

1 **Overall survival with maintenance olaparib in BRCA1/2-mutated**
2 **platinum-sensitive relapsed ovarian cancer (SOLO2/ENGOT-**
3 **Ov21): a randomised, placebo-controlled, phase 3 trial**

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55 **Summary**

56 **Background**

57 The PARP inhibitor olaparib significantly improved progression-free survival versus
58 placebo (HR 0.30 [95% CI 0.22–0.41]) in BRCA-mutated platinum-sensitive relapsed
59 ovarian cancer patients in the SOLO2/ENGOT-Ov21 trial. We report the final overall
60 survival (OS) analysis.

61 **Methods**

62 This double-blind, randomised trial was performed across 123 sites (16 countries).
63 Eligible patients had histologically confirmed, relapsed, high-grade serous ovarian or
64 endometrioid cancer and received ≥ 2 previous platinum regimens. Patients were
65 randomised 2:1 to olaparib tablets (300 mg twice daily) or placebo through a web or
66 voice-response system, with stratification by response to previous chemotherapy
67 (complete or partial) and length of platinum-free interval (>6 -12 or >12 months).
68 Masking occurred in patients, treatment providers, and data assessors. OS
69 (secondary endpoint) was analysed in the intention-to-treat population. Safety
70 analyses included patients who received ≥ 1 treatment dose. This trial, registered with
71 ClinicalTrials.gov (NCT01874353), is not recruiting patients.

72 **Findings**

73 295 patients, enrolled between September 3, 2013, and November 21, 2014, received
74 olaparib (n=196) or placebo (n=99). One patient (randomised in error) did not receive
75 olaparib. Median follow-up was 65.7 months (IQR 63.6–69.3) with olaparib and
76 64.5 months (IQR 63.4–68.7) with placebo. Median OS was longer with olaparib

77 (51.7 months [95% CI 41.5–59.1]) versus placebo (38.8 months [95% CI 31.4–48.6];
78 HR 0.74 [95% CI 0.54–1.00], p=0.054; unadjusted for subsequent PARP inhibitor
79 therapy). The most common grade ≥ 3 treatment-emergent adverse event (TEAE) was
80 anaemia (41 [21%] of 195 olaparib patients; 2 [2%] of 99 placebo patients). Fifty (26%)
81 olaparib patients and eight (8%) placebo patients reported serious TEAEs. TEAEs with
82 a fatal outcome occurred in eight (4%) olaparib patients.

83 **Interpretation**

84 In SOLO2, the first phase 3 trial to our knowledge that provides final OS data on
85 maintenance olaparib, olaparib prolonged median OS by 12.9 months over placebo
86 (unadjusted for subsequent PARP inhibitor therapy).

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89

90 **Introduction**

91 Patients with relapsed ovarian cancer usually receive multiple lines of chemotherapy,
92 with time to relapse typically shortening with each successive line of treatment.¹
93 Treatment goals in the relapsed setting include delaying symptomatic disease
94 progression and prolonging survival.² Improvements in overall survival (OS) are
95 difficult to demonstrate in ovarian cancer trials due to crossover and longer post-
96 progression survival associated with post-progression therapies.^{3,4}

97 The poly(ADP-ribose) polymerase (PARP) inhibitor olaparib is approved in
98 numerous countries as maintenance therapy for patients with platinum-sensitive
99 relapsed ovarian cancer, regardless of *BRCA1* and/or *BRCA2* (BRCA) mutation
100 status.⁵⁻⁸ Olaparib is also approved as maintenance therapy in the newly diagnosed
101 setting.^{5,6,9,10}

102 In the primary analysis of the phase 3 SOLO2/ENGOT Ov-21 trial,
103 maintenance olaparib provided a significant progression-free survival (PFS) benefit
104 versus placebo (hazard ratio [HR] 0.30 [95% confidence interval [CI] 0.22–0.41],
105 $p < 0.0001$; median 19.1 months [95% CI 16.3–25.7] vs 5.5 months [95% CI 5.2–5.8])
106 in patients with platinum-sensitive relapsed ovarian cancer and a BRCA mutation.¹¹
107 Olaparib tablets had a manageable tolerability profile.

108 Here, we report final OS and long-term safety data of maintenance olaparib in
109 patients with platinum-sensitive relapsed ovarian cancer and a BRCA mutation.

110 **Methods**

111 **Study design and participants**

112 This international, randomised, double-blind, placebo-controlled, phase 3 trial
113 (SOLO2/ENGOT-Ov21; NCT01874353) was performed according to the European
114 Network for Gynaecological Oncological Trial groups (ENGOT) Model C,¹² across 123
115 sites in 16 countries (appendix pp 2–3). The trial was conducted in accordance with
116 the Declaration of Helsinki, Good Clinical Practice guidelines, and the AstraZeneca
117 policy on bioethics.¹³

118 Eligible patients were aged ≥ 18 years, had an Eastern Cooperative Oncology
119 Group performance status 0–1 and histologically confirmed, relapsed, high-grade
120 serous ovarian cancer (including primary peritoneal or fallopian tube cancer) or high-
121 grade endometrioid cancer. Patients had received at least two previous lines of
122 platinum-based chemotherapy, were in objective response (according to modified
123 Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1 or CA-125 levels)
124 to their most recent platinum regimen, and had platinum-sensitive disease (disease
125 progression ≥ 6 months after the last dose of platinum-based chemotherapy) following
126 the penultimate line of chemotherapy before enrolment.

127 Eligible patients had a documented deleterious, or suspected deleterious,
128 BRCA mutation based on either blood or tumour testing. All patients consented to
129 providing two blood samples for confirmatory germline BRCA mutation testing using
130 the Myriad BRCAAnalysis[®] test (Myriad Genetic Laboratories, Inc., Salt Lake City, UT,
131 USA). Patients with a known BRCA mutation before randomisation could enter the trial
132 based on this information; patients with unknown BRCA mutation status were

133 screened prior to randomisation. Although patients with either somatic or germline
134 BRCA mutations were eligible for randomisation, all patients randomised in SOLO2
135 were found to harbour a germline BRCA mutation.

136 Patients were ineligible if they were previously treated with a PARP inhibitor or
137 had received any systemic chemotherapy or radiotherapy (except for palliative
138 reasons) within 3 weeks prior to study treatment. Patients with myelodysplastic
139 syndrome (MDS) or acute myeloid leukaemia (AML) were ineligible.

140 The appendix contains the full eligibility criteria (pp 4–6) and latest protocol. All
141 patients provided written, informed consent. The trial is not recruiting patients.

142 **Randomisation and masking**

143 Patients were randomised 2:1 to maintenance olaparib tablets or placebo. A computer
144 software program (AstraZeneca's Global Randomization System) that generates
145 random numbers produced the randomisation scheme; this was loaded into the
146 interactive web or voice-response system database. Investigators or nominated
147 assistants contacted the interactive web or voice-response system centralised
148 randomisation centre for allocation of randomised treatment. Randomisation was
149 performed within 8 weeks of patients' last dose of chemotherapy, with stratification by
150 response to previous chemotherapy (complete or partial) and length of platinum-free
151 interval (>6–12 or >12 months).

152 Treatment masking was achieved using individual treatment codes provided by
153 the interactive web or voice-response system. Patients, treatment providers, data
154 collectors, and analysers were masked to the treatment assignment. Olaparib tablets

155 were manufactured at three sites: AbbVie Deutschland GmbH and Co. KGa
156 (Ludwigshafen, Germany), AbbVie Limited (Barceloneta, Puerto Rico), and
157 AstraZeneca AB (Södertälje, Sweden). Placebo tablets were manufactured at Penn
158 Pharmaceutical Services Limited (Gwent, United Kingdom). Olaparib and placebo
159 tablets appeared identical and were presented in the same packaging. Unmasking
160 was only permitted in medical emergencies where knowledge of the treatment
161 assignment is required for patient management.

162 **Procedures**

163 Patients were randomised to receive oral olaparib tablets (300 mg twice daily) or
164 matching placebo tablets (twice daily) until objective disease progression (modified
165 RECIST version 1.1) or until other discontinuation criteria were met (appendix p 6).
166 Treatment could continue beyond progression if the investigator deemed the patient
167 was experiencing benefit and did not meet other discontinuation criteria. Repeat dose
168 interruptions were permitted for a maximum of 14 days on each occasion (and were
169 required for grade 3–4 treatment-emergent adverse events [TEAEs]; National Cancer
170 Institute Common Terminology Criteria for Adverse Events [CTCAE] version 4.0) until
171 reversion to grade ≤ 1 or complete patient recovery. If toxicities reoccurred after re-
172 challenge with study treatment, and if further dose interruptions were considered
173 inadequate for toxicity management, dose reductions (to 250 mg twice daily and then,
174 if required, to 200 mg twice daily) or permanent treatment discontinuation could be
175 considered. Treatment switching from placebo to olaparib was not permitted; however,
176 patients could receive subsequent PARP inhibitor therapy as part of clinical practice.

177 Adverse events (AEs) were graded using National Cancer Institute CTCAE
178 version 4.0. Tumor assessments were performed with computed tomography or
179 magnetic resonance imaging every 12 weeks until week 72, then every 24 weeks
180 thereafter until disease progression. Physical examinations and measurements of vital
181 signs were performed on day 1, then every 4 weeks until week 72, then every
182 12 weeks thereafter. Measurements of haematology and clinical chemistry were
183 conducted on day 1, then every week until day 29, then every 4 weeks until week 72,
184 then every 12 weeks. After the data cut-off (DCO) for the primary analysis, all patients
185 were followed for disease progression and survival. Patients receiving study treatment
186 were followed up at least every 12 weeks for safety assessments and disease
187 progression. MDS/AML events and new primary malignancies were actively solicited
188 throughout the follow-up for overall survival.

189 **Outcomes**

190 We have previously reported data for PFS (defined as the time from randomisation
191 until objective radiological disease progression or death), which represented the
192 primary endpoint for this study.¹¹

193 Key secondary endpoints included in this final analysis are OS, time to first
194 subsequent therapy or death (TFST), time to second subsequent therapy or death
195 (TSST), time to study treatment discontinuation or death (TDT), exposure to olaparib
196 in patients receiving olaparib, and safety and tolerability.

197 **Statistical analysis**

198 Final OS analysis was planned for 60% maturity (~177 events). Survival outcomes for
199 the two interventions were compared using a log-rank test stratified by the stratification

200 factors and based on a two-sided significance level of 5%. Kaplan-Meier methods
201 were used to generate time-to-event curves, from which medians and survival
202 proportions were calculated. HRs and CIs were calculated with Cox proportional
203 hazards models, adjusting for the stratification factors. The same methods were used
204 to assess TFST, TSST, and TDT. For subgroup analyses of OS, a Cox proportional
205 hazards model including treatment, subgroup of interest and subgroup by treatment
206 interaction was used. SAS[®] version 9.4 (SAS Institute, Cary, NC, USA) was used for
207 the analyses.

208 Final OS, TFST, TSST, and TDT were analysed in the full analysis set (FAS;
209 all randomised patients). Duration of exposure to treatment and safety were analysed
210 in the safety analysis set (patients who received at least one treatment dose).

211 A prespecified exploratory OS analysis was performed using the rank preserving
212 structural failure time model (re-censored), to adjust for subsequent PARP inhibitor
213 therapy in the placebo group. Prespecified OS sensitivity analysis was conducted in
214 patients with a germline BRCA mutation confirmed by the Myriad BRCAAnalysis[®] test.
215 A post-hoc OS sensitivity analysis used electronic case report form (eCRF)
216 stratification variables to correct for patients who were mis-stratified at randomisation
217 (appendix, p 6). The 95% CIs of the HRs of the OS sensitivity, TFST, and TSST
218 analyses were unadjusted for multiplicity and inferences may not be reproducible.

219 An external independent data monitoring committee reviewed accumulating
220 safety data. The latest statistical analysis plan is available in the appendix.

221 **Role of the funding source**

222 The trial was designed by ENGOT and its lead group, GINECO (Groupe
223 d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens), in collaboration with
224 the sponsor, AstraZeneca. This article was written by the authors, with medical writing
225 support funded by the sponsor. All authors had access to the raw data and had roles
226 in data collection, analysis, and interpretation. The corresponding author had full
227 access to all the raw data and had final responsibility for the decision to submit for
228 publication.

229 **Results**

230 From September 3, 2013 to November 21, 2014, 602 patients were screened for
231 eligibility, of whom 295 patients were enrolled and randomised. Of 196 patients
232 assigned to olaparib, 195 received olaparib; one patient was randomised in error (due
233 to ineligibility for the trial) and did not receive olaparib. All 99 patients assigned to the
234 placebo group received placebo (figure 1). Final DCO occurred on February 3, 2020.

235 Baseline characteristics appeared well balanced between the two groups
236 (appendix p 7). A confirmed Myriad germline BRCA mutation was present in 190 (97%)
237 of 196 patients in the olaparib group and 96 (97%) of 99 patients in the placebo group.
238 Subsequent anticancer therapy modalities received following discontinuation of study
239 treatment are provided in the appendix (p 7). Following progression, 20 (10%) and 38
240 (38%) patients in the olaparib and placebo groups, respectively, received subsequent
241 PARP inhibitor therapy as either maintenance therapy following platinum-based
242 chemotherapy or as monotherapy (appendix p 8).

243 The mean total treatment duration was 29.1 (standard deviation [SD] 24.7;
244 interquartile range [IQR] 8.2–56.8) months for olaparib and 13.1 (SD 18.6; IQR 3.7–
245 11.0) months for placebo. At the primary analysis, the mean total treatment duration
246 was 17.4 months (SD 9.8) for olaparib and 9.0 months (SD 8.1) for placebo. At the
247 primary analysis, median follow-up for PFS was 22.1 months (IQR 21.9–27.4) with
248 olaparib and 22.2 months (IQR 8.3–27.5) with placebo in censored patients. At the
249 final analysis, median follow-up for OS was 65.7 months (IQR 63.6–69.3) with olaparib
250 and 64.5 months (IQR 63.4–68.7) with placebo.

251 The final OS analysis was performed after 181 of 295 patients had died (61%
252 maturity: 116 [59%] of 196 patients [olaparib] and 65 [66%] of 99 patients [placebo]).
253 Median OS was 51.7 months (95% CI 41.5–59.1) with olaparib and 38.8 months
254 (95% CI 31.4–48.6) with placebo (HR 0.74 [95% CI 0.54–1.00], $p=0.054$; FAS;
255 figure 2A and appendix p 8). The predefined threshold for statistical significance was
256 not met. By Kaplan-Meier estimates, 42% (95% CI 35–49) of patients in the olaparib
257 group and 33% (95% CI 24–43) of patients in the placebo group were alive at 5 years.

258 In the prespecified exploratory OS analysis that adjusted for subsequent PARP
259 inhibitor therapy in the placebo group in the FAS (181 events in 295 patients: 116
260 events in 196 olaparib patients and 65 events in 99 placebo patients; 61% maturity),
261 median OS was 51.7 months (95% CI 41.5–59.1) with olaparib and 35.4 months (95%
262 CI 24.2–43.5) with placebo (HR 0.56 [95% CI 0.35–0.97]; figure 2B and appendix
263 p 8). In the prespecified sensitivity analysis in patients with a germline BRCA mutation
264 confirmed by Myriad BRCAAnalysis[®] test (175 events in 286 patients: 111 events in
265 190 olaparib patients and 64 events in 96 placebo patients; 61% maturity), median OS
266 was 52.4 months (95% CI 41.5–61.4) with olaparib and 37.4 months (95% CI 29.8–

267 44.2) with placebo (HR 0.71 [95% CI 0.52–0.97], $p=0.031$; appendix pp 8, 16). In the
268 sensitivity analysis of OS using eCRF stratification variables in the FAS (181 events
269 in 295 patients: 116 events in 196 olaparib patients and 65 events in 99 placebo
270 patients; 61% maturity), median OS was 51.7 months (95% CI 41.5–59.1) with
271 olaparib and 38.8 months (95% CI 31.4–48.6) with placebo (HR 0.70 [95% CI 0.52–
272 0.96], $p=0.023$; appendix p 8). This analysis corrected for patients mis-stratified at
273 randomisation based on response to previous chemotherapy and length of platinum-
274 free interval.

275 OS subgroup analyses are shown in the appendix (p 17). Median OS was
276 67.4 months (95% CI 53.4–not calculable) with olaparib ($n=91$) and 49.2 months (95%
277 CI 34.0–not calculable) with placebo ($n=47$) for patients in complete response to prior
278 chemotherapy (HR 0.73 [95% CI 0.45–1.22]), and 39.2 months (95% CI 32.1–45.2)
279 with olaparib ($n=105$) and 34.0 months (95% CI 21.9–40.1) with placebo ($n=52$) for
280 patients in partial response (HR 0.79 [95% CI 0.54–1.18]). Median OS was
281 56.3 months (95% CI 43.9–67.4) with olaparib ($n=110$) and 37.4 months (95% CI
282 27.1–60.3) with placebo ($n=62$) in patients who had received two previous lines of
283 platinum-based chemotherapy (HR 0.78 [95% CI 0.53–1.18]; 41.5 months (95% CI
284 35.1–not calculable) with olaparib ($n=60$) and 38.8 months (95% CI 21.5–49.3) with
285 placebo ($n=19$) in patients who had received three previous lines (HR 0.68 [95% CI
286 0.37–1.30]); and 43.6 months (95% CI 22.7–59.1) with olaparib ($n=25$) and
287 40.1 months (95% CI 21.2–49.2) with placebo ($n=18$) in patients who had received at
288 least four previous lines (HR 0.90 [95% CI 0.45–1.87]).

289 In the final analysis, median TFST (225 events in 295 patients: 139/196 [71%]
290 in the olaparib group vs 86/99 [87%] in the placebo group; 76% maturity) was

291 27.4 months (95% CI 22.6–31.1) with olaparib and 7.2 months (95% CI 6.3–8.5) with
292 placebo (HR 0.37 [95% CI 0.28–0.48], $p < 0.0001$; unadjusted for multiplicity; appendix
293 p 18). By Kaplan-Meier estimates, 28% (95% CI 22.1–34.8) of patients in the olaparib
294 group and 13% (95% CI 7.0–20.3) of patients in the placebo group were alive and had
295 still not received a first subsequent treatment at 5 years. Median TSST (209 events in
296 295 patients: 130/196 [66%] in the olaparib group vs 79/99 [80%] in the placebo group;
297 71% maturity) was 35.8 months (95% CI 29.4–43.9) with olaparib and 18.9 months
298 (95% CI 15.5–21.5) with placebo (HR 0.51 [95% CI 0.39–0.68], $p < 0.0001$; unadjusted
299 for multiplicity; appendix p 18). Results for TDT are shown in the appendix (p 7).

300 Cumulative exposure of ≥ 5 years was seen in 43/195 (22%) patients in the
301 olaparib group and 9/99 (9%) patients in the placebo group, and cumulative exposure
302 of ≥ 2 years was seen in 87/195 (45%) and 13/99 (13%) patients, respectively (figure 3).

303 The most common grade 1–2 TEAEs were nausea, fatigue/asthenia, anaemia,
304 and vomiting (table 1 and appendix pp 9–12). The most common grade ≥ 3 TEAE in
305 the olaparib group was anaemia (table 1).

306 Serious TEAEs were reported in 50/195 (26%) patients receiving olaparib and
307 8/99 (8%) patients receiving placebo. At the primary analysis (DCO September 19,
308 2016), 35/195 (18%) patients receiving olaparib and 8/99 (8%) patients receiving
309 placebo had serious TEAEs. The most common serious TEAE was anaemia (eight
310 [4%] patients) in the olaparib group; and constipation (two [2%] patients) and small
311 intestinal obstruction (two [2%] patients) in the placebo group (appendix p 13).

312 At the primary analysis, one patient in the olaparib group had a TEAE with an
313 outcome of death. At the final analysis, 116/196 (59%) patients in the olaparib group

314 and 65/99 (66%) patients in the placebo group died during the trial; deaths related to
315 the disease under investigation occurred in 98/196 (50%) and 54/99 (55%) patients,
316 respectively. The causes of death for 2/196 (1%) patients in the olaparib group and
317 8/99 (8%) patients in the placebo group were recorded as unknown. TEAEs with an
318 outcome of death occurred in eight (4%) patients in the olaparib group and no patients
319 in the placebo group within the safety follow-up period (between first dose and 30 days
320 after the final treatment dose); in the olaparib group these were attributed to MDS/AML
321 (n=6), gastric adenocarcinoma (n=1), and plasma cell myeloma (n=1), which occurred
322 within the safety follow-up period. MDS/AML events were actively solicited after the
323 safety follow-up period. AEs with an outcome of death occurred in five (3%) patients
324 in the olaparib group after the safety follow-up period; these were all attributed to
325 MDS/AML. AEs with an outcome of death occurred in three (3%) patients in the
326 placebo group after the safety follow-up period; these were attributed to AML (n=1),
327 septic shock with MDS as a secondary cause of death (n=1), and respiratory distress
328 with MDS as a secondary cause of death (n=1). Three deaths, unrelated to AEs or the
329 disease under investigation, occurred in the olaparib group after the safety follow-up
330 period; these were attributed to intestinal obstruction (n=1), myocardial infarction
331 (n=1), and ovarian cancer (n=1, this patient was misclassified as having death not
332 caused by disease progression).

333 At the primary analysis, MDS/AML occurred in four (2%) patients in the olaparib
334 group (median follow-up: 22.1 months) and four (4%) patients in the placebo group
335 (median follow-up: 22.2 months). At the final analysis in the olaparib group (median
336 follow-up: 65.7 months), MDS/AML occurred in 16 (8%) patients; of these, nine (5%)
337 patients developed MDS/AML after the safety follow-up period. In the placebo group

338 (median follow-up: 64.5 months), all four (4%) cases of MDS/AML occurred after the
339 safety follow-up period (appendix p 14).

340 One (6%) olaparib patient and one (25%) placebo patient who developed
341 MDS/AML received subsequent chemotherapy and PARP inhibitor therapy. Five
342 (31%) olaparib patients and two (50%) placebo patients who developed MDS/AML
343 received subsequent chemotherapy only. A swimmer plot summarising the duration of
344 study treatment, subsequent therapy, and onset of MDS/AML is provided in the
345 appendix (p 19). The median time to onset of MDS/AML from randomisation was
346 3.0 years (IQR 2.3–3.8) with olaparib and 1.4 years (IQR 0.8–2.0) with placebo in the
347 FAS.

348 New primary malignancies occurred in eight (4%) patients in the olaparib group
349 and two (2%) patients in the placebo group, and pneumonitis occurred in three (2%)
350 patients and no patients, respectively (appendix p 14).

351 Dose interruptions because of TEAEs occurred in 97 (50%) patients in the
352 olaparib group and 19 (19%) patients in the placebo group at the final analysis, and
353 88 (45%) patients and 18 (18%) patients, respectively, at the primary analysis. Dose
354 reductions because of TEAEs occurred in 54 (28%) patients in the olaparib group and
355 three (3%) patients in the placebo group at the final analysis, and in 49 (25%) patients
356 and three (3%) patients, respectively, at the primary analysis. Treatment
357 discontinuations because of TEAEs occurred in 33 (17%) patients in the olaparib
358 group and three (3%) patients in the placebo group at the final analysis, and in 21
359 (11%) patients and two (2%) patients, respectively, at the primary analysis. Details of

360 TEAEs leading to dose interruptions, dose reductions, and treatment discontinuations
361 are provided in the appendix (pp 14–16).

362 **Discussion**

363 This analysis demonstrated a median OS improvement of 12.9 months with olaparib
364 over placebo (HR 0.74 [95% CI 0.54–1.00], $p=0.054$), despite 38% of patients in the
365 placebo group receiving subsequent PARP inhibitor therapy, although the predefined
366 threshold for statistical significance was not met. By Kaplan-Meier estimates, 28% of
367 patients in the olaparib group were alive and had still not received a first subsequent
368 treatment at 5 years, representing a patient-centred benefit of olaparib.

369 The final OS and sensitivity analyses show consistent OS benefits with olaparib
370 versus placebo. The treatment effect of olaparib was apparent in the analysis adjusted
371 for subsequent PARP inhibitor therapy in the placebo group, the analysis of patients
372 with a Myriad germline BRCA mutation, and the analysis that corrected for patients
373 who were mis-stratified at randomisation; the 95% CIs for the OS HR had upper limits
374 of 0.97, 0.97, and 0.96, respectively.

375 The longer-term tolerability profile of olaparib in this analysis was generally
376 consistent with that reported previously,^{11,14} and will be further explored. There was
377 only a small increase in TEAEs, dose modifications, and treatment discontinuations
378 with olaparib compared with the primary analysis, despite the longer treatment
379 duration.

380 MDS/AML events were actively solicited throughout the study treatment and
381 follow-up. At the final analysis of SOLO2, which investigates patients with BRCA-

382 mutated platinum-sensitive relapsed ovarian cancer who had received ≥ 2 previous
383 lines of platinum-based chemotherapy and received study treatment until disease
384 progression, MDS/AML occurred in 16 (8%) olaparib patients and four (4%) placebo
385 patients with a 5-year follow-up. In the olaparib group, nine (5%) patients developed
386 MDS/AML after the safety follow-up period (>30 days after the final dose of olaparib,
387 and during the survival follow-up). In the olaparib group, cumulative exposure of
388 ≥ 2 years was seen in 45% of patients. The increased incidence of MDS/AML with
389 olaparib versus placebo was observed in the context of the late onset of these events
390 and the extended OS observed with olaparib versus placebo. In the overall clinical trial
391 program across all indications, MDS/AML events occurred in $<1.5\%$ of patients at any
392 time after starting olaparib, including cases that were actively solicited during the long-
393 term follow up for overall survival.^{5,14,15} In the first-line setting, the risk of MDS/AML
394 remains at $<1.5\%$ at 5-year follow-up when maintenance olaparib treatment is
395 provided for a duration of 2 years in patients who had received one previous line of
396 platinum-based chemotherapy.^{14,15} The association between MDS/AML and olaparib
397 is being further explored.

398 Prior to this analysis, there had been difficulties in demonstrating OS
399 improvements in ovarian cancer patients since platinum-based chemotherapy was
400 introduced in the first-line¹⁶ and relapsed¹⁷ settings. Two phase 3 trials on molecularly
401 targeted therapy had not demonstrated significant OS improvements with the addition
402 of bevacizumab to platinum-based chemotherapy, followed by bevacizumab, in
403 women with platinum-sensitive relapsed ovarian cancer.^{18,19} Median OS was
404 33.6 months in the bevacizumab arm versus 32.9 months in the chemotherapy control
405 arm in OCEANS (HR 0.95 [95% CI 0.77–1.18], $p=0.65$),¹⁸ and 42.2 months (95% CI

406 37.7–46.2) versus 37.3 months (95% CI 32.6–39.7), respectively, in GOG-0213 (HR
407 0.83 [95% CI 0.68–1.01], $p=0.056$).¹⁹ In the intention-to-treat population of newly
408 diagnosed ovarian cancer patients from the phase 3 GOG-0218 trial, the bevacizumab
409 concurrent arm (HR 1.06 [95% CI 0.94–1.20]) and bevacizumab concurrent plus
410 maintenance arm (HR 0.96 [95% CI 0.85–1.09]) did not provide an OS advantage
411 compared with the chemotherapy control arm.²⁰ In an exploratory analysis of patients
412 with Stage IV disease, median OS was 42.8 months in the bevacizumab concurrent
413 plus maintenance arm versus 32.6 months in the chemotherapy control arm (HR 0.75
414 [95% CI 0.59–0.95]).²⁰

415 In the phase 2 Study 19 trial (NCT00753545), median OS was 34.9 months
416 (95% CI 29.2–54.6) with maintenance olaparib capsules and 30.2 months (95% CI
417 23.1–40.7) with placebo in patients with a BRCA mutation (HR 0.62 [95% CI 0.42–
418 0.93], $p=0.021$).²¹ In SOLO2, median OS was 51.7 months (95% CI 41.5–59.1) with
419 maintenance olaparib tablets and 38.8 months (95% CI 31.4–48.6) with placebo (HR
420 0.74 [95% CI 0.54–1.00], $p=0.054$), although the predefined threshold for statistical
421 significance was not met. Eleven (15%) of 74 patients with a BRCA mutation in Study
422 19 and 43 (22%) of 195 patients in SOLO2 received olaparib for at least 5 years,
423 demonstrating the patient-centred treatment benefit that olaparib provides in the
424 relapsed setting.²¹

425 OS improvements are difficult to demonstrate in ovarian cancer trials because
426 of crossover and longer post-progression survival associated with post-progression
427 therapies.^{3,4} The PFS benefit translating into OS prolongation with maintenance
428 olaparib in SOLO2 supports the potential use of PFS as a surrogate for OS in the
429 evaluation of PARP inhibitor therapy in ovarian cancer patients. While OS is the gold

430 standard efficacy endpoint in ovarian cancer trials, it is evaluated in combination with
431 PFS and intermediate clinical endpoints (such as time to second disease progression
432 and TSST) as the long post-progression survival and post-progression therapies of
433 ovarian cancer patients lead to difficulty in demonstrating OS improvements.²²
434 Additionally, a consensus statement on recurrent ovarian cancer reported that the
435 preferred endpoint for clinical trials is OS when the expected median OS is ≤ 12 months
436 and PFS when the expected median OS is >12 months.⁴

437 In this analysis, the absolute gain in OS was greater in patients in the olaparib
438 group who had received two or three previous lines of platinum-based chemotherapy
439 than in those who had received at least four previous lines. This favours the earlier
440 use of olaparib to achieve greater benefit in the relapsed setting. In the first-line setting,
441 the early introduction of olaparib could offer the greatest benefit. Substantial PFS
442 benefits were seen with olaparib versus placebo in patients with newly diagnosed
443 advanced ovarian cancer and a BRCA mutation in the phase 3 SOLO1 trial
444 (NCT01844986),¹⁴ and with olaparib plus bevacizumab versus bevacizumab in
445 patients with newly diagnosed advanced ovarian cancer who were positive for
446 homologous recombination deficiency in the phase 3 PAOLA-1 trial (NCT02477644).²³
447 Enduring PFS benefits were seen in patients following their completion of olaparib
448 therapy at 24 months in SOLO1 and PAOLA-1.^{14,23} In SOLO1, median PFS was
449 56.0 months with maintenance olaparib (median follow-up: 4.8 years) and
450 13.8 months (median follow-up: 5.0 years) with placebo (HR 0.33 [95% CI 0.25–
451 0.43]); 48% of olaparib patients versus 21% of placebo patients remained free from
452 disease progression or recurrence at 5 years.¹⁵ This represents a significant milestone
453 for PARP inhibitor therapy in the newly diagnosed setting.

454 SOLO2 is the first phase 3 trial to our knowledge that provides final OS data
455 on maintenance olaparib, the only PARP inhibitor with long-term follow-up data, in
456 patients with platinum-sensitive relapsed ovarian cancer and a BRCA mutation. In this
457 analysis, maintenance olaparib provided an unprecedented OS improvement of
458 12.9 months over placebo.

459 **Contributors**

460 AP was responsible for writing the manuscript. AF, JAL, RA, RTP, AMO, JK, TH, SP,
461 MF, AB, T-WP-S, KT, GSS, AL, J-HK, EAF, IV, and EP-L were responsible for
462 recruiting patients, conducting the trial, and obtaining the data. TM, ESL, and PR
463 analysed the data. All authors interpreted the data, and reviewed the draft and final
464 versions of the manuscript.

465 **Study groups**

466 Grupo Español de Investigación en Cáncer de Ovario (GEICO): AP. Groupe
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469 Research Council (NHMRC) Clinical Trials Centre: RA. SOLO2 US Consortium: RTP.
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480 **Declaration of interests**

481 Authors have completed the ICMJE form for disclosure of potential conflicts of interest
482 and the author statement form.

483 **Data sharing**

484 The redacted study protocol and statistical analysis plan is shared in the online
485 appendix of this Article.

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494 **Research in context**

495 **Evidence before this study**

496 We searched PubMed using the search terms “poly(ADP-ribose) polymerase inhibitor”
497 or “PARP inhibitor”, “ovarian cancer”, “maintenance”, and “platinum-sensitive

498 relapsed”, using no date or language restrictions. We found one trial design (olaparib
499 phase 3b OPINION study), primary and secondary results from the olaparib phase 2
500 Study 19, and primary results from the present olaparib phase 3 study, SOLO2.

501 **Added value of this study**

502 To our knowledge, olaparib is the only poly(ADP-ribose) polymerase (PARP) inhibitor
503 with long-term follow-up data and SOLO2 is the first phase 3 trial that provides final
504 overall survival (OS) data on maintenance therapy with a PARP inhibitor (olaparib) in
505 patients with platinum-sensitive relapsed ovarian cancer and a BRCA mutation.
506 Improvements in OS are difficult to demonstrate in ovarian cancer trials due to
507 crossover and use of post-progression therapies. However, this analysis showed an
508 unprecedented OS improvement of 12.9 months with maintenance olaparib over
509 placebo.

510 **Implications of all the available evidence**

511 Patients with relapsed ovarian cancer represent a challenging population to treat, and
512 usually receive multiple lines of chemotherapy, with time to relapse typically shortening
513 with each successive line of treatment. Prior to this analysis, limited progress had been
514 made in demonstrating OS improvements in ovarian cancer since the introduction of
515 platinum-based chemotherapy. The SOLO2 final analysis shows significant OS benefit
516 of maintenance olaparib for patients with platinum-sensitive relapsed ovarian cancer
517 and a BRCA mutation.

518

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600

601 **Table 1: Summary of treatment-emergent adverse events**

602

	Olaparib (n=195)			Placebo (n=99)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Nausea	142 (72.8%)	6 (3.1%)	0	35 (35.4%)	0	0
Fatigue/asthenia*	119 (61.0%)	11 (5.6%)	0	37 (37.4%)	2 (2.0%)	0
Anaemia [†]	48 (24.6%)	39 (20.0%)	2 (1.0%)	8 (8.1%)	2 (2.0%)	0
Vomiting	73 (37.4%)	5 (2.6%)	0	19 (19.2%)	1 (1.0%)	0
Diarrhoea	65 (33.3%)	2 (1.0%)	0	20 (20.2%)	0	0
Abdominal pain	49 (25.1%)	6 (3.1%)	0	28 (28.3%)	3 (3.0%)	0
Headache	49 (25.1%)	1 (0.5%)	0	14 (14.1%)	0	0
Constipation	46 (23.6%)	0	0	20 (20.2%)	3 (3.0%)	0
Decreased appetite	43 (22.1%)	1 (0.5%)	0	11 (11.1%)	0	0
Leukopenia [‡]	27 (13.8%)	4 (2.1%)	3 (1.5%)	2 (2.0%)	0	0
Neutropenia [§]	32 (16.4%)	11 (5.6%)	3 (1.5%)	2 (2.0%)	3 (3.0%)	1 (1.0%)
Dysgeusia	38 (19.5%)	0	0	6 (6.1%)	0	0

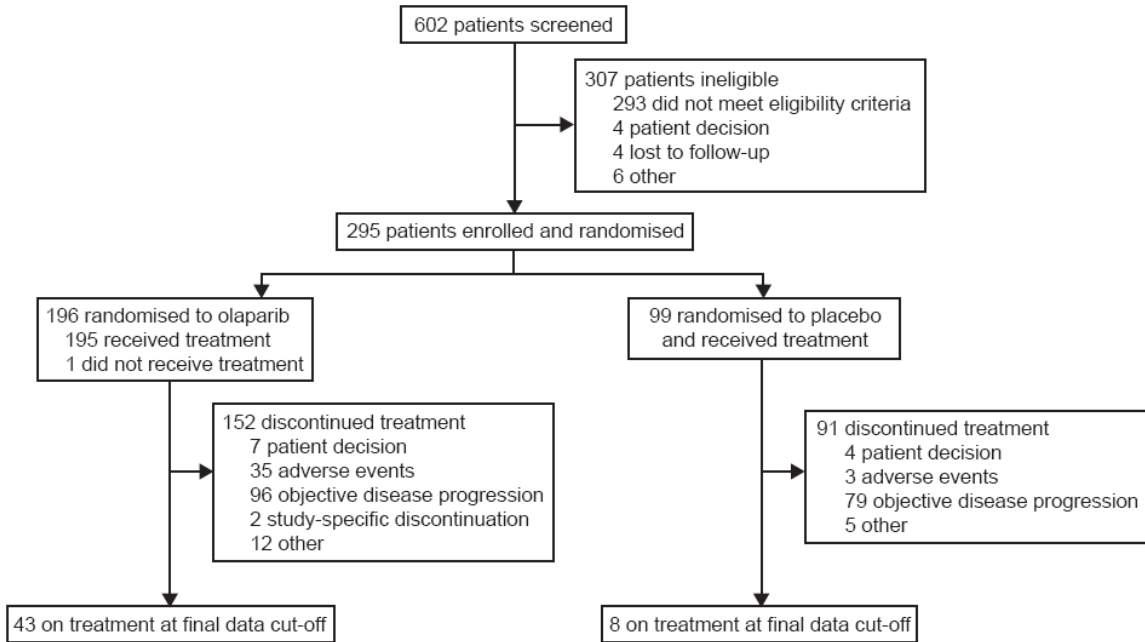
Cough	36 (18.5%)	1 (0.5%)	1 (0.5%)	6 (6.1%)	0	0
Dizziness	33 (16.9%)	1 (0.5%)	0	6 (6.1%)	0	0
Back pain	31 (15.9%)	0	0	12 (12.1%)	2 (2.0%)	0
Thrombocytopenia [¶]	28 (14.4%)	3 (1.5%)	1 (0.5%)	3 (3.0%)	1 (1.0%)	0
Arthralgia	31 (15.9%)	0	0	14 (14.1%)	0	0
Dyspepsia	29 (14.9%)	0	0	9 (9.1%)	0	0
Hypomagnesaemia	28 (14.4%)	1 (0.5%)	0	10 (10.1%)	0	0
Pyrexia	28 (14.4%)	0	0	6 (6.1%)	0	0
Nasopharyngitis	25 (12.8%)	0	0	11 (11.1%)	0	0
Dyspnoea	23 (11.8%)	2 (1.0%)	0	1 (1.0%)	0	0
Upper abdominal pain	23 (11.8%)	1 (0.5%)	0	13 (13.1%)	0	0
Elevated blood creatinine	21 (10.8%)	0	0	1 (1.0%)	0	0
Urinary tract infection	17 (8.7%)	3 (1.5%)	0	10 (10.1%)	0	0

603 Data are n (%). Data are shown for TEAEs that occurred in at least 10% of patients in either treatment group during study
604 treatment or up to 30 days after discontinuation of the intervention. The TEAEs were graded using CTCAE version 4.0. Where
605 indicated, the *Medical Dictionary for Regulatory Activities* (MedDRA) preferred terms for some adverse events have been

606 combined. TEAE= treatment-emergent adverse event. *Includes patients with fatigue and patients with asthenia. †Includes
607 patients with anaemia, decreased haemoglobin level, decreased haematocrit, or decreased red blood cell count. ‡Includes
608 patients with leukopenia and decreased white blood cell count. §Includes patients with neutropenia, febrile neutropenia,
609 neutropenic sepsis, or decreased neutrophil count. ¶Includes patients with thrombocytopenia or decreased platelet count.
610

611 **Figure legends**

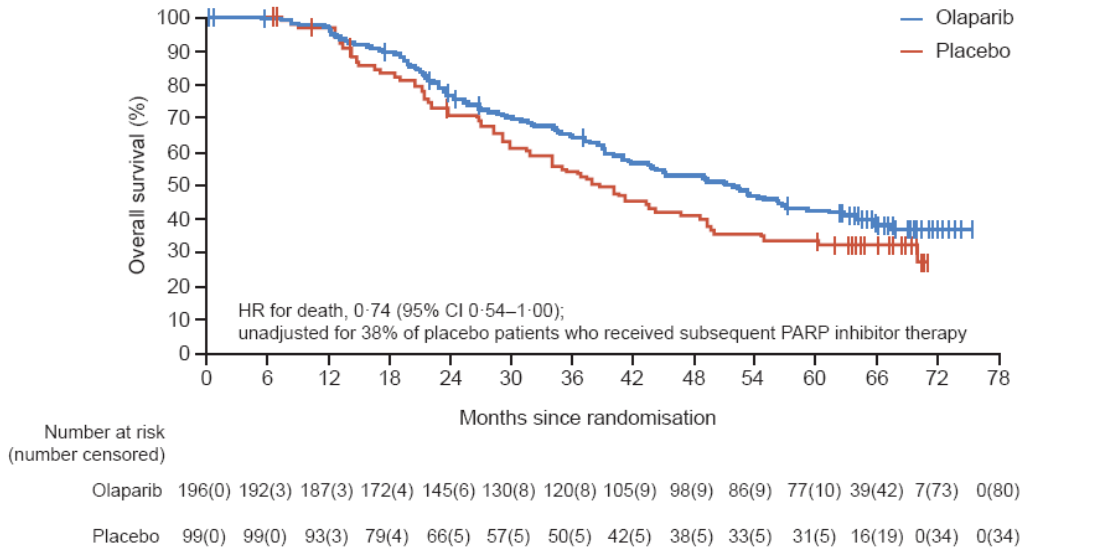
612 **Figure 1: Trial profile**



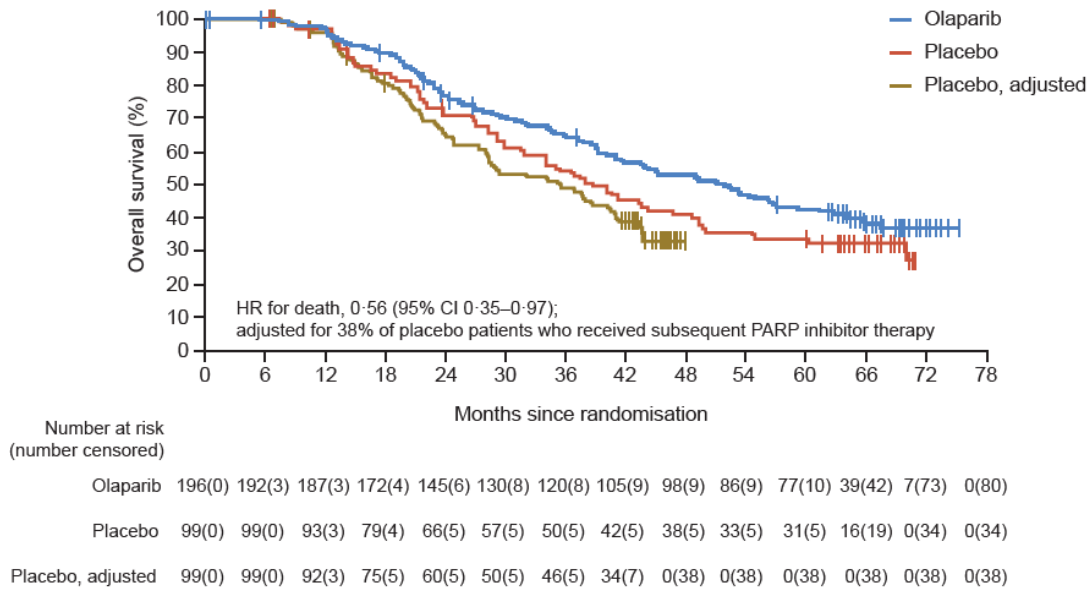
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615 **Figure 2: Kaplan-Meier estimates of (A) overall survival in the full analysis set**
 616 **and (B) overall survival in the full analysis set, adjusted for subsequent PARP**
 617 **inhibitor therapy in the placebo group**



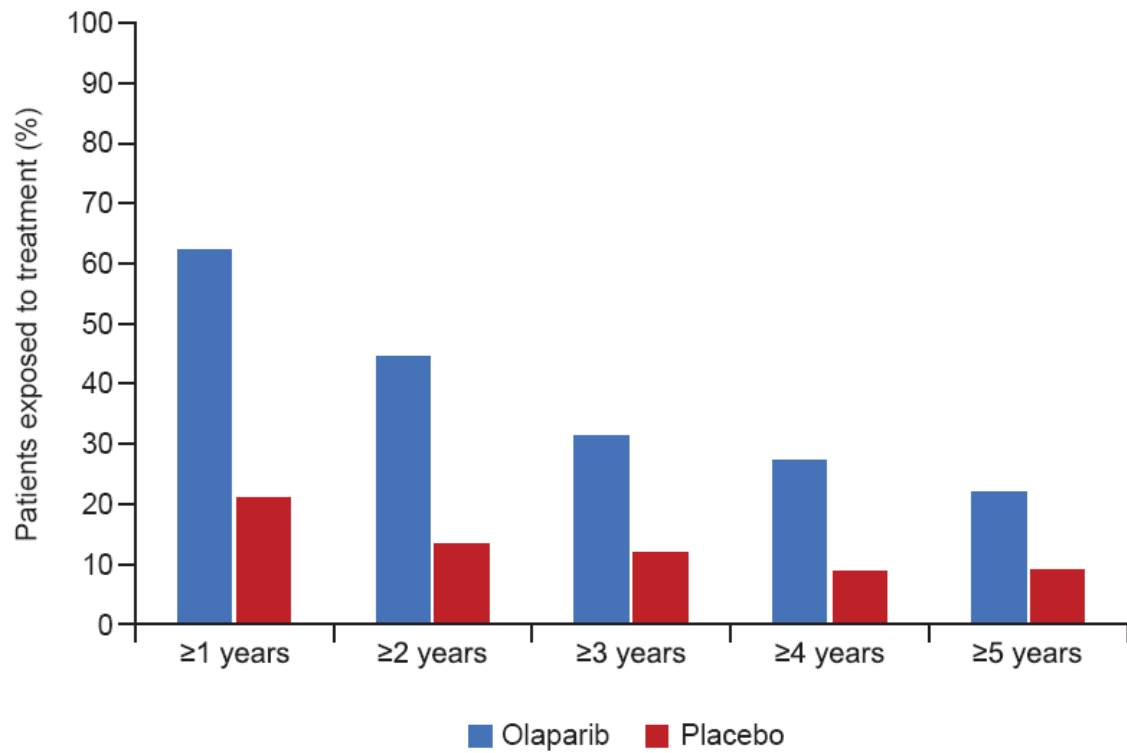
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620 The rank preserving structural failure time model (re-censored) was used to adjust for subsequent
 621 PARP inhibitor therapy in the placebo group. CI=confidence interval. HR=hazard ratio.
 622 PARP=poly(ADP-ribose) polymerase.

623 **Figure 3: Duration of exposure to treatment in the safety analysis set**



624