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Olaparib as maintenance therapy in patients with BRCA 1-2 mutated recurrent platinum sensitive ovarian cancer: Real world data and post progression outcome

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TITLE: Olaparib as maintenance therapy in patients with BRCA 1-2 mutated recurrent platinum sensitive ovarian cancer. A real world experience from the MITO group.

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42 **Abstract**

43 **Objectives:** Olaparib is approved as maintenance therapy in patients with BRCA mutated platinum sensitive
44 (PS) recurrent ovarian cancer (OC) after response to last platinum-based therapy. Few data are available
45 regarding the use out of the registration trials and **on response to further treatments after progression.**

46 **Materials ad methods:** In this non interventional, retrospective study, patients treated with olaparib in 13
47 centers, according to the label, have been collected and analyzed. Primary objectives of the study is to
48 describe effectiveness and safety of olaparib in a real world setting with a focus on post progression
49 treatments and response.

50 **Results:** 234 patients were analyzed. All patients were BRCA mutated and most of them had germline
51 mutations. Around 50% of the patients received olaparib after 3 or more lines of platinum-based
52 chemotherapy achieving a radiologic complete (CR) or partial response. 12.4% patients with stable disease
53 were also included. Median PFS was 14.7 months (95% CI:12.6-18), with statistically longer PFS in patients
54 with normal serum Ca125 at baseline, a CR after last platinum based therapy and that received olaparib after
55 second platinum-based therapy. Median OS was not reached. Most frequent G3-G4 toxicity was anaemia
56 (6%) **with dose discontinuation and dose reduction in 11 (4.7%) and 49 (20.9%) of cases, respectively.**
57 Among 66 patients receiving further treatment after olaparib progression and evaluable for response, ORR
58 was 22.2, 11.1% and 9.5% in patients with Platinum Free interval (PFI) of more than 12 months, between 6
59 and 12 months and less than 6 months, respectively.

60 **Conclusions:** **Olaparib is effective and safe in real world setting. Data on post-progression treatments seem**
61 **to suggest cross resistance with chemotherapy and need to be confirmed in larger studies because of the**
62 **potential importance in clinical practice decisions.**

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68 **Introduction**

69 Ovarian Cancer (OC) is the most lethal gynecological malignancy worldwide [1, 2]. Indeed, it is frequently
70 diagnosed at an advanced stage and despite optimal debulking surgery and platinum based chemotherapy,
71 about 70% of patients relapse [3]. Recurrent patients can be roughly divided in those that are not candidate to
72 receive a platinum rechallenge and those ~~seplatinum-sensitive (PS)~~, that are candidate to receive platinum
73 again [1, 4-6].

74 In the last years, new knowledge on OC biology showed that almost half of the High-Grade Ovarian Cancer
75 shows an alteration of Homologous recombination (HR) that is a high fidelity DSBs DNA repair mechanism,
76 active during cell replication [7, 8]. These alterations lead to HR Deficiency (HRD), causing a less preserved
77 DNA integrity and a higher response to DNA damaging agents like platinum compounds [9]. Among these
78 alterations, BRCA1 and 2 mutations account for 22.6% of mutations in HGSOCC~~and are related to increased~~
79 ~~risk of breast cancer and OC and a younger age at diagnosis, with 2/3 present at germline level and 1/3~~
80 ~~somatic~~. The patients carrying these mutations are highly responsive to platinum and this biological
81 characteristics have been exploited therapeutically with the use of PolyADP Ribose Polymerase Inhibitors
82 (PARPis), that historically act with a synthetic lethal mechanism, leading HRD cells to apoptosis [10, 11].
83 ~~Indeed they inhibit PARPs, a family of enzymes that repair DNA Single strand Break (SSB) via Base~~
84 ~~Excision Repair (BER) and promote a conservative DNA repair facilitatingHR and inhibiting Non~~
85 ~~Homologous End Joining (NHEJ), a less conservative mechanism of repair~~[12, 13]. *In vitro* studies shows
86 that BRCA1/2 mutated cell lines are really sensitive to cytotoxic activity of PARPis and clinical trials
87 confirmed that greatest benefit from PARPis is displayed in BRCA1/2 mutated patients, although an
88 interesting activity was seen also in BRCA wild type OCs [12, 14].

89 Among these drugs, olaparib was the first in class drug to be developed and approved in OC. Olaparib is an
90 oral inhibitor of PARP 1, PARP2 and PARP 3 [15, 16] that has been approved by EMA in 2014 as
91 maintenance for patients with relapsed, platinum sensitive (with interval between last dose of platinum
92 derivatives and progression longer than 6 months) BRCA-mutated (germline and/or somatic) HGSOCC with
93 complete or partial response (CR/PR) to last platinum-based chemotherapy [17]. This approval was based on
94 Study 19, a randomized, placebo controlled phase II trial [18].~~In this study 265 patients with PS recurrent~~

95 ~~OC in response to last platinum based chemotherapy were randomized to receive Olaparib 400 mg twice a~~
96 ~~day or placebo as maintenance therapy. This study showed a significantly longer PFS for experimental arm~~
97 ~~(8.4 vs 4.8 months with HR of 0.35 P<0.001) with a greater benefit in BRCA (germline and somatic)~~
98 ~~mutated subgroup (11.2 vs 4.3 months HR 0.18 P<0.0001) and a trend toward a benefit in OS, with 15~~
99 ~~patients receiving the drug for over 6 years[14, 18-20]Study 19 results that was confirmed by were confirmed~~
100 ~~by the and SOLO2 trial, an international, multicentre, phase III randomized, double blind, placebo controlled~~
101 ~~trial, that enrolled 295 BRCA mutated recurrent OC patients[21]. In this latter trial patients receiving~~
102 ~~olaparib maintenance therapy achieved an improvement These patients, after response to last platinum based~~
103 ~~chemotherapy, were randomized 2:1 to Olaparib in a new formulation (300 mg tablets, twice daily) or~~
104 ~~placebo until toxicity or progression. Primary endpoint was reached with an improvement of 13.6 months in~~
105 ~~PFS (19.1 vs 5.5 months in placebo arms, HR 0.30 p<0.0001) [21, 22].~~

106 In both **Study 19 and SOLO2** trials olaparib showed a safe profile, being the most frequent adverse events
107 nausea, fatigue, vomiting and diarrhea, above all Grade (G) 1-2 and the most frequent G3-G4 toxicity anemia
108 (18%). Treatment compliance was high with around 20% of the patients decreasing the dose due to toxicity
109 [21].

110 Although these results have modified clinical practice in this setting, real world data on the use of PARPis
111 are scarce, with short follow-up and small study populations [23-25], so there is the need to evaluate
112 effectiveness ~~efficacy~~ and safety of olaparib in a real world setting, ~~to understand if the results obtained in~~
113 ~~the selected patients included in the trials can be generalized to a wider and less selected population and,~~
114 ~~particularly if compliance to treatment is preserved also in everyday clinical practice~~[26, 27]. Moreover, we
115 have few data in the literature on post progression treatment and response.

116 MITO therefore has designed a multicentre non interventional retrospective study that analyzed data from
117 patients treated with olaparib in the general clinical practice, with the aim to describe effectiveness and
118 safety data of olaparib in a real life setting, with a focus on post progression treatment and outcome.

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121

122 **Materials and methods**

123

124 This is a non interventional, retrospective study conducted in 13 MITO (Multicenter Italian Trials in Ovarian
125 cancer and gynecologic malignancies) centers. The study has been approved by the ethical committee.

126 Archival data from consecutive patients treated with olaparib (400 mg, capsule formulation) according to the
127 EMA label from September 1st 2015 up to 31 May 2019 have been collected by the centers, centralized in the
128 coordinating institution (Istituto Nazionale per la Cura dei Tumori IRCCS Fondazione “G. Pascale” Napoli)
129 and analyzed. **Patients included in clinical trials were excluded.**

130 Primary objectives of the study is to describe effectiveness and safety of olaparib in a real world setting.
131 Effectiveness of olaparib maintenance treatment was described in terms of Overall Response Rate (ORR)
132 according to RECIST 1.1 [28], Progression Free Survival (PFS), and Overall Survival (OS). Incidence of
133 Adverse events (AEs), as well as dose reductions due to AEs were recorded. **Also, post progression treatment**
134 **and response were recorded and analyzed in all the patients experiencing a progression during olaparib**
135 **therapy.**

136 **Disease assessment was performed according to routine practice (every 3 months) and RECIST 1.1 response**
137 **was calculated locally. No central review was performed.**

138 Centers reported all AEs records, graded according to Common Terminology Criteria for Adverse events
139 (CTCAE) version 5.0 [29].

140

141 *Statistical analysis*

142 Baseline characteristics were analyzed according to descriptive statistics. Continuous variables were
143 described with median values and interquartile range; categorical variables were described in terms of
144 absolute numbers and proportion over the total number of patients analyzed.

145 PFS defined as time from first day of olaparib administration until disease progression (defined as objective
146 radiological disease progression using modified RECIST version 1.1 or clinical progression) or death.

147 Patients who did not experience disease progression were censored on the date of the last follow-up visit. OS
148 was defined from first day of olaparib administration to death for any cause or the last follow up visit for
149 living patients. PFS and OS curves were described according to the Kaplan Meier product-limit method and

150 compared with adjusted Log Rank test. Median follow-up was calculated according to the inverted Kaplan
151 Meier technique [30].

152 HR and 95% confidence interval (CIs) were estimate with multivariable Cox models including number of
153 lines, stage, residual disease at primary surgery, previous treatment with bevacizumab, age (continuous),
154 mutational status, ECOG and RECIST1.1 Response [31].

155 All the analyses were performed with STATA 14 MP (StataCorp. 2015. Stata Statistical Software: Release
156 14. College Station, TX: StataCorp LP.)

157

158

159 **Results**

160 *Patients characteristics*

161 Two hundreds and thirty-four patients were enrolled from 13 centers, treated from 13 June 2015 to 31 May
162 2019, cutoff date. Main characteristics of patients are showed in Table 1. Median age at diagnosis was 53,2
163 (IQR 46.6-59.4) years. About 71% of patients had an ECOG PS of 0, while 24.8% of patients had an ECOG
164 PS of 1 or 2; in 38,5% of the patients comorbidities were reported. All patients were BRCA mutated. About
165 70% of patients had a BRCA1 mutation, while 29.9% carried a BRCA 2 mutation, 1 patient was both BRCA
166 1 and BRCA 2 mutated. Most patients had germline BRCA mutation while 6.0% of patients had somatic
167 mutation. Only 42.7% of the patients had familiar history of ovarian or breast cancer and 15.4% of the cases
168 had personal history of breast cancer.

169 Most patients (75.2%) had FIGO stage III OC at diagnosis, 91.9% of patients had an HGSOE histology,
170 while the remaining patients had OC with other subtypes (above all high grade endometrioid cancer). More
171 than half patients were optimally debulked at diagnosis (60.3%) and almost all patients were treated with a
172 platinum doublet at diagnosis, being Carboplatin-Paclitaxel three weekly (48.3%) and Carboplatin-Paclitaxel
173 three weekly with Bevacizumab (41.5%) the most administered regimens. Median **initial** Platinum Free
174 Interval (time between the last cycle of platinum **during first line** and evidence of disease progression,
175 PFI) **after first line** was 18 (IQR 12-27.5) months.

176 Patient characteristics before olaparib administration are summarized in table 2.

177 Patients that received olaparib had a median PFI **after** last platinum therapy of 9.0 (5.0-14.2) months. In
178 47.4% of the patients olaparib was administered after second platinum-based line. Nevertheless, 41.0% and
179 11.5% of patients received olaparib after 3 and 4 or more lines of platinum based chemotherapy,
180 respectively. As for platinum based regimens, 86.3% of patients received a platinum doublet before
181 maintenance therapy with olaparib, while 10.3% of the patients received a platinum derivative alone. Most
182 patients had a radiologic PR (45.3%) or CR (38.9%) to last platinum based therapy, but 12.4% patients
183 received olaparib after a Stable disease (SD).

184

185 *Treatment effectiveness*

186 With a median follow up of 15.5 months (95% CI 13.0-18.2), 234 patients received at least one dose of
187 olaparib. One hundred and twenty three patients were evaluable for radiologic response with 35 CR, 22 PR
188 and an ORR of 46.3%. Among patients with SD after last platinum therapy, six patients out of 29 achieved a
189 PR or CR per RECIST (20.7%). At time of analysis 150 patients have received olaparib for at least 6 months,
190 85 patients for at least 12 months and 35 patients treated for more than 2 years. About 50% of the patients
191 are still on treatment at time of the analysis.

192 With 116 events recorded, median PFS (mPFS) was 14.7 months (95% CI:12.60-18.03) (Figure 1).

193 Explorative subgroups analysis have been performed (see Table 3 and Figure 2). Median PFS was
194 statistically longer in patients with normal serum Ca125 at baseline (cut off 35 UI/ml) (25.5 months vs7.9
195 months with and an adjusted HR of 2.5 (95% CI 1.5-4.3, p: 0.001). Also patients receiving olaparib after
196 second platinum based had longer PFS compared to those treated in third and in later lines, with a mPFS of
197 16.6, 15.5 and 8.2 months for patients treated in 2nd line, 3rd line and later lines [adjusted HR of 1.9 (95%
198 CI 1.1-3.5, p:0.031) and of 2.5 (95% CI 1.3-4.8, p: 0.004), respectively]. Patients achieving a CR after last
199 platinum based therapy had a statistically significant longer mPFS if compared with patients achieving a PR
200 [(33.4 vs 10.4 months), HR of 3.0 (95% CI 1.6-5.8 p:0.001)], and a SD [(33.4 vs 9.2 months), HR of 2.7
201 (95%CI 1.2-6.1, p: 0.017)], respectively.

202 No difference in mPFS was recorded according to stage and residual disease at primary surgery,
203 administration of Bevacizumab during first line treatment, ECOG PS, BRCA 1 or 2 status, age or previous
204 familiar history of BC or OC. Median OS was not reached with only 32 events recorded (Figure 1).

205 *Dose adjustment and safety*

206 Two hundred and twenty nine patients received olaparib at the recommended starting dose of 400 mg b.i.d,
207 while 5 patients received the drug at a reduced dose of 200 mg b.i.d since the beginning. Median treatment
208 discontinuation was 11.6 months and reason for discontinuation was progression or death in 108 patients

209 (46.2%) and toxicity in 11 (4.7%) of cases. Dose adjustment was required in 49 (20.9%) patients above all
210 for hematologic toxicities (anaemia in 33% of dose adjustments). Most frequently recorded toxicities were
211 nausea (35.7%) anaemia (35.7%) and fatigue (35.1%), above all G1 or 2. Most frequent G3-G4 toxicity was
212 anaemia (6%) (See Table 4 for all G3-G4 AEs).

213 There was no statistical difference in incidence of G3-G4 AEs according to interval between last cycle of
214 chemotherapy and first dose of olaparib maintenance therapy or according to line of therapy (2nd line versus
215 later line). There was no statistical difference in PFS between patients treated with recommended dose of 400
216 mg bid and patients requiring a dose reduction (or treated with reduced dose since the beginning).

217

218 *Post progression treatments*

219 Among 110 patients with progressive disease, 2 patients received endocrine therapy and 86 patients received
220 at least one further line of chemotherapy. Among these women, 25 had a PFI of more than 12 months, 39 a
221 PFI between 6 and 12 months and 24 a PFI of less than 6 months. Sixty-six patients were evaluable for
222 response.

223 Response to post progression therapy is reported in Table 5. Eighteen (72%) patients with PFI of more than
224 12 month were evaluable for response. Among these, 14 cases were treated with a platinum based therapy,
225 with 13 patients receiving platinum doublet and 1 patients receiving carboplatin as single agent. ORR was
226 22.2% (1 CR; 3 RP; 7 SD, 7 PD).

227 Among patients with PFI between 6 and 12 months, the most frequent treatment was a rechallenge with
228 platinum derivatives (35.9%, 14 patients), although 64.1% of patients received other therapies (12 patients
229 received trabectedin alone in the setting of MITO23 trial, 4 patients received trabectedin in combination with
230 liposomal pegilated doxorubicin). Among patients of this group evaluable for response, ORR was 11.1% (3
231 PR, 8SD; 16 PD).

232 Patients with PFI of less than 6 months received a monotherapy in the majority of the cases, being weekly
233 paclitaxel and trabectedin (9 and 4 patients respectively) the most frequently administered regimens. ORR
234 was 9.5% (1 CR and 1 PR) with a PD in 76.2% of the cases.

235 **Discussion**

236 This study analyzed 234 BRCA mutated recurrent patients with OC treated with olaparib as maintenance
237 after a platinum based chemotherapy. Median PFS was 14.7 months (95% CI:12.6-18), that is comparable to
238 the data of the registration trials, and a safe toxicity profile was also observed in this real life setting.
239 Interestingly patients progressed after olaparib and that were treated with chemotherapy had unexpected poor
240 response rate of 22.2, 11.1% and 9.5% in patients with a PFI of more than 12 months, between 6 and 12
241 months and less than 6 months, respectively.

242 Our study is the first work that reports data on post progression treatment and response after maintenance
243 therapy with olaparib, suggesting that RR is lower than expected. With the intrinsic limit of its retrospective
244 nature, this finding shed a light on one of the upcoming urgent clinical research need, being olaparib
245 maintenance therapy, a new standard also in first line treatment.

246 We currently know that olaparib and other PARPi maintenance therapy improved PFS in registration
247 randomized clinical trials in recurrent patients treated as maintenance after response to platinum based
248 chemotherapy. Namely, in Study 19 phase II trial patients receiving olaparib 400 mg twice a day as
249 maintenance therapy had a longer PFS (8.4 vs 4.8 months in placebo arm with HR of 0.35 P<0.001) with a
250 greater benefit in BRCA (germline and somatic) mutated subgroup (11.2 vs 4.3 months HR 0.18 P<0.0001)
251 and a trend toward a benefit in OS, [14, 18-20]. These data were later confirmed by the SOLO2 trial [21], in
252 which BRCA mutated patients receiving olaparib (300 mg tablets, twice daily) maintenance therapy had
253 significant benefit in PFS [21, 22]. After these results olaparib has been rapidly introduced in everyday
254 practice, modifying treatment algorithms. Nevertheless in SOLO2 and Study 19 trial, as usually in all
255 registration trials [14, 21], olaparib was administered to very selected patients from highly experienced
256 providers with very straight rules, timelines and schedules per protocol. This improved PFS obtained in an
257 ideal setting needs external validity in a less selected population.

258 Real world studies could be useful as a *"measure in understanding health care data collected under real life*
259 *practice circumstances"* (European Forum "Relative Effectiveness" Working group) [32], and the results can
260 help defining if drugs are effective also in real world setting. ~~with heterogeneous populations in centers with~~

261 ~~representative providers and outside straight rules of protocols. Moreover defining cost effectiveness of new~~
262 ~~drugs could be easier if results from clinical trials are straightened by real world studies.~~

263 Few results from olaparib real world use have been reported, with short follow up [25] or small population
264 [33], lacking essential clinical information like BRCA status [23] and focusing above all on safety.

265 This study is the first real world experience published *in extenso* including only BRCA mutated patients with
266 OC treated according to EMA label with olaparib maintenance therapy after platinum based therapy. Indeed,
267 as a result of a real world setting, 24.8% of our patients had ad ECOG PS of more than 0 and 38.5% had
268 registered comorbidities. Our study, as in the registration trials, includes patients receiving olaparib ~~after at~~
269 ~~least second line of platinum based therapy, with several cases treated after 3 or 4 lines of chemotherapy.~~

270 In our study median PFS was 14.7 months and ~~was 14.7 months. This result is-is~~ slightly lower than in the
271 SOLO2 trial (19.3 months) [21] (Table 6). This difference could be explained by the less selected population
272 including also some cases treated after a SD at the last platinum received. ~~Subgroup analyses identified~~
273 ~~patients with a longer PFS providing information that could be useful in patient consenting clarifying them~~
274 ~~the expectations of patients in this setting.~~ Indeed our analyses suggest that patients achieving a CR to last
275 platinum therapy and with low Ca 125 at baseline, have a better PFS when treated with olaparib ~~in terms of~~
276 ~~PFS~~, identifying a population that probably includes long responders to olaparib. This results are consistent
277 with data published by other groups [34, 35], although the prognostic role of Ca 125 has never been
278 reported in this setting and, if confirmed, could be an easy tool for clinicians to predict duration of treatment
279 with olaparib. Ca 125 data need also to be taken into account when indirectly comparing efficacy in trials
280 with different PARPi; in fact some registration trials included only patients with normalized Ca 125 [36].
281 ~~Although SOLO2 has demonstrated that the benefit of olaparib is evident independently from the number of~~
282 ~~previous line, we show that patients treated after 3 or 4 chemotherapy lines have significantly shorter PFS.~~
283 ~~We believe that this information can be useful for clinicians and patients when deciding the therapy,~~
284 ~~particularly where alternative regimens are available.~~

285 ~~In our series a small subgroup of patients with SD to last platinum based therapy was treated with olaparib~~
286 ~~achieving a ORR of 20.7%. Although this group of patients is small these data suggested an interesting~~
287 ~~activity also in this setting.~~

288 As for safety, data on AEs and dose reduction do not differ from results of SOLO 2 trial, confirming that
289 olaparib is a manageable drug also in everyday practice in a less fit population. Moreover dose reduction was
290 recorded in 20.9% of patients (a result similar to SOLO2 trial) and does not seem to worsen outcome in our
291 population.

292 We believe that an interesting data from our real world study is the post progression treatment efficacy in
293 this setting. In fact, we found that ORR to chemotherapy in patients evaluable for response is lower than
294 expected according to the PFI [37, 38]. In particular we found an ORR of only 22.2% in patients progressed
295 after a longer olaparib therapy, treated with platinum again after a PFI of more than 12 months. Due to the
296 fact that about 50% of the patients are still on treatment, these data will need further update and have to be
297 considered preliminary. Also, the retrospective nature of the trial that is based on self-reported response rate
298 require that our conclusions need to be confirmed. Nonetheless, we believe that this observation will prompt
299 further research in the field exploring cross resistance between PARPi and chemo, and if confirmed in
300 further studies, might have a significant impact on our clinical decisions.

301 The cross resistance suggested in our study has been demonstrated in preclinical models [39], and could play
302 a role also in the clinic. In fact, although in the registration trials it has been shown that the time to second
303 progression is prolonged in the arms treated with PARPis, the response to chemotherapy has not been
304 described and data may be important in the selection of the drugs to be used in clinical practice, with more
305 sequence studies needed in the future. These data may have also have a potential impact on the strategy of
306 PARPis after PARPis that is currently under investigation (NCT03106987, OReO study).

307 Our results seems to be in contrast with a retrospective study published by Kaye and colleagues [40] that
308 showed an ORR of 36% in 67 patients that progressed to olaparib and were treated with chemotherapy and
309 an ORR of 40% in 48 patients receiving a platinum derivative. Nevertheless they analyzed both platinum
310 sensitive and resistant patients that received olaparib not only as maintenance therapy but also as
311 monotherapy, with a median interval from start of olaparib and subsequent line of only 7.4 months making
312 the comparison between the two studies difficult due to different populations[40].

313 In conclusion we found that olaparib given in a real life setting of less selected patients is active and well
314 tolerated. Patients in CR and with normal Ca125 have longer PFS. Nevertheless Further studies will be
315 needed to clarify if these easy clinical parameters can help to identify the population of long responders cases

316 ~~that have been described with all the PARPi.~~ we found lower response rates than expected according to PFI in
317 patients treated with chemotherapy after olaparib progression. These data, although provocative, need to be
318 confirmed in further studies investigating this important aspect also in the first line scenario, and adding
319 translational studies evaluating the biological meaning of cross resistance between PARPi and
320 chemotherapy.

321

322

323 **Author contributions**

324 Dr. Cecere and Dr. Pignata are responsible for study concept and study design. Dr. Pignata is responsible for
325 Funding acquisition. Dr. Arenare and Dr, Giannone are responsible for quality control of data and
326 algorithms. Dr. Arenare, Dr. Cecere and Dr. Giannone are responsible for data analysis and interpretation.
327 Statistical analysis were performed by Dr. Arenare. Dr. Cecere, Dr. Giannone and Dr. Pignata prepared and
328 edited the manuscript. All authors acquired data and reviewed manuscript.

329 **Conflict of interest statement**

330 Dr. Cecere reports honoraria from AstraZeneca, Tesaro and Pharmamar, outside the submitted work. Dr.
331 Giannone reports grants from Roche, outside the submitted work. Dr. Salutari has been part of advisory
332 boards of AstraZeneca, PharmaMar, Tesaro, MSD, outside the submitted work. Dr. Lorusso has been part of
333 advisory boards and received institutional support for research from Immunogen, Genmab, Pharmamar,
334 Clovis, Tesaro, Merck, AstraZeneca, outside the submitted work. Dr. Bergamini reports honoraria from
335 AstraZeneca outside the submitted work. Dr. Orditura reports personal fees from Tesaro, outside the
336 submitted work. Dr. Valabrega reports speaking honoraria from AstraZeneca, Tesaro, Roche, Amgen,
337 PharmaMar and has been part of advisory boards of Tesaro, Amgen and PharmaMar, outside the submitted
338 work. Dr.Pignata reports honoraria from AstraZeneca, Tesaro Clovis, Roche,Pharmamar, MSD, Pfizer and
339 Research funding from AstraZeneca, MSD, Roche Pfizer outside the submitted work.Dr. Arenare,
340 Dr.Ronzino, Dr. Lauria, Dr. Cormio, Dr.Carella, Dr. Scollo, Dr. Ghizzoni, Dr. Raspagliesi, Dr. Di
341 Napoli,Dr. Mazzoni, Dr. Marchetti, Dr. Scambia, Dr. Maltese, Dr. De Matteis, Dr Cardalesi, Dr. Loizzi, Dr.
342 Boccia, Dr. Naglieri and Dr. Scandurra have nothing to disclose.

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345

347 **Table 1:** patients characteristics at diagnosis of ovarian cancer

Characteristic of patients	N=234 (%)
Age ,years	
Median, IQR	53.2 (46.6-59.4)
ECOG PS, n (%)	
0	167 (71.4)
1	48 (20.5)
2	10 (4.3)
Unknown	9 (3.8)
Comorbidities, n (%)	
Yes	90 (38.5)
No	123 (52.5)
Unknown	21 (9.0)
Familiar history for Breast or Ovarian cancer, n (%)	
Yes	100 (42.7)
No	118 (50.4)
Unknown	16 (6.8)
Personal history of Breast cancer, n (%)	
Yes	36 (15.4)
No	179 (76.5)
Unknown	19 (8.1)
BRCA status, n (%)	
BRCA 1 mutation	163 (69.7)
BRCA 2 mutation	70 (29.9)
BRCA 1 and BRCA 2 mutation	1 (0.4)
Type of mutation, n (%)	
Germline	153 (65.4)
Somatic	14 (6.0)

Unknown	67	(28.6)
Stage (FIGO) at diagnosis, n (%)		
I-II	27	(11.5)
III	176	(75.2)
IV	25	(10.7)
Unknown	6	(2.6)
Histology, n (%)		
Serous	215	(91.9)
Endometrioid	14	(6.0)
Clear cell	2	(0.9)
Mixed	1	(0.4)
Transitional	2	(0.9)
Residual, n (%)		
None	141	(60.3)
≤ 1 cm	41	(17.5)
> 1 cm	41	(17.5)
Unknown	11	(4.7)
Fist line treatment, n (%)		
Carboplatin- Paclitaxel three weekly+ Bevacizumab	97	(41.5)
Carboplatin Single agent	2	(0.9)
Carboplatin- Paclitaxel three weekly	113	(48.3)
Carboplatin Paclitaxel weekly	17	(7.3)
Others	5	(2.1)
PFI after first line,months		
Median, IQR	18.0	(12.0-27.5)

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350 **Table 2:** patients characteristics at time of olaparib administration

Characteristic of patients	N=234	(%)
Number of platinum based lines pre olaparib		
2	111	(47.4)
3-4	96	(41)
>4	27	(11.5)
PFI before last platinum based therapy(months)		
Median, IQR	9	(5-14.2)
Platinum based therapy before olaparib		
Platinum combo	202	(86.3)
Platinum single agent	24	(10.3)
Other	8	(3.4)
Radiologic response to last platinum based therapy		
Complete response	91	(38.9)
Partial response	106	(45.3)
Stable Disease	29	(12.4)
Progressive disease	1	(0.4)
Unknown	7	(3.0)
Ca125 before olaparib administration		
≤35 UI/ml	138	(59.0)
>35 UI/ml	51	(21.8)
Unknown	45	(19.2)

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352 **Table 3:** : Exploratory subgroup analysis of Progression-free Survival

	HR	p	95%CI
Ca 125			
Low vs high	2.5	0.001	1.5-4.3
Number of previous lines			
1 vs 2 previous lines	1.9	0.031	1.1-3.5
1 vs >2 previous lines	2.5	0.004	1.3-4.8
RECIST response to last platinum based therapy			
CR vs PR	3.1	0.001	1.6-5.8
CR vs SD or PD	2.7	0.017	1.2-6.1
FIGO Stage at diagnosis			
I-II vs III	1.0	0.11	0.5-2.3
I-II vs IV	1.1	0.25	0.4-3.0
Residual disease			
R=0 vs R≠0	1.5	0.117	0.9-2.4
Previous treatment with bevacizumab			
Yes vs not	1.15	0.641	0.6-2.1
BRCA status			
BRCA1 vs BRCA2 mutation	0.7	0.165	0.4-1.2
Age			
Old vs young	1	0.169	1.0-1.0
ECOG PS			
0 vs 1	1.6	0.139	0.9-3.0
0 vs 2	1.6	0.289	0.6-4.0

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355 **Table 4:** recorded G3-G4 AEs

Adverse event G3-G4	N=234	(%)
Nausea	8	(3.4)
Fatigue	3	(1.3)
Anemia	13	(5.6)
Thrombocytopenia	5	(2.1)
Leucopenia or Neutropenia	4	(1.7)
Abdominalpain	1	(0.4)
Vomiting	2	(0.9)
MDS	1	(0.4)
Hypomagnesaemia	1	(0.4)

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366 **Table 5:** Response to chemotherapy in patients treated after progression to olaparib.

Platinum free interval	CR	PR	SD	PD
PFI < 6mm	1 (4.8)	1(4.8)	3 (14.3)	16 (76.2)
PFI: 6-12 mm	0	3 (11.1)	8 (29.6)	16 (59.3)
PFI >12 mm	1 (5.6)	3 (16.7)	7 (38.9)	7 (38.9)

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368 **Table 6:**table comparing results from SOLO2 Trial and this real world study.

	SOLO2	MITO Real life study
PFS	19.1 months	14.7 months
ORR	30 (41.1%)	57(46.3%)
Dose reduction	49 (25%)	49 (20.9%)
Dose discontinuation	21 (11%)	11 (4.7%)

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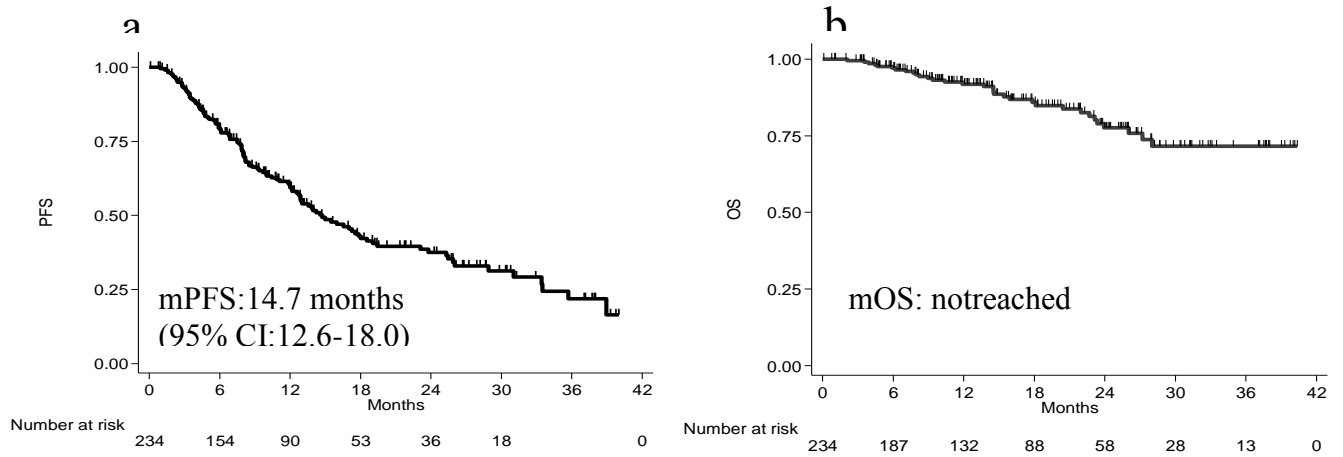
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374 Figure 1: With a median follow up of 15.5 months (95% CI 13.0-18.2), median PFS was 14.7 months (Figure
375 1a) while median OS was not reached (Figure 1b).



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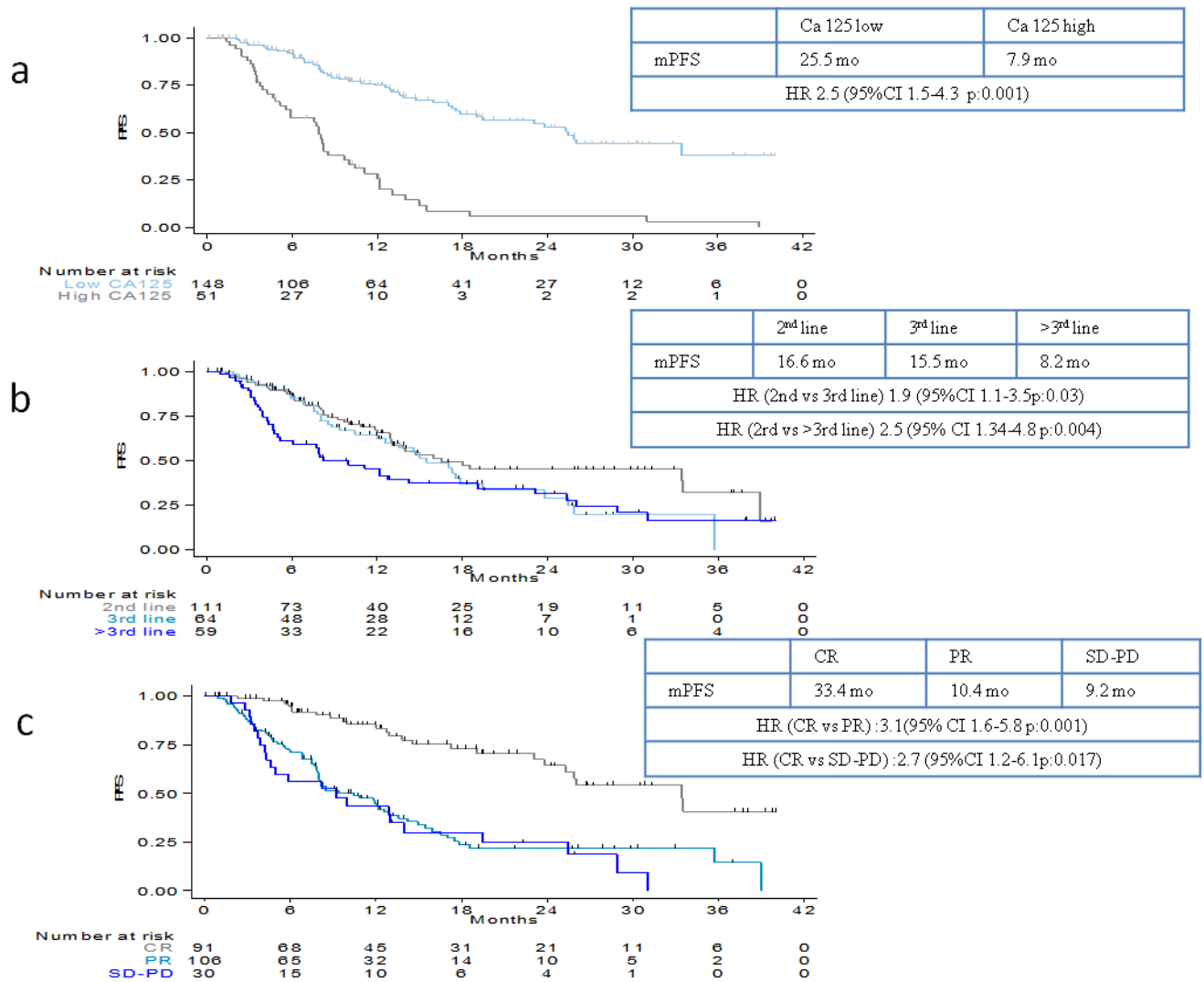
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380 **Figure 2:** Median PFS according to serum Ca125 at baseline (cut off 35 UI/ml, Figure 2a), number of
381 previous platinum based lines (Figure 2b) and response to last platinum based therapy (Figure 2c).

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391 **References**

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393 [1] Colombo N, Sessa C, du Bois A, Ledermann J, McCluggage WG, McNeish I, et al. ESMO-ESGO consensus
394 conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced
395 stages, borderline tumours and recurrent disease†. *Ann Oncol.* 2019.

396 [2] Siegel RL, Miller KD, Jemal A. *Cancer Statistics, 2017.* *CA Cancer J Clin.* 2017;67:7-30.

397 [3] <https://seer.cancer.gov/statfacts/html/ovary.html>.

398 [4] Wilson MK, Pujade-Lauraine E, Aoki D, Mirza MR, Lorusso D, Oza AM, et al. Fifth Ovarian Cancer
399 Consensus Conference of the Gynecologic Cancer InterGroup: recurrent disease. *Ann Oncol.* 2017;28:727-
400 32.

401 [5] Buechel M, Herzog TJ, Westin SN, Coleman RL, Monk BJ, Moore KN. Treatment of patients with
402 recurrent epithelial ovarian cancer for whom platinum is still an option. *Ann Oncol.* 2019;30:721-32.

403 [6] Mirza MR, Pignata S, Ledermann JA. Latest clinical evidence and further development of PARP inhibitors
404 in ovarian cancer. *Ann Oncol.* 2018;29:1366-76.

405 [7] Network CGAR. Integrated genomic analyses of ovarian carcinoma. *Nature.* 2011;474:609-15.

406 [8] Pal T, Permuth-Wey J, Betts JA, Krischer JP, Fiorica J, Arango H, et al. BRCA1 and BRCA2 mutations
407 account for a large proportion of ovarian carcinoma cases. *Cancer.* 2005;104:2807-16.

408 [9] Pennington KP, Walsh T, Harrell MI, Lee MK, Pennil CC, Rendi MH, et al. Germline and somatic
409 mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian
410 tube, and peritoneal carcinomas. *Clin Cancer Res.* 2014;20:764-75.

411 [10] Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of BRCA2-
412 deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature.* 2005;434:913-7.

413 [11] Mittica G, Ghisoni E, Giannone G, Genta S, Aglietta M, Sapino A, et al. PARP Inhibitors in Ovarian
414 Cancer. *Recent Pat Anticancer Drug Discov.* 2018.

415 [12] Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair
416 defect in BRCA mutant cells as a therapeutic strategy. *Nature.* 2005;434:917-21.

417 [13] Scott CL, Swisher EM, Kaufmann SH. Poly (ADP-ribose) polymerase inhibitors: recent advances and
418 future development. *J Clin Oncol.* 2015;33:1397-406.

419 [14] Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance
420 therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective
421 analysis of outcomes by BRCA status in a randomised phase 2 trial. *Lancet Oncol.* 2014;15:852-61.

422 [15] Wahlberg E, Karlberg T, Kouznetsova E, Markova N, Macchiarulo A, Thorsell AG, et al. Family-wide
423 chemical profiling and structural analysis of PARP and tankyrase inhibitors. *Nat Biotechnol.* 2012;30:283-8.

424 [16] Lynparza [package insert], Astra Zeneca 2018,
425 https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208558s001lbl.pdf.

426 [17] <https://www.ema.europa.eu/en/medicines/human/EPAR/lymparza>.

427 [18] Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance
428 therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med.* 2012;366:1382-92.

429 [19] Ledermann JA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Overall survival in patients
430 with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an
431 updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. *Lancet Oncol.*
432 2016;17:1579-89.

433 [20] Friedlander M, Matulonis U, Gourley C, du Bois A, Vergote I, Rustin G, et al. Long-term efficacy,
434 tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian
435 cancer treated with maintenance olaparib capsules following response to chemotherapy. *Br J Cancer.*
436 2018;119:1075-85.

437 [21] Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, et al. Olaparib tablets as
438 maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation
439 (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.*
440 2017;18:1274-84.

441 [22] Penson R, Kaminsky-Forrett M, Ledermann J, Brown C, Plante M, Korach J, et al. Efficacy of olaparib
442 maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer by number
443 of lines of prior chemotherapy: Phase III SOLO2 trial (ENGOT Ov-21). *Annals of Oncology* 2017. p. v330-v54.
444 [23] Eriksson I, Wettermark B, Bergfeldt K. Real-World Use and Outcomes of Olaparib: a Population-Based
445 Cohort Study. *Target Oncol.* 2018;13:725-33.
446 [24] Marme F, Hilpert F, Welslau M, El-Balat A, Grischke E-M, Schinkothe T, et al. Olaparib in German
447 routine clinical practice: Updated interim results of the non-interventional study C-PATROL. *Journal of*
448 *Clinical Oncology* 2018 36 : 15_suppl , e17549-e17549.
449 [25] De La Motte Rouge T, Pautier P, Alexandre, P. Ray-Coquard I, Cottu P, Rodrigues M, et al. 2755 POSTER
450 First real life data on Olaparib in BRCA1/2 mutated Platinum-Sensitive Relapsed Epithelial Ovarian Cancer in
451 France: Analysis of 52 patients enrolled in the French Temporary Authorization for Use (ATU). *European*
452 *Journal of Cancer* 2015. p. S548-S9.
453 [26] Eisenhauer EA. Real-world evidence in the treatment of ovarian cancer. *Ann Oncol.* 2017;28:viii61-viii5.
454 [27] Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, et al. Real-World Evidence - What
455 Is It and What Can It Tell Us? *N Engl J Med.* 2016;375:2293-7.
456 [28] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation
457 criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228-47.
458 [29] NCI. Common Terminology Criteria for Adverse Events Version 5.0.
459 [30] Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials.*
460 1996;17:343-6.
461 [31] Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika.*
462 1982;69:239-241. doi: 10.1093/biomet/69.1. 239.
463 [32] Mahajan R. Real world data: Additional source for making clinical decisions. *Int J Appl Basic Med Res.*
464 2015;5:82.
465 [33] Orbegoso Aguilar M.A., Dumas L. , Davies E., Gore M., George A., S. B. 273P Olaparib maintenance
466 treatment, the Royal Marsden experience. *Annals of Oncology* 2018.

- 467 [34] Lheureux S, Lai Z, Dougherty BA, Runswick S, Hodgson DR, Timms KM, et al. Long-Term Responders on
468 Olaparib Maintenance in High-Grade Serous Ovarian Cancer: Clinical and Molecular Characterization. Clin
469 Cancer Res. 2017;23:4086-94.
- 470 [35] Labidi-Galy Intidhar Sana, De La Motte Rouge Thibault , Derbel Olfa KE, Wolfer Anita , Olivier
471 Timothee , Ketty Hu. Predictive factors for prolonged response to olaparib as maintenance therapy in
472 ovarian cancer patients with BRCA mutations. 2019.
- 473 [36] Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, et al. Rucaparib maintenance
474 treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised,
475 double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390:1949-61.
- 476 [37] Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, et al. BRCA mutation frequency and
477 patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the
478 Australian Ovarian Cancer Study Group. J Clin Oncol. 2012;30:2654-63.
- 479 [38] Madariaga A, Lheureux S, Oza AM. Tailoring Ovarian Cancer Treatment: Implications of. Cancers
480 (Basel). 2019;11.
- 481 [39] Johnson N, Johnson SF, Yao W, Li YC, Choi YE, Bernhardt AJ, et al. Stabilization of mutant BRCA1
482 protein confers PARP inhibitor and platinum resistance. Proc Natl Acad Sci U S A. 2013;110:17041-6.
- 483 [40] Ang JE, Gourley C, Powell CB, High H, Shapira-Frommer R, Castonguay V, et al. Efficacy of
484 chemotherapy in BRCA1/2 mutation carrier ovarian cancer in the setting of PARP inhibitor resistance: a
485 multi-institutional study. Clin Cancer Res. 2013;19:5485-93.

486