase II study D0810C00019 demonstrated the efficacy of olaparib maintenance when using the capsule formulation (8 capsules twice daily). A more patient friendly tablet formulation (2 tablets twice daily) has been developed and this phase III study will investigate the efficacy of the tablet formulation when given as a maintenance therapy to newly diagnosed high risk advanced BRCA mutated ovarian cancer patients. The tablet dose of olaparib that will be investigated in this study is 300 mg twice daily. This tablet dose has been chosen based on data from an ongoing study, D0810C00024. Since it has been shown that the capsule and tablet formulations are not bioequivalent, a formulation switch based on bioequivalence has not been possible. The tablet dose of 300 mg twice daily is considered to have similar efficacy in terms of tumour shrinkage in BRCA mutated ovarian cancer patients to the 400 mg twice daily capsule together with an acceptable tolerability profile.

The tolerability profile of the 300 mg twice daily tablet dose in study D0810C00024 was considered similar to the 400 mg twice daily capsule formulation. The most common adverse events were consistent with the known safety profile of olaparib, namely low grade nausea, vomiting, fatigue and anaemia. Further information is provided in the IB.

A preliminary analysis of the effect of food (a light snack) on the pharmacokinetics of olaparib tablets was also investigated in study D0810C00024 and preliminary analysis of this data suggest that the intake of a light snack does not impact the pharmacokinetics (PK) of olaparib. Patients will be allowed to take olaparib tablets with a light snack during the phase III study.

The findings from study D0810C00019 are supported by clinical data from over 350 additional patients with BRCAm ovarian cancer in six other olaparib trials demonstrating consistent response rates.

### **1.3.1 Rationale for Study Design**

The magnitude of PFS benefit demonstrated in patients with gBRCA mutation positive ovarian cancer in Study D0810C00019 (median PFS delay of approximately 7 months following completion of chemotherapy; (HR, 0.18; 95% CI 0.11-0.31; median: 11.2 vs 4.3 months;  $P<0.0001$ ) is considered to be clinically meaningful and robust, with the upper CI of 0.31 being the most conservative estimate of the PFS benefit that can be expected in this

patient population. This translates to a 69% reduction in the risk of disease progression or death.

The proposed Phase III study will investigate the efficacy of olaparib administered as maintenance therapy in the first line setting for the treatment of newly diagnosed high risk advanced BRCA mutation positive ovarian cancer. PFS is considered the most appropriate primary endpoint for the Phase III study in this patient population because it is a meaningful and widely accepted measure of clinical benefit that can be measured robustly. The primary assessment of PFS will be based on investigator review of objective radiological findings as per the RECIST 1.1 guidelines.

An increased interval between lines of chemotherapy enables patients to delay further hospitalisation, the cumulative toxicities associated with chemotherapy, the associated risks of infection, and/or postpone major surgery. Furthermore, PFS is a clinically significant and clinically meaningful endpoint in its own right, as subsequent disease progression is associated with delayed development or worsening of cancer-related symptoms.

A number of secondary endpoints will provide further support for the clinical benefit of olaparib in this patient population, and will include OS, time from randomisation to progression by RECIST v1.1 or CA-125, time from randomisation to second progression (PFS2; see details in the study plan), time from randomisation to first subsequent therapy or death (TFST), time from randomisation to second subsequent therapy or death (TSST), time from randomisation to study treatment discontinuation or death (TDT), and patient reported outcome (PRO) measures.

All patients will be followed for OS in this study, however it is expected that the OS results will be confounded by an imbalance in subsequent anti-cancer treatment and particularly subsequent PARP inhibitor use between the arms, given the anticipated availability of trials of other PARP inhibitors for BRCAm ovarian cancer patients. Hence, PFS is considered the most robust measure to confirm the clinical benefit in this patient population.

## 1.4 Benefit/risk and ethical assessment

Olaparib in this current study is considered to have a positive benefit-risk profile for the treatment of first line BRCA mutated platinum responsive advanced (FIGO Stage III-IV) ovarian cancer patients who are considered at high risk of disease progression.

Ovarian cancer is the leading cause of death from gynaecological tumors in the Western world. Olaparib has demonstrated a large clinically meaningful prolongation of PFS as a maintenance therapy in BRCA mutated platinum responsive patients in the relapsed ovarian setting (D0810C00019) and has a tolerability profile that is considered suitable for use in the maintenance setting. In the phase II maintenance study in the relapsed ovarian cancer setting (D0810C00019) a number of patients have remained on therapy for periods >3 years (21 patients remained on olaparib maintenance therapy for >3 years and 32 patients for >2 years). Refer to the current IB for a complete description of the safety and tolerability profile.

Platinum-containing therapy is considered the treatment of choice for patients with newly diagnosed advanced ovarian cancer, including those patients with BRCA1/2 mutated high risk ovarian cancer, however the duration of response and the prolongation of the progression free interval are usually brief and these chemotherapy regimens cannot be continued until progression as they are associated with neurological, renal and haematological toxicity and cannot generally be tolerated for more than about 6 cycles. Since chemotherapy is not a viable treatment option in the maintenance setting, there is a need for a well tolerated maintenance treatment (following completion of chemotherapy) that can be taken until disease progression to extend the progression free interval in this patient population. Recently, the European Medicines Agency (EMA) approved bevacizumab, in combination with carboplatin and paclitaxel, for the first-line treatment or first recurrence of platinum sensitive advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer; the approval was based on improved PFS in trials of bevacizumab in combination with chemotherapy followed by bevacizumab maintenance monotherapy.

Patients with BRCA mutation ovarian cancer, however, represent a targeted and clinically identifiable subpopulation for whom, despite the potential for personalised healthcare, no targeted treatment is currently available.

The current study design will allow patients to complete their platinum-containing regimen as per normal clinical practice prior to enrolment. The use of olaparib as a maintenance therapy after completion of chemotherapy may provide further benefit to patients in terms of prolongation of the progression free interval, increasing the interval between lines of chemotherapy, delaying further hospitalisation and the cumulative toxicities associated with chemotherapy. Additionally, PARP inhibition with olaparib is expected to have less effect on normal cells that are wild type or heterozygous for both BRCA1 and BRCA2 ([Farmer et al 2005](#)). In patients with gBRCA mutations, their normal tissues will carry only one mutated copy of the relevant BRCA gene, but their tumours are expected to have lost both functional copies. This is important for the selective therapeutic window of olaparib (i.e., effect on the tumour versus the effect on normal tissue) and leads to an acceptable tolerability profile for



long term clinical use in a clearly identifiable and targeted patient population most likely to derive benefit.

Since ovarian cancer patients who respond to platinum based chemotherapy do not routinely receive additional treatment at this point in their therapy, the use of a placebo comparator to olaparib following completion of the platinum-containing regimen in those patients who, in the investigator's opinion, have achieved a clinical complete response or partial response is acceptable in order to objectively test the hypothesis of improved efficacy with the addition of olaparib maintenance treatment after a platinum regimen. The study will be conducted as a double-blind placebo-controlled study in which patients are randomised 2:1 to receive olaparib or matching olaparib placebo (tablet formulation), with a primary efficacy endpoint of PFS.

The tablet formulation is considered to be a more patient friendly formulation for long term use requiring patients to take up to 2 tablets twice daily as compared to the capsule formulation requiring 8 capsules twice daily.

In view of the potential for olaparib maintenance monotherapy to have a clinically meaningful PFS advantage in BRCA1/2 mutated patients with ovarian cancer, the current study is designed to allow patients to continue on olaparib therapy for up to two years or until progression of disease, whichever is earlier. Patients who continue to have evidence of disease that remains stable (i.e., no evidence of disease progression) at two years or those who have progressed may continue to receive study treatment if, in the opinion of the investigator, it is in the patient's best interest. However, if at two years the patient has no evidence of disease, study treatment should be discontinued. Patients may stop treatment at any time if they choose to do so or if the investigator believes it is in the best interest of the patient. Additionally, in the event of unmanageable toxicity, directions for reducing, interrupting or discontinuing olaparib are provided.

In the current study, prior to entry some patients will already know their germline BRCA mutation status. In addition, in some rare circumstances the patient may know their tumour BRCA mutation status. For those who do not know their BRCA mutation status but wish to participate in the study, patients will have to consent to undergo gBRCA testing. Any counselling procedures required before such testing will be carried out in accordance with local hospital practice. Patients who then chose to undergo testing and in whom a gBRCA mutation is identified will be eligible to continue study screening procedures.

During screening, patients will be required to consent to provide a sample of archival tumour tissue (to be submitted only if they are subsequently randomised), as well as a blood sample to either ascertain or reconfirm their BRCA mutation status.

A further (optional) blood sample will also be collected for future biomarker research. This research may further identify correlates for the response and possible resistance mechanisms that may exist for olaparib, a targeted therapy that is being

developed for ovarian cancer patients with BRCA 1/2 mutations. Such an understanding of response and resistance to olaparib may assist in ultimately ensuring that AstraZeneca will be able to prospectively identify patients most likely to benefit from treatment with olaparib.

## **2. STUDY OBJECTIVES**

### **2.1 Primary objective**

To determine the efficacy by progression free survival (using investigator assessment of scans according to modified RECIST 1.1) of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy.

### **2.2 Secondary objectives**

1. To determine the efficacy of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy by assessment of overall survival (OS), time to earliest progression by RECIST or CA-125, or death, and time from randomisation to second progression (PFS2)
2. To compare the effects of olaparib maintenance monotherapy compared to placebo on Health-related Quality of Life (HRQoL) as assessed by the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy
3. To assess efficacy of olaparib in patients identified as having a deleterious or suspected deleterious variant in either of the BRCA genes using variants identified with current and potential future BRCA mutation assays (gene sequencing and large rearrangement analysis)
4. To determine the efficacy of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy by assessment of time from randomisation to first subsequent therapy or death (TFST), time from randomisation to second subsequent therapy or death (TSST) and time from randomisation to study treatment discontinuation or death (TDT).

## **2.3 Safety objective**

1. To assess the safety and tolerability of olaparib maintenance monotherapy in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy

## **2.4 Exploratory objectives**

- 1.
2. To explore the impact of treatment and disease state on health state utility by EuroQoL five dimensions, five level (EQ-5D-5L)
3. To explore the impact of treatment and disease on resource use
4. To explore the effects of olaparib maintenance monotherapy compared to placebo on Health-related Quality of Life (HRQoL) as assessed by the individual domains of the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O)
5. To explore the efficacy of olaparib by assessment of overall survival (OS) adjusting for the impact of spontaneous switching [outside of study design] to PARP inhibitors or other potentially active investigational agents
- 6.
7. Future exploratory research into factors that may influence development of cancer and/or response to study treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumor samples that were mandatory for entry onto the study or on optional tumor biopsy samples collected during the course of the study
8. To collect and store DNA according to each country's local and ethical procedures) for future exploratory research into genes/genetic variation that may influence response (i.e., distribution, safety, tolerability and efficacy) to study treatments and or susceptibility to disease (optional)

The exploratory analyses may not be reported in the clinical study report, if not, they will be reported separately.

### 3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

#### 3.1 Overall study design and flow chart

This is a phase III, randomised, double-blind, placebo-controlled, multi-centre study to assess the efficacy of olaparib maintenance monotherapy in high risk advanced ovarian cancer patients (including patients with primary peritoneal and / or fallopian tube cancer) with BRCA mutations [documented mutation in BRCA1 or BRCA2] that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) who have responded following first line platinum based chemotherapy.

Approximately 344 patients will be randomised using an Interactive Voice Response System / Interactive Web Response System (IVR/IWR system) in a 2:1 ratio to the treatments as specified below:

- Olaparib tablets *p.o.* 300 mg twice daily
- Placebo tablets *p.o.* twice daily

Eligible patients will be those patients with newly diagnosed, histologically confirmed, high risk advanced (FIGO stage III-IV) BRCA mutated high grade serous or high grade endometrioid (based on local histopathological findings) ovarian cancer, primary peritoneal cancer and / or fallopian-tube cancer who are in clinical complete response or partial response following completion of first line platinum-based chemotherapy. Patients who re-present following prior diagnosis at an earlier stage of disease are not eligible. Stage III patients should have had one attempt at optimal debulking surgery (upfront or interval debulking). Stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery.

Patients must have completed a minimum of six and maximum of nine treatment cycles of first line platinum-based therapy (e.g., carboplatin or cisplatin) before randomisation to the study and should be in the opinion of the investigator in clinical complete response or partial response. However, if platinum based therapy must be discontinued early as a result of toxicities specifically related to the platinum regimen, patients must have received a minimum of four cycles of the platinum regimen.

Patients must not have received bevacizumab (either in combination or as maintenance therapy following combination therapy) or any investigational agent during their first line course of treatment.

Patients known to have germline BRCA mutation/s (gBRCAm i.e., blood) prior to randomisation can enter the study based on this result. The result must be made available to

AstraZeneca. In addition the patients must consent to provide 2 blood samples. One sample will be used for a confirmatory Myriad gBRCA test post randomisation using the current commercial Myriad BRCA*Analysis*<sup>®</sup> (gene sequencing and large rearrangement analysis), which will be paid for by AstraZeneca.

Patients with unknown BRCA status must consent to provide 2 blood samples for germline BRCA testing and follow all local ethical procedures for genetic testing. One sample will be used to test for BRCA mutations using the current commercial Myriad BRCA*Analysis*<sup>®</sup> test prior to study entry. When the result from the Myriad test indicates the patient does have a deleterious or suspected deleterious BRCA mutation, the patient can be randomised into the study (providing they have fulfilled all other screening requirements).

These samples will be required for the study even if the patients are found not to have a BRCA mutation.

Patients will be randomised within 8 weeks after their last dose of chemotherapy (last dose is the day of the last infusion).

Randomisation will be stratified by:

- response to first line platinum chemotherapy (in the opinion of the investigator, clinical complete response or partial response).

Following randomisation patients in both treatment arms will attend clinic visits weekly for the first 4 weeks of treatment (Days 8, 15, 22 and 29). Patients will then attend clinic visits every 4 weeks whilst on study treatment.

Patients should continue to receive study treatment for up to two years or until objective radiological disease progression as per RECIST as assessed by the investigator, whichever is earlier, and as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria as outlined in Section 5.8. Patients should continue with study treatment to RECIST progression as described above despite rises in CA-125. Patients who continue to have evidence of disease that remains stable (i.e., no evidence of disease progression) at two years or those who have progressed may continue to receive study treatment if, in the opinion of the investigator, it is in the patient's best interest. However, if at two years the patient has no evidence of disease, study treatment should be discontinued. A decision about continuing treatment with the investigational product beyond two years should be made after assessing the patient's disease status according to RECIST guidelines at week 108, and/or by assessing the patient's clinical condition. Continuation of treatment beyond week 108, based solely on clinical progression, is permissible only after case-by-case discussion with the AZ study physician.

Once a patient has discontinued study treatment, or has progressed, clinic visits will be reduced to every 12 weeks. Following discontinuation of study treatment, further treatment

will be at the discretion of the investigator. Any further systemic anti-cancer treatment will be collected until death, loss to follow-up or withdrawal of consent. In addition to their regular 12 weekly contact, patients will be contacted in the 7 days following a specified date (data cut off date) for each survival analysis. Assessments will be performed as described in [Table 3](#), and [Table 4](#).

Patients in both treatment arms will have tumour assessments according to RECIST at baseline and every 12 weeks ( $\pm 1$  week) up to 156 weeks and then every 24 weeks ( $\pm 1$  week) relative to date of randomisation until objective radiological disease progression according to RECIST. All CT/MRI scans will be sent to an AstraZeneca appointed Clinical Research Organisation (CRO) for blinded independent central review. All treatment decisions will be based on site assessment of scans. After the primary progression free survival (PFS) analysis, central review of scans will no longer be required and investigators will be advised when to stop sending copies of the scans to the CRO conducting the central review. Ongoing collection of site review tumour assessment is required and must be recorded in the electronic case report form (eCRF).

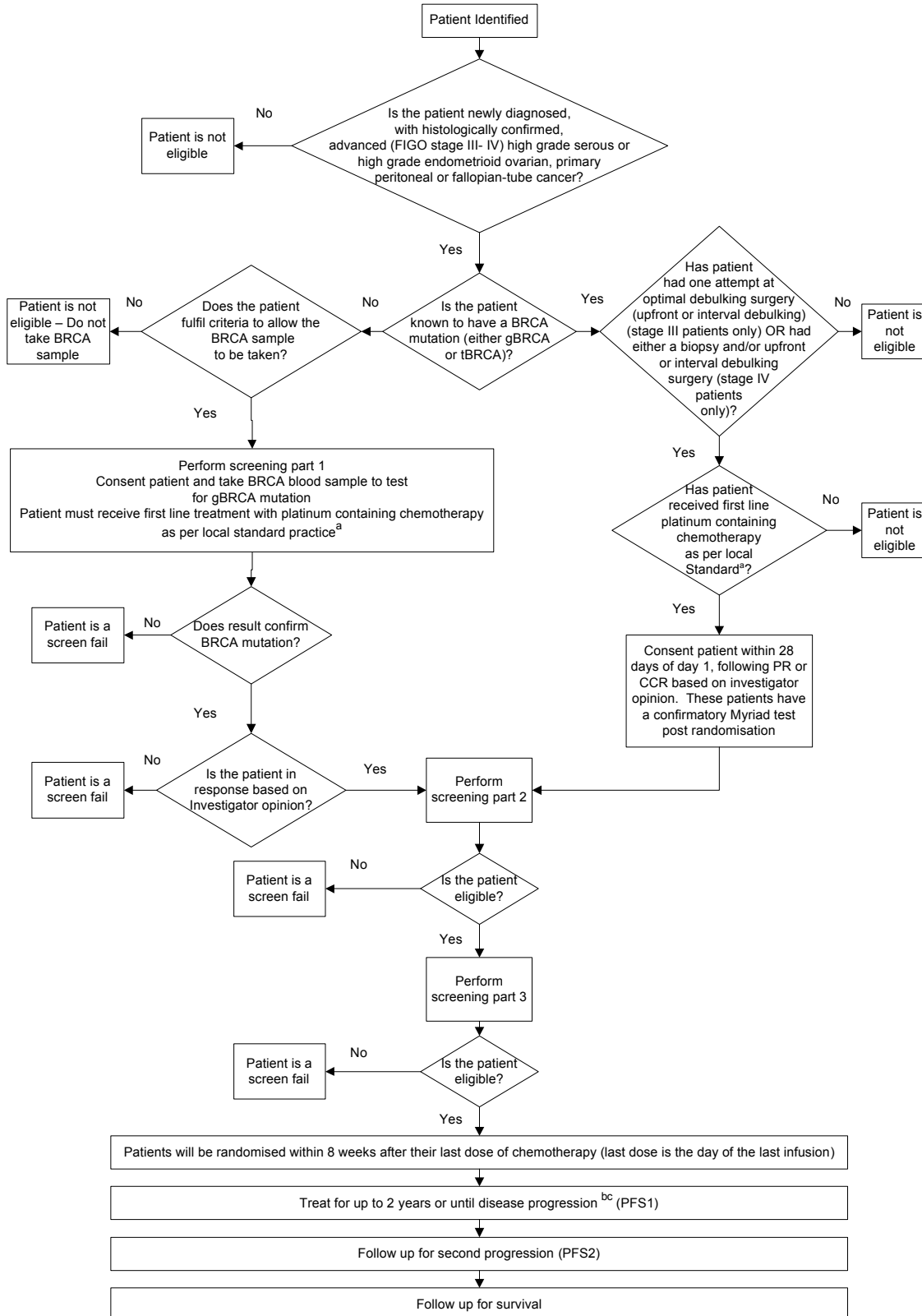
RECIST will be modified to assess patients with clinical CR at entry who will be assessed as having no evidence of disease (NED) unless they have progressed based on the appearance of new lesions.

Any patient who discontinues study treatment for reasons other than objective radiological progression should continue, to undergo scheduled objective tumour assessments according to the study plan (see [Table 3](#) and [Table 4](#)) in order to assess objective radiological progression of disease. Failure to do so may result in bias to the study results.

Once a patient has progressed the patient will be followed for second progression (PFS2) every 12 weeks and then survival until the final analysis. Patients will be contacted in the week following last patient last visit for each analysis of survival.

The primary analysis of the study will occur when approximately 196 events have occurred or after the last patient randomised has had the opportunity to have been on the study for at least 36 months, whichever comes first (there will be no interim analysis of progression free survival). The primary analysis will be based on investigator assessment of scans; however, a sensitivity analysis will be performed using the BICR data. All efficacy variables including overall survival will be analysed at the time of the primary analysis (providing sufficient events are available to make the analyses meaningful).

**Figure 1 Overall Study Design Flow Chart**



- a First line chemotherapy must comprise of a minimum of 6 and a maximum of 9 cycles of platinum based chemotherapy) and not containing bevacizumab. However if platinum based therapy must be discontinued early as a result of toxicities specifically related to the platinum regimen, patients may be eligible if they have received a minimum of four cycles of platinum regimen
- b Patients should continue to receive study treatment for up to two years or until objective radiological disease progression as per RECIST as assessed by the investigator, whichever is earlier, and as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria as outlined in Section 5.8. Patients should continue with study treatment to RECIST progression as described above despite rises in CA-125. Patients who continue to have evidence of disease that remains stable (i.e., no evidence of disease progression) at two years or those who have progressed may continue to receive study treatment if, in the opinion of the investigator, it is in the patient's best interest. However, if at two years the patient has no evidence of disease, study treatment should be discontinued. A decision about continuing treatment with the investigational product beyond two years should be made after assessing the patient's disease status according to RECIST guidelines at week 108, and/or by assessing the patient's clinical condition. Continuation of treatment beyond week 108, based solely on clinical progression, is permissible only after case-by-case discussion with the AZ study physician.
- c All ongoing adverse events/serious adverse events (AEs/SAEs) and any new AEs/SAEs identified during the 30 calendar days follow up period after last dose of study medication must be followed to resolution. See Section 6.4.3 for post 30 day safety follow up adverse event reporting.



## Figure 2          Screening Plan

### **Screening Part 1 (From diagnosis to –28d) applicable to:**

- only those patients who **do not** know their gBRCA or tBRCA mutation status prior to entry in to the study

These patients will undergo screening assessments as described for part 1 in [Table 1](#). Screening part 1 is conducted to determine if the patient is considered **eligible to undergo the BRCA status blood test**. The BRCA test may be performed from diagnosis to –28 days at the discretion of the investigator. To perform the BRCA testing from diagnosis to the end of cycle 3, investigator judgement of patient's potential eligibility to enter the study should be assessed as per [Table 1](#) and by reviewing the inclusion/exclusion criteria. For post cycle 3 of first line chemotherapy gBRCA status testing the patient must meet the inclusion criteria in Section 4.1 and none of the exclusion criteria in Section 4.2, and be showing a response to their current platinum chemotherapy prior to having the blood sample taken for the Myriad gBRCA status test. Once part 1 has been successfully completed these patients will continue to part 2 and have all procedures performed as described for part 2 in [Table 1](#).

### **Screening Part 2 (-28d to –1) applicable to:**

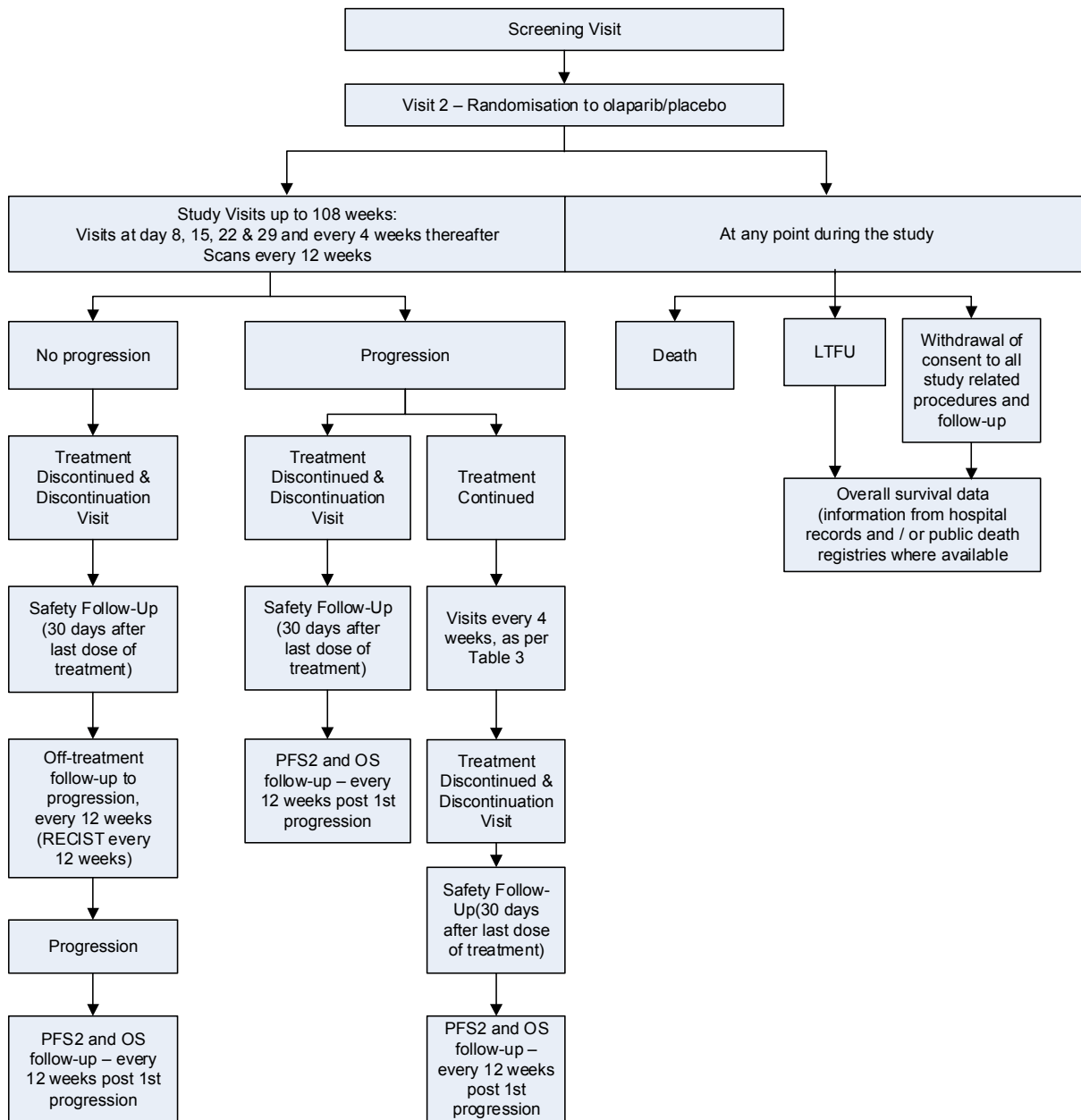
- those patients who already know their BRCA mutation status **and** have a deleterious or suspected deleterious mutation. These patients will undergo screening assessments as described for part 2 in [Table 2](#) and have confirmatory Myriad test post randomisation.
- those patients who have a confirmed mutation after completing screening part 1. These patients will undergo screening assessments as described for part 2 in [Table 1](#).

### **Screening Part 3 (-7d to –1) applicable to:**

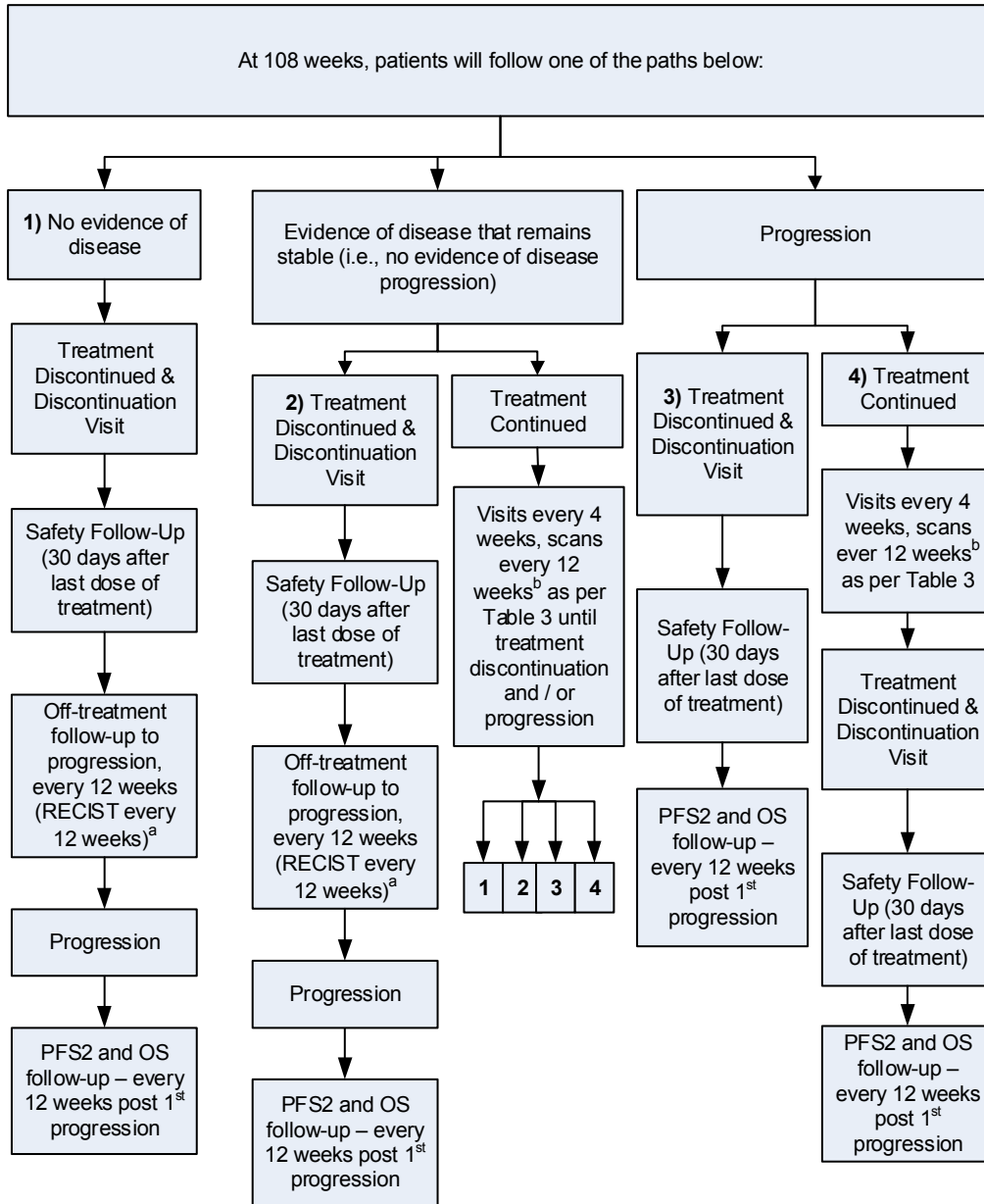
- those patients who are still deemed eligible to continue with screening after completing part 1 and / or part 2.

Once screening has been completed and eligibility confirmed these patients will continue to visit 2 and have procedures performed as described in [Table 3](#).

**Figure 3 Study Flow Chart Up to 108 Weeks on Treatment**



**Figure 4 Study Flow Chart At 108 Weeks on Treatment**



<sup>a</sup> Patients off treatment: Off-treatment follow-up visits and scans will continue to be conducted every 12 weeks (±1 week) up to 156 weeks (3 years), then every 24 weeks (±1 week) relative to date of randomization.

<sup>b</sup> Patients continuing treatment: Treatment visits will continue every 4 weeks (±3 days) up to 156 weeks (3 years), then every 12 weeks (±1 week) relative to date of randomization. Scans will continue every 12 weeks (±1 week) up to 156 weeks (3 years), then every 24 weeks (±1 week) relative to date of randomization.




Revised Clinical Study Protocol  
Drug Substance AZD2281  
Study Code D0818C00001  
GOG Code GOG-3004

i











Revised Clinical Study Protocol  
Drug Substance AZD2281  
Study Code D0818C00001  
GOG Code GOG-3004

d




a

Revised Clinical Study Protocol  
Drug Substance AZD2281  
Study Code D0818C00001  
GOG Code GOG-3004

e

### **3.2 Rationale for study design, doses and control groups**

The proposed Phase III study is designed to investigate the efficacy and clinical benefit of olaparib as maintenance therapy for the treatment of newly diagnosed high risk advanced BRCA mutation positive ovarian cancer based upon the benefit demonstrated in the phase II study D0810C00019 (Section 1.3). The primary assessment of PFS will be based on investigator assessment of objective radiological findings as per the RECIST guidelines. A number of secondary endpoints will provide further support for the clinical benefit of olaparib in this patient population, and will include OS, time from randomisation to progression by RECIST 1.1 or CA-125, time from randomisation to second progression (PFS2; see details in the study plan) and patient reported outcome measures.

The study design will allow patients to complete their platinum-containing regimen as per normal clinical practice prior to enrolment. The use of olaparib as a maintenance therapy after completion of chemotherapy may provide further benefit to patients in terms of prolongation of the progression free interval, increasing the interval between lines of chemotherapy, delaying further hospitalisation and the cumulative toxicities associated with chemotherapy. Additionally, PARP inhibition with olaparib is expected to have no effect on normal cells that are wild type or heterozygous for both BRCA1 and BRCA2 (Farmer et al 2005). In patients with gBRCA mutations, their normal tissues will carry only one mutated copy of the relevant BRCA gene, but their tumours are expected to have lost both functional copies. This is important for the selective therapeutic window of olaparib (i.e., effect on the tumour versus the effect on normal tissue) and leads to an acceptable tolerability profile for long term clinical use in a clearly identifiable and targeted patient population most likely to derive benefit.

Since ovarian cancer patients who respond to platinum based chemotherapy do not routinely receive additional treatment at this point in their therapy, the use of a placebo comparator to olaparib following completion of the platinum-containing regimen in those patients who have achieved in the opinion of the investigator a clinical complete response or partial response is considered acceptable in order to objectively test the hypothesis of improved efficacy with the addition of olaparib maintenance treatment after a platinum regimen. Given the promising phase II data from Study D0810C00019 (Section 1.3), the phase III study will be conducted with a 2:1 randomisation for olaparib:placebo to minimise the number of patients receiving placebo.

A more patient friendly tablet formulation (2 tablets twice daily) has been developed and this phase III study will investigate the efficacy of the tablet formulation when given as a maintenance therapy to BRCA mutated ovarian cancer patients following first line platinum based chemotherapy. The tablet dose of olaparib that will be investigated in this study is 300mg twice daily. This tablet dose has been chosen based on data from an ongoing study, D0810C00024. Since it has been shown that the capsule and tablet formulations are not bioequivalent, a formulation switch based on bioequivalence has not been possible. The tablet dose of 300mg twice daily is considered to have similar efficacy in terms of tumour shrinkage in BRCA mutated ovarian cancer patients to the 400mg twice daily capsule together with an acceptable tolerability profile. The tolerability profile of the 300mg twice daily tablet dose in



study D0810C00024 was considered similar to the 400mg twice daily capsule formulation. The most common adverse events were consistent with the known safety profile of olaparib, namely low grade nausea, vomiting, fatigue and anaemia. Further information is provided in the IB.

## **4. PATIENT SELECTION CRITERIA**

The patient population should be selected without bias.

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

### **4.1 Inclusion criteria**

Patients that already know they have a mutation in BRCA1 or BRCA2 gene that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) must fulfil all of the criteria below. Patients that do not know their mutation status, and who are being considered for this trial should be identified early so that the appropriate BRCA mutation screening procedures can be put in place in a timely manner. Patients that do not know their BRCA mutation status and who are being tested post cycle 3 of their first line chemotherapy must fulfil all of the criteria marked with an asterisk (\*) below prior to BRCA mutation testing being carried out. To perform the BRCA testing from diagnosis to the end of cycle 3, investigator judgement of patient's potential eligibility to the study should be assessed as per [Table 1](#) and by reviewing the inclusion/exclusion criteria. All inclusion criteria will then be assessed following confirmation that they harbour an appropriate BRCA mutation.

Any patient that fulfils the eligibility criteria for the BRCA test, are required to have their eligibility assessed again prior to randomisation.

All patients must provide informed consent prior to any study specific procedures.

1. \*Patients must be  $\geq 18$  years of age.
2. \*Female patients with newly diagnosed, histologically confirmed, high risk advanced (FIGO stage III – IV) BRCA mutated high grade serous or high grade endometrioid (based on local histopathological findings) ovarian cancer, primary peritoneal cancer and / or fallopian-tube cancer who have completed first line platinum based chemotherapy (intravenous or intraperitoneal). Guidance on grading of serous ovarian carcinomas is covered by Appendix J.

3. \* Stage III patients must have had one attempt at optimal debulking surgery (upfront or interval debulking). Stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery.
4. Documented mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function)
5. Patients who have completed first line platinum (e.g. carboplatin or cisplatin), containing therapy (intravenous or intraperitoneal) prior to randomisation:
  - Patients must have, in the opinion of the investigator, clinical complete response or partial response and have no clinical evidence of disease progression on the post-treatment scan or a rising CA-125 level, following completion of this chemotherapy course. Patients with stable disease on the post-treatment scan at completion of first line platinum-containing therapy are not eligible for the study.
  - ‘Response’ is used throughout the protocol and refers to patients being, in the opinion of the investigator, in clinical complete response or partial response on the post-treatment scan. Clinical complete response is defined as no evidence of RECIST measurable or non-measurable disease on the post-treatment scan and a normal CA-125. Partial response is defined as  $\geq 30\%$  reduction in tumor volume demonstrated from the start to finish of chemotherapy OR no evidence of RECIST measurable disease on the post-treatment scan with a CA-125 which has not decreased to within the normal range.
  - Platinum based chemotherapy course must have consisted of a minimum of 6 treatment cycles and a maximum of 9, however if platinum based therapy must be discontinued early as a result of toxicities specifically related to the platinum regimen, patients must have received a minimum of 4 cycles of the platinum regimen.
  - \*Patients must **not** have received bevacizumab during their first line course of treatment, either in combination or as maintenance therapy following combination therapy.
  - Patients must not have received an investigational agent during their first line course of chemotherapy
  - Patients must be randomised within 8 weeks after their last dose of chemotherapy (last dose is the day of the last infusion).
6. Pre-treatment CA-125 measurements must meet criterion specified below:

- If the first value is less than or equal to the upper limit of normal (ULN) the patient is eligible to be randomised and a second sample is not required
  - If the first value is greater than ULN a second assessment must be performed at least 7 days after the first. If the second assessment is  $\geq 15\%$  more than the first the patient is not eligible
7. Patients must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:
- Haemoglobin  $\geq 10.0$  g/dL with no blood transfusion in the past 28 days
  - Absolute neutrophil count (ANC)  $\geq 1.5 \times 10^9/L$
  - Platelet count  $\geq 100 \times 10^9/L$
  - Total bilirubin  $\leq 1.5 \times$  institutional upper limit of normal (ULN)
  - Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT))  $\leq 2.5 \times$  institutional upper limit of normal unless liver metastases are present in which case they must be  $\leq 5 \times$  ULN
  - Serum creatinine  $\leq 1.5 \times$  institutional ULN
8. \*Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (see Appendix G).
9. \*Patients must have a life expectancy  $\geq 16$  weeks.
10. \*Postmenopausal or evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test prior to Myriad BRCA test during screening part 1, within 28 days of study treatment and confirmed prior to treatment on day 1.

Postmenopausal is defined as:

- Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
- Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the post menopausal range for women under 50
- radiation-induced oophorectomy with last menses  $>1$  year ago
- chemotherapy-induced menopause with  $>1$  year interval since last menses

- surgical sterilisation (bilateral oophorectomy or hysterectomy)
11. \*Patients is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations.
  12. \*Formalin fixed, paraffin embedded (FFPE) tumour sample from the primary cancer **must** be available for central testing. If there is not written confirmation of the availability of an archived tumour sample prior to enrolment the patient is **not** eligible for the study.

For inclusion in i) the optional exploratory genetic research and ii) the optional biomarker research, patients must fulfil the following criteria:

- Provision of informed consent for genetic research
- Provision of informed consent for biomarker research

If a patient declines to participate in the optional exploratory genetic research or the optional biomarker research, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study.

## 4.2 Exclusion criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled (any asterisked\* are also applicable as an exclusion criteria for patients that are being screened post cycle 3 of their first line chemotherapy to determine their BRCA mutation status via Myriad. To perform the BRCA testing from diagnosis to the end of cycle 3, investigator judgement of patient's potential eligibility to the study should be assessed as per [Table 1](#) and by reviewing the below exclusion criteria):

1. \*Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
2. BRCA 1 and/or BRCA2 mutations that are considered to be non detrimental (e.g. “Variants of uncertain clinical significance” or “Variant of unknown significance” or “Variant, favor polymorphism” or “benign polymorphism” etc)
3. \*Patients with early stage disease (FIGO Stage I, IIA, IIB or IIC)
4. Stable disease or progressive disease on the post-treatment scan or clinical evidence of progression at the end of the patient's first line chemotherapy treatment
5. \*Patients where more than one debulking surgery has been performed before randomisation to the study. (Patients who, at the time of diagnosis, are deemed to be unresectable and undergo only a biopsy or oophorectomy but then go on to receive chemotherapy and interval debulking surgery are eligible).

6. \*Patients who have previously been diagnosed and treated for earlier stage ovarian, fallopian tube or primary peritoneal cancer.
7. \*Patients who have previously received chemotherapy for any abdominal or pelvic tumour, including treatment for prior diagnosis at an earlier stage for their ovarian, fallopian tube or primary peritoneal cancer. (Patients who have received prior adjuvant chemotherapy for localised breast cancer may be eligible, provided that it was completed more than three years prior to registration, and that the patient remains free of recurrent or metastatic disease).
8. \*Patients with synchronous primary endometrial cancer unless both of the following criteria are met:
  - (i) stage <2
  - (ii) less than 60 years old at the time of diagnosis of endometrial cancer with stage IA or IB grade 1 or 2, or stage IA grade 3 endometrioid adenocarcinoma OR  $\geq$  60 years old at the time of diagnosis of endometrial cancer with Stage IA grade 1 or 2 endometrioid adenocarcinoma. Patients with serous or clear cell adenocarcinoma or carcinosarcoma of the endometrium are not eligible.
9. Patients who have had drainage of their ascites during the final 2 cycles of their last chemotherapy regimen prior to enrolment on the study.
10. \*Previous randomisation in the present study.
11. \*Participation in another clinical study with an investigational product during their chemotherapy course immediately prior to randomisation.
12. \*Any previous treatment with PARP inhibitor, including olaparib.
13. \*Other malignancy within the last 5 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS), Stage 1, grade 1 endometrial carcinoma, or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for  $\geq$ 5 years. Patients with a history of localised breast cancer may be eligible, provided they completed their adjuvant chemotherapy more than three years prior to registration, and that the patient remains free of recurrent or metastatic disease
14. \*Resting ECG with QTc > 470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome

15. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment (or a longer period depending on the defined characteristics of the agents used).
16. \*Concomitant use of known potent CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir.
17. \*Persistent toxicities ( $\geq$ Common Terminology Criteria for Adverse Event (CTCAE) grade 2) caused by previous cancer therapy, excluding alopecia.
18. \*Patients with myelodysplastic syndrome/acute myeloid leukaemia.
19. \*Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.
20. Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.
21. \*Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent.
22. \*Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.
23. \*Breast feeding women.
24. \*Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV).
25. \*Patients with a known hypersensitivity to olaparib or any of the excipients of the product.
26. \*Patients with known active hepatitis (i.e. Hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids
27. \*Previous allogeneic bone marrow transplant

28. \*Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable, for timing refer to inclusion criteria no.7)

Procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

## **5. STUDY CONDUCT**

### **5.1 Restrictions during the study**

The following restrictions apply while the patient is receiving olaparib and for the specified times before and after:

#### **5.1.1 Olaparib and CYP3A4**

Patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 enzyme activity (see Section 5.6.2) from the time they enter the screening period until 30 days after the last dose of study medication.

#### **5.1.2 Contraception**

Female patients of child bearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception in combination throughout the period of taking study treatment and for at least 1 month after last dose of study drug.

For details refer to Appendix E Acceptable Birth Control Methods.

### **5.2 Patient enrolment and randomisation and initiation of investigational product**

The Principal Investigator will:

1. Obtain signed informed consent from the potential patients before any study specific procedures are performed.
2. Assign potential patients a unique enrolment number, beginning with 'E#'. (This number will be obtained through Interactive Voice/Web Response System [IVRS/IWRS]).
3. Determine patient's eligibility. See Sections 4.1 and 4.2.
4. Obtain the randomisation code (patient number) through IVRS/IWRS

As patients are screened for the study, they must be allocated an enrolment code (E-code). The E-code is a 7-digit number made up of the centre number and the patient number within that particular centre (e.g., the first patient screened at centre number 0001 would be assigned the E-code E0001001, the second patient screened would be E0001002 and so on). This number is

the patient unique identifier and is used to identify the patient on the eCRFs. If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

### 5.2.1 Procedures for randomisation

Patient eligibility will be established before treatment randomisation. Once the eligibility of a patient has been confirmed, the Investigator (or nominated assistant) should contact the IVRS/IWRS Centralised Randomisation Centre for allocation of randomised study treatment.

The actual treatment given to individual patients will be determined by a randomisation scheme that has been loaded into the (IVRS/IWRS) database. The randomisation scheme will be produced by a computer software program called GRand (AZ Global Randomisation system) that incorporates a standard procedure for generating random numbers.

A blocked randomisation will be generated and all centres will use the same list in order to minimise any imbalance in the number of patients assigned to each treatment group.

The randomisation scheme will be stratified based on:

- response to first line platinum chemotherapy (clinical complete response or partial response)

Patients will be identified to the Centralised Randomisation Centre using patient initials, Ecode and date of birth.

Randomisation codes will be assigned strictly sequentially within each strata as patients become eligible for randomisation.

Eligible patients will be randomised in a 2:1 ratio as specified below:

- olaparib tablets *p.o.* 300 mg twice daily
- placebo tablets *p.o.* twice daily

It is recommended that patients commence study treatment as soon as possible after randomisation, and ideally within 3 days.

The IVRS/IWRS Centralised Randomisation Centre will inform the Investigator of the Kit ID number to be allocated to the patient at the randomisation visit. The Investigator will call/log in to the IVRS/IWRS for each subsequent dispensing visit for assignment of a new Kit ID number.

The Kit ID number dispensed at each visit will correspond to the treatment to which the patient was originally randomised



### **5.3 Procedures for handling patients incorrectly enrolled or randomised or initiated on investigational product**

**Patients who fail to meet the inclusion/exclusion criteria** should not, under any circumstances, be randomised or receive study medication. There can be no exceptions to this rule.

Where patients that do not meet the selection criteria are randomised in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, a discussion should occur between the AstraZeneca Study Team Physician and the investigator regarding whether to continue or discontinue the patient from treatment. Once a decision is made, Investigators need to ensure they comply with all applicable requirements for human patient protection and ethical review.

The AstraZeneca Study Team Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have their study treatment stopped and be withdrawn from the study.

### **5.4 Blinding and procedures for unblinding the study**

#### **5.4.1 Methods for ensuring blinding**

Olaparib and placebo treatment will be blinded.

The study medication will be labelled using a unique Kit ID number, which is linked to the randomisation scheme. The active and placebo tablets will be identical and presented in the same packaging to ensure blinding of the study medication.

#### **5.4.2 Methods for unblinding the study**

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) or pharmacists from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff. Where a treatment code break is sought for an individual patient in situations other than medical emergencies, it is strongly recommended to discuss with the relevant AstraZeneca staff in collaboration with the Principal Investigator before the patient is unblinded.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

## 5.5 Treatments

### 5.5.1 Identity of investigational product(s)

AstraZeneca's Pharmaceutical Development, R&D Supply Chain will supply olaparib and matching placebo to the investigator as green film-coated tablets.

Investigational product	Dosage form and strength	Manufacturer
Olaparib	Tablet – 150 mg and 100 mg	
Placebo to match olaparib	Tablet to match each strength of olaparib	

<sup>a</sup> Descriptive information for olaparib can be found in the Investigator's Brochure

### 5.5.2 Doses and treatment regimens

#### 5.5.2.1 Olaparib and matching placebo (study treatment)

For all centres, olaparib and matching placebo (study treatment) will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. The randomised study treatment will be dispensed to patients. Each dosing container will contain sufficient medication for at least each treatment period plus overage. Multiple bottles of study treatment may be required for dispensing in order to make up the desired dose.

Patients will be administered their randomised study treatment tablets orally at a dose of 300mg twice daily.

Study treatment is available as a green film-coated tablet containing 150mg or 100mg of olaparib or matching placebo. Tablets are to be taken orally, twice daily (bd). Doses of study treatment should be taken at the same times each day approximately 12 hours apart. All doses should be taken with approximately 240 mL of water. The study treatment tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Study treatment tablets can be taken with a light meal/snack (e.g., two pieces of toast or a couple of biscuits).

If vomiting occurs shortly after the study treatment tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

Patients should continue to receive study treatment for up to two years or until objective radiological disease progression as per RECIST as assessed by the investigator, whichever is earlier, and as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria as outlined in Section 5.8. Patients should

continue with study treatment to RECIST progression as described above despite rises in CA-125. Patients who continue to have evidence of disease that remains stable (i.e., no evidence of disease progression) at two years or those who have progressed may continue to receive study treatment if, in the opinion of the investigator, it is in the patient's best interest. However, if at two years the patient has no evidence of disease, study treatment should be discontinued. A decision about continuing treatment with the investigational product beyond two years should be made after assessing the patient's disease status according to RECIST guidelines at week 108, and/or by assessing the patient's clinical condition. Continuation of treatment beyond week 108, based solely on clinical progression, is permissible only after case-by-case discussion with the AZ study physician.

Once patients have been discontinued from study treatment, other treatment options will be at the discretion of the investigator. Patients and investigators will not be routinely unblinded to study treatment prior to the final OS analysis. Within this study patients are not permitted to switch over to the opposite arm from which they were randomised.

### **5.5.3 Labelling**

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

Specific dosing instructions will not be included on the label, the site must complete the "Patient Dispensing Card" with the details of the dosing instructions at the time of dispensing.

The patient emergency contact details will not be on the label but can be found in the informed consent and the 'Patient Dispensing Card'. For emergency purposes the patient must be in possession of the emergency contact details at all times

### **5.5.4 Storage**

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle specifies the appropriate storage.

### **5.5.5 Management of toxicity of study treatment**

Any toxicity observed during the study treatment phase could be managed by interruption of the dose of study treatment if deemed appropriate by the Investigator. Repeat dose interruptions are allowed as required, for a maximum of 14 days on each occasion. If the interruption is any longer than this the AstraZeneca study team must be informed. Study treatment must be interrupted until the patient recovers completely or the toxicity reverts to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (current version) grade 1 or less.

Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment. Treatment

must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the Investigator considers to be related to administration of study treatment.

NB. In case a patient shows an AST or ALT  $\geq 3 \times \text{ULN}$  or total bilirubin  $\geq 2 \times \text{ULN}$  please refer to Appendix D ‘Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy’s Law’, for further instructions.

### **Management of anaemia:**

Adverse events of anaemia CTCAE grade 1 or 2 (Haemoglobin (Hb)  $\geq 8$  g/dl) should be investigated and managed as deemed appropriate by the investigator with or without interruption of study drug or change in dose, taking into account previous history of anaemia. Common treatable causes of anaemia (e.g. iron, vitamin B12 or folate deficiencies and hypothyroidism) should be excluded. In some cases management of anaemia may require blood transfusions. However, if patient develops anaemia CTCAE grade 3 (Hb  $< 8$  g/dl) or worse, study treatment should be interrupted for up to maximum of 4 weeks to allow for bone marrow recovery and patient should be managed appropriately. Study treatment can be restarted at the same dose if Hb has recovered to  $\geq 9$  g/dl. Any subsequently required anemia related interruptions, considered likely to be dose related, or coexistent with newly developed neutropenia, and or thrombocytopenia, will require study treatment dose reductions to 250 mg bd as a first step and to 200 mg bd as a second step.

If a patient has been treated for anaemia with multiple blood transfusions without study treatment interruptions and becomes blood transfusion dependant as judged by investigator, study treatment should be interrupted for up to a maximum of 4 weeks to allow for bone marrow recovery. Study treatment should be restarted at a reduced dose.

### **Management of neutropenia and leukopenia:**

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if CTC grade 3 or worse neutropenia occurs. Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h of the last dose of study treatment.

Study treatment can be restarted at the same dose if an adverse event of neutropenia or leucopenia have been recovered up to CTCAE grade  $\leq 1$  (ANC  $\geq 1.5 \times 10^9/\text{L}$ ). Growth factor support should be stopped at least 24h before restarting study drug (7 days for pegylated G-CSF).

Any subsequent interruptions will require study treatment dose reductions to 250 mg bd as a first step and to 200 mg bd as a second step.

### **Management of thrombocytopenia**

An adverse event of thrombocytopenia should be managed as deemed appropriate by the investigator. If patient develops thrombocytopenia CTCAE grade 3 or worse study treatment should be interrupted for a max of 4 weeks. In some cases management of thrombocytopenia may require platelet transfusions. Platelet transfusions should be done according to local hospital guidelines.

### **Management of prolonged haematological toxicities while on study treatment:**

If patient develops prolonged haematological toxicity such as:

- $\geq 2$  week interruption/delay in study treatment due to CTC grade 3 or worse anaemia and/or development of blood transfusion dependence
- $\geq 2$  week interruption/delay in study treatment due to CTC grade 3 or worse neutropenia ( $ANC < 1 \times 10^9/L$ )
- $\geq 2$  week interruption/delay in study treatment due to CTC grade 3 or worse thrombocytopenia (Platelets  $< 50 \times 10^9/L$ )

Weekly differential blood counts including reticulocytes (calculate reticulocyte index (RI),  $RI = \text{reticulocyte count} \times \text{haematocrit (Hct)}/\text{normal Hct}$ ; a value of 45 is usually used for normal Hct) (Bessman JD 1990) and peripheral blood smear should be performed. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice.

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the Investigator to AstraZeneca Patient Safety. Study treatment should be discontinued if diagnosis of myelodysplastic syndrome is confirmed.

### **Management of new or worsening pulmonary symptoms:**

If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormality occurs, an interruption in study treatment dosing is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the AstraZeneca Study Physician.

## Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. They are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment with the incidence of nausea and vomiting not showing an increase over the treatment cycles.

No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter in accordance with local treatment practice guidelines.

## Interruptions for intercurrent non-toxicity related events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with AstraZeneca study physician.

If a patient discontinues treatment for intercurrent condition and progresses while off treatment, they can restart study treatment if the investigator feels the patient is receiving clinical benefit. Please note that evidence of objective radiological disease progression is required.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

**Table 5**                      **Dose reductions for study treatment**

<b>Initial Dose</b>	<b>Following re-challenge post interruption: Dose reduction 1</b>	<b>Dose reduction 2</b>
300mg	250mg	200mg

## **5.6 Concomitant and post-study treatment(s)**

Any medications (with the detailed exceptions) which are considered necessary for the patient's welfare, and which it is believed will not interfere with the study medication, may be given at the discretion of the investigator, providing the medications, the doses, dates and reasons for administration are recorded.

In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded. This includes any blood transfusions.

The reasons for the use, doses and dates of treatment should be recorded in the patient's medical records and appropriate sections of the eCRF.

All medications (prescriptions or over the counter medications) continued at the start of study or started during the study or until 30 days from the end of the last protocol treatment and different from the study medication must be documented as per [Table 1](#), [Table 2](#), [Table 3](#) and [Table 4](#).

### **5.6.1 Medications that may NOT be administered**

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (Hormone replacement therapy (HRT) is acceptable), radiotherapy, biological therapy or other novel agent) is to be permitted while the patient is receiving study medication.

Live virus and bacterial vaccines should not be administered whilst the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

### **5.6.2 CYP3A4**

The use of any natural/herbal products or other "folk remedies" should be discouraged but use of these products, as well as use of all vitamins, nutritional supplements and all other concomitant medications must be recorded.

Olaparib is an investigational drug for which no data on in vivo interactions are currently available. Olaparib can inhibit CYP3A4 and UGT1A1 in vitro. These findings suggest that olaparib has the potential to cause clinically significant interactions with other CYP3A4 substrates or UGT1A1 substrates in the liver or gastrointestinal tract. Therefore, caution should be exercised when substrates of CYP3A4 are combined with olaparib, in particular those with a narrow therapeutic margin (e.g. simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozone, sirolimus, tacrolimus and quetiapine). Substrates of UGT1A1 should also be given with caution in combination with olaparib (e.g. irinotecan, nintedanib, ezetimibe, raltegravir or buprenorphine). In vitro data have also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, to ensure patient safety, the following potent inhibitors of CYP3A4 must not be used during this study for any patient receiving olaparib.

While this is not an exhaustive list, it covers the known potent inhibitors, which have most often previously been reported to be associated with clinically significant drug interactions:

- ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir

For patients taking any of the above, the required wash-out periods prior to starting study treatment is one week.

In addition, to avoid potential reductions in exposure due to drug interactions, the following CYP3A4 inducers should be avoided:

- Phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbitone, nevirapine, modafinil and St John's Wort (*Hypericum perforatum*)

For patients taking any of the above, the required wash-out periods prior to starting study treatment are phenobarbitone 5 weeks, and for any of the others, 3 weeks.

After randomisation if the use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient's safety and welfare, the investigator must contact the AstraZeneca Study Physician. A decision to allow the patient to continue in the study will be made on a case-by-case basis.

### **5.6.3 Anticoagulant Therapy**

Patients who are taking warfarin may participate in this trial; however, it is recommended that prothrombin time (international normalised ratio (INR) and activated partial thromboplastin time (APTT)) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted.

### **5.6.4 Anti-emetics/Anti-diarrhoeals**

From screening part 2 onwards, should a patient develop nausea, vomiting and / or diarrhoea, then these symptoms should be reported as AEs (see Section 6.4.3) and appropriate treatment of the event given.

### **5.6.5 Palliative radiotherapy**

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.



### **5.6.6 Administration of other anti-cancer agents**

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.

### **5.6.7 Subsequent therapies for cancer**

Details of first and subsequent therapies for cancer and/or details of surgery for the treatment of the cancer, after discontinuation of treatment, will be collected. Reasons for starting subsequent anti-cancer therapies including access to other PARP inhibitors or investigational drugs will be collected and included in the exploratory assessments of OS.

## **5.7 Treatment compliance**

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the eCRF.

Patients should be given clear instructions on how and when to take their study treatment. Patients will self-administer study treatment. Study site staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the eCRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the investigative site until reconciliation is completed by the study monitor. All patients must return their bottle(s) of study treatment at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded by the site staff on the eCRF.

Patients must return all containers and any remaining tablets at the end of the study.

### **5.7.1 Accountability**

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the patient.

Study site personnel will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction and return should be signed. Any discrepancies must be accounted for on the appropriate forms.

## **5.8 Discontinuation of investigational product**

Patients may be discontinued from investigational product (IP) in the following situations:

- Patients decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance to study protocol
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML).
- Objective radiological disease progression according to RECIST criteria (unless in the Investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria as outlined in Section 5.8)
- If at two years of study treatment the patient has no evidence of disease. Presence of structural disease should be assessed according to RECIST guidelines at week 108.

#### **5.8.1 Procedures for discontinuation of a patient from investigational product**

A patient that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); questionnaires (e.g., for patient reported outcomes) and all study drugs should be returned by the patient.

By discontinuing from treatment, the patient is not withdrawing from the study. Patients should be followed for progression (if discontinuation in the absence of progression), PFS2 and OS following treatment discontinuation as per the protocol schedule. If a patient is withdrawn from study, see Section 5.9.

Any patient discontinuing investigational product should be seen at 30 days post discontinuation for the evaluations outlined in the study schedule. The patient's tumour status should be assessed clinically and, if appropriate, disease progression should be confirmed by radiological assessment. After discontinuation of study medication, the principal Investigator/Sub-Investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the patient. In addition, they will record on the eCRF the date of discontinuation, the reasons, manifestation and treatment at the time of discontinuation. If patients discontinue study treatment, the AstraZeneca monitor must be informed immediately. Patients will be required to attend the treatment discontinuation visit. The patient should return all study medication.

After discontinuation of the study medication at any point in the study, all ongoing AEs or SAEs must be followed until resolution unless, in the Investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow up (see Sections 6.4.3 and 6.4.4). All new AEs and SAEs occurring during the 30 calendar days

after the last dose of study medication must be reported (if SAEs, they must be reported to AstraZeneca within 24 hours as described in Section 6.4.4) and followed to resolution as above. Patients should be seen at least 30 days after discontinuing study medication to collect and / or complete AE information. Procedures for handling of any untoward events occurring subsequent to the 30-day follow-up AE reporting period are described in Section 6.4.3 under Post follow-up adverse event reporting.

Any patient who has not yet shown objective radiological disease progression at withdrawal from IP should continue to be followed as per RECIST as detailed in Section 6.2.3.1.

All patients must be followed for survival, up to the final analysis.

## **5.9 Withdrawal from study**

Patients are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (see Sections 6.4.3 and 6.4.4); questionnaires (e.g., for patient reported outcomes) and all study drugs should be returned by the patient.

The status of ongoing, withdrawn (from the study) and “lost to follow-up” patients at the time of an overall survival analysis should be obtained by the site personnel by checking the patient notes, hospital records, contacting the patient’s general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

Withdrawn patients will not be replaced.

Reasons for withdrawal from the study:

- Voluntary withdrawal by the patient who is at any time free to discontinue their participation in the study, without prejudice to further treatment.
- Severe non-compliance to protocol as judged by the Investigator and/or AstraZeneca.
- Incorrectly enrolled patients i.e., the patient does not meet the required inclusion/exclusion criteria for the study.
- Patient lost to follow-up.
- Death

\*If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to:

- to further participation in the study including any further follow up (e.g., survival calls)
- withdrawal of consent to the use of their study generated data
- withdrawal to the use of any samples (see Section 7.5)

## **6. COLLECTION OF STUDY VARIABLES**

### **6.1 Recording of data**

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA).

The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

### **6.2 Data collection at enrolment and follow-up**

A study initiation visit must be conducted at the centre prior to the commencement of any study activities requiring informed consent. A schedule for the tests and evaluations to be conducted in this study is contained in this section and [Table 1](#), [Table 2](#), [Table 3](#) and [Table 4](#).

#### **6.2.1 Enrolment/Screening procedures**

The following assessments and procedures should be performed during screening prior to –28 days and / or within 28 days prior to first dose of study treatment as per [Table 1](#) and [Table 2](#). For details of the schedule and nature of the assessments, see below:

- Date of birth, race and ethnicity
- Current and concomitant medications including previous cancer therapies
- Medical and surgical history including previous cancer and radiotherapy, history of blood transfusions in previous 120 days and response to current therapies
- Physical examination, ECOG performance status, vital signs (blood pressure and pulse; body temperature), body weight, height and ECG (within 7 days prior to the start of the study treatment).

- Haematology/Clinical chemistry/Urinalysis
- Menopausal status; serum or urine pregnancy test for women of childbearing potential. The pregnancy test should be within 28 days prior to the start of study treatment and confirmed on day 1 prior to dosing.
- Blood sample for disease specific marker (CA-125) (see Section 6.4.5.4)
- BRCA1/2 mutation status:

All patients must have a known deleterious or suspected deleterious BRCA mutation to be randomised, this may have been determined prior to study entry or may be assessed as part of the enrolment procedure for the study (via Myriad). Patients must consent to provision of duplicate blood samples, to be taken at the same time. One sample will be used to assess the presence of a germline BRCA mutation by the Myriad test.

For patients with an unknown BRCA status one sample will be used to assess the presence of a germline BRCA mutation by the Myriad test prior to first dose of study treatment. It is recommended that the Myriad gBRCA test is undertaken during the patients last chemotherapy regimen to allow sufficient time for:

- (i) all associated local procedures for genetic testing
- (ii) the return of the Myriad BRCA result
- (iii) the patient to be randomised to study treatment within 8 weeks after their last dose of chemotherapy (last dose is the day of the last infusion)

Provision of an archival tumour sample is also mandated for subsequent analysis for randomised patients only. See Section 6.8.1.1 for gBRCA Myriad testing criteria.

- Tumour assessment (scans of chest, abdomen and pelvis with other regions as clinically indicated for the assessment of disease. [CT/MRI]).
  - Baseline assessments should be performed no more than 28 days before randomisation, and ideally should be performed as close as possible to the start of study treatment. Scans that were performed as part of standard of care prior to signature of the informed consent form can be analysed for the purposes of the study if they were performed within the correct time frame and consistent with the acquisition guidelines for CT or MRI provided by the central imaging CRO. To note the scan taken after completion of platinum containing regimen, can serve as the baseline scan as long as it was performed no more than 28 days prior to start of treatment (see Section 6.3.1).

- In screening part 1 only SAEs related to study procedures (e.g. blood sampling for BRCA & pregnancy test [if applicable]) must be reported (AEs do not require reporting). From screening part 2 onwards - all AEs/SAEs must be reported.
- Confirmed availability and collection of an archival paraffin embedded tumour tissue sample (see Section 6.7.2)
- Tumour biopsy (optional) (see Section 6.7.3)
- Baseline scores (prior to dosing on Day 1) for patient reported outcomes and quality of life will be obtained (EQ-5D-5L and FACT-O) (see Section 6.5 and Appendix H)

The Principal Investigator/Sub-Investigator should adhere to the study plan, procedures and perform tests/observations in accordance with the protocol.

### 6.2.2 On study assessments

Study treatment is self administered by the patient twice daily as instructed. The visit schedule is based on 28-day periods. Patients will attend the clinic on days 1 (1<sup>st</sup> day of treatment), 8, 15, 22, 29, and every 4 weeks from visit 7 until 108 weeks (if not progressed and still on treatment). Patients who remain on treatment post progression or after week 108 continue to attend clinic visits every 4 weeks for up to 156 weeks (3 years), after which they will attend clinic for every 12 weeks (relative to date of randomisation), unless more visits are clinically indicated. Treatment beyond 108 weeks can only be continued at the discretion of the investigator and only after fulfilling specific conditions (see Table 3). The following assessments will be performed at time points specified in the study schedule (see Table 3):

- Physical examination (data is not required to be captured on an eCRF, however any significant changes from baseline must be reported as an AE).
- ECOG performance status: required at day 1 of 1<sup>st</sup> day of study treatment, if it has not been assessed within 7 days of randomisation, then every 4 weeks up to 108 weeks (if not progressed and still on treatment); see Table 3 for details.
- Vital signs: day 1 and day 29. Body weight is only required at day 1 of 1<sup>st</sup> day of study treatment, if it has not been assessed within 7 days of randomization and then any other time as clinically indicated. From visit 7, temperature and weight are only required if clinically indicated, blood pressure and pulse are to be taken in line with RECIST assessments.
- ECG: Day 57 (i.e., week 9), at safety follow up and at any other time if clinically indicated.
- Haematology and clinical chemistry: Safety blood samples do not need to be repeated on Day 1 of study treatment if assessed at least 3 weeks after the last dose

of chemotherapy and within 7 days before starting study treatment, unless the investigator believes that it is likely to have changed significantly

- Serum or urine pregnancy test for women of childbearing potential (prior to treatment on day 1 of 1<sup>st</sup> day of study treatment). If the test is positive then a confirmatory test should be performed.
- gBRCA1/2 mutation status: Confirmation of BRCA mutation status result using Myriad test (for those patients that knew their gBRCA status prior to study entry)
- tBRCA1/2 mutation status: Determination of germline BRCA mutation status using the Myriad test for those patients that knew their tumour BRCA status prior to study entry. Confirmation of tumour BRCA mutation status for all patient result using a central laboratory
- Disease specific Tumour marker (CA-125)
- Tumour assessments scans of the chest\*, abdomen and pelvis with other regions as clinically indicated for assessment of disease (CT/MRI) (see Section 6.3).
  - \*Chest, abdomen and pelvis CT/MRI scans should be performed at base-line.
  - \*In those patients with disease present in the chest or upper abdomen lymphadenopathy chest, abdomen and pelvis should be performed at follow-up.
  - \*In those patient with no disease present in the chest and no upper abdomen lymphadenopathy then follow-up is by abdomen and pelvis only.
- AE and concomitant medications (including any blood transfusions) at every visit.
- Patient Reported Outcomes and Quality of Life questionnaire: EQ-5D- 5L and FACT-O: at baseline, Day 29, every 12 weeks (+/- 7 days) for 156 weeks, then every 24 weeks (+/- 7 days) or until the data cut off for the primary analysis. In addition, Quality of Life questionnaire will be collected at the discontinuation of study treatment visit and 30 days post last dose. Patients who had RECIST 1.1 disease progression will complete the questionnaires during the 12 weekly survival follow-ups either in person or over the phone.
- Resource use will be captured including inpatient admissions, ICU and length of stay in hospital
- An optional pharmacogenetic sample will be obtained from consenting patients and stored for future exploratory pharmacogenetic analysis (Section 6.8.4)
- Optional tumour biopsy at objective progression (Section 6.7.3)

- Optional blood sample for biomarker analysis (e.g. cfDNA) at randomisation (Section 6.8.3)

Patients will continue with study treatment for up to two years or until objective radiological disease progression by RECIST, whichever is earlier. Patients who continue to have evidence of stable disease at two years or who have progressed may continue to receive study treatment if, in the opinion of the investigator, it is in the patient's best interest. However, if at two years the patient has no evidence of disease, study treatment should be discontinued. A decision about continuing treatment with the investigational product beyond two years should be made after assessing the patient's disease status according to RECIST guidelines at week 108, and/or by assessing the patient's clinical condition. Continuation of treatment beyond week 108, based solely on clinical progression, is permissible only after case-by-case discussion with the AZ study physician. Once patients have been discontinued from study treatment, other treatment options will be at the discretion of the Investigator. Within this study patients are not permitted to switch over to the opposite arm from which they were randomised.

### **6.2.3 Follow-up procedures**

#### **6.2.3.1 Treatment Discontinuation Visit**

Patients should be discontinued from study treatment if any discontinuation criteria are fulfilled (see Section 5.8). The assessments to be carried out at the visit are detailed in the study schedule (Table 3).

#### **6.2.3.2 Treatment discontinuation due to objective radiological disease progression or any other discontinuation criteria**

Patients should be discontinued from study treatment if they have radiological objective disease progression according to RECIST (see Appendix F), unless in the investigator's opinion they are benefiting from treatment, or if they meet any other discontinuation criteria as outlined in Section 5.8. The assessments to be carried out are detailed in the study schedule (Table 3) and include:

- An optional tumour biopsy sample
- An optional blood sample for biomarker analysis (e.g. cfDNA)
- EQ-5D-5L and FACT-O questionnaires

Following the discontinuation visit and safety follow up visit patients who have discontinued due to radiological disease progression will be followed for PFS2 and OS as per Table 4 and patients who have discontinued but do not have radiological disease progression will continue to be followed for PFS1 as per Table 4.

#### **6.2.4 Follow-up 30 day after last dose of study medication (follow-up visit)**

A follow-up visit should be conducted 30 days after the last dose of study treatment. Any serious and/or non-serious AEs ongoing at the time of the Discontinuation Visit or which have



occurred during the defined 30-day follow-up period must be followed-up (in accordance with Section 6.4.3). Appropriate safety evaluations should be repeated and/or additional tests performed at any time when clinically indicated, or at the discretion of the investigator, until resolution, unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. If the patient is lost to follow-up, then this should be noted in the eCRF. The assessments to be carried out at the 30 day follow up visit are detailed in the study schedule (Table 3).

### 6.2.5 Survival

Assessments for survival should be made every 12 weeks following radiological objective disease progression according to RECIST. Survival information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician. Survival data will be collected up to the time of the final overall survival (OS) analysis. In addition, patients should be contacted in the week following the data cut-off for the primary PFS and final survival analyses to provide complete survival data.

Patients will be followed up as per Table 3 or Table 4 to the point of the final analysis. At this point Investigators will be notified that no further data collection for the study is required. Monitoring and recording of SAEs will continue as per Section 6.4.4. Since some cases MDS/AML or new primary malignancies developed after discontinuing treatment with olaparib, investigators will be asked during the regular follow up for overall survival if the patient has developed MDS/AML or a new primary malignancy and prompted to report any cases as SAE (or AE for non-melanoma skin cancers, if at least one of the criteria for SAE is not met, see Section 6.4.2) even after discontinuation of therapy and regardless of investigator's assessment of causality or knowledge of the treatment arm.

The status of ongoing, withdrawn (from the study) and lost to follow up patients at the time of an overall survival analysis should be obtained by the site personnel by checking the patient notes, hospital records, contacting the patient's general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

### 6.2.6 Second Progression

Following objective progression, copies of the patient's radiological scans are no longer required to be sent for blinded independent central review. Patients will be assessed every 12 weeks for a second progression (using the patients status at first progression as the reference for assessment of second progression). A patient's progression status is defined according to local standard clinical practice and may involve any of; objective radiological, CA-125, symptomatic progression or death. RECIST measurements will not be collected for assessment of PFS2. The date of PFS2 assessment and investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF.

### **6.2.7 Patient management post primary analysis**

The data cut off date for the statistical analysis for the primary objective of the study will be established when approximately 196 confirmed progression events have occurred or after the last patient randomised has had the opportunity to have been on the study for at least 36 months, whichever comes first.

Patients on study treatment at the time of the data cut-off will continue to receive study treatment until they meet any discontinuation criteria as per Section 5.8.

Patients on study treatment will be followed for core safety assessments and disease progression (haematology, clinical chemistry, AEs/SAEs and concomitant medications (including any subsequent cancer therapy), study treatment dosing details, objective radiological disease progression according to RECIST, as per Table 3). These patients should be followed according to routine clinical practice but visits should take place at least every 12 weeks see Table 3.

All patients (patients still on study treatment and patients withdrawn from study treatment) will be followed for survival and disease progression.

### **6.2.8 Patient management post final analysis**

The data cut off date for the final statistical analysis of the study will be established when ~206 confirmed OS (~60% maturity for OS analysis) are expected to have occurred.

At this time point, the clinical study database will close to new data and post the data cut off all patients will be unblinded. Patients who are receiving active treatment can either choose to discontinue from the study or where the investigator believes patients are gaining clinical benefit; patients may continue to receive study treatment. All patients will receive follow up care in accordance with standard local clinical practice.

Patients that are on placebo will not be offered olaparib as a study treatment.

AstraZeneca will continue to supply olaparib after completion of this study until either olaparib is licenced in that country, or it is determined that the benefit to risk profile does not support continued development of olaparib, or the national health authority has deemed the drug not approvable. In all these scenarios, AstraZeneca will work with investigators on the proper transition of patients to alternative therapies if possible.

SAEs will continue to be reported to AstraZeneca Patient Safety Department, for any patients who continue on olaparib until 30 days after study treatment is discontinued, in accordance with Section 6.4.4. Additionally as stated any SAE or non-serious adverse event, that is ongoing at the end of the study, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up. If an investigator learns of any SAEs, including death, at any time after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify AstraZeneca, Patient Safety.

Drug accountability should continue to be performed until the patient stops study treatment completely.

## **6.3 Efficacy**

### **6.3.1 CT and MRI scans Tumour assessments (modified RECIST 1.1)**

Following the baseline assessment, subsequent tumour assessments according to RECIST should be performed at the end of every 12 weeks ( $\pm 1$  week) up to 156 weeks then every 24 weeks ( $\pm 1$  week) relative to date of randomisation, according to the planned study schedule (see [Table 3](#) and [Table 4](#)) up to objective progression by RECIST.

For those patients with no evidence of disease at baseline, following a clinical complete response to chemotherapy, progression is defined by the detection of new lesions on follow up radiological assessments (modified RECIST 1.1).

The imaging modalities used for RECIST assessment will be CT or MRI scans of the chest, abdomen and pelvis with other regions as clinically indicated for the assessment of disease, see Section [6.2.2](#). Any other sites at which new disease is suspected should also be appropriately imaged.

Radiological examinations performed in the conduct of this study should be retained at site as source data.

Anonymised copies of the scans are to be sent to an AstraZeneca appointed CRO for blinded independent central review.

All treatment decisions will be based on site assessment of scans. After the primary PFS analysis, central review of scans will no longer be required and investigators will be advised when to stop sending copies of the scans to the CRO conducting the central review. Ongoing collection of site review tumour assessment is required and must be recorded in the eCRF.

It is important to follow the assessment schedule as closely as possible. If scans are performed outside of scheduled visit  $\pm 1$  week window interval and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points. Patients will be evaluated until objective radiological disease progression by RECIST as per the study schedule (see [Table 3](#) and [Table 4](#)), and then followed for second progression and survival, regardless of whether study treatment is discontinued or delayed and/or protocol violations, unless they withdraw consent.

### **6.3.2 Tumour Evaluation**

Modified RECIST 1.1 criteria will be used to assess patient response to treatment by determining progression free survival (PFS) times. (The modified RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria (complete response, partial response, stable disease or progression of disease, no evidence of disease) are presented in Appendix F).

Although CA-125 is measured in this study it will not be directly used for assessing objective response or progression and patients should be continued on treatment until objective radiological disease progression as defined by RECIST.

The methods of assessment of tumour burden used at baseline - CT or MRI scans of chest, abdomen and pelvis, with other regions as clinically indicated for the assessment of disease must be used at each subsequent follow-up assessment, see Section 6.2.2.

Following the baseline assessment, efficacy for all patients will be assessed by objective tumour assessments every 12 weeks ( $\pm 1$  week) up to 156 weeks then every 24 weeks ( $\pm 1$  week) relative to date of randomisation, according to the planned study schedule [Table 3](#) and [Table 4](#) until objective radiological disease progression as defined by RECIST.

If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression then the patient should still continue to be followed until objective radiological disease progression as defined by RECIST.

Categorisation of objective tumour response assessment will be based on the RECIST criteria of response: complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD), no evidence of disease (NED) and not evaluable (NE). Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (i.e., smallest sum of diameters previously recorded on study). In the absence of a best response of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before randomisation.

For patients with non-measurable disease only at baseline, categorisation of objective tumour response assessment will be based on the RECIST criteria of response: CR (complete response), PD (progression of disease) and Non CR/Non PD.

Patients with no disease at baseline will be assessed according to RECIST criteria for new lesions with responses of No Evidence of Disease (NED) or progression of disease.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to NTL (non-target lesion) or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of study treatment. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

Following progression, patients should continue to be followed up for survival every 12 weeks as outlined in the study plan ([Table 4](#) or [Table 5](#)). It is important to follow the assessment

schedule as closely as possible. Please refer to the study plan ([Table 4](#) or [Table 5](#)) and CT/MRI scans in Section [6.3.1](#).

### **6.3.3 Central reading of scans**

An independent review of all scans used in the assessment of tumours according to RECIST will be conducted. All imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to an AstraZeneca appointed Contract Research Organisation (CRO) for central analysis. Results of this independent review will not be communicated to investigators, and the management of patients will be based solely upon the results of the RECIST assessment conducted by the investigator.

A sensitivity analysis for this study will be based on the independent central review (ICR) of the radiological scans.

## **6.4 Safety**

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

### **6.4.1 Definition of adverse events**

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

### **6.4.2 Definitions of serious adverse event**

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect

- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

### **6.4.3 Recording of adverse events**

#### **Time period for collection of adverse events**

Adverse Events, including Serious Adverse Events, will be collected from time of signature of informed consent\*, throughout the treatment period and up to and including the 30-day follow-up period. All ongoing and any new AEs/SAEs identified during the 30 calendar days follow up period after last dose of study medication must be followed to resolution. After any interim analysis, any ongoing AEs/SAEs need to be unlocked and followed for resolution.

\*Exception: In screening part 1 only SAEs related to study procedures must be reported (AEs do not require reporting). From screening part 2 onwards - all AEs/SAEs must be reported.

#### **Follow-up of unresolved adverse events**

Any SAE or non-serious adverse event that is ongoing at the time of the 30 day follow up, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up

AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

#### **Post Follow-up adverse events**

For Pharmacovigilance purposes and characterisation of events of special interest, any case of MDS/AML or new primary malignancy occurring after the 30 day follow up period should be reported as SAE (or AE for non-melanoma skin cancers, if at least one of the criteria for SAE is not met, see Section 6.4.2) to AstraZeneca Patient Safety regardless of investigator's assessment of causality or knowledge of the treatment arm. A Questionnaire will be sent to any investigator reporting MDS/AML or new primary malignancy as an aid to provide detailed information on the case.

At any time after a patient has completed the study, if an Investigator learns of any SAEs, including death, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify AstraZeneca, Patient Safety.

If patients who are gaining clinical benefit are allowed to continue study treatment post data cut off and / or post study completion then all SAEs must continue to be collected and reported to Patient Safety within the usual timeframe.

Otherwise, after study treatment completion (i.e. after any scheduled post treatment follow-up period has ended) there is no obligation to actively report information on new AEs or SAEs occurring in former study patients. This includes new AEs/SAEs in patients still being followed up for survival but who have completed the post treatment follow up period (30 days).

### **Variables**

The following variables will be collect for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Description of AE.



## **Severity of AE**

For each episode on an adverse event, all changes to the CTCAE grade attained as well as the highest attained CTC grade should be reported.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE (this would be recorded as an SAE as per the guidance found in this section (Section 6.4.3)).

The grading scales found in the National Cancer Institute (NCI) CTCAE version 4.0 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades the recommendation is that the CTCAE criteria that convert mild, moderate and severe events into CTCAE grades should be used.

A copy of the CTCAE version can be downloaded from the [Cancer Therapy Evaluation Program](#) website.

## **Causality collection**

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

## **Adverse Events based on signs and symptoms**

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

## **Adverse Events based on examinations and tests**

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory



values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign/ECG is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign/ECG will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

**NB.** Cases where a patient shows an AST **or** ALT  $\geq 3xULN$  **or** total bilirubin  $\geq 2xULN$  may need to be reported as SAEs, please refer to Appendix D ‘Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy’s Law’, for further instructions.

### **Disease progression**

Disease progression can be considered as a worsening of a patient’s condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the signs and symptoms of the cancer. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

### **New cancers**

The development of a new primary cancer (including skin cancer) should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 6.4.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

### **Lack of efficacy**

When there is deterioration in the ovarian cancer, for which the study treatment(s) is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the Sponsor or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

## Deaths

All deaths that occur in screening part 1 related to study procedures should be reported as a SAE.

All deaths that occur from screening part 2 onwards, including within the protocol-defined 30-day post-study follow-up period after the administration of the last dose of study treatment, must be reported as follows:

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the DEATH eCRF but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within **24 hours** (see Section 6.4.4 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the ‘death eCRF’.
- Deaths with an unknown cause should always be reported as a SAE. A post mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to AstraZeneca within the usual timeframes.

### 6.4.4 Reporting of serious adverse events

In Screening part 1, only SAEs related to study procedures must be reported. From Screening part 2 onwards, all SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any reportable SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

#### **6.4.5 Laboratory safety assessment**

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the times indicated in the Study Schedule (see [Table 1](#), [Table 2](#) and [Table 3](#)).

These tests will be performed by the hospital's local laboratory. Additional analyses may be performed if clinically indicated.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF.

The following laboratory variables will be measured:

##### **6.4.5.1 Full haematology assessments for safety;**

- haemoglobin,
- red blood cells [RBC]
- platelets
- mean cell volume [MCV]
- mean cell haemoglobin concentration [MCHC],
- mean cell haemoglobin [MCH],
- white blood cells [WBC],
- absolute differential white cell count
  - (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and absolute neutrophil count or segmented neutrophil count and Band forms should be performed at each visit and when clinically indicated. If absolute differentials not available please provide % differentials.

#### 6.4.5.2 Coagulation

- activated partial thromboplastin time {APTT} will be performed if clinically indicated
- international normalised ratio {INR} will be performed if clinically indicated unless the patient is receiving warfarin. Patients taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

#### 6.4.5.3 Biochemistry assessments for safety

- sodium
- potassium
- calcium
- magnesium
- creatinine
- total bilirubin
- gamma glutamyltransferase [GGT]
- alkaline phosphatase [ALP]
- aspartate transaminase [AST]
- alanine transaminase [ALT]
- urea or blood urea nitrogen [BUN]
- total protein
- albumin
- lactic dehydrogenase [LDH])

**NB.** In case a patient shows an AST **or** ALT  $\geq 3xULN$  **or** total bilirubin  $\geq 2xULN$  please refer to Appendix D ‘Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy’s Law’, for further instructions.

#### **6.4.5.4 Disease specific tumour marker samples (CA-125)**

As part of the routine safety blood samples, all patients will supply blood sample for CA-125 (2 mL) for assessment at the beginning of each 28 day period prior to the patient receiving study treatment.

It is important to follow the assessment schedule as closely as possible. If CA-125 assessment is performed outside of scheduled visit  $\pm$  1 week window interval, every attempt should be made to assess the CA-125 at the scheduled time points. Patients will be evaluated until objective disease progression, based on progressive serial elevation of serum CA-125 according to the modified Gynecologic Cancer InterGroup criteria GCIG criteria (note GCIG criteria is not validated for this trial population). See Section [11.1.2.2](#).

Further assessment of CA 125 post serological progression will be at the discretion of the investigator according to local clinical practice.

For blood volume see Section [7.1](#).

#### **6.4.5.5 Urinalysis**

Urinalysis by dipstick should be performed as stated in [Table 1](#), [Table 2](#) and [Table 3](#). Microscopic analysis should be performed by the hospital's local laboratory if required.

#### **6.4.5.6 Bone marrow or blood cytogenetic samples**

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged haematological toxicities as defined in Section [5.5.5](#).

Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. Full reports must be provided by the investigator for documentation on the Patient Safety database.

#### **6.4.6 Physical examination**

For timing of individual measurement refer to study schedule (see [Table 1](#), [Table 2](#) and [Table 3](#)).

A physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities) and neurological systems.

## **6.4.7 ECG**

### **6.4.7.1 Resting 12-lead ECG**

ECGs are required prior to obtaining the Myriad blood samples during screening for patients with unknown BRCA status, within 7 days prior to starting study treatment, at week 9 after starting study treatment when clinically indicated and at the follow up visit after patient has discontinued study medication.

Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. The Investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected.

ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the Investigator will record it as an AE on the eCRF. The original ECG traces must be stored in the patient medical record as source data.

## **6.4.8 Vital signs**

Height will be assessed at screening only.

Weight will be assessed according to the Study Schedule (see [Table 1](#), [Table 2](#) and [Table 3](#)) and as clinically indicated at any other time.

Any changes in vital signs should be recorded as an AE, if applicable.

### **6.4.8.1 Pulse and blood pressure**

Blood pressure and pulse rate will be measured preferably using a semi automatic BP recording device with an appropriate cuff size after 10 minutes rest on a bed. For timings of assessments refer to the Study Schedule (see [Table 1](#), [Table 2](#) and [Table 3](#)).

The date of collection and measurement will be recorded on the appropriate eCRF.

### **6.4.8.2 Body temperature**

Body temperature will be measured in degrees Celsius using an automated thermometer at the times indicated in the Study Schedule (see [Table 1](#), [Table 2](#) and [Table 3](#)).

The date of collection and measurement will be recorded on the appropriate eCRF.

## **6.4.9 Other safety assessments**

### **6.4.10 Serum or urine pregnancy test**

Pregnancy tests on blood or urine samples will be performed for pre-menopausal women of childbearing potential, prior to obtaining the Myriad blood samples during screening for patients with unknown BRCA status, within 28 days prior to the start of study treatment and

on Day 1 of the study prior to commencing treatment. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated.

## **6.5 Patient reported outcomes (PRO): FACT-O and EQ-5D-5L**

### **6.5.1 Administration of PRO questionnaires**

Paper questionnaires will be given to the patient at baseline, at Day 29 and then every 12 weeks (+/- 7 days) for 156 weeks, then every 24 weeks (+/- 7 days) or until the data cut off for the primary analysis. In addition, Quality of Life questionnaire will be collected at the discontinuation of study treatment visit and 30 days post last dose. Patients who had RECIST 1.1 disease progression will complete the questionnaires during the 12 weekly survival follow-ups either in person or over the phone (see [Table 3](#) and [Table 4](#)). Following collection of the paper questionnaire (in person or over the phone), the site staff can either enter the information directly into the WBDC (RAVE) electronic database system or arrange to have the paper questionnaires transcribed into the WBDC (RAVE) database.

Each centre must allocate the responsibility for the administration of the questionnaires to a specific individual (e.g., a research nurse, study coordinator) and if possible assign a back-up person to cover if that individual is absent. The AZ Study Delivery Team (or delegate) will provide relevant training in administration of the questionnaires. The significance and relevance of the data need to be explained carefully to participating patients so that they are motivated to comply with data collection.

The instructions for completion of the PRO questionnaires are as follows:

- It must be completed prior to any other study procedures (following informed consent) and before discussion of disease progress to avoid biasing the patient's responses to the questions
- It must be completed in private by the patient, where a visit to the clinic is not planned, i.e. for patients followed up for survival with no scheduled clinic visits, the site staff will administer questionnaires via telephone.
- The patient should be given sufficient time to complete at their own speed
- The patient should not receive help from relatives, friends or clinic staff to answer the questionnaire. However, if the patient is unable to read the questionnaire (e.g., is blind or illiterate) the questionnaire may be read out by trained clinic staff and responses recorded
- On completion of the questionnaire it should be handed back to the person responsible for questionnaires who should check for completeness

Only 1 answer should be recorded for each question

### 6.5.2 FACT-O

Patient-reported health-related quality of life (HRQoL) will be assessed using the FACT-O questionnaire ([Basen-Engquist K et al 2001](#)). The FACT-O is composed of the following subscales: physical, social/family, emotional, and functional well-being as well as the additional concerns scales consisting of specific ovarian cancer symptoms.

### 6.5.3 PRO method or questionnaire for other purposes

The end point for health-related quality of life analysis will be the Trial Outcome Index (TOI), an established single targeted index derived from the FACT-O questionnaire and it is considered to target the most relevant symptoms together with function and physical well-being and can be directly related to signs and symptoms and AEs. The TOI is composed of the following scales of the FACT-O: physical and functional well-being and additional concerns.

### 6.5.4 EQ-5D-5L

Patient reported health state utility will be assessed using the EQ-5D-5L. The instrument asks patients to respond to 5 different dimensions covering mobility, self-care, usual activities, pain/discomfort, anxiety/depression, as well as rate how they feel on the day of assessment via a visual analogue scale.

## 6.6 Pharmacokinetics – Not Applicable

## 6.7 Biomarkers

Tumour and blood samples will be collected for mandated and optional biomarker work as detailed in [Table 6](#).

### 6.7.1 Biomarker samples

The archival tumour sample, and the baseline blood samples for BRCA mutation status are all mandated samples.

**Table 6 Samples for Biomarker Research**

Sample Type	Visits	Optional or Mandatory
Whole blood (for prospective germline BRCA testing at central laboratory or retrospective confirmation of BRCA mutation at central laboratory)	Screening sample	Mandatory



**Table 6 Samples for Biomarker Research**

<b>Sample Type</b>	<b>Visits</b>	<b>Optional or Mandatory</b>
Whole blood sample (to be used for the retrospective determination of gBRCA mutation status by Myriad).	Screening sample	Mandatory
Archival tumour sample	Screening	Mandatory for all randomised patients
On-study baseline tumour biopsy	Baseline	Optional
On-study progression tumour biopsy	At progression as defined in Section 6.3.1	Optional
Blood sample for biomarker analysis (e.g. cfDNA)	At randomisation and progression	Optional
Blood for optional exploratory pharmacogenetics	Baseline	Optional

The samples and data from this research will be coded and not labelled with any personal details. Each sample will be identified with the study and patient enrolment number. In this way biomarker data may be correlated with clinical data, samples destroyed in the event of withdrawal of consent and regulatory audit enabled. However, only the investigator will be able to link the biomarker sample to the individual patient.

However, the samples and any results will remain the responsibility of AstraZeneca at all times. AstraZeneca will not give samples, sample derivatives or data derived from the samples to any other parties except as required by law.

Biomarker data may be generated in real time during the study or retrospectively and will have unknown clinical significance. AstraZeneca will not provide biomarker results to patients, their family members, any insurance company, an employer, clinical study investigator, general physician or any other third party unless required to do so by law. The patient's samples will not be used for any other purpose other than those described in the protocol.

The exception to the above is the gBRCA status result from the Myriad assessment for patients with previously unknown local BRCA status. This result will be provided to the investigator and will be collected as part of the patient's demography and medical history details.

### **6.7.2 Exploratory Biomarker Research on Archival Tumour Samples (Mandatory)**

These samples will be collected from the site pathologist once patient has been randomised. An adequately sized (minimum of 2 mm x 2 mm) historical tumour tissue paraffin block from resection or a core biopsy from the primary tumour or metastases should be provided. This sample will have been collected anytime since the time of original diagnosis but prior to study entry. Alternatively, sections mounted on glass slides prepared from the block can be provided.

Collection of an archival tumour sample is mandated for all randomised patients for the assessment of tissue BRCA mutation status, however further exploratory work is planned on surplus tissue. This material may be used for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, improve the understanding of disease progression (including tumour BRCA mutation status and its role in response).

Please refer to Investigator Laboratory Manual for further details of archival tissue collection, shipping and storage.

### **6.7.3 Exploratory Biomarker Research on Tumour Biopsy Samples (Optional)**

Biopsies may be particularly valuable where there is a marked phenotypic change in a particular lesion and investigators are encouraged to contact AstraZeneca in these cases.

When a patient presents with a biopsiable tumour, an on-study tumour biopsy sample should be obtained, (only in patients that have signed the additional optional consent). A sample should be taken prior to dosing with study drug but must be taken after the baseline RECIST scan has been performed and a second tumour biopsy sample taken at documented RECIST progression. The provision of tumour tissue is encouraged only if clinically appropriate and not considered detrimental to patient care.

The biopsied tumour must not be used as part of the RECIST assessments.

Patients will not be excluded from the study if these samples are not collected.

On-study tumour tissue collected during the study should be immediately fixed and processed to a FFPE block.

Please refer to Investigator Laboratory Manual for further details of on-study tumour tissue collection, shipping and storage.

## **6.8 Pharmacogenetics**

### **6.8.1 Collection of blood sample for Myriad germline BRCA1 and BRCA2 testing**

All patients must have a known deleterious or suspected deleterious BRCA mutation to be randomised; this may have been determined prior to study entry or may be assessed as part of the enrolment procedure for the study (via Myriad).

### **6.8.1.1 Guidance for BRCA testing of patients with known BRCA status**

For patients that can be randomised to the study on the basis of a pre-existing known BRCA mutation test result, a blood sample for a confirmatory BRCA mutation test by Myriad must be taken once the patient has consented to the study. Should the result from the Myriad test indicates the patient does not have a deleterious or suspected deleterious BRCA mutation, the patient can continue in the study and can continue to receive their allocated study treatment.

For blood volume see Section 7.1.

### **6.8.1.2 Guidance for BRCA testing of patients with unknown BRCA status**

Patients that do not know their BRCA status, must have a Myriad test prior to randomisation to the study. If the result shows that the patient has a deleterious/suspected deleterious gBRCA mutation, the patient can then be randomised to the study. In order to limit the time that the patient is not receiving study treatment after their last dose of chemotherapy, it may be necessary for the patient to have a Myriad BRCA test performed after initial diagnosis. Patients will need to have met the local ethical requirements for such genetic tests (e.g., genetic counseling) prior to the test procedure.

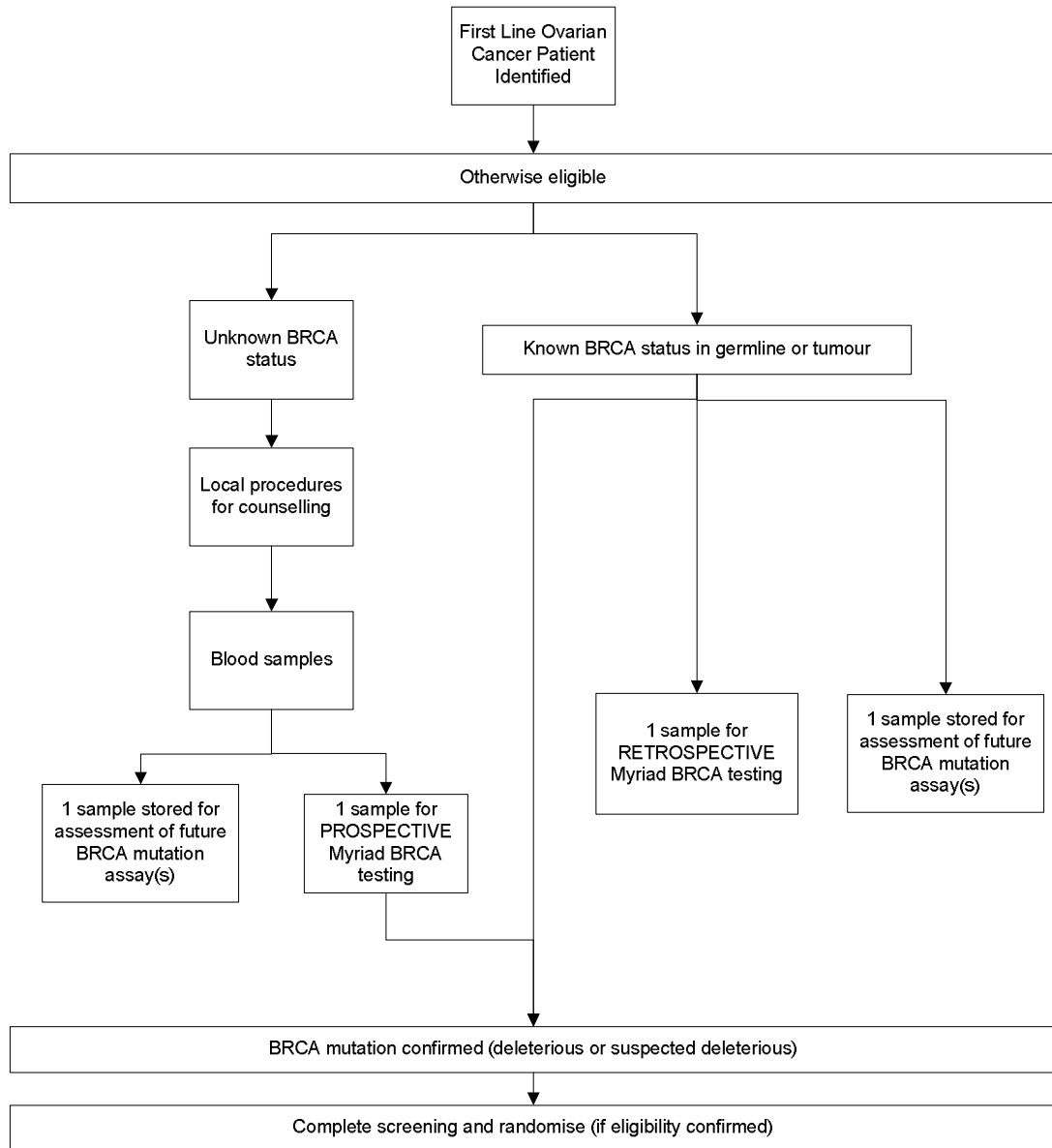
The following clinicopathological features are known to be associated with an increased probability of BRCA mutations:

1. Family history of breast or ovarian cancer, ethnicity and age ([Pal et al 2005](#); [Risch et al 2006](#))
2. High grade serous ovarian cancer ([Alsop et al 2012](#))

The BRCA test may be performed from diagnosis to – 28 days at the discretion of the investigator. To perform the BRCA testing from diagnosis to the end of cycle 3, investigator judgement of patient's potential eligibility to the study should be assessed as per [Table 1](#) and by reviewing the inclusion/exclusion criteria. For post cycle 3 of first line chemotherapy gBRCA status testing the patient must meet the inclusion criteria in Sections [4.1](#) and [4.2](#), and be showing a response to their current platinum chemotherapy prior to having the blood sample taken for the Myriad gBRCA status test. This response is in the opinion of the investigator but there should be documented evidence eg CA-125 results, radiological assessments.

The blood and tumour sample collection algorithm for patients with known or unknown BRCA mutation status is documented in the flow diagram below:

**Figure 5**      **Flow diagram for patients with known or unknown BRCA mutation status**



### **6.8.3 Exploratory blood sample for biomarker analysis (e.g. cfDNA) (Optional)**

A 12 mL blood sample will be collected from all patients at randomisation and at progression for exploratory biomarker work.

### **6.8.4 Collection of pharmacogenetic samples (optional)**

An optional pharmacogenetic sample will be obtained from consenting patients and stored for future exploratory pharmacogenetic analysis. The sample will be taken after randomisation on day 1 of the first randomised treatment preferably or at subsequent visits. Patients do not have to consent to this sample in order to participate in the study

Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume see Section 7.1.

## **6.9 Health economics**

### **6.9.1 Resource Use**

Resource use will be captured including inpatient admissions, ICU and length of stay in hospital.

## **7. BIOLOGICAL SAMPLING PROCEDURES**

### **7.1 Volume of blood**

The volume of blood that will be drawn from each patient will vary, dependent upon the length of time that the patient remains in the trial and on treatment. However the volume of blood to be drawn from each patient during screening and up to Day 29 should not exceed 110 mL.

The total volume of blood to be drawn from each patient in the study, assuming they complete screening, 6 months of treatment, a treatment discontinuation visit and the 30-day follow-up visit, should not exceed 195 mL.

Safety laboratory assessments will be performed locally at each centre's laboratory by means of their established methods. The number of samples/blood volumes is therefore subject to site-specific change.

Extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments.

The estimated total volume of blood that will be drawn from each patient in this study is as follows:

**Table 7 Estimated maximum volume of blood to be drawn from each patient**

Assessment		Sample volume (mL)	No. of samples - screening	No. of samples -month 1 (including day 29)	Months 2-6	Treatment discontinuation visit and 30 day follow-up visit	Objective radiological disease progression	Total volume (mL)
Safety	Clinical chemistry (locally assessed)	5	1	5	1(x4)	1(x2)		60
	Haematology (locally assessed)	5	1	5	1(x4)	1(x2)		60
Whole blood sample: Prospective Myriad BRCA test for patients with unknown BRCA status or for confirmation of BRCA status for those with previous results)		9	1					9
Blood sample for biomarker analysis (e.g. cfDNA)		12		1			1	24
Blood cytogenetic analysis		Site dependent	Depends on the blood smear result					

**Table 7 Estimated maximum volume of blood to be drawn from each patient**

<b>Assessment</b>	<b>Sample volume (mL)</b>	<b>No. of samples - screening</b>	<b>No. of samples -month 1 (including day 29)</b>	<b>Months 2-6</b>	<b>Treatment discontinuation visit and 30 day follow-up visit</b>	<b>Objective radiological disease progression</b>	<b>Total volume (mL)</b>
Serum pregnancy test	Site dependent	Site may use urine instead	Site may use urine instead				
Blood sample for CA-125 (locally assessed)	2	3	1(x2)	1x4	1(x1) (only treatment discontinuation visit)		20
<b>Total volume (ml)</b>		34	75	48	22	12	191

## **7.2 Handling, storage and destruction of biological samples**

The samples will be used up or disposed of after analyses or retained for further use as described here.

Biological samples for future research can be retained at R&D site or CRO, on behalf of AstraZeneca for a maximum of 15 years following the Last Patient's Last Visit in the study. The results from future additional exploratory analysis will not be reported in the Clinical Study Report but separately in a Scientific Report.

### **7.2.1 Pharmacogenetic (optional exploratory) samples**

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access within the relevant sample tracking system at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analysed.

## **7.3 Labelling and shipment of biohazard samples**

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'International Air Transport Association (IATA) 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.



## **7.4 Chain of custody of biological samples**

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

## **7.5 Withdrawal of informed consent for donated biological samples**

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

BRCA sample: As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

Archival tumour sample: Although mandatory, the patient may continue in the study if the patient is already randomised.

Tumour biopsy sample: As collection of the biological samples is an optional part of the study, the patient may continue in the study.

Blood samples for biomarker analysis (e.g. cfDNA): As collection of the biological samples is an optional part of the study, the patient may continue in the study.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca.
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented.

- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed (the archival tumour samples may be returned to site), the action documented and the signed document returned to the study site.
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

## **8. ETHICAL AND REGULATORY REQUIREMENTS**

### **8.1 Ethical conduct of the study**

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

### **8.2 Patient data protection**

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

The exception to the above is the result of the Myriad gBRCA test, this will be made available to the investigator and patient.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

### **8.3 Ethics and regulatory review**

An Institutional Review Board (IRB)/Ethics Committee (EC) should approve the final study protocol, including the final version of the Informed Consent Form(s) including biomarker and/or pharmacogenetic sample consents and any other written information and/or materials to

be provided to the patients. The investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the IRB/Ethics Committee should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The IRB/Ethics Committee should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB/Ethics Committee annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions (SUSARs), where relevant.

Each Principal Investigator is responsible for providing the IRB/Ethics Committees with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

## **8.4 Informed consent**

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study, including any information on the mandatory and optional sampling; e.g. BRCA testing and tumour biopsies.
- Ensure each patient is notified that they are free to discontinue from the study at any time.
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study.

- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File.
- Ensure a copy of the signed Informed Consent Form is given to the patient.
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

## **8.5 Changes to the protocol and informed consent form**

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator, the Principal Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section [8.3](#).

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

## **8.6 Audits and inspections**

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

## **9. STUDY MANAGEMENT BY ASTRAZENECA**

### **9.1 Pre-study activities**

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities.
- Determine availability of appropriate patients for the study.
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a CSA between AstraZeneca and the investigator.

### **9.2 Training of study site personnel**

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

### **9.3 Monitoring of the study**

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed.
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the

study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., clinic charts).

- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the investigator(s) or other staff at the centre needs information and advice about the study conduct.

### **9.3.1 Source data**

Refer to the CSA for location of source data.

## **9.4 Study agreements**

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

### **9.4.1 Archiving of study documents**

The Investigator follows the principles outlined in the CSA.

## **9.5 Study timetable and end of study**

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The study is expected to start in Quarter 3 2013 and to end by Quarter 1 2023. The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with olaparib.

## **10. DATA MANAGEMENT BY ASTRAZENECA**

Data management will be performed by AstraZeneca Data Management Centre staff.

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at the AstraZeneca Data Management.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Data associated with biological samples will be transferred from laboratories internal or external to AstraZeneca. Data from external providers (e.g. central laboratories) will be validated as appropriate to ensure it is consistent with the clinical data and included in the final database. In the case of biomarker (tumour tissue or blood for exploratory analyses) data, the results of any analyses will not be recorded in the database, but information relating to the processing of the sample, including the original date of biopsy (historical tumour tissue sample and the actual date the sample(s) were collected) will be recorded in the eCRF and database.

Exploratory genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples. The results from this exploratory research will not be reported in the CSR.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

## **11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA**

A comprehensive SAP will be prepared before the first patient is entered.

### **11.1 Calculation or derivation of efficacy variable(s)**

At each visit patients will be programmatically assigned a RECIST visit response of CR, PR, SD, PD, NED, NE depending on the status of their disease compared to baseline and previous assessments, based on the BICR review. This will be repeated using the investigator assessed RECIST data.

### 11.1.1 Progression Free Survival (PFS)

PFS is defined as the time from randomisation until the date of objective radiological disease progression according to RECIST or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised study treatment or receives another anti-cancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment. If the patient has no evaluable visits or does not have a baseline assessment they will be censored at day 1 unless they die within two visits of baseline. (25 weeks allowing for visit window).

The PFS time will always be derived based on scan/assessment dates not visit dates.

RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- (a) Date of progression will be determined based on the **earliest** of the RECIST assessment/scan dates of the component that triggered the progression
- (b) When censoring a patient for PFS the patient will be censored at the **latest** of the RECIST assessment/scan dates contributing to a particular overall visit assessment

Overall visit assessments will be determined for each assessment (scheduled or unscheduled) and will contribute to the derivation of PFS.

Objective progression is defined as at least a 20% increase in the sum of the diameters of the target lesions (compared to previous minimum sum) or an overall non-target lesion assessment of progression or a new lesion. For patients with no evidence of disease at baseline, following a clinical complete response to chemotherapy, progression is defined by the detection of new lesions on follow-up radiological assessments.

The primary analysis will be based on the programmatically derived PFS based on investigator-recorded assessment of the radiological scans. A sensitivity analysis based on the independent central review (ICR) of the radiological scans will be carried out. A charter for the ICR will be developed in advance of the start of the study.

### 11.1.2 Secondary endpoints

#### 11.1.2.1 Overall Survival

Overall survival is defined as the time from the date of randomisation until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.



Note: Survival calls will be made in the week following the date of Data Cut Off (DCO) for the analysis, and if patients are confirmed to be alive or if the death date is post the DCO date these patients will be censored at the date of DCO.

#### **11.1.2.2 Time to earliest progression by RECIST 1.1 or CA-125 or death**

Progression or recurrence based on serum CA-125 levels will be defined on the basis of a progressive serial elevation of serum CA-125, according to the following modified GCIG criteria (note GCIG criteria is not validated for this trial population):

- Patients with elevated CA-125 pre-treatment (i.e. greater than the upper limit of normal (ULN)):-
  - (a) If CA-125 does not fall to within the normal range whilst on treatment then there must be evidence of CA-125 greater than, or equal to, 2 times the nadir value in the 28 day period before day 1 on 2 occasions at least 1 week apart.
  - (b) Where CA-125 does fall to within the normal range whilst on study treatment (and the patient has not already progressed by way of (a) above) then there must be evidence of CA-125 greater than, or equal to, 2 times the ULN on 2 occasions at least 1 week apart.
- Patients with CA-125 in the normal range pre-treatment must show evidence of CA-125 greater than, or equal to, 2 times the ULN on 2 occasions at least 1 week apart CA-125 progression will be assigned the date of the first measurement that meets the criteria as noted.

Time to progression by RECIST or CA-125 progression or death is defined as the time from randomisation to the earlier date of RECIST or CA-125 progression or death by any cause. Patients without a CA-125 progression or a RECIST progression who are still alive at the time of analysis will be censored at their last evaluable RECIST assessment or their last available CA-125 measurement, whichever is the most recent at the time of the analysis. If a patient progresses or dies after two or more missed RECIST and CA-125 assessments, then the patient will be censored at the time of their last evaluable assessment. If only one assessment is missing during this period, no censoring is required.

#### **11.1.2.3 Time from randomisation to second progression (PFS2)**

Time from randomisation to second progression is defined as the time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS or death. The date of second progression will be recorded by the investigator and defined according to local standard clinical practice and may involve any of; objective radiological, CA-125 or symptomatic progression or death. Second progression status will be reviewed every 12 weeks following the progression event used for the primary variable PFS (the first progression) and status recorded. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second

disease progression, i.e. censored at the latest of the PFS or PFS2 assessment date if the patient has not had a second progression or death).

#### **11.1.2.4 Time to first subsequent therapy or death (TFST)**

Time to start of first subsequent therapy or death (TFST) will be assessed (see Section 12.2.3.3). TFST is defined as the time from the date of randomisation to the earlier of the date of therapy start date following study treatment discontinuation, or death. Subsequent therapies will be reviewed to assess which represent clinically important treatments intended to control ovarian cancer. Any patient not known to have died at the time of the analysis and not known to have had a further intervention of this type will be censored at the last known time to have not received subsequent therapy, i.e. the last follow-up visit where this was confirmed.

#### **11.1.2.5 Time to second subsequent therapy or death (TSST)**

Time to start of second subsequent therapy or death (TSST) will be assessed (see Section 12.2.3.3). TSST is defined as the time from the date of randomisation to the earlier of the date of second subsequent therapy start date following study treatment discontinuation, or death. Any patient not known to have died at the time of the analysis and not known to have had a second further intervention of this type will be censored at the last known time to have not received second subsequent therapy, i.e. the last follow-up visit where this was confirmed.

#### **11.1.2.6 Time to study treatment discontinuation or death (TDT)**

Time to study treatment discontinuation or death (TDT) will be assessed (see Section 12.2.3.3). TDT is defined as the time from the date of randomisation to the earlier of the date of study treatment discontinuation or death. Any patient not known to have died at the time of analysis and not known to have discontinued study treatment will be censored based on the last recorded date on which the patient was known to be alive.

Note: Survival calls will be made in the week following the date of Data Cut Off (DCO) for the analysis, and if patients are confirmed to be alive or if the death date is post the DCO date these patients will be censored at the date of DCO.

#### **11.1.2.7 Best Overall RECIST Response (BoR)**

Best overall RECIST response (BoR) is calculated based on the overall visit responses from each RECIST assessment, described in Appendix F. It is the best response a patient has had during their time in the study following randomisation but prior to starting any subsequent cancer therapy and prior to RECIST progression or the last evaluable assessment in the absence of RECIST progression.

Categorisation of best overall response will be based on the RECIST criteria (Appendix F) using the following response categories: complete response (CR), partial response (PR), stable disease (SD), No Evidence of Disease (NED; applies only to those patients entering the study with no disease at baseline), progressive disease (PD) and not evaluable (NE).

Best overall response will be determined programmatically based on the RECIST criteria using investigator data.

For patients whose progression event is death, BoR will be calculated based on data up until the last evaluable RECIST assessment prior to death.

For patients who die with no evaluable RECIST assessments, if the death occurred  $\leq 25$  weeks (i.e. 24 weeks  $\pm 1$  week) after randomisation then BoR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST assessments, if the death occurred  $> 25$  weeks (i.e. 24 weeks  $\pm 1$  week) after randomisation then BoR will be assigned to the non-evaluable (NE) category.

Progression events that have been censored due to them being  $> 25$  weeks after the last evaluable assessment will not contribute to the BoR derivation.

A patient will be classified as a responder if the RECIST criteria for a CR or PR are satisfied at any time up to the earliest of the defined analysis cut-off point or the start of subsequent therapy. For each treatment group, the objective response rate (ORR) is the number of CR and PR divided by the number of patients in the group in the FAS with measurable disease at baseline. Only patients with PR and measurable disease at enrolment can achieve an objective response of CR or PR, other permissible categories of BoR are NE, PD.

## **11.2 Calculation or derivation of safety variable(s)**

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs and ECG. These will be collected for all patients. Appropriate summaries of these data will be presented as described in Section [12.2](#).

### **11.2.1 Other significant adverse events (OAE)**

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and Discontinuation of Investigational Product due to Adverse Events (DAEs). Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

Revised Clinical Study Protocol  
Drug Substance AZD2281  
Study Code D0818C00001  
GOG Code GOG-3004

---

---

---

---

---

---

**11.4 Calculation or derivation of pharmacokinetic variables – Not Applicable**

**11.5 Calculation or derivation of pharmacodynamic variables – Not Applicable**

**11.6 Calculation or derivation of pharmacogenetic variables**

To be defined in the exploratory analysis plan.

**11.7 Calculation or derivation of resource use**

Frequency and estimates of resource use, including length of stay and number of hospital admissions, will be derived from the resource use information.

## 12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

### 12.1 Description of analysis sets

A comprehensive statistical analysis plan (SAP) will be prepared and finalised before first subject in (FSI).

Table 10 gives a summary of outcome variables and analysis populations.

#### 12.1.1 Full analysis set

**Intention to treat (ITT):** The primary statistical analysis of the efficacy of olaparib will include all patients who are randomised as part of the global enrolment. The global recruitment to the study will close when approximately 344 patients are randomised.

The primary analysis will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised as part of the global enrolment but did not subsequently go on to receive study treatment are included in the Full Analysis Set (FAS). Therefore, all efficacy and health related QoL data will be summarised and analysed using the FAS on an intention-to-treat (ITT) basis.

#### 12.1.2 Safety analysis set

All patients who received at least one dose of randomised investigational product, olaparib or placebo and as part of the global enrolment will be included in the primary safety analysis set. Throughout the safety results sections, erroneously treated patients (e.g., those randomised to treatment A but actually given treatment B) will be accounted for in the treatment group of the treatment they actually received.

**Table 10 Summary of Outcome Variables and Analysis Populations**

Outcome Variable	Populations
<b>Efficacy Data</b>	
- PFS	ITT
- OS, PFS2, TFST, TSST, TDT, symptom/QoL endpoints	ITT
Demography	ITT
<b>Safety Data</b>	
- Adverse Events	Safety
- Lab measurements	Safety
- Vital Signs	Safety

## 12.2 Methods of statistical analyses

The treatment comparison is olaparib 300 mg bd vs placebo.

All efficacy analyses will be performed on the ITT population. In addition, as a sensitivity to the main analyses of PFS, PFS2, OS, TDT, TFST and TSST, analyses of these endpoints will be performed in those patients whose gBRCAm status is confirmed by the central Myriad test.

Results of all statistical analysis will be presented using a 95% confidence interval and 2-sided p-value.

The following table details which endpoints are to be subject to formal statistical analysis, together with pre-planned sensitivity analyses making clear which analysis is regarded as primary for that endpoint

**Table 11 Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses**

Endpoints Analysed	Notes
PFS (Time from randomisation to first progression or death)	Primary analysis: stratified log-rank test using investigator data
	Sensitivity Analyses <sup>a</sup>
	1) Evaluation time bias analysis; stratified log-rank test using investigator data
	2) Attrition bias analysis (using alternative censoring rules); stratified log-rank test using investigator data
	3) Ascertainment bias analysis; stratified log-rank test using BICR data
	4) Deviation bias (if meaningful to do); stratified log-rank test using investigator data
5) Analysis in randomised patients confirmed as gBRCA mutation positive by central Myriad test; stratified log rank test using investigator data	



**Table 11 Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses**

<b>Endpoints Analysed</b>	<b>Notes</b>
Overall Survival (Time from randomisation to death due to any cause)	Stratified log-rank test Sensitivity analysis: Stratified log rank test using investigator data in randomised patients confirmed as gBRCA mutation positive by central Myriad test
PFS2 (Time from randomisation to second progression or death)	Stratified log rank test based on investigator assessment of second progression Sensitivity analysis: Stratified log rank test using investigator data in randomised patients confirmed as gBRCA mutation positive by central Myriad test
TFST (Time to first subsequent therapy or death)	Stratified log rank test using investigator data Sensitivity analysis: Stratified log rank test using investigator data in randomised patients confirmed as gBRCA mutation positive by central Myriad test
TSST (Time to second subsequent therapy or death)	Stratified log rank test using investigator data Sensitivity analysis: Stratified log rank test using investigator data in randomised patients confirmed as gBRCA mutation positive by central Myriad test
Change from baseline in TOI score	Mixed model for repeated measures (MMRM) analysis of the change from baseline in TOI score
Time to earliest progression by RECIST 1.1, CA-125 or death	Stratified log rank test using investigator data
TDT (Time to study treatment discontinuation or death)	Stratified log rank test using investigator data Sensitivity analysis: Stratified log rank test using investigator data in randomised patients confirmed as gBRCA mutation positive by central Myriad test

<sup>a</sup> See Section 12.2.2.1 for further details

### 12.2.1 Multiplicity strategy for primary and key secondary endpoints

In order to describe the nature of the benefits of olaparib maintenance treatment, PFS, PFS2, TFST, TSST, change from baseline in TOI score and OS will be tested at a 2-sided significance level of 5%.

In addition to these planned analyses, which will be performed and reported in the CSR, in order to strongly control the type I error at 2.5% 1-sided for key label claims, a multiple testing

procedure (MTP) will also be employed across the primary endpoint (PFS) and key secondary endpoints (PFS2 and OS). There is no requirement to adjust for multiplicity due to PFS interim analyses, since there are no planned interim PFS analyses with the opportunity to make an early claim of efficacy.

A hierarchical testing strategy will be employed where PFS is tested first using the full test mass (full test mass =  $\alpha$ ) and key secondary endpoints of PFS2 and OS will then be tested using a MTP with a recycling strategy (i.e., the MTP will recycle the test mass to the endpoint not yet rejected in the hierarchy outlined in [Figure 6](#)). The MTP is detailed below.

**Figure 6 Multiple Testing Procedure**



PFS2 will only be tested (with the test mass split between interim and final PFS2 analyses) if statistical significance is shown for PFS. OS will only be tested if the null hypothesis (of no difference) is rejected for PFS2.

Both PFS2 and OS will be tested at the time of the primary analyses of PFS and again when there are approximately 60% deaths. A proportion of alpha will be spent at this first analyses time point for both endpoints to control for multiple testing however different spending functions will be applied for each.

An interim analysis for PFS2 will be performed at the time of the PFS analysis (approximately 180 PFS2 events expected at this time). Statistical significance will be declared at the interim analysis for PFS2 if the 1-sided  $p < 0.0125$ . Assuming 180 PFS2 events, a  $HR \leq 0.70$  would equate to a 1-sided  $p$ -value  $< 0.0125$ .

If the null hypothesis for PFS2 is not rejected at this first analyses time point then PFS2 will be tested again when the final analysis of OS occurs (approximately 300 PFS2 events expected when approximately 206 death events have occurred). The type I error will be controlled at 2.5% 1-sided by assigning approximately 1.8% significance level (1-sided) to the final analysis of PFS2 (final significance level to be determined accounting for correlation between the interim and final PFS2 analyses) ([Stone 2010](#)). Assuming 300 PFS2 events, a  $HR \leq 0.77$  would equate to a 1-sided  $p$ -value  $< 0.018$ . If PFS2 is significant at either the interim or final analyses, the full test mass (alpha) will be carried forward to OS.

An interim analysis for OS will be performed at the time of the PFS analysis (approximately 100 OS events). Statistical significance will be declared at the interim analysis for OS if the null hypothesis for PFS2 is rejected at the PFS analysis and the observed p-value for OS is  $p < 0.0001$ . This allows the significance level at the final analysis for OS to be controlled at the 2.5% level (1-sided) (Haybittle J L 1971)).

### 12.2.2 Analysis of primary endpoint

PFS will be analysed when approximately 196 events have occurred or after the last patient randomised has had the opportunity to have been on the study for at least 36 months, whichever comes first. No further analyses of PFS are planned beyond this point unless requested by Health Authorities.

PFS will be analysed using a log rank test stratified by response to first line platinum chemotherapy (clinical complete response partial response) for generation of the p-value and using the Breslow approach for handling ties. The hazard ratio (HR) and confidence interval will be estimated from a Cox Proportional Hazards model (with ties = Efron and the stratification variable as a covariate) and the CI will be calculated using a profile likelihood approach.

Stratification variables will be defined according to data from the interactive voice/web response system (IVRS/IWRS). If there are any patients who were mis-stratified, a sensitivity analysis will be carried out using the (correct) baseline data collected in the eCRF.

The HR (olaparib vs placebo) together with its corresponding 95% confidence interval (CI) and p-value will be presented (a HR less than 1 will favour olaparib).

A Kaplan-Meier (KM) plot of PFS will be presented by treatment group. Summaries of the number and percentage of subjects experiencing a PFS event, and the type of event (RECIST or death) will be provided along with median PFS for each treatment.

The assumption of proportionality will be assessed. Note that in the presence of non-proportionality, the HR will be interpreted as an average HR over the observed extent of follow-up. Proportionality will be tested firstly by examining plots of complementary log-log (event times) versus log (time) and, if these raise concerns, a time dependent covariate would be fitted to assess the extent to which this represents random variation.

The primary analysis will be based on the programmatically derived PFS based on Investigator recorded assessments, and using all scans regardless of whether they were scheduled or not.

The proportion of patients alive and progression free at 6 months and 12 months will be summarised (using the KM curve) and presented by treatment group.

The number of patients prematurely censored will be summarised by treatment arm together with baseline prognostic factors of the prematurely censored patients. A patient is defined as prematurely censored if they had not progressed and the latest scan prior to DCO was more than one scheduled tumour assessment interval (+ 2 weeks) prior to the DCO date.

Subgroup analyses will be conducted comparing PFS between treatments in the following subgroups of the full analysis set:

- Response to previous platinum chemotherapy (clinical complete response or partial response)
- 
- ECOG performance status at baseline (0 or 1)
- Baseline CA-125 value ( $\leq$  ULN vs  $>$  ULN)
- 
- Age at randomisation ( $<65$  vs.  $\geq 65$ )
- Stage of disease at initial diagnosis (III or IV)

A minimal number of patients that are tBRCAm *and* gBRCA wt are expected to be randomised into this study. Assuming the number of progression events in this population is less than 20, these patients will be summarised with a Kaplan Meier of PFS by treatment. If the number of events is  $\geq 20$ , this factor will be added to the forest plot (i.e. gBRCA and tBRCA mutated vs tBRCA mutated only).

Other baseline variables may also be assessed if there is clinical justification. For each subgroup, the HRs (olaparib: placebo) and associated CIs will be calculated from a Cox proportional hazards model (ties = Efron) that contains the treatment term, factor (subgroup) and treatment-by-factor interaction term. The treatment effect HRs for each treatment comparison along with their confidence intervals will be obtained for each level of the subgroup from this single model. The HRs and 95% CIs will be presented on a forest plot including the HR and 95% CI from the overall population (using the primary analysis).

The purpose of the subgroup analyses is to assess the consistency of treatment effect across potential or expected prognostic factors. The results observed in Phase II (D0810C00019) do not suggest that these factors will be predictive factors for a qualitatively different treatment effect.

If there are too few events available for a meaningful analysis of a particular subgroup (where there are less than 20 events per subgroup level no formal statistical tests will be performed), the relationship between that subgroup and PFS will not be formally analysed. In this case, only descriptive summaries will be provided.

No adjustment to the significance level for testing will be made since all these subgroup analyses will be considered exploratory and may only be supportive of the primary analysis of PFS.

The presence of quantitative interactions will be assessed by means of an overall global interaction test. This will be performed in the overall population by comparing the fit of a Cox proportional hazards model including treatment, all covariates, and all covariate-by-treatment interaction terms, with one that excludes the interaction terms and will be assessed at the 2-sided 10% significance level. If the fit of the model is not significantly improved then it will be concluded that overall the treatment effect is consistent across the subgroups.

If the global interaction test is found to be statistically significant, an attempt to determine the cause and type of interaction will be made. Stepwise backwards selection will be performed on the saturated model, whereby (using a 10% level throughout) the least significant interaction terms are removed one-by-one and any newly significant interactions re-included until a final model is reached where all included interactions are significant and all excluded interactions are non-significant. Throughout this process all main effects will be included in the model regardless of whether the corresponding interaction term is still present. This approach will identify the factors that independently alter the treatment effect and prevent identification of multiple correlated interactions.

Any quantitative interactions identified using this procedure will then be tested to rule out any qualitative interaction using the approach of [Gail and Simon 1985](#).

A further analyses of PFS (using investigator assessed RECIST) may be performed at the time of the OS analyses, if requested by Health authorities.

#### **12.2.2.1 Sensitivity Analyses for Primary Endpoint**

As a sensitivity analysis to the primary endpoint of PFS, the primary analysis will be repeated excluding any patients who did not have a gBRCA mutation status confirmed by the central Myriad test. The same methodology and model will be used and the HR and associated 95% CI from a Cox Proportional Hazards model will be reported. A KM plot of PFS in this subset of patients will be presented by treatment group.

Sensitivity analyses will be performed to assess the possible presence of time-assessment bias (i.e., differential assessment times between treatment groups).

Summary statistics for the number of weeks between the time of progression and the last evaluable RECIST assessment prior to progression will be presented for each treatment group.

##### **(a) Evaluation-Time bias**

Sensitivity analyses will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled time points. The midpoint between the time of progression and the previous evaluable RECIST assessment will be analysed using a stratified log rank test, as described for the primary analysis of PFS. This approach has

been shown to be robust to even highly asymmetric assessment schedules ([Sun and Chen 2010](#)). This approach will use the investigator RECIST assessments.

(b) Attrition bias

Attrition bias will be assessed by repeating the primary PFS analysis except that the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression immediately following two, or more, non-evaluable tumour assessments will be included. In addition, patients who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy.

Additionally a Kaplan-Meier plot of the time to censoring where the censoring indicator of the primary PFS analysis is reversed will be presented.

(c) Ascertainment bias

A stratified log-rank test will be repeated using BICR assessed RECIST data to programmatically derive PFS. The HR and 95% Confidence Interval will be presented.

If there is an important discrepancy between the primary analysis using investigator assessments and this sensitivity analysis using ICR assessments, then the proportion of subjects with central but no site confirmation of progression will be summarised. The approach of imputing an event at the next visit in the investigator assessed analysis may help inform the most likely HR value, but only if an important discrepancy exists.

(d) Deviation bias (if meaningful to do)

As a sensitivity to the primary endpoint of PFS, an analyses excluding patients with deviations that may affect the efficacy of the trial study treatment will be performed if >10% of patients:

- Did not have the intended disease or indication or
- Did not receive any randomised study treatment

A stratified log-rank test will be repeated using the investigator RECIST data, using the same ties and stratification factor as described for the primary analysis of PFS. The HR and 95% Confidence Interval will be presented.

### **12.2.3 Analysis of secondary endpoints**

#### **12.2.3.1 Analysis of PFS2 endpoint**

An initial PFS2 analysis will be performed at the same time as the primary analysis of PFS and will use the same methodology and model. A further analysis of PFS2 will be performed when the OS data are approximately 60% mature.

As a sensitivity, the analysis of PFS2 will be repeated in those patients whose gBRCAm status is confirmed by the central Myriad test. A KM plot of PFS2 in this subset of patients will be presented by treatment group.

The sensitivity analysis outlined for 12.2.2.1 will not be repeated for PFS2 with the exception of a Kaplan-Meier plot of the time to censoring where the censoring indicator of the primary PFS2 is reversed.

### **12.2.3.2 Analysis of OS endpoint**

OS data will be analysed at the time of the primary analysis of PFS and will use the same methodology and model (provided there are sufficient events available for a meaningful analysis [ $\geq 20$  deaths], if not descriptive summaries will be provided). A further analysis of OS will be performed when the OS data are approximately 60% mature.

As a sensitivity, the analysis of OS will be repeated in those patients whose gBRCAm status is confirmed by the central Myriad test. A KM plot of OS in this subset of patients will be presented by treatment group.

The sensitivity analysis outlined for 12.2.2.1 will not be repeated for OS with the exception of a Kaplan-Meier plot of the time to censoring where the censoring indicator of the primary OS is reversed.

### **12.2.3.3 Analysis of TFST, TSST, TDT endpoints**

Time to first subsequent therapy or death (TFST), time to second subsequent therapy or death (TSST) and time to study treatment discontinuation or death (TDT) will be analysed at the same time as the primary analysis of PFS and using the same methodology and model. The HRs for the treatment effect together with 95% CIs will be presented. Kaplan Meier plots will be presented by treatment arm. In addition, the time between first progression and starting first subsequent therapy will be summarised.

Summary tables of first and second subsequent therapies by treatment arm will be provided, as well as response to first and second subsequent therapy by treatment arm.

Further analyses of these endpoints will be performed when the OS data are approximately 60% mature.

As a sensitivity, the analyses of TFST, TSST and TDT will be repeated in those patients whose gBRCAm status is confirmed by the central Myriad test. KM plots of TFST, TSST and TDT in this subset of patients will be presented by treatment group.

### **12.2.3.4 Analysis of time to earliest progression by RECIST 1.1 or CA-125 or death**

Time to progression by RECIST 1.1 or CA-125 will be performed at the same time as the primary analysis of PFS and will use the same methodology and model.

The number (%) of patients reporting a CA-125 progression, an objective RECIST 1.1 progression and both a CA-125 and/or objective RECIST progression will be tabulated.

No multiplicity adjustment will be applied as this is viewed as a supportive endpoints (to PFS).

#### **12.2.3.5 Summary of Best overall RECIST Response (BoR)**

For each treatment arm, Best Overall Response (BoR) will be summarised by n (%) for each category (CR, PR, SD, NED, PD, NE). No formal statistical analyses are planned.

The objective response rate (ORR) will be summarised (i.e., number of patients (%)) by treatment group.

#### **12.2.3.6 Analysis of PRO endpoints**

The analysis population for HRQoL data will be the subset of the FAS (ITT) set.

Change from baseline in TOI score will be regarded as the primary analysis of the FACT-O questionnaire and will be analysed using a mixed model for repeated measures (MMRM) analysis of the change from baseline in TOI score for each visit. The primary analysis will be to compare the average treatment effect from the point of randomisation for the first 24 months (which will include visit data obtained at baseline, day 29 (week 4), weeks 12, 24, 36, 48, 60, 72, 84, 96 and the discontinuation and follow-up visits if occurring within the first 24 months) unless there is excessive missing data (defined as >75% missing data). If the time to first subsequent chemotherapy when approximately 50% of placebo patients receive chemotherapy does not occur by 24 months post-randomisation then additional time periods will be analysed and will be included on supportive summaries and graphical displays as appropriate.

The MMRM model will include patient, treatment, visit and treatment by visit interaction as explanatory variables and the baseline TOI score as a covariate. Treatment, visit and treatment by visit interaction will be fixed effects in the model; patient will be included as a random effect. The treatment by visit interaction will remain in the model regardless of significance. Calculation of a suitable adjusted mean estimate will be detailed in the SAP that will estimate the average treatment effect over visits which gives each visit equal weight. The adjusted mean estimates and corresponding 95% confidence intervals will be presented for the overall treatment comparison and by visit for each treatment group.

Descriptive statistics and graphs will be reported for the TOI by visits as well as change in these scores from baseline. These will also be reported for the physical well being (PWB), social well being (SWB), emotional well being (EWB), functional well being (FWB) and the ovarian cancer subscale (Additional Concerns) domains.

Summary tables of Trial Outcome Index (TOI) best change rates will be provided.



### **12.2.3.7 Health State Utility – EQ-5D-5L**

Descriptive statistics will be reported for EQ-5D-5L health state utility values and the visual analogue score by visit, as well as change in these scores from baseline. Further details of the exploratory analysis will be outlined in the statistical analysis plan (SAP).

The scores for each of the EQ-5D-5L health state utility values and visual analogue will be summarised in terms of mean changes from baseline at each post-baseline assessment (with n, standard deviation, min, max presented). If less than 50% of the items in one health state are missing, the mean scores for the completed items will be used for imputation. If 50% or more of the items in one health state are missing, that subscale will be treated as missing.

### **12.2.3.8 Impact of Switching to PARP inhibitors (or other potentially active investigational agents) on Overall Survival Analyses**

Exploratory analyses of OS adjusting for impact of subsequent PARP inhibitor trial or treatment may be performed if a sufficient proportion of patients switch. Methods such as Rank Preserving Structural Failure Time (RPSFT) (Robins et al 1991), Inverse Probability of Censoring Weighting (IPCW) (Robins 1993) and other methods in development will be explored. The decision to adjust and final choice of methods will be based on a blinded review of the data and the plausibility of the underlying assumptions. Baseline and time-dependent characteristics will be explored, and summaries of baseline characteristics will be summarised for placebo patients, splitting between those that have and haven't switched at the time of the analyses. Further detail will be provided in the SAP and Payer Analysis Plan.

### **12.2.4 Exploratory endpoints**

Exploratory endpoints are covered by PRO endpoints. For analysis description please see Section 12.2.3.6.

### **12.2.5 Interim analyses**

No interim analyses of PFS prior to the primary analysis will be performed, however additional analyses of PFS and/or OS may be performed to meet Regulatory Agency requests.

Revised Clinical Study Protocol  
Drug Substance AZD2281  
Study Code D0818C00001  
GOG Code GOG-3004

### 12.3 Determination of sample size

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.

The primary endpoint of the study is PFS.

In total 206 PFS events in the study would have 90% power to show statistically significant PFS at the 2-sided 5% level if the assumed true treatment effect were HR 0.62; this translates to a 8 month benefit in median PFS over 13 months on placebo (estimated from data reported by [Alsop et al 2012](#)) if PFS is exponentially distributed.

Approximately 344 patients will be recruited (2:1 ratio) so that data maturity for the PFS analysis is approximately 60%.

Assuming 18 months non-linear recruitment, 206 PFS events are expected to occur approximately 36 months after first subject in is enrolled in the study (FSI). This will be the primary analysis of PFS. No further analyses of PFS are planned beyond this point unless requested by Health Authorities.

At this time, an analysis of OS will also be performed. It is anticipated that approximately 100 OS events (29% maturity) will have occurred. Assuming that the true OS treatment effect is 0.85 and if this point estimate for the HR of 0.85 was observed, the 95% upper confidence limit (UCL) for the HR would be 1.29.

A further analysis of OS may be performed at approximately 60% maturity (~206 events); this is anticipated to occur approximately 80 months after FSI. Assuming that the true OS treatment effect is 0.85 and this point estimate for the HR of 0.85 was observed, the 95% UCL for the HR would be 1.13. Note that these estimates are based on the assumption that no confounding will occur. AstraZeneca anticipates potential confounding of OS data due to availability of PARP inhibitors for BRCA mutated ovarian cancer patients during follow up in this study, which are likely to disproportionately affect OS in one arm of the study (placebo-treated patients).

**Pharmacogenetic research (PGx)** The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

### 12.4 Data monitoring committee

This study will use an external Independent Data Monitoring Committee (IDMC) to perform interim reviews of accumulating study safety data. This committee will be composed of therapeutic area experts and a statistician, who are not employed by AZ, and do not have any major conflict of interest. Following the review, the IDMC will recommend whether the study should continue unchanged, be terminated, or be modified in any way. Once the IDMC has reached a recommendation, a report will be provided to AstraZeneca. The report will only

include the recommendation and any potential protocol amendments. It will not contain any unblinded information. A separate IDMC charter will be developed which will contain details of the IDMC members and clearly define the responsibilities of the IDMC.

In addition to the periodic review of safety data by an IDMC, the safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with the Patient Safety Department. Issues identified will be addressed; this could involve, for instance, amendments to the study protocol and letters to investigators.

### 13. MEDICAL EMERGENCIES AND ASTRAZENECA CONTACTS

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4**

In the case of a medical emergency the investigator may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician/other physician at the AstraZeneca Research and Development site.

Name	Role in the study	Address & telephone number
	Clinical Development Manager responsible for the protocol at central R&D site	
	SDT Physician responsible for the protocol at central R&D site	
	Global Safety Physician	
	24-hour emergency cover at central R&D site	

## 13.1 Overdose

There is currently no specific treatment in the event of overdose of olaparib and possible symptoms of overdose are not established.

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 30 days.

## 13.2 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

### 13.2.1 Maternal exposure

If a patient becomes pregnant during the course of the study investigational product should be discontinued immediately.

The outcomes of any conception occurring from the date of the first dose of study medication until 3 months after the last dose of study medication must be followed up and documented.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.4.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

## 14. LIST OF REFERENCES

### **Alsop et al 2012**

Alsop K, Fereday S, Meldrum C, DeFazio A, Emmanuel C, George J, et al. BRCA Mutation Frequency and Patterns of Treatment Response in BRCA Mutation–Positive Women With Ovarian Cancer: A Report From the Australian Ovarian Cancer Study Group. *J Clin Oncol* 2012;30:2654-63.

### **Basen-Engquist K et al 2001**

Basen-Engquist K, Bodurka-Bevers D, Fitzgerald MA, Webster K, Cella D, Hu S, Gershenson DM. Reliability and validity of the functional assessment of cancer therapy-ovarian. *J Clin Oncol*. 2001 Mar 15;19(6):1809-17.

### **Bessman JD 1990**

Bessman JD. Reticulocytes. In: Walker HK, Hall WD, Hurst JW, editors. *Clinical Methods: The History, Physical, and Laboratory Examinations*. 3rd edition. Boston: Butterworths; 1990. Chapter 156. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK264/>

### **Cancer Therapy Evaluation Program**

<http://ctep.cancer.gov>

### **Cella D et al 1993**

Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*. 1993 Mar;11(3):570-9.

### **Chen J et al 2011**

Chen J, Quan H, Gallo P, Menjoge S, Luo X, Tanaka Y, Li G, Ouyang S, Binkowitz B, Ibia E, Talerico S, and Ikeda K. Consistency of treatment effect across regions in multiregional trials, part I: design considerations. *Drug Information Journal* 2011;45:595-602.

### **Colombo et al 2010**

Colombo N, Peiretti M, Parma G, Lapresa M, Mancari R, Carinelli S, et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. *Ann Oncol* 2010; 21 (Suppl 5) v23-v30.

## **FACT-O Scoring Manual**

[www.facit.org](http://www.facit.org)

### **Farmer et al 2005**

Farmer H, McCabe N, Lord CJ, Tutt ANJ, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Letter to Nature* 2005; 434:917-921.

### **Fleming et al 2009**

Fleming GF, Ronnett BM, Seidman J. Epithelial ovarian cancer. In: Barakat RR, Markman M, Randall ME, eds. *Principles and practice of Gynecologic oncology*, 5<sup>th</sup> edition. Philadelphia: Lippincott Williams & Wilkins; 2009:763-836.

### **Fong et al 2009**

Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med*. 2009;361(2):123-34.

### **Gail and Simon 1985**

Gail M, Simon R. Testing for qualitative interactions between treatment effects and patient subsets. *Biometrics* 1985;41:361-72.

### **Gallo P et al 2011**

Gallo P, Chen J, Quan H, Menjoge S, Luo X, Tanaka Y, Li G, Ouyang S, Binkowitz B, Ibia E, Talerico S, and Ikeda K. Consistency of treatment effect across regions in multiregional trials, part II: monitoring, reporting, and interpretation. *Drug Information Journal* 2011;45:603-608.

### **Hay et al 2009**

Hay T, Matthews JR, Pietzka L, Lau A, Cranston A, Nygren AO, et al. Poly(ADP-ribose) polymerase-1 inhibitor treatment regresses autochthonous Brca2/p53-mutant mammary tumors in vivo and delays tumor relapse in combination with carboplatin. *Cancer Res* 2009;69(9):3850-5.

### **Haybittle J L 1971**

Haybittle, J L 1971. Repeat assessment of results in clinical trials of cancer treatment. *British Journal of Radiology*. 1971 Oct;44:793-7.

### **Helleday 2011**

Helleday T. The underlying mechanism for the PARP and BRCA synthetic lethality: Clearing up the misunderstandings. *Molecular Oncology* 2011;5:387-393.

### **Huang 2012**

Qin Huang, Gang Chen, Zhilong Yuan, K K Gordan Lan: Design and sample size considerations for simultaneous global drug development program. *J Biopharm Stat* 2012 Sep;22(5):1060-73.

**Jemal et al 2010**

Jemal A, Siegel R, Xu J, Ward E. Cancer Statistics, 2010. *CA Cancer J Clin* 2010; Sep-Oct; 60(5):277-300.

**Ledermann et al 2012**

Ledermann J, Harter P, Gourley C. Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer. *N Engl J Med* 2012;366:1382-92.

**Li G et al 2013**

Li G, Chen J, Quan H, and Shentu Y. Consistency assessment with global and bridging development strategies in emerging markets. *Contemp Clin Trials* 2013 Nov;36(2):687-96.

**McGuire et al 1996**

McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 1996;334:1-6.

**Murai et al 2012**

Murai J, Huang SN, Das BB, Renaud A, et al. Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. *AACR* 2012;72(21);5588–99.

**NCCN Clinical Practice Guidelines in Oncology**

NCCN Clinical Practice Guidelines in Oncology; Ovarian cancer version 1.2013, [www.nccn.com](http://www.nccn.com)

**Osoba et al 2005**

Osoba D, Bezjak A, Brundage M, et al: Analysis and interpretation of health-related quality-of-life data from clinical trials: Basic approach of The National Cancer Institute of Canada Clinical Trials Group. *Eur J Cancer* 2005;41:280-287.

**Pal et al 2005**

Pal T, Permuth-Wey J, Betts JA, Krischer JP, Fiorica J, Arango H, et al. BRCA1 and BRCA2 Mutations Account for a Large Proportion of Ovarian Carcinoma Cases. *Cancer* 2005;104(12):2807-16.

**Richards et al 2008**

Richards SC, Bale S, Bellissimo DB. ACMG recommendations for standards for interpretation and reporting of sequence variations. *Genet Med* 2008;10(4):294–300.

**Risch et al 2006**

Risch HA, McLaughlin JR, Cole DEC, Rosen B, Bradley L, Fan I, et al. Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. *J Natl Cancer Inst* 2006;98:1694–1706.



**Robins et al 1991**

Robins JM, Tsiatis AA. Correcting for noncompliance in randomized trials using rank preserving structural failure time models. *Communications in Statistics - Theory and Methods* 1991;20:2609-2631.

**Robins 1993**

Robins J. Information recovery and bias adjustment in proportional hazards regression analysis of randomized trials using surrogate markers. *Proceedings of the Biopharmaceutical Section, American Statistical Association* 1993;24-33.

**Rottenberg et al 2008**

Rottenberg S, Jaspers JE, Kersbergen A, van der Burg E, Nygren AO, Zander SA, et al. High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. *Proc Natl Acad Sci.* 2008;105(44):17079-84.

**Stone 2010**

Stone, A. The application of bespoke spending functions in group sequential designs and the effect of delayed treatment crossover in survival trials. *Pharm Statistics* 5 2010:151-161.

**Sun and Chen 2010**

Sun X and Chen C. Comparison of Finkelstein's Method With the Conventional Approach for Interval-Censored Data Analysis. *Stat Biopharm Research* 2010;2:1:97-108.

---

**Statistical Analysis Plan**

Drug Substance	Olaparib
Study Code	D0818C00001
GOG Code	GOG-3004

---

---

**A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients with BRCA Mutated Advanced (FIGO Stage III-IV) Ovarian Cancer following First Line Platinum Based Chemotherapy**

---

Statistical Analysis Plan  
Drug Substance Olaparib  
Study Code: D0818C00001  
GOG Code: GOG-3004

---

**A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients with BRCA Mutated Advanced (FIGO Stage III-IV) Ovarian Cancer following First Line Platinum Based Chemotherapy**

---

Study Statistician

Statistical Analysis Plan  
Drug Substance Olaparib  
Study Code D0818C00001  
GOG Code GOG-3004

---

**A Phase III Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed BRCA Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy**

---

**Global Product Statistician**

<b>TABLE OF CONTENTS</b>	<b>PAGE</b>
TITLE PAGE.....	1
SIGNATURE OF STUDY STATISTICIAN.....	2
SIGNATURE OF GLOBAL PRODUCT STATISTICIAN .....	3
LIST OF ABBREVIATIONS .....	7
1 STUDY DETAILS.....	12
1.1 Study Objectives .....	12
1.2 Study Design.....	13
1.3 Number of Subjects.....	19
2 ANALYSIS SETS .....	19
2.1 Definition of Analysis Sets.....	19
2.2 Violations and Deviations .....	21
3 PRIMARY AND SECONDARY VARIABLES.....	22
3.1 Derivation of RECIST Visit Responses.....	22
3.1.1 Target lesions (TLs).....	23
3.1.2 Non-target lesions (NTLs) and new lesions.....	28
3.1.3 Overall visit response.....	29
3.1.4 Independent review .....	30
3.2 Outcome Variables.....	30
3.2.1 Progression free survival (PFS).....	31
3.2.2 Time from randomisation to second progression or death (PFS2).....	32
3.2.3 Overall survival (OS).....	32
3.2.4 Time to first subsequent therapy or death (TFST).....	33
3.2.5 Time to second subsequent therapy or death (TSST) .....	33
3.2.6 Time to study treatment discontinuation or death (TDT) .....	33
3.2.7 Time to earliest progression by RECIST or CA-125 or death .....	33
3.2.8 Best overall RECIST response (BoR).....	34
3.3 Patient Reported Outcome (PRO) Variables.....	36
3.3.1 FACT-O .....	36
3.3.2 EQ-5D-5L (exploratory analysis) .....	39
3.3.3 General consideration for patient reported outcome variables.....	39
3.4 Safety.....	40
3.4.1 Adverse events.....	40
3.4.2 Treatment exposure.....	41

3.4.3	Dose intensity .....	41
3.4.4	Laboratory data .....	43
3.4.5	ECGs .....	43
3.4.6	Vital signs .....	43
3.4.7	General consideration for safety assessments .....	43
3.5	Health Care Resource Use.....	45
3.6	China cohort .....	45
4	ANALYSIS METHODS.....	46
4.1	General Principles .....	47
4.2	Analysis Methods.....	47
4.2.1	Multiplicity .....	50
4.2.2	Primary variable - progression free survival (PFS) .....	51
4.2.3	Time from randomisation to second progression (PFS2).....	58
4.2.4	Overall survival (OS).....	59
4.2.5	Time to first subsequent therapy or death (TFST) and time to second subsequent therapy or death (TSST).....	60
4.2.6	Time to study treatment discontinuation or death (TDT) .....	60
4.2.7	Time to earliest progression by RECIST 1.1, CA-125 or death.....	61
4.2.8	Best overall RECIST response (BoR).....	61
4.2.9	Patient reported outcomes (PROs).....	61
4.2.10	Exploratory analyses .....	64
4.2.11	Safety.....	65
4.2.12	Demographic and baseline characteristics data .....	69
4.2.13	Treatment exposure.....	72
4.2.14	Data cut-offs .....	72
5	INTERIM ANALYSES .....	73
6	CHANGES OF ANALYSIS FROM PROTOCOL .....	73
7	REFERENCES .....	73

## LIST OF TABLES

Table 1	Summary of Outcome Variables and Analysis Populations.....	20
Table 2	TL Visit Responses .....	24
Table 3	NTL Visit Responses .....	28
Table 4	Overall Visit Responses .....	29
Table 5	Health-Related Quality of Life .....	37
Table 6	Health-Related Quality of Life : Change rates - overall score .....	37

Table 7	Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses .....	48
---------	---	----

## **LIST OF FIGURES**

Figure 1	Study Flow Chart Up to 108 Weeks on Treatment.....	17
Figure 2	Study Flow Chart At 108 Weeks on Treatment.....	18
Figure 3	Example of Dose Intensity Calculations for Olaparib .....	42
Figure 4	Multiple Testing Procedure .....	51

## LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this study Statistical Analysis Plan.

<b>Abbreviation or special term</b>	<b>Explanation</b>
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
Baseline	Refers to the most recent assessment of any variable prior to dosing with study treatment
BD	Twice daily
BICR	Blinded independent central review
BoR	Best overall RECIST response
BP	Blood pressure
BRCA	Breast cancer susceptibility gene
<i>BRCAnalysis</i> <sup>®</sup>	Gene sequencing and large rearrangement analysis for Hereditary Breast and Ovarian Cancer, registered trademark of Myriad Genetics, Inc
BRCA mutation or BRCAm	Breast cancer susceptibility gene mutation (see gBRCA mutation or gBRCAm)
CA-125	Cancer Antigen – 125
cfDNA	Circulating free DNA
CLIA	Clinical Laboratory Improvement Amendments
CCR	Clinical complete response. ‘Response’ is used throughout the protocol and refers to patients being, in the opinion of the investigator, in clinical complete response or partial response on the post-treatment scan. Clinical complete response is defined as no evidence of either RECIST measurable or non-measurable disease on the post-treatment scan and a normal CA-125. Partial response is defined as $\geq 30\%$ reduction in tumour volume demonstrated from the start to finish of chemotherapy OR no evidence of RECIST measurable disease on the post-treatment scan with a CA-125 which has not decreased to within the normal range.
CI	Confidence interval
CR	Complete response
CRF / eCRF	Case Report Form (electronic)
CRO	Clinical Research Organisation
CSP	Clinical Study Protocol



<b>Abbreviation or special term</b>	<b>Explanation</b>
CSR	Clinical Study Report
CT	Computed tomography
CTC / CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of investigational product due to adverse event
DBP	Diastolic blood pressure
DCO	Data cut-off
DCR	Disease control rate
DNA	Deoxyribonucleic acid
DOR	Duration of response
d.p.	Decimal places
ECG	Electrocardiogram
E-code	Enrolment code (allocated by IVRS/IWRS)
ECOG	Eastern Cooperative Oncology Group: A performance status using scales and criteria to assess how a patient's disease is progressing
EQ-5D-5L / EQ-5D	EuroQoL five dimensions, five level (EQ-5D-5L) health state utility index
EWB	Emotional well being
FACIT	Functional Assessment of Chronic Illness Therapy
FACT-O	Functional Assessment of Cancer Therapy – Ovarian: A multidimensional questionnaire for patients with ovarian cancer
FAS	Full analysis set
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
FSI	First subject in
FWB	Functional well being
gBRCA	Germline BRCA
gBRCA mutation or gBRCAm	The term "gBRCA mutation" is used to refer to a germline BRCA1 or BRCA2 mutation classified as "deleterious" or "suspected deleterious" in accordance with the American College of Medical Genetics and Genomics recommendations for standards for interpretation and reporting of sequence variants.
gBRCA wt	gBRCA wildtype
GCIG	Gynecologic Cancer Intergroup
GOG	Gynecologic Oncology Group

<b>Abbreviation or special term</b>	<b>Explanation</b>
HR	Hazard ratio
HRQoL	Health-related quality of life
ICR	Independent Central Review
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IP	Intraperitoneal
IPCW	Inverse probability of censoring weighting
ITT	Intention to treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LD	Longest Diameter
LPLV	Last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milli-gram
MMRM	Mixed model for repeated measures
MRI	Magnetic resonance imaging
MTP	Multiple testing procedure
NA	Not applicable
NC	Not calculable
NCI	National Cancer Institute
NE	Not evaluable
NED	No evidence of disease
NTL	Non-target lesions
OAE	Other significant adverse event (see definition in Section 3.4.1)
ORR	Objective response rate
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation
PD	Progressive disease
PFS	Progression free survival

<b>Abbreviation or special term</b>	<b>Explanation</b>
PFS2	Time from randomisation to second progression
PID	Percentage intended dose
p.o.	Per os (by mouth, orally)
PR	Partial response
PRO	Patient reported outcome
PWB	Physical well being
QoL	Quality of life
QSR	Quality System Regulation
QTcB	QT interval (corrected for heart rate using Bazett's correction)
QTcF	QT interval (corrected for heart rate using Fridericia's correction)
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumours. This study will use modified RECIST version 1.1
REML	Restricted maximum likelihood
RPSFT	Rank preserving structural failure time
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SWB	Social well being
Study treatment	Olaparib or matching placebo
SBP	Systolic blood pressure
tBRCA mutation or tBRCAm	The term "tBRCA mutation" is used to refer to a somatic tumour BRCA1 or BRCA2 mutation classified as "deleterious" or "suspected deleterious" in accordance with the American College of Medical Genetics and Genomics recommendations for standards for interpretation and reporting of sequence variants.
TDT	Time from randomisation to study treatment discontinuation or death
TFST	Time from randomisation to first subsequent therapy or death
TL	Target lesions
TOI	Trial Outcome Index
TSST	Time from randomisation to second subsequent therapy or death
UCL	Upper confidence limit

---

<b>Abbreviation or special term</b>	<b>Explanation</b>
ULN	Upper limit of normal
VUS	Variant of uncertain significance
wt	Wildtype (patients without evidence of BRCA1 or BRCA2 deleterious or suspected deleterious mutations)

---

# 1 STUDY DETAILS

## 1.1 Study Objectives

### Primary:

To determine the efficacy by progression free survival (PFS) using investigator assessment according to modified Response Evaluation Criteria In Solid Tumours (RECIST) 1.1) of olaparib maintenance monotherapy compared to placebo in Breast Cancer susceptibility gene (BRCA) mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy.

### Secondary:

1. To determine the efficacy of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy by assessment of overall survival (OS), time to earliest progression by RECIST or Cancer Antigen-125 (CA-125), or death, and time from randomisation to second progression (PFS2).
2. To compare the effects of olaparib maintenance monotherapy compared to placebo on health-related quality of life (HRQoL) as assessed by the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy.
3. To assess efficacy of olaparib in patients identified as having a deleterious or suspected deleterious variant in either of the BRCA genes using variants identified with current and future BRCA mutation assays (gene sequencing and large rearrangement analysis).
4. To determine the efficacy of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy by assessment of time from randomisation to first subsequent therapy or death (TFST), time from randomisation to second subsequent therapy or death (TSST) and time from randomisation to study treatment discontinuation or death (TDT).

### Safety:

1. To assess the safety and tolerability of olaparib maintenance monotherapy in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy.

## **Exploratory:**

- 1.
2. To explore the impact of treatment and disease state on health state utility by EuroQoL five dimensions, five level (EQ-5D-5L).
3. To explore the impact of treatment and disease on resource use.
4. To explore the effects of olaparib maintenance monotherapy as assessed by the individual domains of the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O).
5. To explore the efficacy of olaparib by assessment of overall survival (OS) adjusting for the impact of spontaneous switching [outside of study design] to Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitors or other potentially active investigational agents.
- 6.
7. Future exploratory research into factors that may influence development of cancer and/or response to study treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumour samples that were mandatory for entry into the study or on optional tumour biopsy samples collected during the course of the study.
8. To collect and store Deoxyribonucleic acid (DNA) (according to each country's local and ethical procedures) for future exploratory research into genes/genetic variation that may influence response (i.e., distribution, safety, tolerability and efficacy) to study treatments and or susceptibility to disease (optional).

The exploratory analyses may not be reported in the Clinical Study Report (CSR). If not, they will be reported separately.

## **1.2 Study Design**

This is a Phase III, randomised, double-blind, placebo-controlled, multi-centre study to assess the efficacy of olaparib maintenance monotherapy in high risk advanced ovarian cancer patients (including patients with primary peritoneal and / or fallopian tube cancer) with BRCA mutations [documented mutation in BRCA1 or BRCA2] that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) who have responded following first line platinum based chemotherapy.

Patients will be randomised (using an Interactive Voice Response System (IVRS) / Interactive Web Response System (IWRS)) in a 2:1 ratio to the treatments as specified below:

- olaparib tablets p.o. 300 mg twice daily
- placebo tablets p.o. twice daily

In addition a separate China cohort will be randomised in the same way (see Section 3.6 for further details).

Eligible patients will be those patients with newly diagnosed, histologically confirmed, high risk advanced (FIGO stage III-IV) BRCA mutated high grade serous or high grade endometrioid (based on local histopathological findings) ovarian cancer, primary peritoneal cancer and / or fallopian-tube cancer who are in clinical complete response or partial response following completion of first line platinum-based chemotherapy. Patients who re-present following prior diagnosis at an earlier stage of disease are not eligible. Stage III patients should have had one attempt at optimal debulking surgery (upfront or interval debulking). Stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery.

Patients must have completed a minimum of six and maximum of nine treatment cycles of first line platinum-based therapy (e.g., carboplatin or cisplatin) before randomisation to the study and should be in the opinion of the investigator in clinical complete response or partial response. However, if platinum based therapy must be discontinued early as a result of toxicities specifically related to the platinum regimen, patients must have received a minimum of four cycles of the platinum regimen.

Patients must not have received bevacizumab (either in combination or as maintenance therapy following combination therapy) or any investigational agent during their first line course of treatment.

Patients known to have deleterious or suspected deleterious germline BRCA mutation/s (gBRCAm i.e., blood) prior to randomisation can enter the study based on this result. The result must be made available to AstraZeneca. In addition the patients must consent to provide 2 blood samples. One sample will be used for a confirmatory Myriad gBRCA test post randomisation using the current commercial Myriad *BRCAnalysis*<sup>®</sup> (gene sequencing and large rearrangement analysis),

Patients with unknown BRCA status must consent to provide 2 blood samples for germline BRCA testing and follow all local ethical procedures for genetic testing. One sample will be used to test for BRCA mutations using the current commercial Myriad *BRCAnalysis*<sup>®</sup> test prior to study entry.

These samples will be required for the study even if the patients are found not to have a BRCA mutation. When the result from the Myriad test indicates the

patient does have a deleterious or suspected deleterious BRCA mutation, the patient can be randomised into the study.

Patients will be randomised within 8 weeks after their last dose of chemotherapy (last dose is the day of the last infusion).

Randomisation will be stratified by:

- Response to first line platinum chemotherapy (in the opinion of the investigator, clinical complete response (CCR) or partial response (PR)).

Following randomisation patients in both treatment arms will attend clinic visits weekly for the first 4 weeks of treatment (Days 8, 15, 22 and 29). Patients will then attend clinic visits every 4 weeks whilst on study. Patients should continue to receive study treatment for up to two years or until objective radiological disease progression as per RECIST as assessed by the investigator and as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria (see Section 5.8 of the Clinical Study Protocol (CSP)). Patients who continue to have evidence of disease that remains stable (i.e. no evidence of disease progression) at two years or those who have progressed may continue to receive study treatment if, in the opinion of the investigator, it is in the patient's best interest. However, if at two years the patient has no evidence of disease, study treatment should be discontinued.

Once a patient has progressed and discontinued study treatment, clinic visits will be reduced to every 12 weeks. Following discontinuation of study treatment, further treatment will be at the discretion of the investigator. Any further systemic anti-cancer treatment data will be collected until death, loss to follow-up or withdrawal of consent. In addition to their regular 12 weekly contact, patients will be contacted in the 7 days following a specified date (data cut off date) for each survival analysis. Assessments will be performed as described in Tables 1, 2, 3 and 4 of the CSP. Patients in both treatment arms will have tumour assessments according to RECIST at baseline and every 12 weeks ( $\pm 1$  week) up to 156 weeks and then every 24 weeks ( $\pm 1$  week) relative to date of randomisation, until objective radiological disease progression according to RECIST. All Computed tomography (CT)/ Magnetic resonance imaging (MRI) scans will be sent to an AstraZeneca appointed Clinical Research Organisation (CRO) for blinded independent central review. All treatment decisions will be based on site assessment of scans. After the primary PFS analysis, central review of scans will no longer be required and investigators will be advised when to stop sending copies of the scans to the CRO conducting the central review. Ongoing collection of site review tumour assessment is required and must be recorded in the electronic case report form (eCRF).

RECIST will be modified to assess patients with CR at entry who will be assessed as having no evidence of disease (NED) unless they have progressed based on the appearance of new lesions.



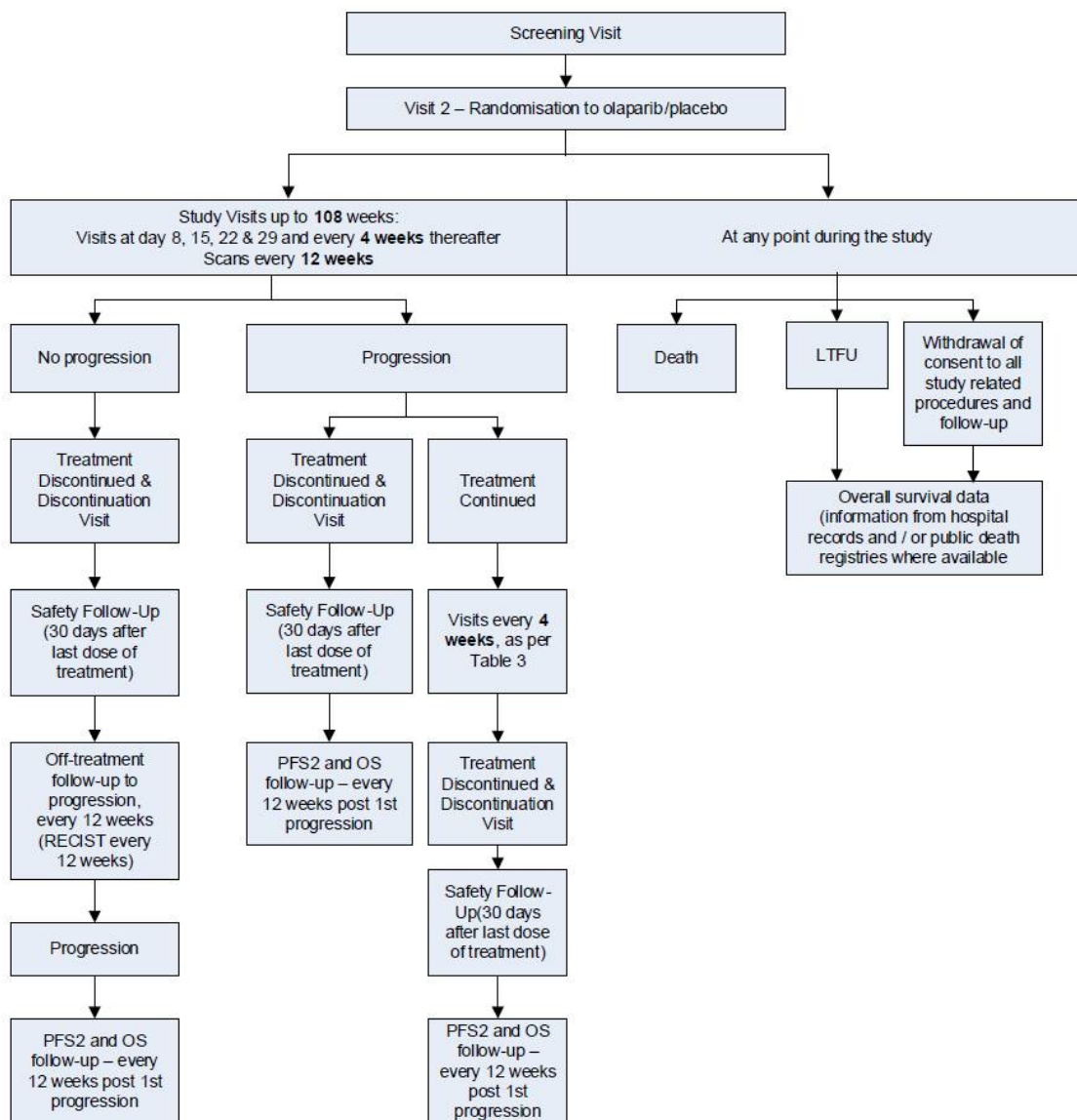
Any patient who discontinues study treatment for reasons other than objective radiological progression should continue to undergo scheduled objective tumour assessments according to the study plan (see Tables 3 and 4 of the CSP) in order to assess objective radiological progression of disease. Failure to do so may result in bias to the study results.

Once a patient has progressed, the patient will be followed for second progression (PFS2) every 12 weeks and then survival until the final analysis. Patients will be contacted in the week following last patient last visit (LPLV) for each analysis of survival.

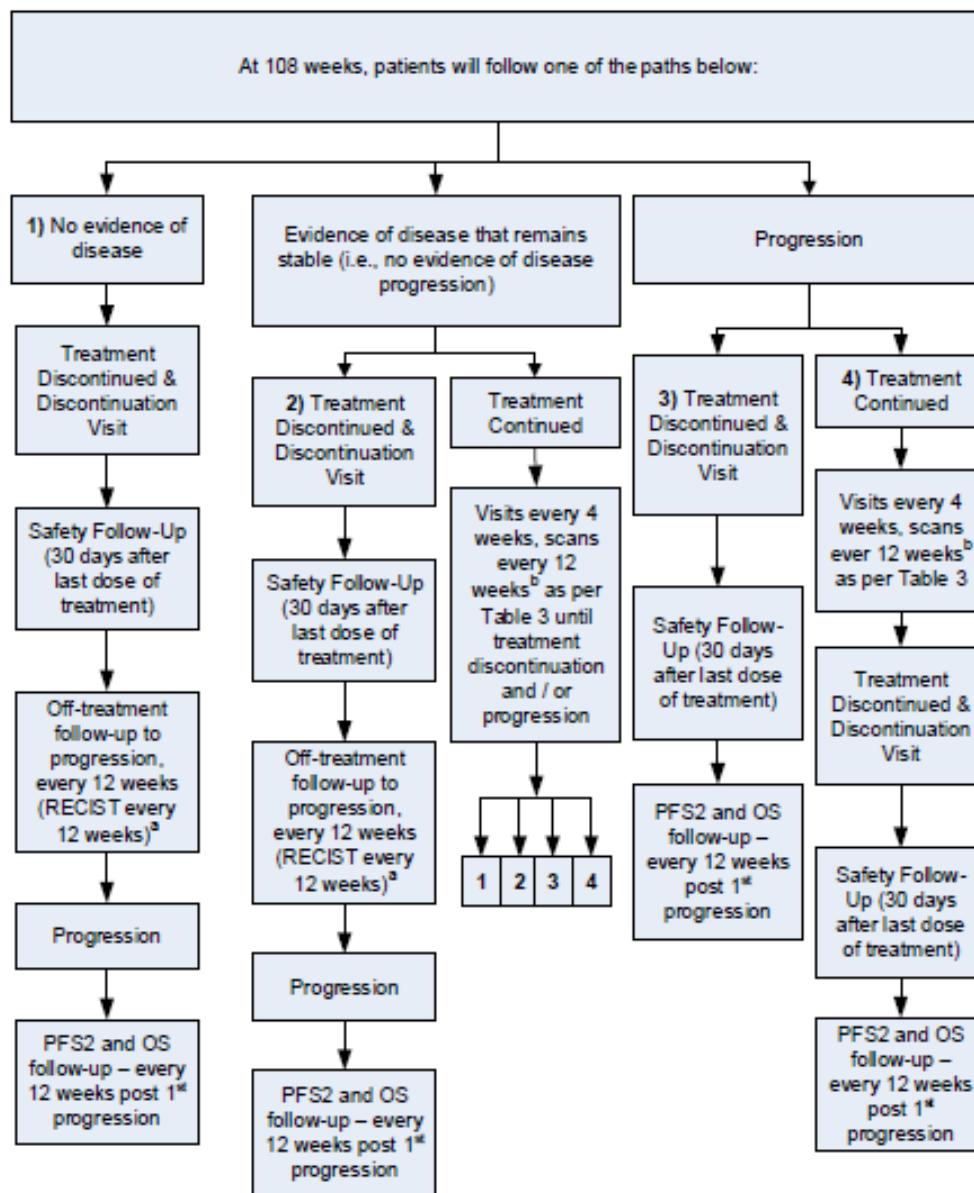
The primary analysis will be based on investigator assessment of disease progression by RECIST; however, a sensitivity analysis will be performed using blinded independent central review (BICR). All efficacy variables including overall survival will be analysed at the time of the primary analysis (providing sufficient events are available to make the analyses meaningful).

The overall study design is shown in Figure 1 of the CSP, the screening plan is shown in Figure 2 of the CSP and the study flow chart in Figure 1 and Figure 2 below. Screening schedules are detailed in Tables 1 and 2 of the CSP. The study schedule is detailed in Tables 3 and 4 of the CSP.

**Figure 1 Study Flow Chart Up to 108 Weeks on Treatment**



**Figure 2 Study Flow Chart At 108 Weeks on Treatment**



<sup>a</sup> Patients off treatment: Off-treatment follow-up visits and scans will continue to be conducted every 12 weeks ( $\pm 1$  week) up to 156 weeks (3 years), then every 24 weeks ( $\pm 1$  week) relative to date of randomization.

<sup>b</sup> Patients continuing treatment: Treatment visits will continue every 4 weeks ( $\pm 3$  days) up to 156 weeks (3 years), then every 12 weeks ( $\pm 1$  week) relative to date of randomization. Scans will continue every 12 weeks ( $\pm 1$  week) up to 156 weeks (3 years), then every 24 weeks ( $\pm 1$  week) relative to date of randomization.

### 1.3 Number of Subjects

In total 206 PFS events in the study would have 90% power to show statistically significant PFS at the 2-sided 5% level if the assumed true treatment effect were hazard ratio (HR) 0.62; this translates to a 8 month benefit in median PFS over 13 months on placebo (estimated from data reported by [Alsop et al 2012](#)) if PFS is exponentially distributed.

Approximately 344 patients will be recruited (2:1 ratio) so that data maturity for the PFS analysis is approximately 60%.

Assuming 18 months non-linear recruitment, 206 PFS events are expected to occur approximately 36 months after first subject in is enrolled in the study (FSI). At this time, an analysis of OS will also be performed.

PFS will be analysed when approximately 196 events have occurred or after the last patient randomised has had the opportunity to have been on the study for at least 36 months, whichever comes first. No further analyses of PFS are planned beyond this point unless requested by Health Authorities.

A further analysis of OS may be performed at approximately 60% maturity (~206 events); this is anticipated to occur approximately 80 months after FSI. Assuming that the true OS treatment effect is 0.85 and this point estimate for the HR of 0.85 was observed, the 95% UCL for the HR would be 1.13. Note that these estimates are based on the assumption that no confounding will occur. AstraZeneca considers there will be potential confounding of OS data due to availability of PARP inhibitors for BRCA mutated ovarian cancer patients during follow up in this study, which are likely to disproportionately affect OS in one arm of the study (placebo-treated patients).

## 2 ANALYSIS SETS

### 2.1 Definition of Analysis Sets

Two main analysis sets are defined for this study for the analysis of patients who have been included in the study as part of the global enrolment.

#### Full analysis sets

**Intention to treat (ITT):** The primary statistical analysis of the efficacy of olaparib will include all patients who are randomised as part of the global enrolment. The primary analysis will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised as part of the global enrolment but did not subsequently go on to receive study treatment are included in the Full Analysis Set (FAS). Therefore, all efficacy and HRQoL data will be summarised and analysed using the

FAS on an intention to treat (ITT) basis.

No centres will be provided with all of the treatment codes within that centre until completion of the study following the final analysis of overall survival.

### Safety analysis set

All patients who received at least one dose of randomised investigational product, olaparib or placebo and are part of the global enrolment will be included in the safety analysis set (regardless of whether that was the randomised therapy intended or indeed whether, in rare cases, they received therapy without being randomised). Throughout the safety results sections, erroneously treated olaparib patients (those randomised to olaparib but actually received placebo) will be accounted for in the placebo treatment group. Erroneously treated placebo patients (those randomised to placebo but actually received olaparib) will be accounted for in the olaparib treatment group. Patients receiving treatment from more than one treatment arm will be accounted for based upon their initial treatment started

**Table 1 Summary of Outcome Variables and Analysis Populations**

<b>Outcome Variable</b>	<b>Populations</b>
<b>Efficacy Data</b>	
- PFS	FAS (ITT)
- OS, PFS2, TFST, TSST, TDT, symptom/HRQoL endpoints	FAS (ITT)

**Table 1 Summary of Outcome Variables and Analysis Populations**

<b>Outcome Variable</b>	<b>Populations</b>
<b>Study Population/ Demography Data</b>	
- Demography characteristics (e.g. age, sex etc)	FAS (ITT)
- Baseline and disease characteristics	FAS (ITT)
- Important deviations	FAS (ITT)
- Medical/Surgical history	FAS (ITT)
- Previous anti-cancer therapy	FAS (ITT)
- Concomitant medications/procedures	FAS (ITT)
- Subsequent anti-cancer therapy	FAS (ITT)
<b>Safety Data</b>	
- Exposure	Safety
- Adverse Events	Safety
- Laboratory measurements	Safety
- ECGs	Safety
- Vital Signs	Safety

## 2.2 Violations and Deviations

The important protocol deviations will be listed and summarised by randomised treatment group. None of the deviations will lead to any patients being excluded from any of the analysis sets described in Section 2.1. If the deviations are serious enough to have the potential to impact the primary analysis, sensitivity analyses may be performed.

The following general categories will be considered important deviations and be listed and discussed in the CSR as appropriate.

- Patients randomised but who did not receive olaparib/matching placebo.
- Patients who deviate from key entry criteria, which will be documented ahead of database lock.
- Baseline RECIST scan > 28 days before study treatment is started
- Baseline RECIST scan after randomised treatment is started.
- Patients who have a RECIST scan outside of a scheduled visit window on > 2 occasions.

- Disallowed concomitant medication use.

Misrandomisations in terms of errors in treatment dispensing patients receiving treatment other than that to which they were randomised as well as incorrect stratifications, will also be summarised and listed. A misrandomisation is when a patient is not randomised or treated according to the randomisation schedule. It is envisaged that there will be 2 sub categories of this:

- (a) Patients who receive no treatment whatsoever for a period of time due to errors in dispensing of medication. Note, this is not due to tolerability issues where patients may stop taking drug.
- (b) The patient receives a treatment pack with a different code to their randomisation code. However, the actual treatment may still match the randomised treatment. For example, a patient is given randomisation code 0001, which according to the randomisation schedule is olaparib. However, at the randomisation visit they are given treatment pack 0003, but this still contains olaparib.

Patients who receive the wrong treatment at any time will be included in the safety analysis set as described in Section 2.1. During the study, decisions on how to handle misrandomisations will be made on an individual basis with written instruction from the study team leader and the study statistician.

In addition to the programmatic determination of the deviations above, monitoring notes or summaries will be reviewed to determine any important post entry deviations that are not identifiable via programming, and to check that those identified via programming are correctly classified. The final classification will be made prior to database lock and all decisions will be made whilst blinded to study treatment allocation.

### **3 PRIMARY AND SECONDARY VARIABLES**

#### **3.1 Derivation of RECIST Visit Responses**

Patients with measurable or non measurable disease or no evidence of disease assessed at baseline by CT/MRI will be entered in this study. RECIST 1.1 has been modified to allow the assessment of progression due to new lesions in patients with no evidence of disease at baseline.

For all patients, the RECIST tumour response data will be used to determine each patient's visit response according to modified RECIST version 1.1. It will also be used to determine if and when a patient has progressed in accordance with RECIST and also their best objective response (BoR).

Baseline radiological tumour assessments are to be performed no more than 28 days before randomisation and ideally should be performed as close as possible to the start of study treatment. Tumour assessments are then performed every 12 weeks ( $\pm 1$  week) up to 156 weeks and then every 24 weeks ( $\pm 1$  week) following randomisation until disease progression.

If an unscheduled assessment was performed and the patient had not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

At each visit, an overall visit response will be determined - using the information from target lesions (TL), non-target lesions (NTL) and new lesions. For the investigator assessments this will be done programmatically and the RECIST outcomes will be calculated using a computer program.

### **3.1.1 Target lesions (TLs)**

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is  $\geq 10$  mm in the longest diameter (LD) (except lymph nodes which must have short axis  $\geq 15$  mm) with CT or MRI and which is suitable for accurate repeated measurements.

A patient can have a maximum of 5 measurable lesions recorded at baseline with a maximum of 2 lesions per organ (representative of all lesions involved suitable for accurate repeated measurement) and these are referred to as target lesions (TLs). If more than one baseline scan is recorded then measurements from the one that is closest to randomisation will be used to define the baseline sum of TLs. It may be the case that, on occasion, the largest target lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits.

Note: For patients who do not have measurable disease at entry (i.e. no TLs) but have non-measurable disease, evaluation of overall visit responses will be based on the overall NTL assessment and the absence/presence of new lesions (see Section 3.1.3 for further details). If a patient does not have measurable disease at baseline then the TL visit response will be not applicable (NA).

For patients with no evidence of disease (NED) at baseline (i.e. no TLs and no NTLs), evaluation of overall visit responses will be based on absence/presence of new lesions. If no TLs and no NTLs are recorded at a visit, both the TL and NTL visit response will be recorded as NA and the overall visit response will be NED.



**Table 2 TL Visit Responses**

<b>Visit Responses</b>	<b>Description</b>
Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to <10 mm
Partial Response (PR)	At least a 30% decrease in the sum of diameters of TL, taking as reference the baseline sum of diameters
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also indicate an absolute increase of at least 5 mm
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response
Not Applicable (NA)	No target lesions are recorded at baseline

The percentage increase/decrease taking baseline as a reference for post-baseline visit will be calculated as:

$$[\text{Post-baseline sum of diameters of TL} - \text{Baseline sum of diameters of TL}] * 100 / (\text{Baseline sum of diameters of TL})$$

And similarly for the percentage change at a post-baseline visit using previous study minimum as a reference. If more than one baseline scan is recorded then measurements from the one that is closest to and prior to randomisation will be used to define the baseline sum of diameters of TLs.

**Rounding of TL data**

For calculation of PD and PR for TLs, percentage changes from baseline and previous minimum should be rounded to 1 decimal place. before assigning a TL response. For example 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%

### **Missing TL data**

For a visit to be evaluable, all target lesion measurements should be recorded. However, a visit response of PD should still be assigned if any of the following occurred:

- A new lesion is recorded.
- A NTL visit response of PD is recorded.
- The sum of TLs is sufficiently increased to result in a 20% increase, and an absolute increase of  $\geq 5$ mm, from nadir even assuming the non-recorded TLs have disappeared. Note: the nadir can only be taken from assessments where all the TLs had a LD recorded.

### **Lymph nodes**

For lymph nodes, if the size reduces to  $< 10$  mm then these are considered non-pathological. However a size will still be given and this size should still be used to determine the TL visit response as normal. In the special case where all lymph nodes are  $< 10$  mm and all other TLs are 0 mm then although the sum may be  $>0$  mm the calculation of TL response should be over-written as a CR.

### **TL visit responses subsequent to CR**

A CR can only be followed by CR, PD or NE. If a CR has occurred then the following rules at the subsequent visits must be applied:

- Step 1: If all TLs meet the CR criteria (i.e. 0 mm or  $< 10$  mm for lymph nodes) then response will be set to CR irrespective of whether the criteria for PD of TL is also met i.e. if a lymph node LD increases by 20% but remains  $< 10$  mm.
- Step 2: If some TL measurements are missing but all other lesions meet the CR criteria (i.e. 0 mm or  $< 10$  mm for lymph nodes) then response will be set to NE irrespective of whether when referencing the sum of TL diameters the criteria for PD is also met.
- Step 3: If not all TLs meet the CR criteria and the sum of lesions meets the criteria for PD then response will be set to PD
- Step 4: If after steps 1 – 3 a response can still not be determined the response will be set to remain as CR

### **TL too big to measure**

If a TL becomes too big to measure this should be indicated in the database and a size ('x') above which it cannot be accurately measured should be recorded. If using a value of x in the calculation of TL response would not give an overall visit response of PD, then this will be

flagged and reviewed by the study team blinded to treatment assignment. It is expected that a visit response of PD will remain in the vast majority of cases.

### **TL too small to measure**

If a TL becomes too small to measure a value of 5 mm will be entered into the database and used in TL calculations, unless the radiologist has indicated and entered a smaller value that can be reliably measured. If a TL response of PD results then this will be reviewed by the study team blinded to treatment assignment.

### **Irradiated lesions/lesion intervention**

Previously irradiated lesions (i.e. lesion irradiated prior to entry into the study) should be recorded as NTLs and should not form part of the TL assessment.

Any TL (including lymph nodes), which has had intervention during the study (for example, irradiation / palliative surgery / embolisation), should be handled in the following way and once a lesion has had intervention then it should be treated as having intervention for the remainder of the study noting that an intervention will most likely shrink the size of tumours:

- Step 1: the diameters of the TLs (including the lesions that have had intervention) will be summed and the calculation will be performed in the usual manner. If the visit response is PD this will remain as a valid response category.
- Step 2: If there was no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and scale up as described below as long as there remain  $\leq 1/3$  of the TLs with missing measurements. If the scaling results in a visit response of PD then the patient would be assigned a TL response of PD.
- Step 3: If after both steps PD has not been assigned, then if appropriate, a scaled sum of diameters will be calculated (as long as  $\leq 1/3$  of the TLs have interventions, and PR or SD then assigned as the visit response. Patients with intervention are evaluable for CR as long as all non-intervened lesions are 0 (or  $<10$ mm for lymph nodes) and each lesion that has experienced intervention also has a value of 0 recorded. If scaling-up is not appropriate due to too few non-missing measurements then the visit response will be set as NE.

If  $\leq 1/3$  of the TL measurements have interventions then the results will be scaled up based on the measurements at the nadir visit to give an estimated sum of diameters and this will be used in calculations; this is equivalent to comparing the visit sum of diameters of the non-intervention lesions to the nadir sum of diameters excluding the lesions with interventions.

### Example of scaling

Lesion	Longest diameter at nadir visit	Longest diameter at follow-up visit
1	7.2	7.1
2	6.7	6.4
3	4.3	4.0
4	8.6	8.5
5	2.5	Intervention
<b>Sum</b>	<b>29.3</b>	<b>26</b>

Lesion 5 has had an intervention at the follow-up visit.

The sum of lesions 1-4 at the follow-up is 26 cm. The sum of the corresponding lesions at baseline visit is 26.8 cm.

Scale up as follows to give an estimated TL sum of 28.4cm:

$$\frac{26}{26.8} \times 29.3 = 28.4cm$$

At subsequent visits the above steps will be repeated to determine the TL and overall visit response. When calculating the previous minimum, lesions with intervention should be treated as missing and scaled up where appropriate (as per step 2 above).

### Lesions that split in two

If a TL splits in two, then the LDs of the split lesions should be summed and reported as the LD for the lesion that split.

### Lesions that merge

If two TLs merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL size should be recorded as 0 mm.

### Change in method of assessment of TLs

CT and MRI are the only methods of assessment that can be used within the trial. If a change in method of assessment occurs between CT and MRI, this will be considered acceptable and no adjustment within the programming is needed.

If a change in method involves clinical examination (e.g. CT changes to clinical examination or vice versa), any affected lesions should be treated as missing.

### 3.1.2 Non-target lesions (NTLs) and new lesions.

At each visit an overall assessment of the NTL response should be recorded by the investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

NTL response will be derived based on the investigator’s overall assessment of NTLs as follows:

**Table 3 NTL Visit Responses**

<b>Visit Responses</b>	<b>Description</b>
Complete Response (CR)	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10 mm short axis).
Progression (PD)	Unequivocal progression of existing non-target lesions. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression <b>MUST</b> be clinically significant for the physician to consider changing (or stopping) therapy.
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression.
Not Evaluable (NE)	Only relevant when one or some of the non-target lesions were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit.  Note: For patients without target lesions at baseline, this is relevant if any of the non-target lesions were not assessed at this visit and the progression criteria have not been met.
Not Applicable (NA)	Only relevant if there are no NTLs at baseline

To achieve ‘unequivocal progression’ on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in TLs, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest ‘increase’ in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

New lesions will be identified via a Yes/No tick box. The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

A new lesion indicates progression so the overall visit response will be PD irrespective of the TL and NTL response.

If the question ‘Any new lesions since baseline’ has not been answered with Yes or No and the new lesion details are blank this is not evidence that no new lesions are present and should be treated as NE in the derivation of overall visit response.

Symptomatic deterioration is not a descriptor for progression of NTLs: it is a reason for stopping study therapy and will not be included in any assessment of NTLs.

Patients with ‘symptomatic deterioration’ requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

### 3.1.3 Overall visit response

Table 4 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

**Table 4 Overall Visit Responses**

Target Lesions	Non-target lesions	New Lesions	Overall Response
CR	CR or NA	No (or NE)	CR
NA	CR	No (or NE)	CR
CR	Non CR/Non PD (or NE)	No (or NE)	PR
PR	CR, Non CR/Non PD or NE, NA	No (or NE)	PR
SD	CR, Non CR/Non PD or NE, NA	No (or NE)	SD
NA	Non CR/Non PD	No (or NE)	SD

**Table 4 Overall Visit Responses**

Target Lesions	Non-target lesions	New Lesions	Overall Response
NE	CR, Non CR/Non PD or NE, NA	No (or NE)	NE
NA	NE	No (or NE)	NE
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD
NA	NA	No	NED

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NED = no evidence of disease, NA = not applicable (only relevant if there were no TL/NTL at baseline).

### 3.1.4 Independent review

The independent review charter contains the details of the independent central review conducted by the AstraZeneca-appointed central Core Imaging Laboratory and will be developed in advance of the start of the study. The independent data review will provide RECIST measurements for each visit for each patient at the time of primary data cut-off (DCO). After the primary PFS analysis, central review of scans will no longer be required.

For each patient, the independent reviewer will provide time point response data and the relevant scan dates for each time point (i.e. for visits where progression is/is not identified) with supporting measurements and assessments.

## 3.2 Outcome Variables

At each visit patients will be assigned a RECIST visit response of CR, PR, SD, PD, NED (applies only to those patients entering the study with no evidence of disease at baseline), NE depending on the status of their disease compared to baseline and previous assessments, using programmatically derived overall visit response from Investigator RECIST assessments. This will be repeated using the time point responses and relevant dates from the BICR.

Where applicable, outcome variables will be programmatically derived using data from Investigator RECIST assessments unless otherwise stated.

### 3.2.1 Progression free survival (PFS)

PFS is defined as the time from randomisation until the date of objective radiological disease progression according to RECIST or death (by any cause in the absence of progression) regardless of whether the patient discontinues randomised therapy or receives another anti-cancer therapy prior to progression (i.e. date of RECIST progression/death or censoring – date of randomisation + 1). Patients who have not progressed or died at the time of analysis, or who progress or die after two or more missed visits, are censored at the time of the latest evaluable visits or does not have a baseline assessment they will be censored at day 1 unless they die within two visits of baseline (25 weeks allowing for visit window).

Given the scheduled visit assessment scheme and the change in scanning frequency after 156 weeks then the following rules will be used to define two missed visits:

- If the latest evaluable assessment was on or prior to Week 133/Day 931 (Week 132 + one week) then two missed visits will equate to more than 26 weeks ( $12 \times 2 + 2$ )
- If the latest evaluable assessment was post Week 133/ Day 931 and prior to Week 155/Day 1085 (Week 156 - one week) then two missed visits will equate to more than 38 weeks ( $12 + 24 + 2$ )
- If the latest evaluable assessment was on or post Week 155/Day 1085 (Week 156 - one week) then two missed visits will equate to more than 50 weeks ( $24 \times 2 + 2$ )

The PFS time will always be derived based on scan/assessment dates not visit dates.

RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- (a) For BICR assessment, date of progression will be determined based on the earliest of the scan dates of the component that triggered the progression for the adjudicated reviewer selecting PD or for either reviewer where both select PD as time point response and there is no adjudication.
- (b) For investigational site assessments, date of progression will be determined based on the earliest of the RECIST assessment/scan dates of the component that triggered the progression.
- (c) When censoring a patient for PFS the patient will be censored at the latest of the RECIST assessment/scan dates contributing to the last evaluable overall visit assessment.

Overall visit assessments will be determined for each assessment (scheduled or unscheduled) and will contribute to the derivation of PFS.



Objective progression is defined as at least a 20% increase in the sum of the diameters of the target lesions (compared to previous minimum sum) and an absolute increase of > 5 mm, or an overall non-target lesion assessment of progression or a new lesion. For patients with no evidence of disease at baseline, following a complete radiological response to chemotherapy, progression is defined by the detection of new lesions on follow-up radiological assessments.

The primary analysis will be based on investigator-recorded assessment of the radiological scans.

A sensitivity analysis based on the BICR review of the radiological scans will be carried out.

The baseline RECIST assessment should be performed prior to randomisation but if an evaluable RECIST assessment occurs after randomisation but before treatment (and there is no available RECIST assessment before randomisation), then this assessment will be used as the baseline assessment. If a patient does not have a baseline RECIST scan performed prior to the date of first dose of study treatment (olaparib/placebo) then the patients will be censored at Day 1 in the analysis.

### **3.2.2 Time from randomisation to second progression or death (PFS2)**

Time from randomisation to second progression or death is defined as the time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS or death. The date of second progression will be recorded by the Investigator and defined according to local standard clinical practice and may involve any of; objective radiological, CA-125 or symptomatic progression or death. Second progression status will be reviewed every 12 weeks following the progression event used for the primary variable PFS (the first progression) and status recorded. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression, i.e. censored at the latest of the PFS or PFS2 assessment date if the patient has not had a second progression or death. If, however the patient progresses for the second time or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable investigator - recorded assessment (see Section 3.2.1 for details).

### **3.2.3 Overall survival (OS)**

Overall survival (OS) is defined as the time from the date of randomisation until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive (SUR\_DAT, recorded within the SURVIVE module of the eCRF).

Note: Survival calls will be made in the week following the date of DCO for the analysis, and if patients are confirmed to be alive or if the death date is post - DCO date these patients will be censored at the date of DCO. Death dates may be found by checking publicly available death registries.

### **3.2.4 Time to first subsequent therapy or death (TFST)**

Time to start of first subsequent therapy or death (TFST) will be assessed. TFST is defined as the time from randomisation to the earlier of first subsequent therapy start date following study treatment discontinuation, or death. Subsequent therapies will be reviewed to assess which represent clinically important treatments intended to control ovarian cancer. Any patient not known to have died at the time of the analysis and not known to have had a further intervention of this type will be censored at the last known time to have not received subsequent therapy, i.e. the last follow-up visit where this was confirmed.

### **3.2.5 Time to second subsequent therapy or death (TSST)**

Time to start of second subsequent therapy or death (TSST) will be assessed. TSST is defined as the time from randomisation to the earlier of the second subsequent therapy start date following study treatment discontinuation, or death. Any patient not known to have died at the time of the analysis and not known to have had a further intervention of this type will be censored at the last known time to have not received second subsequent therapy, i.e. the last follow-up visit where this was confirmed.

### **3.2.6 Time to study treatment discontinuation or death (TDT)**

Time to permanent study treatment discontinuation or death (TDT) will be assessed. TDT is defined as the time from randomisation to the earlier of the date of permanent study treatment discontinuation or death. Any patient not known to have died at the time of analysis and not known to have discontinued study treatment will be censored based on the last recorded date on which the patient was known to be alive.

Note: Survival calls will be made in the week following the date of DCO for the analysis, and if patients are confirmed to be alive or if the death date is post the DCO date these patients will be censored at the date of DCO.

### **3.2.7 Time to earliest progression by RECIST or CA-125 or death**

Progression or recurrence based on serum CA-125 levels will be defined on the basis of a progressive serial elevation of serum CA-125, according to the following modified Gynecologic Cancer Intergroup (GCIIG) criteria (note GCIIG criteria is not validated for this trial population):

- For patients with elevated CA-125 on or before the date of randomisation (i.e. greater than the upper limit of normal (ULN)):
  - (a) If CA-125 does not fall to within the normal range post-randomisation then there must be evidence of CA-125 greater than, or equal to, 2 times the nadir value in the 28 day period before day 1 on 2 occasions at least 1 week apart

- (b) Where CA-125 does fall to within the normal range post-randomisation then there must be evidence of CA-125 greater than, or equal to, 2 times the ULN on 2 occasions at least 1 week apart
- Patients with CA-125 in the normal range on or before the date of randomisation and no results greater than ULN on or before the date of randomisation must show evidence of CA-125 greater than, or equal to, 2 times the ULN on 2 occasions post-randomisation at least 1 week apart.
  - CA-125 progression will be assigned the date of the first measurement that meets the above criteria.

Time to progression by RECIST or CA-125 progression or death is defined as the time from randomisation to the earlier date of RECIST or CA-125 progression or death by any cause.

Patients without a CA-125 progression or a RECIST progression who are still alive at the time of analysis will be censored at the time of their last evaluable RECIST assessment or their last available CA-125 measurement, whichever is the earliest at the time of the analysis. Since CA-125 is assessed more frequently than RECIST the two missed visit rule is based upon the RECIST schedule. Therefore if a patient dies, has RECIST progression or has CA-125 progression after two or more missed RECIST assessments, then the patient will be censored using at the last evaluable RECIST assessment where CA-125 was also collected. This will be defined as a RECIST assessment where the date of CA-125 sample is +/- 11 days (note the earliest date of the RECIST/CA-125 assessment will be used).

If only one assessment is missing during this period, no censoring is required. Patients that do not have any evaluable RECIST assessments or any CA-125 results post-randomisation will be censored at the date of randomisation.

Similarly to the primary analysis of PFS, RECIST progression will be determined from the investigator assessment of RECIST data.

### **3.2.8 Best overall RECIST response (BoR)**

Best overall response (BoR) is calculated based on the overall visit responses from each RECIST assessment (Table 4). It is the best response a patient has had following randomisation but prior to starting any subsequent cancer therapy and prior to RECIST progression or the last evaluable assessment in the absence of RECIST progression.

Categorisation of BoR will be based on the RECIST criteria using the following response categories: complete response (CR), partial response (PR), stable disease (SD), No Evidence of Disease (NED; applies only to those patients entering the study with no disease at baseline), progressive disease (PD) and not evaluable (NE).

Best overall response will be programmatically derived from the investigator data.

For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment will be used. SD should be recorded at least 12 weeks +/- 1 week, i.e. at least 77 days (to allow for the assessment window), after randomisation. For CR/PR, the initial overall visit assessment which showed a response will use the latest of the dates contributing towards a particular overall visit assessment.

For patients whose progression event is death, BoR will be calculated based on data up until the last evaluable RECIST assessment prior to death.

For patients who die with no evaluable RECIST assessments, if the death occurred  $\leq 25$  weeks (i.e. 24 weeks  $\pm 1$  week) after randomisation then BoR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST assessments, if the death occurred  $>25$  weeks (i.e. 24 weeks  $\pm 1$  week) after randomisation then BoR will be assigned to the non-evaluable (NE) category.

Progression events that have been censored due to them being more than two missed visits after the last evaluable assessment will not contribute to the BoR derivation.

A patient will be classified as a responder if the RECIST criteria for a CR or PR are satisfied at any time prior to RECIST progression or the last evaluable assessment in the absence of RECIST progression, up to the earliest of the defined analysis cut-off point or the start of subsequent therapy. For each treatment group, the objective response rate (ORR) is the number of patients with a CR or PR post-baseline divided by the number of patients in the group in the FAS with measurable disease at baseline. Only patients with measurable disease at enrolment can achieve an objective response of CR or PR.

Duration of response will be defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR. If a subject does not progress following a response, then their duration of response will use the PFS censoring time.

Time to onset of objective response is defined as the time from the date of randomisation until the date of first documented response. The date of first documented response should coincide with that used for the RECIST 1.1 BoR endpoint. Time to response will not be defined for those patients who do not have documented response.

The disease control rate (DCR) is defined as the percentage of patients who have at least one confirmed visit response of CR or PR or have demonstrated SD or NED for at least 23 weeks (i.e. 24 weeks  $\pm 1$  week) prior to any evidence of progression. In the case of SD and NED, follow up assessments must have met the SD or NED criteria for a minimum interval of 23 weeks following randomisation.

### 3.3 Patient Reported Outcome (PRO) Variables

#### 3.3.1 FACT-O

Patient reported health-related quality of life (HRQoL) will be assessed using the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) questionnaire ([Basen-Enquist K et al 2001](#)). The FACT-O is composed of the following sub-scales: physical, social/family, emotional, and functional well-being as well as the additional concerns scales consisting of specific ovarian cancer symptoms.

The endpoint for HRQoL analysis will be the Trial Outcome Index (TOI), ([Cella D et al 1993](#)) an established single targeted index derived from the FACT-O questionnaire and it is considered to target the most relevant symptoms together with function and physical well-being and can be directly related to signs and symptoms and AEs. The TOI is composed of the following scales of the FACT-O: physical and functional well-being and additional concerns (ovarian cancer subscale).

Data relating to the FACT-O will be self-reported through patient questionnaires according to the study plan. Patients will be asked to report their HRQoL over the course of the previous 7 days. All patients will be asked to complete the FACT-O. The FACT-O questionnaire will be administered at baseline, at Day 29, then in line with the RECIST assessments every 12 weeks (+/- 7 days) for 156 weeks, then every 24 weeks (+/- 7 days) up to the data cut off for the primary analysis. In addition, HRQoL questionnaires will be collected at the discontinuation of study treatment visit and 30 days post last dose. Patients who had RECIST 1.1 disease progression will complete the questionnaires during the 12 weekly survival follow-up visits either in person or over the phone.

The Trial Outcome Index (TOI) score will be derived from the sum of the scores of three of the derived subscale scores; physical well-being (7 items), functional well-being (7 items), and ovarian cancer subscale (11 items) of the FACT-O questionnaire version 4. The total FACT-O score will also be calculated which is made up of the sum of the individual subscale scores: physical well being (PWB), social well being (SWB), emotional well being (EWB), functional well being (FWB) and ovarian cancer subscale (Additional Concerns) (11 items).

The scores will be derived in accordance with the [FACT-O Scoring Manual](#). A number of items are negatively stated and need to be reversed by subtracting the response from “4”. The scoring manual identifies that the following items need to be reversed prior to summarising: GP1-7, GE1, GE3-6, O1-3, C2, and B5. After reversing proper items, scores are summarised and multiplied by the number of items in the domain. For each subscale (domain), if less than 50% of the subscale items are missing, the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscale. If at least 50% of the items are missing, that subscale also will be treated as missing. The reason for any missing assessment will be identified. If data are missing at random, the above techniques will be used. If there is evidence that the missing data are systematic, missing values will be

handled to ensure that any possible bias is minimised. The TOI score ranges from 0-100 and the FACT-O from 0-152. For all Functional Assessment of Chronic Illness Therapy (FACIT) scales and symptom indices, a higher score indicates a higher HRQoL.

The actual change from baseline in TOI score will be derived for each visit where there is available data. For example; at visit X, the calculation will be (TOI score at visit X – baseline TOI score). Actual change from baseline for the individual FACT-O subscale scores will be calculated in a similar way. The baseline score is defined as last non-missing score prior to dosing with study treatment (olaparib or placebo). Any questionnaires completed on day 1 of dosing will be considered pre-dose.

A change of at least 10 points in TOI will be considered as a clinically relevant or a minimally important difference (Osobo et al 2005).

The threshold for a clinically important change is outlined below (Table 5):

**Table 5 Health-Related Quality of Life**

Score	Change from baseline	Visit response
TOI	$\geq +10$	Improved
	$\leq -10$ or “Subject too heavily affected by symptoms of disease under investigation” is answered as the reason for not completing HRQoL at visit.	Worsened
	Otherwise	No change

Best overall TOI improvement (in absence of starting any subsequent cancer therapy) will be defined as a change from baseline in the TOI of + 10 points or more (Osoba et al 2005) sustained for at least 28 days, the denominator consisting of a subset of the FAS population who have baseline TOI. It will be derived as the best symptom improvement response the patient achieved, based on evaluable HRQoL data collected from randomisation up to the earliest of starting any subsequent cancer therapy or death. Therefore, at the conclusion of the trial, the following criteria, will be used to assign a best overall score response based on the individual visit responses (Table 6).

**Table 6 Health-Related Quality of Life : Change rates - overall score**

Best overall TOI score response	Criteria
---------------------------------	----------

**Table 6 Health-Related Quality of Life : Change rates - overall score**

Best overall TOI score response	Criteria
Improved	Two visit responses of “improved” a minimum of 28 days apart without an intervening visit response of “worsened”
No change	Does not qualify for overall score response of “improved”. Two visit responses of either “no change” or “improved and “no change” a minimum of 28 days apart without an intervening visit response of “worsened”
Worsened	Does not qualify for overall score response of “improved” A visit response of “worsened” without a subsequent response of “improved” or “no change” within 28 days.
Other	Does not qualify for one of the above.

In the calculation of the proportion of patients that have a response of Improved, No Change or Worsened, the denominator used in the calculation will use the number evaluable patients with a TOI score at baseline.

Summary measures of overall compliance and compliance over time will be derived for the FACT-O questionnaire. These will be based upon:

- Received forms = number of FACT-O forms received back plus the number not received back where the reason was ‘Subject too heavily affected by symptoms of disease under investigation’.
- Expected forms = number of patients still under HRQoL follow-up at the specified assessment time excluding patients in countries with no available translation. For patients that have progressed, the latest of progression and safety follow-up will be used to assess whether the patient is still under HRQoL follow-up at the specified assessment time. Date of study discontinuation will be mapped to the nearest visit date to define the number of expected forms.
- Evaluable forms = subset of expected FACT-O forms with at least one subscale that can be determined; or where REVPRDI form is ticked ‘Subject too heavily affected by symptoms of disease under investigation’.

Thus the overall compliance rate is defined as the number of patients with an evaluable baseline and at least one evaluable follow-up form (as defined above), divided by the number of patients expected to have completed at least a baseline FACT-O form.

Compliance over time will be calculated separately for each visit, including baseline, as the number of patients with an evaluable baseline form and a form at the time point (as defined above), divided by number of patients still expected to complete forms at that visit. Similarly the evaluability rate over time will be calculated separately for each visit, including baseline, as the number of evaluable forms (per definition above), divided by the number of received forms.

### **3.3.2 EQ-5D-5L (exploratory analysis)**

The EQ-5D-5L, developed by the EuroQol Group, is a generic questionnaire that provides a simple descriptive profile and a single index value for health status for economic appraisal. The questionnaire comprises six questions that cover five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and how the patient feels. For each dimension, patients select which statement best describes their health on that day from a possible five options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems and unable to/ extreme problems). A visual analogue scale (VAS) which ranges from 0 (worst imaginable health) to 100 (best imaginable health) is used to assess how the patient feels.

The EQ-5D-5L index comprises six questions that cover five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a VAS. A unique health state, the EQ-5D-5L profile, based on the five dimensions is reported as a five-digit code with a possible total of 3,125 health state. For example, state 11111 indicates no problems on any of the five dimensions. This EQ-5D-5L profile will be converted into a weighted health state utility value, termed the EQ-5D index, by applying a country-specific equation to the profile that represents the comparative value of health states. This equation is based on national valuation sets elicited from the general population and the base case will be the UK perspective. Where a valuation set has not been published, the EQ-5D-5L profile will be converted to the EQ-5D index using a crosswalk algorithm (van Hout et al 2012). The visual analogue scale, the EQ-VAS, is reported separately.

The evaluable population will comprise the FAS population.



to be 54 days between Day 29 and Day 85). If an odd number of days exist between two

### **3.4 Safety**

Safety and tolerability will be assessed in terms of AEs (including SAEs), deaths, laboratory data, vital signs, ECG and exposure. These will be collected for all patients.

#### **3.4.1 Adverse events**

AEs and SAEs will be collected throughout the study, from informed consent until 30 days after the last dose of olaparib/placebo.

#### **Other significant adverse events (OAE)**

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and 'Discontinuation of Investigational Product due to Adverse Events' (DAEs). Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

### 3.4.2 Treatment exposure

Exposure will be defined as follows:

Total (or intended) exposure of olaparib/placebo

- Total (or intended) exposure = last dose date – first dose date + 1

Actual exposure of olaparib/placebo

- Actual exposure = intended exposure – total duration of dose interruptions, where intended exposure will be calculated as above.

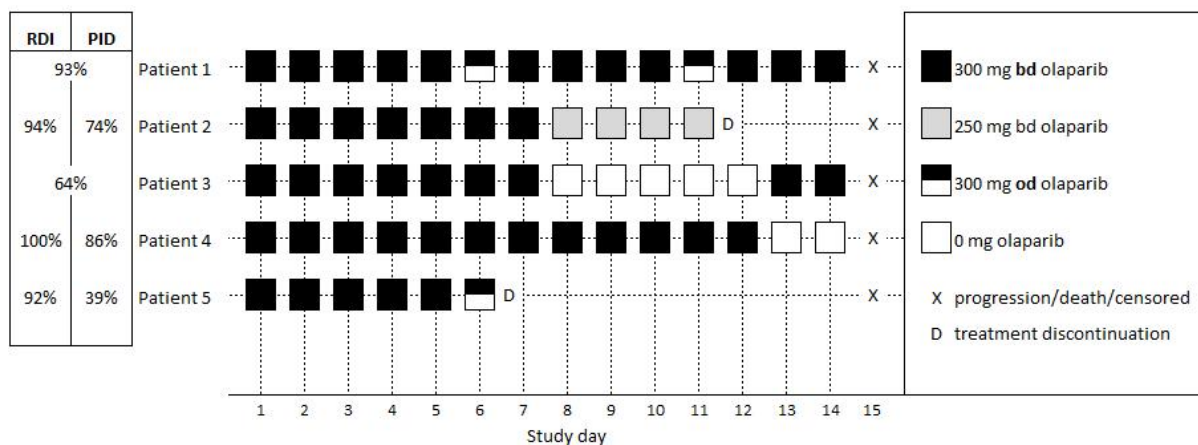
### 3.4.3 Dose intensity

Relative dose intensity (RDI) is the percentage of the actual dose intensity delivered relative to the intended dose intensity through to treatment discontinuation. Percentage intended dose (PID) is the percentage of the actual dose delivered relative to the intended dose through to progression. Both will be derived using study treatment data up to three years or until the date of objective disease progression (whichever is earliest) as defined by RECIST using the investigator site assessments. If the investigator considered that it was in the patient's best interest to continue study treatment past this time, this was not included in the derivation of dose intensity.

Relative dose intensity (RDI) and percent intended dose (PID) will be defined as follows:

- $RDI = 100\% * d/D$ , where d is the actual cumulative dose delivered up to the earlier of progression (or a censoring event) or the actual last day of dosing and D is the intended cumulative dose up to the earlier of progression (or a censoring event) or the actual last day of dosing plus the protocol-defined post-dose rest period.
- $PID = 100\% * d/D$ , where d is the actual cumulative dose delivered up to progression (or a censoring event) and D is the intended cumulative dose up to progression (or a censoring event). D is the total dose that would be delivered, if there were no modification to dose or schedule.

**Figure 3 Example of Dose Intensity Calculations for Olaparib**



In this example, patients 1-4 progressed or were censored on Day 15. All four patients received less treatment than intended due to:

- Missed/forgotten doses (Patient 1)
- Dose reduction and early stopping (Patient 2)
- Dose interruption (Patient 3)
- Progression whilst on dose interruption (Patient 4)
- Early stopping (Patient 5)

**Patient 1:**  $RDI = PID = ((12 * 300 \text{ mg} * 2) + (2 * 300 \text{ mg})) / (14 * 300 \text{ mg} * 2) = 93\%$

**Patient 2:**  $RDI = ((7 * 300 \text{ mg} * 2) + (4 * 250 \text{ mg} * 2)) / (11 * 300 \text{ mg} * 2) = 94\%$   
 $PID = ((7 * 300 \text{ mg} * 2) + (4 * 250 \text{ mg} * 2)) / (14 * 300 \text{ mg} * 2) = 74\%$

**Patient 3:**  $RDI = PID = (9 * 300 \text{ mg} * 2) / (14 * 300 \text{ mg} * 2) = 64\%$

**Patient 4:**  $RDI = (12 * 300 \text{ mg} * 2) / (12 * 300 \text{ mg} * 2) = 100\%$   
 $PID = (12 * 300 \text{ mg} * 2) / (14 * 300 \text{ mg} * 2) = 86\%$

**Patient 5:**  $RDI = ((5 * 300 \text{ mg} * 2) + (1 * 300 \text{ mg})) / (6 * 300 \text{ mg} * 2) = 92\%$   
 $PID = ((5 * 300 \text{ mg} * 2) + (1 * 300 \text{ mg})) / (14 * 300 \text{ mg} * 2) = 39\%$

### **3.4.4 Laboratory data**

Laboratory data will be collected throughout the study, from screening to follow-up visit as described in Table 1, 2 and 3 of the CSP. Blood and urine samples for determination of haematology, clinical chemistry, and urinalysis will be collected as described in Section 3.1.9 of the CSP. For derivation of post baseline visit values considering visit window and how to handle multiple records, derivation rules as described in Section 3.4.7 below will be used.

### **3.4.5 ECGs**

ECG data obtained up until the 30 days from date of last dose of olaparib/placebo treatment will be used for reporting. At screening, overall evaluation of ECG, QTcF (QT interval corrected for heart rate using Fridericia's correction) and QTcB (QT interval corrected for heart rate using Bazett's correction) will be collected. For all post-baseline visits overall evaluation of ECG will be collected.

### **3.4.6 Vital signs**

Vital signs data obtained up until the 30 days from date of last dose of olaparib/placebo treatment will be used for reporting. For derivation of post baseline visit values considering visit window and to handle multiple records, derivation rules as described in Section 3.4.7 below will be used.

### **3.4.7 General consideration for safety assessments**

Time windows will need defining for any presentations that summarise values of laboratory and vital signs data by visit. The following conventions should also apply:

- The time windows should be exhaustive so that data recorded at any time point has the potential to be summarised. Inclusion within the time window should be based on the actual date and not the intended date of the visit.
- All unscheduled visit data should have the potential to be included in the summaries.
- The window for the visits following baseline up to and including 30 days after the last dose of study drug will be constructed in such a way that the upper limit of the interval falls half way between the two visits. The lower limit of the first post-baseline visit will be Day 2. The halfway point is assumed to be the midpoint of the number of days between the visits, excluding both visit days (for example there are assumed to be 27 days between day 29 and day 57). If an odd number of days exist between two consecutive visits then the upper limit will be taken as the midpoint value plus 0.5 days.

For example, the visit windows for vital signs data are:

- Day 29, visit window 2 – 43
- Day 57, visit window 44 – 71
- Day 85, visit window 72 – 99
- Day 113, visit window 100 – 127

In addition an End of Treatment visit will be identified as the visit occurring between 1 and 8 days (inclusive) after the end of treatment. And similarly a 30 day follow up visit will be identified as the visit between 9 and 31 days (inclusive) following end of treatment. These additional points will allow summaries to be presented for these visits separately as well as the inclusion of this data in mapped on-treatment visit summaries.

- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval).
- Listings should display all values contributing to a time point for a patient.
- For visit based summaries:
  - If there is more than one value per patient within a time window then the closest value should be summarised, or the earlier in the event the values are equidistant from the nominal visit date. The listings should highlight the value for that patient that went into the summary table, wherever feasible.
  - To prevent very large tables or plots being produced that contain many cells with meaningless data, for each treatment group visit data should only be summarised if the number of observations is greater than the minimum of 20 or  $> 1/3$  of patients dosed.
- For summaries at a patient level, all values should be included, regardless of whether they appear in a corresponding visit based summary, when deriving a patient level statistic such as a maximum.
- Baseline will be defined as the last non-missing measurement prior to dosing with study treatment (olaparib or placebo). For laboratory data and vital signs data, any assessments made on day 1 will be considered pre-dose. Where safety data are summarised over time, study day will be calculated in relation to date of first treatment (olaparib or placebo)

Missing safety data will generally not be imputed. However, safety assessment values of the form of “ $< x$ ” (i.e., below the lower limit of quantification) or “ $> x$ ” (i.e., above the upper limit of quantification) will be imputed as “ $x$ ” in the calculation of summary statistics but displayed as “ $< x$ ” or “ $> x$ ” in the listings.

### **3.5 Health Care Resource Use**

The assessments to be carried out at each visit are detailed in the study schedule and include the HOSPAD module.

The assessment of health care resource use will increase the understanding regarding the relationship between treatment and tumour related cancer symptoms on resource use, such as the need for palliative procedures to address obstruction and bleeding. This will be captured and analysed to inform submissions to payers.

#### **Calculation or derivation of health care resource use**

To investigate the impact of treatment and disease on health care resource use the following variables will be captured:

- Planned and unplanned hospital attendances beyond trial protocol mandated visits (including physician visits, emergency room visits, day cases and admissions)
- Primary sign or symptom the patient presents with
- Length of hospital stay
- Length of any time spent in an intensive care unit (ICU)

Where admitted overnight, the length of hospital stay will be calculated as the difference between the date of hospital discharge (or death date) and the start date of hospitalisation or start of study drug if the start of study drug is after start date of hospitalisation (length of hospital stay = end date of hospitalisation – start date of hospitalisation + 1). Patients with missing discharge dates will be calculated as the difference between the last day with available data and the start date of hospitalisation. The length of ICU stay will be calculated using the same method.

Approximately 53 patients from sites in China will be recruited and randomised in a 2:1 ratio to receive olaparib or placebo and will follow the same study plan and procedures as patients recruited to the global study. The safety and efficacy data collected will be summarised and analysed separately to the global study safety and ITT analysis sets (as defined in section 2.1). A standalone SAP will be written for the China cohort.

Analyses of the China cohort will be performed after a minimum of 29 PFS events have been observed. The primary statistical analysis of the efficacy of olaparib for China cohort ITT patients will be an assessment of progression free survival based on investigator assessment. A KM plot of PFS will be presented by treatment group. Summaries of the number and percentage of subjects experiencing a PFS event, and the type of event (RECIST or death) will be provided along with median PFS for each treatment. In addition, an analysis of PFS will be performed. The HR (olaparib:placebo) and associated CI will be calculated from a Cox proportional hazards model (ties = Efron) that contains the treatment term and a term for response to first line platinum chemotherapy. The HRs and 95% CIs will be presented on a forest plot including the HR and 95% CI from the overall ITT population (using the primary analysis). Exploratory p-values from a log rank test stratified by response to first line platinum chemotherapy will also be presented. If there are issues with this approach a Cox proportional hazards model with a treatment term only and an unadjusted log rank test will be implemented.

Summaries and analysis of secondary supportive efficacy endpoints (including OS, PFS2, ORR, time to first subsequent therapy (TFST), time to second subsequent therapy (TSST) time to earliest progression by RECIST or CA-125 or death and TDT) will be performed for the China cohort as described for the ITT analysis set.

In addition, an exploratory analysis may be performed using a weighted average or “borrowing evidence” approach (Huang 2012) to combine data from non-China cohort and China cohort patients to estimate the PFS treatment effect if required to support a future China HA request. This will be done outside of the China CSR

When assessing safety and tolerability, summaries will be produced separately for the China cohort based on the China Safety Analysis Set as defined in section 2.1. The China safety data will be summarised descriptively and will not be formally analysed.

Updated safety summaries may also be produced which include safety data from all subjects who received at least one dose of randomised treatment (olaparib or placebo) if requested by health authorities.

## 4 ANALYSIS METHODS

PFS will be analysed when approximately 196 events have occurred or after the last patient randomised has had the opportunity to have been on the study for at least 36 months,

whichever comes first. No further analyses of PFS are planned beyond this point unless requested by Health Authorities.

An initial analysis of OS, PFS2, TFST and TSST will be performed at the same time as the primary analysis of PFS and will use the same methodology and model.

Supportive analyses of time to earliest progression by RECIST or CA-125 or death and TDT will be provided, using the same methodology as specified for the primary analyses of PFS; however no multiple adjustment will be applied as these are viewed as supportive endpoints.

#### **4.1 General Principles**

The primary statistical analysis of the efficacy of olaparib will include all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised but did not subsequently go on to receive study treatment are included in the Full Analysis Set (FAS). Therefore, all efficacy and HRQoL data will be summarised and analysed using the FAS on an ITT basis.

When assessing safety and tolerability, summaries will be produced based on the Safety Analysis Set. This will include all patients who receive at least one dose of randomised treatment (olaparib or placebo). Patients in the safety analysis set will be analysed by their initial treatment received. The safety data will be summarised descriptively and will not be formally analysed.

Relevant parametric analyses of time to event endpoints required for payer submissions will be outlined in a separate payer analysis plan.

#### **4.2 Analysis Methods**

The treatment comparison is olaparib 300 mg bd versus placebo.

All efficacy analyses will be performed on the ITT population. In addition, as a sensitivity to the main analyses of PFS, PFS2, OS, TDT, TFST and TSST, analyses of these endpoints will be performed in those patients whose gBRCAm status is confirmed by Myriad centrally. Each randomised patient will have one of either the Myriad BRACAnalysis CDx performed under Quality Systems Regulations (QSR) or the Myriad Integrated BRACAnalysis assay that is performed under Clinical Laboratory Improvement Amendments (CLIA). Patients randomised in the China Cohort had gBRCAm testing performed by BGI.

Key efficacy (PFS, PFS2, OS, TDT, TFST and TSST) and safety estimates associated with patients whose tBRCAm status is confirmed by Foundation Medicine will also be reported as a separate subset.

Results of all statistical analysis will be presented using 95% confidence intervals and two-sided p-values.



The following table details which endpoints are to be subject to formal statistical analysis, together with pre-planned sensitivity analyses making clear which analysis is regarded as primary for that endpoint.

**Table 7 Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses**

Endpoints Analysed	Notes
PFS (Time from randomisation to first progression or death)	Primary analysis: stratified log-rank test using investigator data
	Key sensitivity analyses: <ul style="list-style-type: none"> <li>• stratified log rank test using investigator data in randomised patients confirmed as gBRCA mutation positive by Myriad centrally</li> <li>• stratified log rank test using investigator data in randomised patients confirmed as tBRCA mutation positive by Foundation Medicine</li> </ul>
	Additional sensitivity analyses:
	1) Evaluation time bias analysis; stratified log-rank test using investigator data
	2) Attrition bias analysis (using alternative censoring rules); stratified log-rank test using investigator data
	3) Ascertainment bias analysis; stratified log-rank test using BICR data
	4) Deviation bias analysis (if meaningful to do); stratified log-rank test using investigator data
5) Stratified log rank test using U and V statistics to calculate HR and CI based on investigator data	
OS (Time from randomisation to death due to any	Stratified log-rank test

**Table 7 Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses**

Endpoints Analysed	Notes
cause)	Key sensitivity analyses: <ul style="list-style-type: none"> <li>• stratified log rank test in randomised patients confirmed as gBRCA mutation positive by Myriad centrally</li> <li>• stratified log rank test in randomised patients confirmed as tBRCA mutation positive by Foundation Medicine</li> </ul>
PFS2 (Time from randomisation to second progression or death)	Stratified log rank test based on investigator assessment of second progression
	Key sensitivity analyses: <ul style="list-style-type: none"> <li>• stratified log rank test using investigator data in randomised patients confirmed as gBRCA mutation positive by Myriad centrally</li> <li>• stratified log rank test in randomised patients confirmed as tBRCA mutation positive by Foundation Medicine</li> </ul> Additional sensitivity analysis: marginal model approach of <a href="#">Wei et al 1989</a>
TFST (Time to first subsequent therapy or death)	Stratified log rank test
	Key sensitivity analyses: <ul style="list-style-type: none"> <li>• stratified log rank test in randomised patients confirmed as gBRCA mutation positive by Myriad centrally</li> <li>• stratified log rank test in randomised patients confirmed as tBRCA mutation positive by Foundation Medicine</li> </ul>
TSST (Time to second subsequent therapy or death)	Stratified log rank test
	Key sensitivity analyses: <ul style="list-style-type: none"> <li>• stratified log rank test in randomised patients confirmed as gBRCA mutation positive by Myriad centrally</li> <li>• stratified log rank test in randomised patients confirmed as tBRCA mutation positive by Foundation Medicine</li> </ul>
TDT (Time to study treatment discontinuation or	Stratified log rank test

**Table 7 Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses**

Endpoints Analysed	Notes
death)	Key sensitivity analyses: <ul style="list-style-type: none"> <li>• stratified log rank test in randomised patients confirmed as gBRCA mutation positive by Myriad centrally</li> <li>• stratified log rank test in randomised patients confirmed as tBRCA mutation positive by Foundation Medicine</li> </ul>
Change from baseline in TOI score	MMRM analysis of the change from baseline in TOI score
Time to earliest progression by RECIST 1.1, CA-125 or death	Stratified log rank test using investigator data

#### 4.2.1 Multiplicity

In order to describe the nature of the benefits of olaparib maintenance treatment, PFS, PFS2, TFST, TSST, TDT change from baseline in TOI score and OS will be tested at a 2-sided significance level of 5%.

In addition to these planned analyses, which will be performed and reported in the CSR, in order to strongly control the type I error at 2.5% one-sided for key label claims, a multiple testing procedure (MTP) will also be employed across the primary endpoint (PFS) and key secondary endpoints (PFS2 and OS). There is no requirement to adjust for multiplicity due to PFS interim analyses, since there are no planned interim PFS analyses with the opportunity to make an early claim of efficacy.

A hierarchical testing strategy will be employed where PFS is tested first using the full test mass (full test mass = alpha) and key secondary endpoints of PFS2 and OS will then be tested using a MTP with a recycling strategy (i.e., the MTP will recycle the test mass to the endpoint not yet rejected in the hierarchy outlined in [Figure](#) ). The MTP is detailed below.

**Figure 4 Multiple Testing Procedure**



PFS2 will only be tested (with the test mass split between interim and final PFS2 analyses) if statistical significance is shown for PFS. OS will only be tested if statistical significance is shown for PFS2.

Both PFS2 and OS will be tested at the time of the primary analyses of PFS and again when there are approximately 60% deaths. A proportion of alpha will be spent at this first analysis time point for both endpoints to control for multiple testing however different spending functions will be applied for each.

An interim analysis for PFS2 will be performed at the time of the PFS analysis. Statistical significance will be declared at the interim analysis for PFS2 if the 1-sided  $p < 0.0125$ .

If the null hypothesis for PFS2 is not rejected at this first analysis time point then PFS2 will be tested again when the final analysis of OS occurs. The type I error will be controlled at 2.5% 1-sided by assigning approximately 1.8% significance level (1-sided) to the final analysis of PFS2 (final significance level to be determined accounting for correlation between the interim and final PFS2 analyses) (Stone 2010). If PFS2 is significant at either the interim or final analyses, the full test mass (alpha) will be carried forward to OS.

An interim analysis for OS will be performed at the time of the PFS analysis. Statistical significance will be declared at the interim analysis for OS if the null hypothesis for PFS2 is rejected at the PFS analysis and the observed p-value for OS is  $p < 0.0001$ . This allows the significance level at the final analysis for OS to be controlled at the 2.5% level (1-sided) (Haybittle J L 1971).

#### **4.2.2 Primary variable - progression free survival (PFS)**

PFS will be analysed using a log-rank test stratified by response to first line platinum chemotherapy (in the opinion of the investigator, clinical complete response (CR) or partial response (PR)) for generation of the p-value and using the Breslow approach for handling ties. The hazard ratio (HR) and confidence interval (CI) will be estimated from a Cox Proportional

Hazards model (with ties = Efron and the stratification variable as a covariate) and the CI will be calculated using a profile likelihood approach.

Stratification variables will be defined according to data from the randomisation. If there are any patients who were mis-stratified, a sensitivity analysis will be carried out using the (correct) baseline data collected in the eCRF. Although not anticipated, if patients are randomised in error when they have not previously had a response to first line platinum chemotherapy, they will be categorised in the “PR” category for the sensitivity analysis using eCRF stratification data.

The HR (olaparib versus placebo) together with its corresponding 95% CI and p-value will be presented (a HR less than 1 represents the reduction in risk for those patients allocated olaparib).

A KM plot, with tick marks to identify censored observations, of PFS will be presented by treatment group. Summaries of the number and percentage of subjects experiencing a PFS event, and the type of event (RECIST or death) will be provided along with median PFS and corresponding 95% CI for each treatment.

The assumption of proportionality will be assessed. Note that in the presence of non-proportionality, the HR will be interpreted as an average HR over the observed extent of follow-up. Proportionality will be tested firstly by producing plots of complementary log-log (event times) versus log (time) and, if these raise concerns, a time dependent covariate would be fitted to assess the extent to which this represents random variation. The primary analysis will be based on the PFS based on investigator assessments, and using all scans regardless of whether they were scheduled or not.

The proportion and corresponding 95% CI of patients alive and progression free at 6 monthly intervals will be summarised (using the KM plot) and presented by treatment group.

The number of patients prematurely censored will be summarised by treatment arm together with baseline prognostic factors of the prematurely censored patients. A patient is defined as prematurely censored if they did not progress and the latest scan prior to DCO was more than one scheduled tumour assessment interval (+ 2 weeks) prior to the DCO date.

In addition, duration of follow-up will be summarised using median time from randomisation to date of censoring (date last known to be non-progressor) in censored (not progressed) patients only, presented by treatment group. The interquartile range will also be presented by treatment group.

As patients will be randomised, imbalances in demographic factors between the treatment groups are not anticipated. However, if any imbalances should occur, the HR and associated CI calculated from a Cox Proportional Hazards model containing treatment, the stratification variable and these additional demographic variables, may be reported.

Summary statistics will be provided for the PFS events due to death and those due to RECIST progression, and also for censored events. In addition, the reason for censoring across treatment arms will be provided. In the case where the distribution of discrepancy in progression assessment between BICR and local investigator across treatment groups is not similar, the PFS analysis may be biased due to informative censoring. The potential impact of informative censoring on parameter estimate will be assessed through sensitivity analysis, using either the methods of Jackson et al or Hsu and Taylor ([Jackson et al 2014](#), [Hsu and Taylor 2009](#)) when considering time dependent covariates. This work will be presented separately and will not form part of the CSR.

Subgroup analyses will be conducted comparing PFS between treatments. Median PFS will be reported. The purpose of the subgroup analyses is to assess the consistency of treatment effect across potential or expected prognostic factors. The results observed in Phase II (D0810C00019) do not suggest that these factors will be predictive factors for a qualitatively different treatment effect. If there are too few events available for a meaningful analysis of a particular subgroup (where there are less than 20 events per subgroup level no formal statistical tests will be performed), the relationship between that subgroup level and PFS will not be formally analysed. In this case, only descriptive summaries will be provided. When there are less than 20 events per a subgroup, consideration will be given to combining relevant subgroups if appropriate to do so.

The following subgroups of the full analysis set will be analysed for PFS:

- Response to previous platinum chemotherapy (obtained from the randomisation schedule)
- gBRCAm status-confirmed by Myriad test or gBRCA wildtype (wt) or gBRCA variant of uncertain significance (VUS) or missing by Myriad test]\*. This will be determined from the Myriad central laboratory tests.
- ECOG performance status at baseline (normal activity [PSTAT=0] or restricted activity [PSTAT=1]).

This will be determined from the response to “Performance status” (PSTAT module) on the eCRF at screening.

- Baseline CA-125 value ( $\leq$  ULN or  $>$  ULN).

The baseline CA-125 value will be defined as the measurement nearest to but prior to date of randomisation.

- BRCA mutation type (BRCA1 or BRCA2 or BRCA1/2 (both)).

This will be determined from the Myriad central laboratory tests. If there are less than 20 events in the “BRCA1/2 both” category, these patients will be excluded from this analysis.

- Age (<65 or ≥ 65).

This will be determined from the date of birth (BIRTHDAT in the DEM module) and date of randomization. See section 4.2.13 for rules on deriving age for partial dates of birth.

- Stage of disease at initial diagnosis (III [FIGO\_STG=30 or 31 or 32 or 33] or IV [FIGO\_STG=40]).

This will be determined from the response to “FIGO stage” (PATHGEN module) on the eCRF at screening.

- Residual macroscopic disease following debulking surgery prior to entry into the study [HISPOUT=1] or no residual macroscopic disease [HISPOUT=2].

This will be determined from the response to the “Last debulking surgery outcome” on the history of debulking surgery page (HISHC module) of the eCRF at screening.

- Region 1 (North America or Rest of World).

This will be determined from the centre number (CENTRE). A ‘North America’ patient is defined as any patient randomised at a site in USA or Canada. Otherwise a patient is defined as ‘Rest of World’. This selection is based on potential differences in clinical practice between the regions.

- Region 2 (Brazil, Poland, Russia, Japan, Korea or Rest of World)

This will be determined from the centre number (CENTRE). A ‘Brazil, Poland, Russia, Japan, Korea’ patient is defined as any patient randomised at a site in either Brazil, Poland, Russia, Japan or Korea. Otherwise a patient is defined as ‘Rest of World’. This selection is based on a comparison of Asia/non Western Europe versus Rest of World.

- Race (White or Black/African-American or Asian or Native Hawaiian/Pacific Islander or American Indian/Alaska Native or Others).

This will be determined from the response to “Race” (DEM module) on the eCRF at screening.

\* Some patients may only have a tumour mutation or are from China where no sample will be supplied for Myriad testing.

Other baseline variables may also be assessed if there is clinical justification, for example, patients who received intravenous (IV) chemotherapy versus patients who received intraperitoneal (IP) chemotherapy in their first line regimen.

A minimal number of patients that are tBRCAm (by local testing) and gBRCA wt (by Myriad testing) are expected to be randomised into this study. Assuming the number of progression events in this population is less than 20, the number and proportion of events will be summarised by treatment arm. If the number of events is  $\geq 20$ , this factor will be added to the forest plot (i.e. gBRCA by Myriad testing and tBRCA mutated versus tBRCA mutated only).

For each subgroup, the HRs (olaparib: placebo) and associated CIs will be calculated from a Cox Proportional Hazards model (ties = Efron) that contains the treatment term, factor (subgroup) and treatment-by-factor interaction term. The treatment effect HRs for each treatment comparison along with their CIs will be obtained for each level of the subgroup from this single model. The HRs and 95% CIs will be presented on a forest plot including the HR and 95% CI from the overall population (using the primary analysis). In addition, summaries of the number and percentage of patients experiencing a PFS event for each subgroup will be provided along with the median PFS for each treatment.

No adjustment to the significance level for testing will be made since all these subgroup analyses will be considered exploratory and may only be supportive of the primary analysis of PFS.

The presence of quantitative interactions will be assessed by means of an overall global interaction test. This will be performed in the overall population by comparing the fit of a Cox Proportional Hazards model including treatment, all covariates, and all covariate-by-treatment interaction terms, with one that excludes the interaction terms and will be assessed at the 2-sided 10% significance level. If a covariate does not have  $\geq 20$  events per level (of the covariate) it will be included as a covariate in the model but the covariate-by-treatment interaction term will be omitted. If the fit of the model is not significantly improved then it will be concluded that overall the treatment effect is consistent across the subgroups.

If the global interaction test is found to be statistically significant, an attempt to determine the cause and type of interaction will be made. Stepwise backwards selection will be performed on the saturated model, whereby (using a 10% level throughout) the least significant interaction terms are removed one-by-one and any newly significant interactions re-included until a final model is reached where all included interactions are significant and all excluded interactions are non-significant. Throughout this process all main effects will be included in the model regardless of whether the corresponding interaction term is still present. This approach will identify the factors that independently alter the treatment effect and prevent identification of multiple correlated interactions.



Any quantitative interactions identified using this procedure will then be tested to rule out any qualitative interaction using the approach of [Gail and Simon 1985](#)

A further analysis of PFS (using investigator assessed RECIST) may be performed at the time of the OS analyses, if requested by health authorities.

### **PFS sensitivity analyses**

As a key sensitivity analysis to the primary endpoint of PFS, the primary analysis will be repeated excluding any patients who did not have a gBRCA mutation status confirmed by Myriad centrally. The same methodology and model will be used and the HR and associated 95% CI from a Cox Proportional Hazards model will be reported. A KM plot of PFS in this subset of patients will be presented by treatment group. This sensitivity analysis will also be repeated excluding any patients who did not have a tBRCA mutation status confirmed by Foundation Medicine.

Sensitivity analyses will be performed to assess the possible presence of time-assessment bias (i.e. differential assessment times between treatment groups)

Summary statistics for the number of weeks between the time of progression and the last evaluable RECIST assessment prior to progression will be presented for each treatment group.

Summaries of the number and percentage of patients who miss two or more consecutive RECIST assessments and the number of patients who miss one RECIST assessment will be presented for each treatment group.

#### **(a) Evaluation-time bias**

Sensitivity analyses will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled time points. The midpoint between the time of progression and the previous evaluable RECIST assessment will be analysed using a stratified log-rank test, as described for the primary analysis of PFS. This approach has been shown to be robust to even highly asymmetric assessment schedules ([Sun and Chen 2010](#)). To support this analysis, the mean of subject-level average inter-assessment times will be tabulated for each treatment. This approach will use the investigator RECIST assessments.

#### **(b) Attrition bias**

Attrition bias will be assessed by repeating the primary PFS analysis except that the actual PFS event times, rather than the censored times, of subjects who progressed or died in the absence of progression immediately following two, or more, non-evaluable tumour assessments will be included. In addition, subjects who take subsequent therapy prior to their last evaluable RECIST assessments or progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy. Additionally a KM plot of the time to censoring where the censoring indicator of the primary PFS analysis is reversed (what

was originally a censored event in the primary PFS analysis becomes an actual event and what originally was a PFS event becomes a censored event) will be presented.

**(c) Ascertainment bias**

A stratified log-rank test will be repeated using BICR RECIST data to programmatically derive PFS. The HR and 95% CI will be presented.

The type of event (RECIST or death) will also be provided.

If there is an important discrepancy between the primary analysis using investigator assessments and this sensitivity analysis using BICR assessments, then the proportion of subjects with site but no central confirmation of progression will be summarised. This scenario is possible as at the time of the primary analysis data cut off all scans will be sent for central review assessment regardless of whether or not a patient has been assessed as having progressed by the site. The approach of imputing an event at the next visit in the BICR assessed analysis may help inform the most likely HR value, but only if an important discrepancy exists.

Disagreements between investigator and BICR assessment of RECIST progression will be presented for each treatment group. The summary will include the early discrepancy rate which is the frequency of BICR progressions declared before the investigator review progressions ( $\geq 2$  weeks earlier and including progressions declared by BICR but not investigator) as a proportion of all BICR progressions, and the late discrepancy rate which is the frequency of BICR progressions declared after the investigator review ( $\geq 2$  weeks later and including progressions declared by investigator but not BICR as a proportion of all discrepancies (including early and late discrepancies) ([Amit et al 2011](#)).

**(d) Deviation bias (if meaningful to do)**

As a sensitivity analysis to the primary endpoint of PFS, an analysis excluding patients with deviations that may affect the efficacy of the trial therapy will be performed if  $> 10\%$  of patients:

- did not have the intended disease or indication or
- did not receive any randomised therapy

A stratified log-rank test will be repeated using the investigator RECIST data, using the same ties and stratification factor as described for the primary analysis of PFS. The HR and 95% CI will be presented.

An additional sensitivity analysis of PFS will be performed based on a log-rank test stratified by the stratification variable, i.e. response to first line platinum chemotherapy, and using the Breslow approach for handling ties. The HR and CI will be estimated from the U and V

statistics obtained directly from the LIFETEST model with inclusion of STRATA terms for the stratification variable.

The HR and its CI will be estimated from the log-rank as follows ([Berry et al 1999](#) and [Sellke and Siegmund 1983](#)):

$$\text{HR} = \exp(U/V)$$

$$95\% \text{ CI for HR} = (\exp\{U/V - 1.96/\sqrt{V}\}, \exp\{U/V + 1.96/\sqrt{V}\})$$

Where  $U = \sum_k U_k = \sum_k \sum_i (d_{1ki} - e_{1ki})$  is the stratified log-rank test statistic obtained from the SAS LIFETEST procedure,  $\sqrt{V} = \sqrt{\sum_k V_k}$ , is its standard deviation, k denotes the stratum and  $d_{1ki}$  and  $e_{1ki}$  are the observed and expected events in Group 1, stratum k, ith event time.

**(e) Event rate at 24 months**

The proportion of patients progression free at 24 months (PFS24) will be defined as the Kaplan-Meier estimate of PFS at 24 months.

The stratified KM estimates (95% CI) of PFS24 stratified by response to first line platinum chemotherapy will be estimated by treatment group. The difference (95% CI) in the stratified estimates of PFS24 between treatments will also be calculated. For estimating the confidence intervals, Greenwood’s estimate of the variance of the KM proportion will be used ([Collett 2003](#)). The hypothesis of no difference in PFS24 between treatment groups across the levels of response to first line platinum chemotherapy will also be tested.

**4.2.3 Time from randomisation to second progression (PFS2)**

PFS2 analysis will be performed using the same methodology and model as PFS. If PFS2 is not statistically significant at the primary PFS analysis, then a further analysis of PFS2 will be performed when the OS data are approximately 60% mature. If PFS2 is statistically significant at the primary PFS analysis, then no further analysis of PFS2 will be performed unless requested by a regulatory authority. The type of progression (objective progression by RECIST, progression by CA-125, symptomatic progression or other) will also be summarised by treatment arm.

As a key sensitivity, the analysis of PFS2 will be repeated in those patients whose gBRCAm status is confirmed by Myriad centrally. A KM plot of PFS2 in this subset of patients will be presented by treatment group. This sensitivity analysis will also be repeated excluding any patients who did not have a tBRCA mutation status confirmed by Foundation Medicine. The sensitivity analysis outlined for PFS in Section 4.2.2 will not be repeated for PFS2 with the exception of a KM plot of the time to censoring where the censoring indicator of the primary

PFS2 is reversed (what was originally a censored event in the primary PFS2 analysis becomes an actual event and what originally was a PFS2 event becomes a censored event).

In addition, a sensitivity analysis of PFS2 using the marginal model approach of Wei, Lin and Weissfeld (Wei LJ et al 1989) will be undertaken where patient risks will be partitioned from randomisation to PFS and from PFS to PFS2.

Time from second progression to previous assessment will be summarised by treatment arm.

#### **4.2.4 Overall survival (OS)**

OS data will be analysed at the time of the primary analysis of PFS and will use the same methodology and model (provided there are sufficient events available for a meaningful analysis [ $\geq 20$  deaths], if not descriptive summaries will be provided). A further analysis of OS will be performed when the OS data are approximately 60% mature.

As a key sensitivity, the analysis of OS will be repeated in those patients whose gBRCAm status is confirmed by Myriad centrally. A KM plot of OS in this subset of patients will be presented by treatment group. This sensitivity analysis will also be repeated excluding any patients who did not have a tBRCA mutation status confirmed by Foundation Medicine.

The remaining sensitivity analyses outlined for PFS in Section 4.2.2 will not be repeated for OS with the exception of a KM plot of the time to censoring where the censoring indicator of the primary OS is reversed (what was originally a censored event in the primary PFS2 analysis becomes an actual event and what originally was a PFS2 event becomes a censored event).

A summary of survival status at the time of analysis will be produced. This will summarise the number of patients who have died, who are still in survival follow-up, who are lost to follow-up or who have withdrawn consent.

In addition, duration of follow-up will be summarised using medians:

- In censored (not died) patients only: Time from randomisation to date of censoring (date last known to be alive)
- In all patients: Time from randomisation to the date of death or to the date of censoring for censored patients.

At the time of the further analysis of OS, the subgroup analyses and global interaction test detailed for PFS in Section 4.2.2 will be repeated for OS.

## **Exploratory analyses of OS**

Exploratory analyses of OS adjusting for impact of subsequent PARP inhibitor trial or treatment may be performed if a sufficient proportion of patients switch. The decision to adjust and final choice of methods will be based on a blinded review of the data and the plausibility of the underlying assumptions. Baseline and time-dependent characteristics will be explored, and summaries of baseline characteristics will be summarised for placebo patients, splitting between those that have and haven't switched at the time of the analyses. This will be performed outside of the CSR.

### **4.2.5 Time to first subsequent therapy or death (TFST) and time to second subsequent therapy or death (TSST)**

Time to first subsequent therapy or death (TFST) and time to second subsequent therapy or death (TSST) will be analysed at the same time as the primary analysis of PFS and using the same methodology and model. The HRs for the treatment effect together with 95% CIs will be presented. KM plots will be presented by treatment arm. In addition, the number of patients who received further therapy relative to progression (before, after, no progression) will also be presented by treatment arm.

Summary tables of first and second subsequent therapies by treatment arm will be provided, as well as response to first and second subsequent therapy by treatment arm.

Further analyses of these endpoints will be performed when the OS data are approximately 60% mature.

As a key sensitivity, the analyses of TFST and TSST will be repeated in those patients whose gBRCAm status is confirmed by Myriad centrally. KM plots of TFST and TSST in this subset of patients will be presented by treatment group. These sensitivity analyses will also be repeated excluding any patients who did not have a tBRCA mutation status confirmed by Foundation Medicine.

### **4.2.6 Time to study treatment discontinuation or death (TDT)**

Time to study treatment discontinuation or death (TDT) will be analysed at the same time as the primary analysis of PFS and using the same methodology and model. The HR for the treatment effect together with 95% CIs will be presented. A KM plot will be presented by treatment arm. No multiplicity adjustment will be applied as this is viewed as a supportive endpoint.

Further analysis of this endpoint will be performed when the OS data are approximately 60% mature.

As a key sensitivity, the analyses of TDT will be repeated in those patients whose gBRCAm status is confirmed by Myriad centrally. A KM plot of TDT in this subset of patients will be

presented by treatment group. This sensitivity analysis will also be repeated excluding any patients who did not have a tBRCA mutation status confirmed by Foundation Medicine.

#### **4.2.7 Time to earliest progression by RECIST 1.1, CA-125 or death**

Time to progression by RECIST 1.1, CA-125 or death will be performed at the same time as the primary analysis of PFS and will use the same methodology and model.

The number (%) of patients reporting a CA-125 progression, and a combined objective progression and/or CA- 125 progression will be tabulated.

No multiplicity adjustment will be applied as this is viewed as a supportive endpoint (to PFS).

#### **4.2.8 Best overall RECIST response (BoR)**

For each treatment arm, Best Overall Response (BoR) derived programmatically from investigator data will be summarised by n (%) for each category (CR, PR, SD, NED, PD, NE). No formal statistical analyses are planned.

The ORR and DCR will be summarised (i.e., number of patients (%)) by treatment group, in patients in the FAS (ITT population) with measurable disease at baseline. In addition, for patients who have an objective response, the duration and onset of the response will be summarised.

#### **4.2.9 Patient reported outcomes (PROs)**

The analysis population for HRQoL data will be the subset of the FAS (ITT set).

It should be noted that some centres erroneously collected patient data using the FACT-O at non-protocol visits. These data will not be used in any analyses or summaries, but will be listed in the appendices and flagged accordingly.

The HRQoL benefit of the long PFS delay with olaparib is expected to be observed when placebo patients require chemotherapy earlier as this is when HRQoL may be expected to deteriorate. It is expected that the stability in “HRQoL” over the 24 months following start of randomised treatment will be longer for patients randomised to olaparib than placebo. This will be investigated using the TOI derived from the FACT-O questionnaire.

#### **Change from baseline TOI scores**

Change from baseline in TOI score will be regarded as the primary analysis of the FACT-O questionnaire and will be analysed using a mixed model for repeated measures (MMRM) analysis of the change from baseline (defined as prior to first dose) in TOI scores for each visit.

The primary analysis will be to compare the average treatment effect from the point of randomisation for the first 24 months (which will include analysis visits obtained within the

first 24 months, i.e. baseline, day 29 (week 4), weeks 12, 24, 36, 48, 60, 72, 84, 96, see Section 3.3.2) unless there is excessive missing data (defined as >75% missing data). If the time to first subsequent chemotherapy when approximately 50% of placebo patients receive chemotherapy does not occur by 24 months post-randomisation then additional time periods will be analysed and will be included on supportive summaries and graphical displays as appropriate.

The MMRM model will include patient, treatment, visit (analysis) and treatment by visit interaction as explanatory variables, the baseline TOI score as a covariate along with the baseline TOI score by visit interaction. Treatment, visit and treatment by visit interaction will be fixed effects in the model; patient will be included as a random effect. Restricted maximum likelihood (REML) estimation will be used. An overall adjusted mean estimate will be derived that will estimate the average treatment effect over visits giving each visit equal weight. For this overall treatment comparison, adjusted mean estimates per treatment group and corresponding 95% CIs will be presented along with an estimate of the treatment difference, 95% CI and p-value. The treatment by visit interaction will remain in the model regardless of significance.

An unstructured covariance matrix will be used to model the within-subject error and the Kenward-Roger approximation will be used to estimate the degrees of freedom. The following provides sample code for implementing the MMRM analysis:

```
proc mixed data=TOI method = reml;  
  class TRT VISIT SUBJECT;  
  model TOISC = TRT VISIT TRT*VISIT TOIBL TOIBL*VISIT / s ddfm=kr;  
  repeated VISIT / type=UN subject=SUBJECT;  
  random intercept / subject= SUBJECT;  
  lsmeans TRT / at means pdiff diff alpha=0.05 cl;
```

where TRT is the randomised treatment, VISIT is the visit, TOISC is the change from baseline in the TOI score, and TOIBL is the baseline TOI score.

For the estimation of trt\*visit means an additional model will be run using all visits and the following lsmeans statement:

```
lsmeans TRT*VISIT / slice=VISIT pdiff diff alpha=0.05 cl;
```

If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached: toeplitz with heterogeneity, autoregressive with heterogeneity, toeplitz, and autoregressive. If there are still issues with the

fit of the model or estimation of the treatment effects, SUBJECT will be treated as a fixed effect.

For each treatment and visit, the adjusted (least squares) mean estimates, corresponding 95% CIs, estimates of the treatment difference, corresponding 95% CIs and p-values will be presented.

During the randomised treatment phase, it is expected that olaparib will not cause harm to HRQoL, this will be demonstrated by comparing the Trial Outcome Index (TOI) best response rates (improved/no change/worsened) whilst on randomised treatment. A contingency table summarising the TOI best change rates will be provided and a CMH analysis including the randomisation stratification factor will be performed.

An AUC (Area Under the Curve) analysis will also be performed for TOI. For each patient, the AUC will be derived using the trapezoidal rule and including all available scheduled visits. Time-adjusted AUC will be calculated as AUC divided by time from baseline to last HRQoL visit where the patient provides data. The mean time-adjusted AUC will be analysed using analysis of variance (ANOVA) including using the same stratification factor as described for the primary analysis of PFS. Time-adjusted AUC summary statistics (mean, median, minimum, maximum, StD) per treatment arm will be presented. In addition, the analysis table will provide the estimated mean difference between treatment groups, 95% CI and p-value. This analysis will be done using the first 24 months of data provided by a patient. For this analysis, for any patient who dies during the first 24 months, data for each question in the FACT-O from the time of death until 24 months will be set to 0. In addition, an analysis using all available data for each patient will be performed.

If deemed appropriate alternative methods may be used (e.g. piecewise linear modelling).

Descriptive statistics and graphs will be reported for the TOI by visits as well as change in these scores from baseline.

### **Total FACT-O and subscales scores**

Descriptive statistics, by visit and change from baseline, will be reported for physical well-being (PWB), functional well-being (FWB) and the ovarian cancer subscale (Additional Concerns) domains. Descriptive statistics will also be provided for the individual questions that make up the additional concerns subscale.

Descriptive statistics, by visit and change from baseline, will also be reported for the emotional well being (EWB) and social well being (SWB) subscales, these two subscales do not form part of the TOI itself.

FACT-O questionnaire compliance (overall compliance and by visit compliance) will be summarised for each treatment group.



For the FACT-O questionnaire compliance table and subsequent tables of descriptive statistics on a visit basis, in addition to individual visits being presented, additional entries will be given for End of treatment and 30 day follow up visits (see section 3.3.3 for description of visit windowing). These visits will not be presented in corresponding figures.

In order to assess the amount of missing data and the reasons for missing data, plots including the number of questionnaires completed/partially completed/missing at each visit will be produced.

#### **4.2.10 Exploratory analyses**

##### **EQ-5D-5L**

The evaluable population will comprise all patients in the FAS (ITT population).

Descriptive statistics will be calculated for each scheduled visit/time point in the study, for each trial arm and as a total. These will report the number of patients, the number of EQ-5D questionnaires completed at each visit, the number and proportion responding to each dimension of the EQ-5D-5L. Additionally summary statistics (e.g. n, mean, median, StD, min, max) will be reported for the EQ-5D index score and the EQ-VAS score, and the change from baseline for the EQ-5D index score and the EQ-VAS score.

Graphical plots of the mean EQ-5D index score and EQ-VAS score, including change from baseline, and associated 95% CI by scheduled visits/time points in the study will be produced. To support submissions to payers, additional analyses may be undertaken and these will be outlined in a separate Payer Analysis Plan.

##### **Health care resource use**

The potential impact the disease and treatment has on health care resource use will be analysed for the purposes of submissions to payers. Descriptive statistics (as appropriate, including means, median, ranges or frequencies and percentages) will be provided for each arm on the different types of hospital admissions, the length of stay of people admitted in to hospital for at least one overnight stay and length of stay of people admitted to intensive care / high dependency units, as well as the primary sign or symptom the patient presents with. To support submissions to payers, additional analyses may be undertaken and these will be outlined in a separate Payer Analysis Plan.

##### **Tumour BRCA**

A summary table will be produced comparing BRCA mutation/s in tumour to germline BRCA mutation status.

##### **Subsequent therapy**

Subsequent therapies received after discontinuation of olaparib will be summarised and listed by treatment group, together with number of regimens received. Patients who subsequently received a PARP inhibitor or entered a PARP inhibitor trial will be summarised and listed by treatment arm according to line of subsequent therapy.

#### 4.2.11 Safety

Safety data will be summarised and listed only. No formal statistical analyses will be performed on the safety data. All safety data will be summarised by actual treatment group (olaparib or placebo) including patients who have dose reduction for blinded period of study. Any patient who received an initial dose of olaparib will be included in the olaparib group, even if the patient was planned to receive placebo. Similarly, any patient who received an initial dose of placebo will be included in the placebo group, even if the patient was planned to receive olaparib. However, some listings such as AEs listings will display the actual dose the patient received at onset of an AE.

##### Adverse events

All AEs, both in terms of Medical Dictionary for Regulatory Activities (MedDRA) preferred term and Common Toxicity Criteria for Adverse Events (CTCAE) grade, will be listed and summarised descriptively by count (n) and percentage (%) for each treatment arm. MedDRA dictionary will be used for coding. Any AE occurring before olaparib/placebo treatment (i.e. before Study Day 1) will be included in the AE listings, but will not be included in the summary tables (unless otherwise stated). These will be referred to as 'pre-treatment'.

The summary tables will include all AEs that occurred after the start of treatment up until the end of the 30 day follow-up period. The 30 day follow-up period will be defined as 30 days following discontinuation of olaparib/placebo treatment.

All reported AEs will be listed along with the date of onset, date of resolution (if AE is resolved), investigator's assessment of severity and relationship to study drug. Frequencies and percentages of patients reporting each preferred term will be presented (i.e. multiple events per patient will not be accounted for apart from on the episode level summaries).

Partially missing dates will be imputed as per the phUSE guidelines ([http://www.phusewiki.org/wiki/index.php?title=Imputing\\_Partial\\_Dates](http://www.phusewiki.org/wiki/index.php?title=Imputing_Partial_Dates))

For date of onset:

- Missing day - Impute the 1st of the month unless month is same as month of first dose of study drug then impute first dose date
- Missing day and month – impute 1st January unless year is the same as first dose date then impute first dose date
- Completely missing – impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.

When imputing a start date ensures that the new imputed date is sensible i.e. is prior to the end date of the AE.

For date of resolution:

- Missing day - Impute the last day of the month unless month is same as month of first dose of study drug then impute last dose date
- Missing day and month – impute 31st December unless year is the same as first dose date then impute last dose date
- Completely Missing – need to look at whether the AE is still ongoing before imputing a date and also when it started in relation to study drug. If the ongoing flag is missing then assume that AE is still present (i.e. do not impute a date). If the AE has stopped and start date is prior to first dose date then impute the 1st dose date, if it started on or after first dose date then impute a date that is after the last dose date.

Summary information (the number and percent of patients by treatment) will be tabulated for:

- All AEs
- All AEs causally related to study medication
- AEs with CTCAE grade 3 or higher
- AEs with CTCAE grade 3 or higher, causally related to study medication
- AEs with outcome of death
- AEs with outcome of death causally related to study medication
- All serious adverse events (SAEs)
- All SAEs causally related to study medication
- AEs leading to discontinuation of olaparib/placebo
- AEs leading to discontinuation of olaparib/placebo, causally related to olaparib/placebo
- Other significant AEs
- Other significant AEs causally related to olaparib/placebo

An overall summary of the number and percentage of patients in each category will be presented, as will an overall summary of the number of episodes in each category. In addition, a truncated AE table of most common AEs, showing all events that occur in at least

5% of patients overall will be summarised by preferred term, by decreasing frequency. This cut-off may be modified after review of the data.

Each AE event rate (per 1000 patient years) will also be summarised by preferred term within each system organ class. For each preferred term, the event rate will be presented and will be defined as the number of patients with that AE divided by the sum of the duration from the start of treatment to 30 days after the last treatment dose (for patients without the event) and the time to the AE (for patients with the event) in each group multiplied by 1000.

AEs will be assigned CTCAE grades (National Cancer Institute (NCI) CTCAE version 4.0) and summaries of the number and percentage of patients will be provided by maximum reported CTCAE grade, system organ class, preferred term and actual treatment group. Fluctuations observed in CTCAE grades during study will be listed.

Summaries of the number and percentage of patients with AEs leading to dose modification of olaparib/placebo by preferred term and treatment group will be presented for the following:

- AEs leading to a dose reduction of olaparib/placebo
- AEs leading to a dose interruption of olaparib/placebo
- AEs leading to a dose modification, defined as a dose interruption and/or dose reduction of olaparib/placebo.

In addition, AEs with outcome of death, SAEs, AEs leading to discontinuation of treatment, AEs causally related to olaparib/placebo and OAEs will be listed.

A summary of deaths will be provided with number and percentage of patients by actual treatment group, categorised as:

- Death related to disease under investigation only
- Death related to disease under investigation only (death > 30 days after last treatment dose)
- AE with outcome of death only
- AE related to disease under investigation and with AE outcome of death
- AE with outcome of death only (AE start date falling >30 days after last treatment dose)
- Deaths > 30 days after last treatment dose, unrelated to AE or disease under investigation

- Deaths >30 days after last treatment dose, AE related to disease under investigation and with AE outcome of death,
- Patients with unknown reason for death.

A corresponding listing will also be produced.

A separate summary will be produced that presents any events that occur prior to dosing or starting more than 30 days after discontinuing therapy.

Summary tables will also be produced for the following common adverse events, based on grouped preferred terms:

- Anaemia
- Neutropenia
- Thrombocytopenia
- Nausea
- Vomiting
- Fatigue/Asthenia

The specific preferred terms to be included in the summaries will be provided prior to database lock.

### **Summary of long term tolerability**

For each AE, median time to first onset of the AE will be presented in patients in the safety analysis set by actual treatment group. Patients who did not experience the AE will not be included in the summaries. Summary tables of time to first onset for each AE will also be produced (e.g. 1-28 days, 29-56 days, 57-84 days, 85-112 days, >112 days). Median duration of the AE will be presented in patients who experienced each AE.

### **Laboratory assessments**

Box-plots of absolute values and change from baseline for a selection of continuous laboratory assessments will be presented.

For all continuous laboratory assessments, absolute value, change from baseline and percentage change from baseline will be summarised using descriptive statistics at each scheduled assessment time by actual treatment group. For categorical laboratory assessments, shift from baseline will be summarised using frequency and proportion at each scheduled assessment time by actual treatment group.

Shift tables for laboratory values by worst common toxicity criteria (CTC) grade will be produced, and for specific parameters separate shift tables indicating hyper- and hypo-directionality of change will be produced. For parameters with no CTCAE grading, shift tables from baseline to worst value on-treatment will be provided (i.e. on-treatment is defined as data collected up until 30 days after the last dose of olaparib/placebo).

A scatter plot of ALT versus total bilirubin, both expressed as multiples of ULN, will be produced. The scatter plot will be repeated for AST versus total bilirubin.

Liver biochemistry test results over time for patients with elevated ALT or AST, and elevated total bilirubin (at any time) will be plotted. Individual patient data where ALT or AST plus total bilirubin are elevated at any time will be listed also.

Urinalysis results (categorical data collected at baseline and only if clinically indicated post-baseline) will be listed only.

Clinically significant laboratory results will be flagged and listed. Reference ranges will also be listed. All laboratory summaries and listings will be presented by actual treatment group.

### **ECGs**

ECG data will be listed by actual treatment group.

### **Vital signs**

Vital signs (SBP, DBP, pulse rate, body temperature and weight) will be summarised over time in terms of absolute values and changes from baseline at each scheduled measurement by actual treatment group. Vital signs data will be listed by actual treatment group.

Selected safety data will also be summarised and listed at the time of updated OS analysis (approximately 60% maturity for OS).

#### **4.2.12 Demographic and baseline characteristics data**

The following will be listed and summarised by randomised treatment group:

- Patient disposition (including screening failures and reason for screening failure)  
This will also include the number (%) of patients who at two years had no evidence of disease and so discontinued study treatment
- Important deviations
- Inclusion in analysis populations
- Demographics (age, age group, sex, race and ethnicity)

- Patient characteristics at baseline (height, weight, weight group (<65, 65-90, > 90), body mass index (BMI) and body mass index group ('Normal (<25)', 'Overweight (25-30)' and 'Obesity (>30)')
- Stratification factors recorded on the eCRF
- Stratification factors according to the randomisation
- Patient recruitment by country and centre
- Previous ovarian cancer therapy
- Previous therapy for other cancer
- Disease characteristics at baseline (ECOG performance status, *BRCA* gene name at screening [*BRCA1*, *BRCA2* or Both or Missing] confirmed locally and by Myriad, *gBRCA* status confirmed locally and by Myriad testing [*gBRCAm*, *gBRCA wt*, *gBRCA VUS*, Missing], *tBRCA* status confirmed by Foundation Medicine testing [*BRCAm*, *BRCA wt*, *BRCA VUS*, Missing], primary tumour location, histology type, tumour grade, International Federation of Gynecology and Obstetrics (FIGO) stage, time from previous platinum chemotherapy to reandomisation, baseline CA-125 value, On-study baseline tumour biopsy and overall disease classification)
- Extent of disease
- Disease related medical history (including number of regimens of previous platinum chemotherapy)
- Relevant surgical history
- History of debulking surgery
- Number of blood transfusions
- Physical examination at baseline
- Time from completion of first line platinum chemotherapy to randomisation
- Disallowed concomitant medications
- Allowed concomitant medications
- Post-discontinuation cancer therapy

- Radiotherapy (previous, on randomised treatment and post-treatment discontinuation)
- BRCA mutation status (by Local germline and Myriad germline, by Myriad germline and tumour BRCA and by Local germline and tumour BRCA)
- Deleterious and suspected deleterious mutation types in germline and tumour BRCA patients

AZ drug dictionary (AZDD) will be used for concomitant medication coding.

Age will be derived as age at last birthday in whole years using the date of randomisation and date of birth. Where a partial date of birth has been collected, the following imputation rules will be applied in order to calculate the patient's age for use in listings and summaries tables presenting age and/or age group and subgroup analyses based on age:

- If only the month and year of birth has been collected, the day of birth will be imputed as 15<sup>th</sup>
- If only the year of birth has been collected the day and month of birth will be imputed as 1<sup>st</sup> July
- If the date of birth is completely missing, the derived age of the patient will also be missing.

Date of birth will be listed as it has been collected on the eCRF.

Overall disease classification will be categorised as follows:

- If a patient has any site of metastatic disease, they are classified as 'Metastatic',
- If a patient has no sites of metastatic disease and does have sites of local disease they are classified as 'local'
- Else if they have no sites of disease identified and no target lesions present at baseline and no non-target lesions present at baseline (as assessed by the investigator) and they do have a valid investigator assessed baseline scan, they are classified as 'NED',
- Else classified as 'unknown'

Partial dates for start and end of concomitant medications will be derived as per date of onset and date of resolution for adverse events, respectively.



Patients who were unblinded (a) prior to disease progression and (b) prior to or on the day of treatment discontinuation will be listed.

A listing containing both the eCRF BRCA results and the Myriad gBRCA and Foundation Medicine tBRCA results will be produced.

Patients disposition data will also be summarised and listed at the time of updated OS analysis (approximately 60% maturity for OS).

#### **4.2.13 Treatment exposure**

The following summaries related to study treatment will be produced for the safety analysis set by actual treatment group:

- Total exposure of olaparib/placebo.
- Actual exposure of olaparib/placebo.
- Reasons for dose reductions, dose interruptions, and dose modifications of olaparib/placebo. Dose reductions and dose interruptions will be based on investigator initiated dosing decisions. Dose interruptions due to “Subject Forgot to Take Dose” will be omitted from these summaries.
- Number of dose reductions, dose interruptions, and dose modifications of olaparib/placebo that last for a period of three days or more.
- PID and RDI of olaparib/placebo (entire intended treatment period).

For patients on study treatment at the time of the PFS analysis, the DCO date will be used to calculate exposure.

All treatment information data will be listed for the safety analysis set by actual treatment group.

Selected exposure data will also be summarised and listed at the time of updated OS analysis (approximately 60% maturity for OS).

#### **4.2.14 Data cut-offs**

The status of ongoing, withdrawn (from the study) and “lost to follow-up” patients at the time of the PFS analysis (initial OS analysis) and at the time of the final OS analysis should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patients general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

## 5 INTERIM ANALYSES

No interim analyses of PFS prior to the primary analysis will be performed; however additional analyses of PFS and/or OS may be performed to meet Regulatory Agency requests.

This study will use an external independent data monitoring committee (IDMC) to perform interim reviews of accumulating study safety data. This committee will be composed of therapeutic area experts and statisticians, who are not employed by AZ, and do not have any major conflict of interest. Following the review the IDMC will recommend whether the study should continue unchanged, be terminated, or be modified in any way. Once the IDMC has reached a recommendation, a report will be provided to AstraZeneca. The report will only include the recommendation and any potential protocol amendments and will not contain any unblinding information.

A separate IDMC charter will be developed which will contain details of the IDMC members and clearly define the responsibilities of the IDMC.

A set of outputs using the data from subjects recruited in Japan will be produced at the time of the primary analysis for Japanese regulatory purposes. The outputs will be repeats of a selection of the main set of outputs and the results will not be described in the clinical study report, but rather will be described in a separate standalone report. In addition some repeats of output will be produced for subjects recruited in Japan at OS timepoint.

## 6 CHANGES OF ANALYSIS FROM PROTOCOL

All efficacy and HRQoL will be analysed using FAS.

### *Section 3.2.1 Progression free survival*

Added clarification that according to the RECIST 1.1 guidelines an overall visit response of PD also requires an absolute increase of  $> 5$  mm in the sum of the diameters of the target lesions.

### *Section 3.2.7 Time to earliest progression by RECIST or CA-125 or death*

Derivations will be relative to randomization (CSP states start of study treatment). Also, censoring will use the earliest of the last evaluable RECIST assessment or the last available CA-125 measurement (CSP states most recent).

## 7 REFERENCES

### **Alsop et al 2012**

Alsop K, Fereday S, Meldrum C, DeFazio A, Emmanuel C, George J, et al. BRCA Mutation Frequency and Patterns of Treatment Response in BRCA Mutation–Positive Women With

Ovarian Cancer: A Report From the Australian Ovarian Cancer Study Group. *J Clin Oncol* 2012;30:2654-63.

**Amit et al 2011**

Amit O, Mannino F, Stone Am et al. Blinded independent central review of progression in cancer clinical trials: results from a meta-analysis and recommendations from a PhRMA working group. *European J Cancer* 2011; 47:1772-1778.

**Basen-Engquist K et al 2001**

Basen-Engquist K, Bodurka-Bevers D, Fitzgerald MA, Webster K, Cella D, Hu S, et al. Reliability and validity of the functional assessment of cancer therapy-ovarian. *J Clin Oncol*. 2001 Mar 15;19(6):1809-17.

**Berry et al 1999**

Berry G, Kitchin RM and Mock PA. A comparison of two simple hazard ratio estimators based on the logrank test. *Statistics in Medicine* 1991; 10(5):749-755

**Cella D et al 1993**

Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*. 1993 Mar;11(3):570-9.

**Collett 2003**

Modelling Survival Data in Medical Research, Second Edition. CRC Press, 2003

**FACT-O Scoring Manual**

FACT-O Scoring Manual. See URL: [www.facit.org](http://www.facit.org)

**Gail and Simon 1985**

Gail M, Simon R. Testing for qualitative interactions between treatment effects and patient subsets. *Biometrics* 1985;41:361-72.

**Haybittle J L 1971**

Haybittle, J L 1971. Repeat assessment of results in clinical trials of cancer treatment. *British Journal of Radiology*. 1971 Oct; 44:793-7

**Hsu and Taylor 2009**

Hsu CH and Taylor J: Nonparametric comparison of two survival functions with dependent censoring via nonparametric multiple imputation, *Statist. Med.* 2009; 28:462–475

**Huang 2012**

Qin Huang, Gang Chen, Zhilong Yuan, K K Gordan Lan: Design and sample size considerations for simultaneous global drug development program. *J Biopharm Stat* 2012 Sep;22(5):1060-73

**Jackson et al 2014**

Jackson D, White IR, Seaman S, Evans H, Baisley K, Carpenter J. Relaxing the independent censoring assumption in the Cox proportional hazards model using multiple imputation, *Statist. Med.* 2014; 33(27): 4681-94

**Osoba et al 2005**

Osoba D, Bezjak A, Brundage M, et al: Analysis and interpretation of health-related quality-of-life data from clinical trials: Basic approach of The National Cancer Institute of Canada Clinical Trials Group. *Eur J Cancer* 41:280-287, 2005

**Sellke and Siegmund 1983**

Sellke, T. and Siegmund, D. Sequential analysis of the proportional hazards model. *Biometrika* 1983 70: 315-326

**Stone 2010**

Stone, A. The application of bespoke spending functions in group sequential designs and the effect of delayed treatment crossover in survival trials. *Pharm. Statistics* 5 (2010) 151-161

**Sun and Chen 2010**

Sun X and Chen C. Comparison of Finkelstein's Method With the Conventional Approach for Interval-Censored Data Analysis. *Stat Biopharm Research* 2010;2:1:97-108.

**van Hout et al 2012**

Ben van Hou, M.F. Janssen, You-Shan Feng, Thomas Kohlmann,, Jan Busschbach et al. Interim Scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L Value Sets. *Value in Health* 2012; 15: 708-715.

**Wei LJ et al 1989**

Wei LJ, Lin DY, Weissfeld L. Regression-analysis of multivariate incomplete failure time data by modelling marginal distributions. *Journal of the American Statistical Association* 1989; 84:1065-73.