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Regorafenib or Tamoxifen for platinum-sensitive recurrent ovarian cancer with rising CA125 and no evidence of clinical or RECIST progression: A GINECO randomized phase II trial (REGOVAR)

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1 **Regorafenib or Tamoxifen for platinum-sensitive recurrent ovarian cancer**
2 **with rising CA125 and no evidence of clinical or RECIST progression: a GINECO**
3 **randomized phase II trial (REGOVAR)**

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45 **ABSTRACT**

46 **Objective**

47 To evaluate the efficacy and safety of regorafenib versus tamoxifen in platinum-sensitive ovarian
48 cancer biological recurrence, defined by CA-125 increase without radiological (RECIST criteria) or
49 symptomatic evidence of progression.

50 **Patients and methods**

51 116 patients with platinum-sensitive ovarian cancer presenting an isolated increase of CA-125 were
52 planned to be randomized. Regorafenib was administered orally at 160 or 120 mg daily, 3 weeks
53 on/1 week off or tamoxifen at 40 mg daily, until disease progression or development of unacceptable
54 toxicity. The primary endpoint was Progression-Free Survival, assessed by progression according to
55 RECIST 1.1 or death (by any cause). Secondary endpoints included Overall Survival, Best Response
56 and CA-125 response rate.

57 **Results**

58 68 patients were randomized. Median age was 67 years (range: 30-87). Primary site of cancer was
59 ovarian for most patients (92.6%). Tumors were predominantly serous / (89.7%), high grade (83.6%)
60 and initial FIGO staging was III for 69.6% of the patients. Most (79.4%) patients were included after
61 the first line of platinum-based treatment.

62 After a median follow-up of 32 months, there was no difference of progression-free survival (PFS)
63 between regorafenib and tamoxifen groups ($p = 0.72$), with median PFS of 5.6 months (CI 90%: 3.84-
64 7.52) for the tamoxifen arm and 4.6 months (CI 90%: 3.65-7.33) for the regorafenib arm. There was
65 also no difference in term of overall survival, best response or CA-125 response, delay to next
66 therapy.

67 Regorafenib presented a less favorable safety profile than tamoxifen, with grade 3/4 events
68 occurring for 90.9% of the patients compared to 54.3% for tamoxifen. The most frequent were
69 cutaneous, digestive, and biological events. Notably, hand-foot syndrome occurred in 36.4% of these
70 patients.

71 **Conclusion**

72 Regorafenib presented an unfavorable toxicity profile compared to tamoxifen, with no superior
73 efficacy in this population of patients.

74 INTRODUCTION

75 The standard of care for advanced epithelial ovarian cancer consists of cytoreductive surgery
76 followed by platin-based chemotherapy, allowing clinical remission for at least 70% of the patients
77 [1]. However, the disease often relapses [2] and is then considered being incurable, with a 5-years
78 survival of 30% [3].

79 Increase of the tumoral marker CA-125 precedes symptoms by 3 to 6 months [4] and is considered as
80 an early indicator of ovarian cancer (OC) recurrence. However, it was shown that early initiation of
81 chemotherapy based on isolated CA-125 increase does not improve survival [5]. For this reason, all
82 guidelines recommend continuing to follow the patients with blood tests and CT scan until
83 radiological progression is observed. This situation highly increase anxiety for many patients and can
84 have deleterious impact on quality of life (QoL). These patients therefore represent a group with an
85 unmet clinical need and clinical trials in this population are warranted. With the introduction of
86 targeted therapies considered to be less toxic than chemotherapies in ovarian cancer, these patients
87 could benefit from alternative therapies and enter in the setting clinical trials [6].

88 Angiogenesis is a critical driver of tumor development. The expression of Vascular Endothelial
89 Growth Factor (VEGF) is increased on ovarian cancer cells and malignant ascites, and correlates
90 negatively with patient survival [7]. Bevacizumab has been the first antiangiogenic drug approved as
91 first-line and maintenance therapy for advanced ovarian cancer. But despite the increase of PFS
92 assessed in clinical trials, PFS does not exceed a median of 20 months [8,9]. Several antiangiogenic
93 multi-kinase inhibitors, like cediranib [10] and pazopanib [11] have shown interesting results for
94 recurrent ovarian cancer. In the context of symptom-free biological recurrence, the main objective is
95 to delay symptomatic manifestations while preserving quality of life. Agents that inhibit tumor
96 angiogenesis and invasion may be considered to be suitable candidates given their potential to
97 extend the duration of remission and disease progression while exhibiting a more favorable toxicity
98 profile than cytotoxic drugs given at maximally tolerated doses. This study investigated the use of
99 regorafenib, a multi-kinase inhibitor targeting angiogenic (VEGFR1-3, TIE2), stromal (PDGFR-b, FGFR),

100 oncogenic kinases (KIT, RET, and RAF) and tumor immunity (CSF1R) [12]. It is approved in many
101 countries, including in Europe for the treatment of refractory metastatic colorectal cancer,
102 unresectable or metastatic gastrointestinal stromal tumors and hepatocellular carcinoma previously
103 treated with sorafenib. A phase I study showed efficacy of regorafenib, with acceptable toxicity, on
104 several advanced solid tumors including OC [13].

105 The GINECO group has focused considerable effort on extending the duration of remission and
106 improving survival through the evaluation of novel agents as well as different routes of
107 chemotherapy administration, combinations, sequences and types of consolidation/maintenance
108 regimens. In 2015, the GINECO initiated this original study, REGOVAR, in response to a paucity of
109 data from clinical trials evaluating the benefit of early therapeutic intervention in patients with
110 asymptomatic biochemical-recurrent epithelial ovarian cancer, primitive peritoneal carcinoma or
111 fallopian tube cancer (EOC/PPC/FTC). A no treatment arm when this study was initiated was deemed
112 to be unacceptable due to patient anxiety over a rising CA-125, compelling a significant proportion of
113 physicians to intervene therapeutically. The use of tamoxifen as reference arm seemed justified
114 based on a favorable toxicity profile compared with available cytotoxic agents and the lack of
115 interference with subsequent interventions after documentation of clinical progression [4].

116 Tamoxifen is a well-known molecule usually well tolerated for long-term treatment of breast cancer
117 [14]. It inhibits estrogen by competitive binding to the estrogen receptor, which is often expressed by
118 ovarian cancer cells [15]. Multiple clinical trials showed a response rate of 10-15% and a disease
119 stabilization rate of 30-40% for recurrent OC [16]. Tamoxifen was already used as comparator in a
120 clinical trial on biological recurrent OC and showed a favorable safety profile [17].

121 The GINECO group undertook a phase II trial to evaluate the safety and efficacy of regorafenib versus
122 those of tamoxifen for biological recurrence in platinum-sensitive epithelial ovarian cancer
123 population (REGOVAR).

124

125 PATIENTS AND METHODS

126 Study design and treatments

127 REGOVAR is a comparative, open label, randomized, phase II trial (NCT NCT02584465, EudraCT 2015-
128 001116-35). The objective of the study was to compare the efficacy and safety of regorafenib versus
129 those of tamoxifen in patients with platinum-sensitive ovarian carcinoma and elevated serum CA-125
130 but no symptomatic progressive disease.

131 After inclusion, the patients were randomized to the regorafenib or tamoxifen arm in a 1:1 ratio.

132 The 2 study treatments were administered until disease progression or unacceptable toxicities.

133 Tamoxifen was administered orally at 40 mg/day and regorafenib at 120 mg/day for 3 weeks on, then
134 1 week off. Of note, a dose of 160 mg/day of regorafenib was used for first patients, but the safety
135 interim analysis performed on the first 20 enrolled patients showed an unfavorable safety profile for
136 regorafenib. Therefore, the independent Data Safety Monitoring Committee (iDSMC) decided to
137 decrease the dose to 120 mg/day. A second iDSMC meeting was organized after inclusion of 68
138 patients to review the benefit/risk balance. Given the higher toxicity of regorafenib compared to
139 tamoxifen and preliminary efficacy results which cannot exclude futility bounds, decision was made
140 to stop prematurely study inclusions from September 2018.

141 The study was conducted in accordance with the Declaration of Helsinki and approved by the
142 relevant local ethic committee according to local regulations. All patients provided written informed
143 consent prior to study enrollment.

144

145 Patients

146 Eligible patients (≥ 18 years) had a histologically confirmed epithelial ovarian, fallopian, or primitive
147 peritoneal carcinoma with elevated serum CA-125 (according to Rustin/GCIG criteria [18]) occurring
148 more than 6 months after a platinum-based first line or second line chemotherapy. Chemotherapy
149 administered or not in combination with bevacizumab could be followed either by surveillance or by

150 bevacizumab maintenance. Other key inclusion criteria were adequate bone marrow, liver and renal
151 functions. The patients had to be without symptoms related to ovarian cancer progression and have
152 an ECOG Performance Status ≤ 1 .

153 The main exclusion criteria were a past or concurrent history of neoplasm other than ovarian cancer,
154 radiological progression (RECIST criteria), any prior radiotherapy to the pelvis or abdomen, surgery
155 within 4 weeks before study, endocrine therapy within 3 years prior to randomization, prior
156 unresolved toxicity $>$ grade 1, history of abdominal fistula, gastrointestinal perforation, intra-
157 abdominal abscess, any malabsorption condition, Congestive heart failure \geq class 2 according to New
158 York Heart Association (NYHA), uncontrolled hypertension, ongoing infection $>$ grade 2 according to
159 NCI-CTCAE version 4.0.

160

161 **Study endpoints and assessments**

162 The primary endpoint was progression free survival (PFS), defined as the time from randomization
163 until the date of first radiological progression or death (by any cause). Progression was assessed by
164 the investigator according to RECIST version 1.1 [19]. Patients who had not progressed or died at the
165 time of analysis were censored at the time of the latest date of RECIST assessment. Secondary
166 endpoints included safety, overall survival (OS), objective response rate (ORR), response rate on CA-
167 125, time to first subsequent therapy or death (TFST), and health-related quality of life (HRQoL).

168 A radiological tumor assessment was performed at baseline, every 8 weeks during treatment, at the
169 end of treatment, then every 3 months during the 36 months follow-up. Clinical evaluation, adverse
170 events assessment and CA-125 measurement were performed at baseline, every 4 weeks for the first
171 3 months then every 8 weeks until the end of treatment or progression.

172 HRQoL was assessed using the EORTC QLQ-C30 cancer specific questionnaire and the QLQ-OV28
173 ovarian cancer module at baseline, every 8 weeks during treatment, at the end of treatment visit,
174 and then every 3 months during the follow-up up to 36 months.

175 **Translational research**

176 Blood and archival tumor samples were collected for exploratory analysis of factors that may
177 influence development of cancer or response to study treatment.

178 Genetic profiling of 18 regorafenib target genes (*RET*, *FLT1* (*VEGFR1*), *KDR* (*VEGFR2*), *FLT4* (*VEGFR3*),
179 *KIT*, *PDGFR α* , *PDGFR β* , *FGFR1*, *FGFR2*, *TEK*, *DDR2*, *NTRK1*, *EPHA2*, *RAF1*, *BRAF*, *MAPK11*, *FRK* and
180 *ABL1*) was performed on tumor samples. We used a prediction algorithm (SUMSCAN), based on the
181 presence of specific gene gains and losses, previously validated to predict the tumors sensitivity to
182 regorafenib [20].

183

184 **Statistical methods**

185 For determination of the sample size, we hypothesized that introduction of regorafenib would
186 increase the progression-free interval to 7.5 months, compared to 4.5 months for tamoxifen [17]
187 (HR=0.6). A total of 95 events with a sample size of 58 patients per arm (116 patients in total) would
188 have 80% power to show statistically significant PFS at a 2-sided alpha of 10%.

189 PFS was estimated using Kaplan Meier method. Patients who had not progressed or died at the time
190 of analysis were censored at the time of the latest date of RECIST assessment. PFS distributions were
191 compared between arms using the Log-Rank test. The tests were adjusted according to 3
192 stratification factors: previous strategy (surveillance; progressive disease under bevacizumab or
193 within 3 months; progressive disease more than 3 months after bevacizumab), platinum sensitivity (
194 to 12 months vs > 12 months) and initial global quality of life (QoL score /general health of QLQ-C30:
195 <50 vs. \geq 50). The hazard ratio for progression between the 2 arms was also provided with its 90%
196 confidence interval (CI).

197 For the secondary endpoints, overall survival (OS) and time to start of subsequent therapy or death
198 (TFST) were estimated using the Kaplan-Meier method. TFST was defined as the time from the date
199 of randomization to the date of event defined as start of a new anticancer therapy following study
200 treatment discontinuation, or death (by any cause in the absence of a new anti-cancer therapy

201 initiation). Best objective response rate (ORR) and Response Rate on CA-125 (RRCA-125) were
202 summarized by arm using proportion together with their 90% confidence interval. RRCA-125 was the
203 proportion of patients with a biological response according to the GCIg criteria (at least a 50%
204 reduction in CA 125 levels from a pretreatment sample)[18]. Response Rates were compared
205 between the 2 study arms using a chi-square test.

206 The assessment of safety was based on the frequency of adverse events (AE), graded according to
207 CTCAE version 4.3.

208 The change from baseline for each HRQoL score was assessed using a mixed model for repeated
209 measures (MMRM) including all post baseline QoL scores up to the latest scheduled visit during
210 treatment, if there were at least 10 patients in each treatment arm who had a score. The MMRM
211 model included treatment, visit and treatment by visit interaction as explanatory variables and the
212 baseline score as a covariate and the baseline QoL score by visit interaction. To compare the
213 treatment arms over time, adjusted mean estimates per treatment arm was reported with the
214 estimate of the treatment difference and corresponding p-value. The minimal clinically important
215 difference was fixed to 10 points to interpret the clinically significance of the results.

216

217 **RESULTS**

218 **Patients**

219 Between September 2015 and August 2018, 74 patients were enrolled and 68 (6 patients were
220 screen failures) were randomized in the study (35 in the tamoxifen arm and 33 in the regorafenib
221 arm). The 2 treatment groups were generally well balanced with respect to baseline characteristics.
222 Relevant patient demographic details are listed in [Table 1](#). The median age was 67 years (range: 30-
223 87). Primary site of cancer was ovarian for most patients (92.6%). Tumors were predominantly serous
224 (89.7%) and high grade (83.6%). FIGO staging was III for 39 patients (69.6%); 64.2% of the patients
225 had an ECOG Performance status of 0 and 35.8% of 1. For the patients for whom BRCA status was
226 available, 7 were BRCA1 and 2 BRCA2 mutated.

227 Median time from initial diagnosis to randomization was 2.2 years (range 0.9-8.1). Previous
228 treatments are described in [Table 1](#): 54 patients (79.4%) were included after one line of treatment,
229 14 patients (20.6%) after the second line. Sixty-three patients (92.6%) had received a platinum +
230 taxane combination as 1st line of treatment. 48 patients (70.6 %) received bevacizumab or another
231 antiangiogenic agent at least once before enrollment: 22 patients of the tamoxifen arm and 25
232 patients of the regorafenib arm received bevacizumab immediately before inclusion, respectively.

233

234 **Treatment exposure**

235 Median duration of exposure to study treatment was 3.7 months (range: 0.1-25.7) for tamoxifen and
236 3.6 months (range: 0-14.9) for regorafenib. Thirty-four patients (43 patients in the regorafenib arm, 6
237 patients in the tamoxifen arm) had experienced at least one treatment modification (21 dose
238 reduction and/or 28 treatment interruption). Sixty-five patients had definitely discontinued the
239 treatment at the date of cut-off data which is 31-Dec-2019. Reason for discontinuation was
240 progression for 47 patients: 27 in tamoxifen arm and 20 in regorafenib arm. Treatment withdrawn
241 for toxicity occurred in 11 patients (3 in tamoxifen arm and 8 in regorafenib arm) ([Table 3](#)). The

242 reasons for discontinuation for the 7 other patients were: patient choice (4 patients); investigator
243 decision (1 patients); deterioration of general status/non response (2 patients). In total, 48 patients
244 received bevacizumab before inclusion.

245 In the regorafenib arm, 6 of the 25 patients who received bevacizumab before inclusion stopped the
246 treatment for toxicity, and 2 of the 7 patients who did not received bevacizumab.

247

248

249 **Efficacy**

250 The median follow up was 32 months (range: 1.2 - 51.8 months). Progression was notified for 60
251 patients out of 68 and 30 patients died. The Kaplan-Meier curve of PFS is presented as [Figure 1](#).

252 There was no significative difference of PFS between arms ($p = 0.72$). The median PFS estimate was
253 5.6 months for the tamoxifen arm (CI 90%: 3.84-7.52) and 4.6 months for the regorafenib arm (CI
254 90%: 3.65-7.33), and Hazard Ratio (HR) was 1.21(CI 90%: 0.78-1.86).

255 Swimmer plots representing individual exposure to treatments, progressions and deaths are
256 provided as supplemental figures S1 and S2. One patient was still under regorafenib treatment and 2
257 patients still under tamoxifen at the time of the analysis.

258 Objective response to treatment was observed in 7 patients (four complete response and one partial
259 response in tamoxifen arm; two partial response in regorafenib arm). There was no significant
260 difference between arms ($p = 0.27$).

261 Response on CA-125 was observed in 20 (30.3%) patients (9 (26.5%) on tamoxifen arm and 11
262 (34.4%) on regorafenib arm), with no statistical difference between treatment arms ($p = 0.49$)([Table](#)
263 [3](#)). This does not account for the high individual variability of CA-125 rates, therefore a spider plot
264 representing the evolution of individual CA-125 values is presented as [Supplemental Figure S3](#).

265 There was no significant difference of Overall Survival (OS) between arms ($p = 0.34$) ([Figure 2](#)). The
266 survival rate at 24 months was 0.78 (CI 90%: 0.63-0.88) in the tamoxifen arm and 0.66 (CI 90%: 0.49-
267 0.78) in the regorafenib arm, HR was 1.32 (CI 90%: 0.70-2.47).

268 63 patients of the 65 who discontinued study therapy had started another treatment (33 after
269 tamoxifen and 30 after regorafenib). We did not report significant difference of TFST between arms
270 ($p = 0.38$). The median time to the first subsequent line of treatment was 5.2 months (CI 90%: 4.17-
271 7.79) in the tamoxifen arm and 4.5 months (CI 90%: 2.96-5.52) in the regorafenib arm respectively.

272

273 **Safety**

274 Adverse events (AE) have been reported in 100% of patients in tamoxifen arm and 97% in
275 regorafenib arm. 90.9% of patients had at least 1 grade 3/4 AE in the regorafenib group, and 54.3%
276 of the patients of the tamoxifen group. The summary of grade 3/4 adverse events is provided in
277 Table 2. Most common grade 3/4 AE in the regorafenib arm were cutaneous or digestive toxicities
278 and biological abnormalities: hand-foot skin reactions (36.4%), cutaneous rash (18.2%),
279 mucositis/stomatitis (15.2%), gastrointestinal obstruction (15.2%), diarrhea (12.1%), arterial
280 hypertension (21.2%), fatigue (15.2%), thrombocytopenia (15.2%), lymphopenia (12.1%) and
281 neutropenia (12.1%). The most common grade 3/4 AE in the tamoxifen arm were arterial
282 hypertension (20.0%), biological abnormalities (neutropenia for 17.1% of the patients, anemia for
283 14.3% and Gamma-GT increase for 14.3%) and gastrointestinal obstruction (11.4%).
284 Eighteen serious adverse events (SAEs) were reported in 9 patients (13.2%), including 3 patients
285 (8.6%) of the tamoxifen arm and 6 patients (18.2%) of the regorafenib arm. SAE notified in
286 regorafenib arm were myelodysplastic syndrome (n=1), cutaneous rash (n=4) and gastrointestinal
287 toxicities (n=1). SAE reported in tamoxifen arm were occlusive syndrome (n=1), duodenal obstruction
288 (n=1) and liver ASAT increased (n=1), Gamma GT increased (n=1), ALAT increased (n=1) and grade 1
289 PAL increased (n=1) all for the same patient.
290 Four deaths unrelated to disease progression were reported: 1 patient died of self-induced drug
291 intoxication, 2 patients from general health deterioration (both in regorafenib arm), 1 died of acute
292 pulmonary edema (tamoxifen arm) and 1 died of voluntary drug intoxication (regorafenib arm).

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Health-related quality of life

Compared to tamoxifen arm, patients of regorafenib arm experienced over the first 16 weeks of treatment a higher level of fatigue (adjusted mean difference 14.9 (90% CI 4.7, 25.0)), as well as appetite loss (16.2 (5.5, 26.9)), diarrhea (13.3 (4.4, 22.1)), upset by hair loss (31.4 (21.1, 41.2)), a lower level of their body image (-13.4 (-22.6, -4.2)) and of their hormonal/menopausal symptoms (-20.0 (-32.4, -7.7)) (Supplementary Table 1). No difference between treatment arms was observed on global health/QoL level.

In contrast, patients randomized in the tamoxifen arm experienced an increase of their hormonal/menopausal symptoms (-20.0 (-35.0; -5.1), $p=0.01$) as well as their upset about hair loss (31.4 (19.0; 43.8), $p<0.01$).

Translational research: SUMSCAN analysis

40 (59%) patients had SUMSCAN analysis performed on tumor samples. Among them, 18 (45%) had an “Unfavorable” SUMSCAN score (predicted resistant) and 22 (55%) a “Favorable” score (predicted sensitive), equally distributed between the two treatment arms. No PFS or OS benefit was observed for the SUMSCAN favorable group. The only 2 patients who responded to regorafenib treatment were classified in the SUMSCAN favorable group, 1 of them was still on regorafenib at the time of database freeze, with more than 19 months of treatment (first patient on the swimmer plot provided as supplemental figure S2) 3 patients responding to tamoxifen were also in the SUMSCAN favorable group (the 2 others had no SUMSCAN analysis). Conversely, all the patients predicted to be resistant had not responded ($n=15$; 3 patients were with missing response), regardless of the treatment group (Supplemental Table 2). Because of the small number of patients, no conclusion could be drawn from these results.

318 **DISCUSSION**

319 This study was stopped prematurely because of regorafenib poor tolerance in this population of
320 patients already pretreated with chemotherapy +/- bevacizumab, despite the use of a reduced 120
321 mg daily dose. There were no unexpected adverse events, the most frequent were fatigue,
322 hypertension, diarrhea and hand-foot syndrome. But in the regorafenib arm, 91% of the patients
323 presented at least one grade 3/4 adverse event. It led to dose reduction for 61% of the patients
324 receiving regorafenib and treatment withdrawn for 8 of them.

325 Furthermore, regorafenib showed disappointing efficacy compared to tamoxifen, with no significant
326 difference in term of PFS (4,6 months vs 5,6 months respectively, $p=0.7227$) or OS ($p=0.3437$). These
327 results are in line with another recent study that showed a similar lack of efficacy of regorafenib on
328 relapsed ovarian cancer. In an interim analysis on 14 patients treated by regorafenib (120 mg/day)
329 for the treatment of OC after ≥ 2 lines of chemotherapy, Tan et al. reported a lack of efficacy and skin
330 toxicities of regorafenib. The previous treatment lines that may have contained other antiangiogenic
331 agents, such as bevacizumab like in our study, may also explain the limited drug efficacy [21].

332 However, an interesting finding of this study was regorafenib efficacy in the histological subset of
333 clear cell carcinomas, and the trial is still ongoing on these patients. Clear cell ovarian carcinoma is a
334 distinct subset of OC, histologically close to renal cells and poorly responding to therapy. It has been
335 shown that the transcription factor HIF1 α is over-expressed in these cells and drives expression of
336 several angiogenic pathways. This could explain the sensibility of these cells to the anti-angiogenic,
337 multi-kinase inhibitor regorafenib [22]. In the present study, only 1 patient presented clear cell
338 carcinoma (randomized in the regorafenib arm), making it impossible to show a potential effect on
339 this sub-population. Of note, this patient received regorafenib for 7.1 months, whereas the median
340 treatment duration was 3.6 months in this group.

341 Epithelial ovarian cancer is a highly heterogeneous disease, with different molecular, histological, and
342 clinical characteristics, that require specific therapeutic options [1]. At least 15 oncogenes are
343 implicated in ovarian cancer. Thus, it will be probably required to target multiple pathways to impede

344 OC progression [1]. As the available treatment arsenal for advanced epithelial OC expands, molecular
345 markers need to be identified to tailor therapeutic strategy to each individual situation. It is however
346 challenging to find reliable biomarkers to predict drug sensibility, because multiple and intricate
347 pathways are implicated in OC progression. In an effort to identify predictive markers of regorafenib
348 response, we conducted an original ancillary study on the tumor samples of 40 patients. We
349 performed profiling of 18 regorafenib target genes, and applied an algorithm, SUMSCAN, previously
350 shown to successfully predict regorafenib sensitivity [20]. However, no relation was found between
351 predicted the score and treatment response. The absence of positive statistical effect on a small
352 number of analyzed samples made it impossible to conclude. Analysis of the individual profile of the
353 patient still under regorafenib treatment (for more than 19.3 months) showed that the tumor was
354 predicted to be regorafenib sensitive, with a gain ≥ 6 copies of the KIT gene and breakage on the
355 FGFR1 gene.

356 In addition, no relation was found between ER or BRCA status and the response to treatment, the
357 low number of patients precluding again any statistical analysis.

358 The originality of this study was to evaluate therapeutic options for the particular population of
359 patients, experiencing OC biological relapse without symptoms. Since the beginning of our study, the
360 treatment landscape of ovarian cancer has dramatically changed with the onset of systematic
361 maintenance therapy in 1st and 2nd line with bevacizumab then polyADP-ribose polymerase inhibitors
362 (PARPi). Untreated patients with CA-125-defined recurrence does not represent a frequent situation
363 anymore. Furthermore, for patients under PARPi maintenance treatment, there is most of the time
364 no more CA-125 increase before RECIST progression [23]. Although this population of untreated
365 patients does not represent anymore the majority of patient in clinical practice, this study provides
366 valuable information about treatment options for asymptomatic patients. Regorafenib and
367 tamoxifen allowed to delay the next line of chemotherapy for several months (for 4.5 and 5.2
368 months, respectively) and therefore hinder potential adverse events associated with more toxic
369 therapy. This applied particularly to 2 patients, who are still on tamoxifen after more than 30 months

370 (Supplemental figure S1). It is therefore valuable to explore these therapeutic options. Furthermore,
371 most of the patients being already on maintenance treatment, they can therefore more easily switch
372 between target therapies.

373 Tamoxifen exhibited a relatively low toxicity profile in this trial. Regorafenib was more toxic with a
374 higher proportion of patients experiencing grades 3 and 4 toxicities (90.9% versus 54.3%) and
375 discontinuing therapy due to adverse events (25% versus 9.1%) compared to tamoxifen. This high
376 toxicity of regorafenib was surprisingly higher than what was observed in the context of recurrent,
377 metastatic osteosarcoma treatment [24]. The second iDSMC noted a reduction of SAEs and of
378 cutaneous toxicities after the dose modification (at 120 mg) and recommended the continuation of
379 study treatment at the dose of 120mg (at investigator discretion).

380 The toxicity observed in the present study was more similar to that in patients with colorectal cancer,
381 treated by regorafenib after several lines of chemotherapy. In this situation, dose-escalation strategy
382 may be an option [25]. However, the toxicity profile may implicate that quality of life during the
383 strategy of delaying the chemotherapy (with regorafenib or tamoxifen treatment) can be worsen
384 compared to not receiving any treatment. Indeed, results of HRQoL were in coherence with the
385 toxicity profile, with a globally lower HRQoL over the 16 first weeks of treatment in regorafenib arm
386 compared to tamoxifen, including a higher level of fatigue, diarrhea and appetite loss.

387 In summary, the premature closure of the study did not allow to conclude on efficacy of regorafenib
388 treatment compared to tamoxifen. Maintenance treatment or surveillance remain the standard of
389 care in this situation of biochemical-recurrent EOC/PPC/FTC without radiological progression [5].

390

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392

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408 **RESEARCH HIGHLIGHTS**

409• Ovarian cancer recurrences can be detected by CA-125 increase before apparition of radiological or
410 clinical manifestations.

411• There is an unmet medical need for asymptomatic patients with CA-125 increase.

412• Regorafenib has modest efficacy and poor tolerance in recurrent ovarian cancer patients.

413• Maintenance treatment or surveillance remain the standard of care in this situation of biochemical-
414 recurrent EOC/PPC/FTC without radiological progression.

415

416

417

418 **CONFLICTS OF INTEREST STATEMENT**

419 Dr Trédan reports supports from the present manuscripts to ARCAGY GINECO from Bayer
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445 Writing – review & editing)

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470 Isabelle Ray-Coquard (Conceptualization; Investigation; Methodology; Resources; Writing–original
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472

473 **REFERENCES**

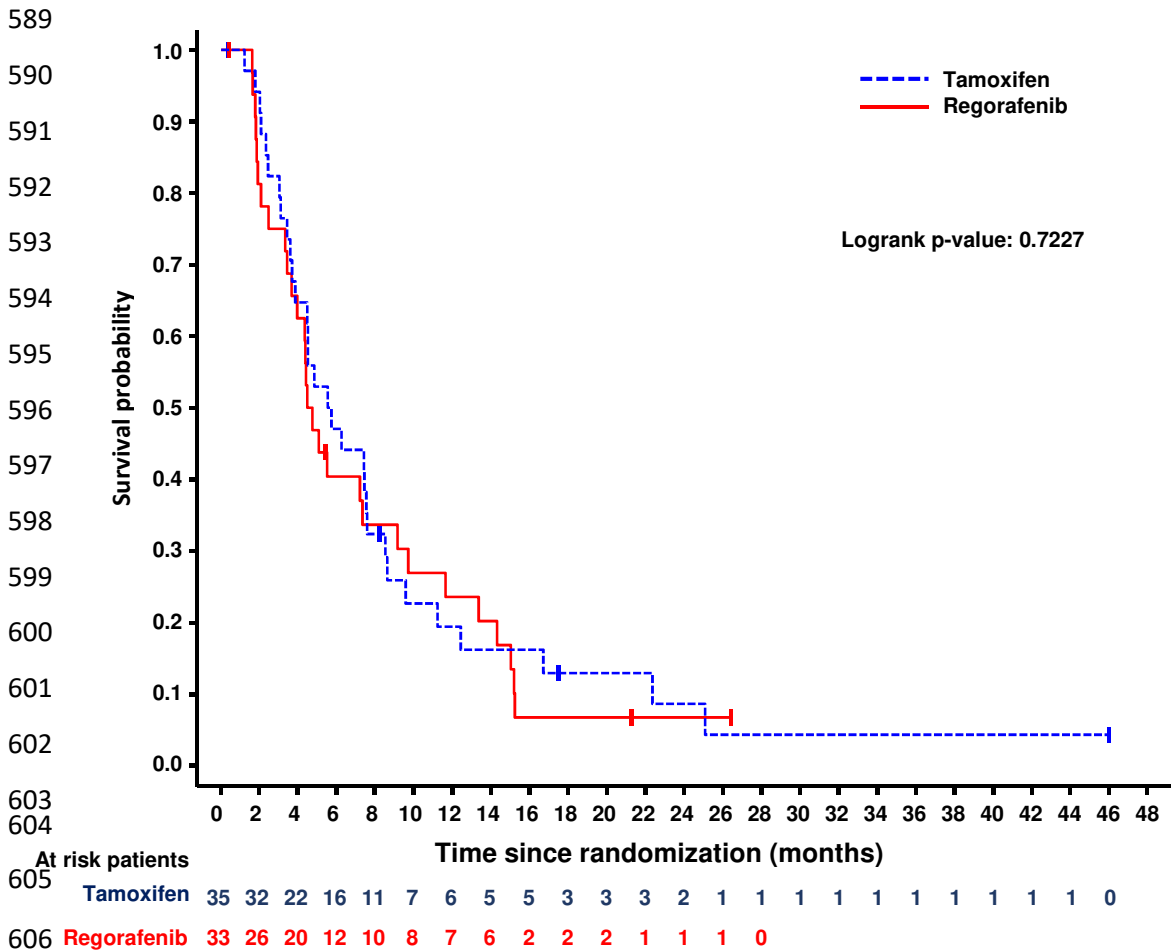
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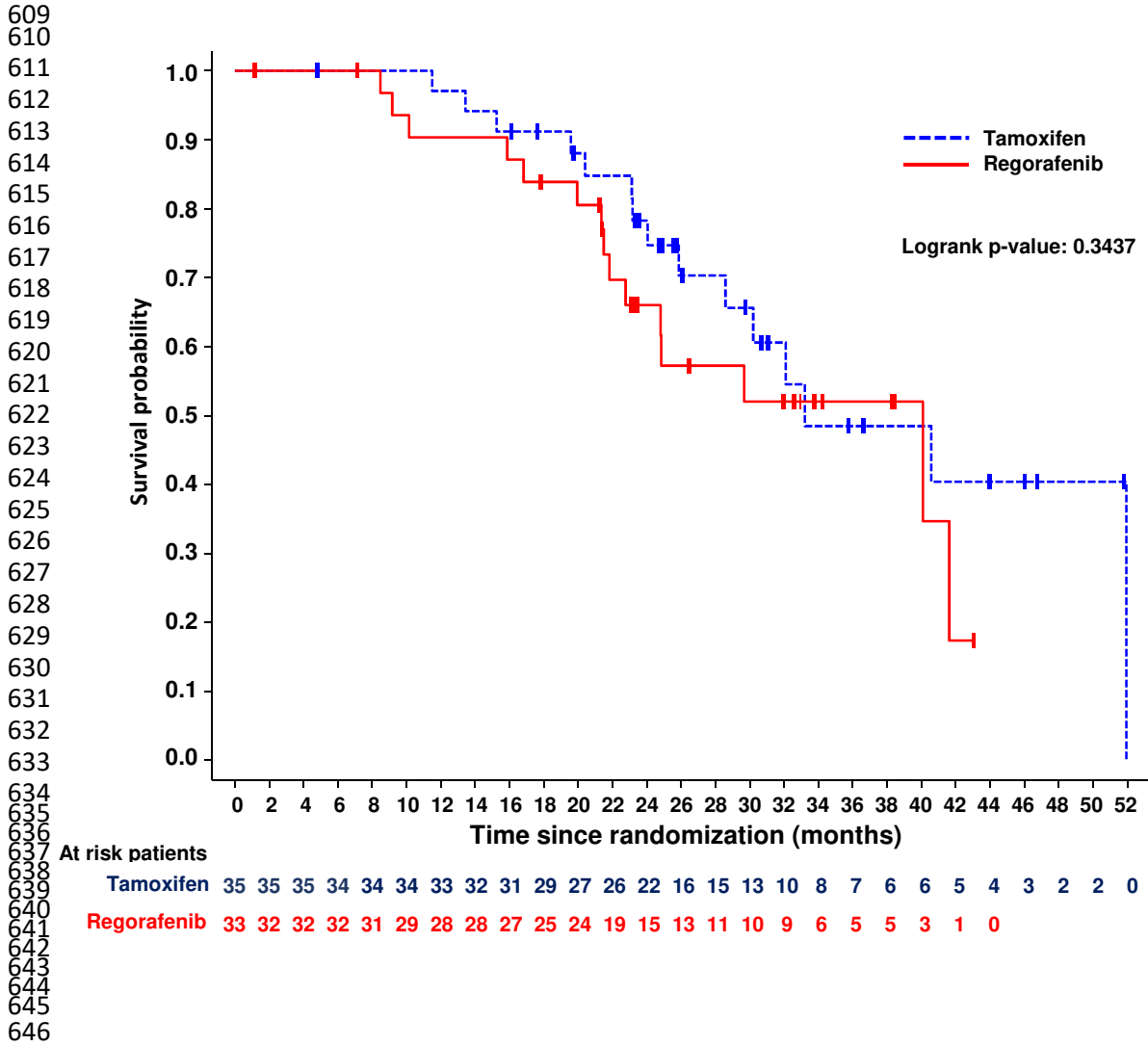
587

588 **Figure 1: Kaplan-Meier estimate of Progression Free Survival (PFS) by randomized treatment group**



607

608 Figure 2: Kaplan-Meier estimate of Overall Survival (OS) by randomized treatment group



	Randomization Arm	All patients	Test
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	Arm 1: Tamoxifen n = 35	Arm 2: Regorafenib n = 33	n = 68	
Age at inclusion^a: median (min; max)	66.7 (29.8;86.7)	67.3 (41.6;79.2)	66.8 (29.8;86.7)	Wilcoxon P = 0.533
ECOG^b				
Performance status = 0	24 (68.6%)	19 (59.4%)	43 (64.2%)	Fisher Exact P = 0.457
Performance status = 1	11 (31.4%)	13 (40.6%)	24 (35.8%)	
Medical Background				
Arterial hypertension	14 (40.0%)	13 (39.4%)	27 (39.7%)	Fisher Exact P = 1
Diabetes	2 (5.7%)	2 (6.1%)	4 (5.9%)	Fisher Exact P = 1
Cardiovascular	2 (5.7%)	6 (18.2%)	8 (11.8%)	Fisher Exact P = 0.144
History of the disease				
Time from diagnosis (years)				
Median (min; max)	2.3 (1.1; 8.1)	2.0 (0.9; 7.1)	2.2 (0.9; 8.1)	Wilcoxon P = 0.370
FIGO 2014 initial status^c				
IA	0 (0.0%)	3 (10.7%)	3 (5.4%)	Fisher Exact P = 0.526
IIB	1 (3.6%)	1 (3.6%)	2 (3.6%)	
IIIA/B	2 (7.1%)	3 (10.7%)	5 (8.9%)	
IIIC	18 (64.3%)	16 (57.1%)	34 (60.7%)	
IV	7 (25.0%)	5 (17.9%)	12 (21.4%)	
Origin of the cancer				
Ovary	33 (94.3%)	30 (90.9%)	63 (92.6%)	Fisher Exact P = 0.478
Fallopian tubes	0 (0.0%)	2 (6.1%)	2 (2.9%)	
Peritoneum	1 (2.9%)	1 (3.0%)	2 (2.9%)	
Not determined	1 (2.9%)	0 (0.0%)	1 (1.5%)	
Histological type				
Serous / Sero-papillary	33 (94.3%)	28 (84.8%)	61 (89.7%)	Fisher Exact P = 0.361
Clear cell	0 (0.0%)	1 (3.0%)	1 (1.5%)	
Endometrioide	0 (0.0%)	1 (3.0%)	1 (1.5%)	
Mucinous	0 (0.0%)	1 (3.0%)	1 (1.5%)	
Undifferentiated	0 (0.0%)	1 (3.0%)	1 (1.5%)	
Other	2 (5.7%)	1 (3.0%)	3 (4.4%)	
Histological grade^d				
High grade	31 (88.6%)	25 (78.1%)	56 (83.6%)	Fisher Exact P = 0.581
Low grade	2 (5.7%)	2 (6.3%)	4 (6.0%)	
NA	2 (5.7%)	3 (9.4%)	5 (7.5%)	
Other	0 (0.0%)	2 (6.3%)	2 (3.0%)	
Tumor biomarkers				
CA 125 (UI/mL)^e: median (min; max)	127.0 (39.0; 896.0)	166.3 (51.4; 3206.0)	161.7 (39.0; 3206.0)	Wilcoxon P = 0.226
BRCA Status				
Non mutated	16 (45.7%)	18 (54.5%)	34 (50.0%)	Fisher Exact P = 0.303
Mutated BRCA1	2 (5.7%)	5 (15.2%)	7 (10.3%)	
Mutated BRCA2	1 (2.9%)	1 (3.0%)	2 (2.9%)	
Unknown	16 (45.7%)	9 (27.3%)	25 (36.8%)	
Hormonal receptor status^f				
Negative	3 (15.0%)	3 (20.0%)	6 (17.1%)	Fisher Exact P = 1.000
Positive	17 (85.0%)	12 (80.0%)	29 (82.9%)	
Previous treatment				
Patients included after one line	27 (77.1%)	27 (81.8%)	54 (79.4%)	
Patients included after two lines	8 (22.9%)	6 (18.2%)	14 (20.6%)	
1st line characteristics				
Carboplatin	2 (5.7%)	1 (3.0%)	3 (4.4%)	Fisher Exact P = 1.000
Platinum + Taxane	32 (91.4%)	31 (93.9%)	63 (92.6%)	
Carboplatin + Taxane + Doxorubicin	1 (2.9%)	1 (3.0%)	2 (2.9%)	
2nd line characteristics				
Carboplatin + Taxane	1 (12.5%)	2 (33.3%)	3 (21.4%)	Fisher Exact P = 0.501
Carboplatin + Doxorubicin	4 (50.0%)	1 (16.7%)	5 (35.7%)	
Carboplatin + Gemcitabine	3 (37.5%)	3 (50.0%)	6 (42.9%)	
At least one occurrence of Bevacizumab or other anti-angiogenics maintenance treatment	23	25	48 (70.6%)	
At least one occurrence of PARP-inhibitor as maintenance treatment	1	1	2 (2.9%)	

648 a Missing data for 2 patients of arm 1 and 1 patient of arm 2; b Missing data for 1 patient of arm 2; c Missing data for 7 patients of arm 1 and 5 patients of arm
 649 2; d Missing data for 1 patient of arm 2; e Missing data for 1 patient of arm 1; f Missing data for 18 patients of arm 1 and 15 patients of arm 2

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651 **Table 2: Grade 3/4 adverse events with frequency \geq 5% in any arm**

	Tamoxifen n=35		Regorafenib n=33		All patients n=68	
	n	%	n	%	n	%
Digestive toxicity						
Gastrointestinal obstruction	4	11.4	5	15.2	9	13.2
Abdominal pain	2	5.7	2	6.1	4	5.9
Diarrhea	0	0.0	4	12.1	4	5.9
Vomiting	0	0.0	2	6.1	2	2.9
Cutaneous toxicity						
Hand-foot skin reactions	0	0.0	12	36.4	12	17.6
Cutaneous rash	0	0.0	6	18.2	6	8.8
Stomatitis / mucositis	0	0.0	5	15.2	5	7.4
Biological abnormalities						
Neutropenia	6	17.1	4	12.1	10	14.7
Anemia	5	14.3	3	9.1	8	11.8
Lymphopenia	3	8.6	4	12.1	7	10.3
Thrombocytopenia	2	5.7	5	15.2	7	10.3
Gamma GT increased	5	14.3	2	6.1	7	10.3
Leukopenia	3	8.6	2	6.1	5	7.4
AST ^a increased	3	8.6	1	3.0	4	5.9
ALT ^b increased	2	5.7	1	3.0	3	4.4
Creatinine increased	2	5.7	0	0.0	2	2.9
PAL ^c increased	2	5.7	0	0.0	2	2.9
Other						
Arterial hypertension	7	20.0	7	21.2	14	20.6
Fatigue	3	8.6	5	15.2	8	11.8
Pain	2	5.7	2	6.1	4	5.9
General physical health deterioration	2	5.7	1	3.0	3	4.4
Infection without neutropenia	0	0.0	3	9.1	3	4.4
Dyspnea	0	0.0	2	6.1	2	2.9

652 a aspartate aminotransferase; b alanine aminotransferase; c alkaline phosphatase

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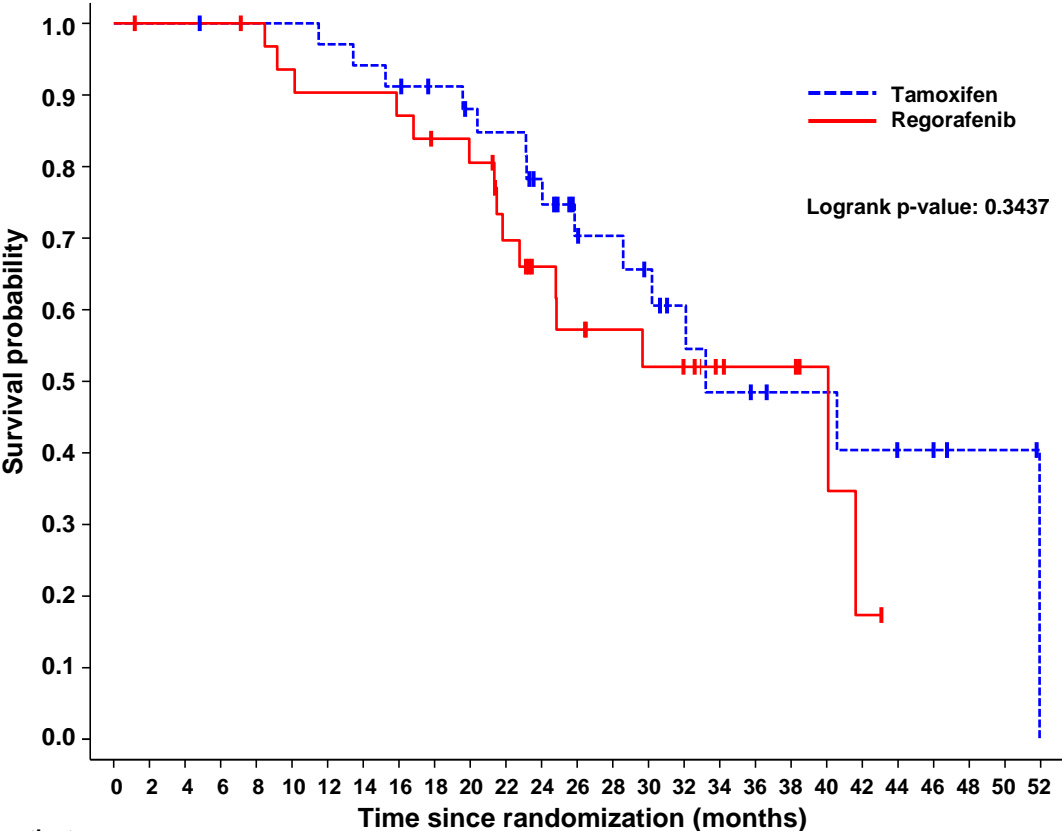
Table 3: Treatment exposure and outcomes for patients in the tamoxifen and regorafenib arms

	Randomization Arm		All patients n = 68	Test
	Arm 1: Tamoxifen n = 35	Arm 2: Regorafenib n = 33		
Duration of treatment, months Median (min; max)	3.7 (0.1; 25.7)	3.6 (0.0; 14.9)	3.7 (0.0; 25.7)	Wilcoxon P = 0.208
At least one dose reduction	1 (2.9%)	20 (60.6%)	21 (30.9%)	Fisher Exact P = <0.001
Reason for permanent discontinuation^a				
Tumor progression	27 (81.8%)	20 (62.5%)	47 (72.3%)	Fisher Exact P = 0.015
Toxicity	3 (9.1%)	8 (25.0%)	11 (16.9%)	
Patient choice	0 (0.0%)	4 (12.5%)	4 (6.2%)	
Investigator decision	1 (3.0%)	0 (0.0%)	1 (1.5%)	
Deterioration of general status/non-response	2 (6.1%)	0 (0.0%)	2 (3.1%)	
Outcomes				
Progression	31 (88.6%)	29 (87.9%)	60 (88.2%)	Fisher Exact P = 1.000
Increased CA-125	23 (74.2%)	23 (79.3%)	46 (76.7%)	Fisher Exact P = 0.763
Symptomatic deterioration related to the disease	5 (16.1%)	9 (31.0%)	14 (23.3%)	Fisher Exact P = 0.227
Death	15 (42.9%)	15 (45.5%)	30 (44.1%)	Fisher Exact P = 1.000
Efficacy				
Best response^b				
CR	4 (12.1%)	0 (0.0%)	4 (6.2%)	Fisher Exact P = 0.124
PR	1 (3.0%)	2 (6.3%)	3 (4.6%)	
SD	22 (66.7%)	19 (59.4%)	41 (63.1%)	
PD	6 (18.2%)	10 (31.3%)	16 (24.6%)	
NE	0 (0.0%)	1 (3.1%)	1 (1.5%)	
Objective response rate^c [90% confidence interval]	5 (15.2%) [6.2%; 29.3%]	2 (6.5%) [1.2%; 18.9%]	7 (10.9%) [5.2%; 19.6%]	Chi-2 p = 0.265
Response rate on CA-125 [90% confidence interval]	9 (26.5%) [14.6%; 41.6%]	11 (34.4%) [20.6%; 50.4%]	20 (30.3%) [21.1%; 40.9%]	Chi-2 p = 0.485

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a Missing data for 2 patients of arm 1 and 1 patient of arm 2; b Missing data for 2 patients of arm 1 and 1 patient of arm 2; c Missing data for 2 patients of arm 1 and 2 patients of arm 2

Figure 2: Kaplan-Meier estimate of Overall Survival (OS) by randomized treatment group



At risk patients

Tamoxifen	35	35	35	34	34	34	33	32	31	29	27	26	22	16	15	13	10	8	7	6	6	5	4	3	2	2	0
Regorafenib	33	32	32	32	31	29	28	28	27	25	24	19	15	13	11	10	9	6	5	5	3	1	0				

	Randomization Arm	All patients n = 68	Test
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Table 1: Patient characteristics at baseline

	Arm 1: Tamoxifen n = 35	Arm 2: Regorafenib n = 33		
Age at inclusion^a: median (min; max)	66.7 (29.8;86.7)	67.3 (41.6;79.2)	66.8 (29.8;86.7)	Wilcoxon P = 0.533
ECOG^b				
Performance status = 0	24 (68.6%)	19 (59.4%)	43 (64.2%)	Fisher Exact P = 0.457
Performance status = 1	11 (31.4%)	13 (40.6%)	24 (35.8%)	
Medical Background				
Arterial hypertension	14 (40.0%)	13 (39.4%)	27 (39.7%)	Fisher Exact P = 1
Diabetes	2 (5.7%)	2 (6.1%)	4 (5.9%)	Fisher Exact P = 1
Cardiovascular	2 (5.7%)	6 (18.2%)	8 (11.8%)	Fisher Exact P = 0.144
History of the disease				
Time from diagnosis (years)				
Median (min; max)	2.3 (1.1; 8.1)	2.0 (0.9; 7.1)	2.2 (0.9; 8.1)	Wilcoxon P = 0.370
FIGO 2014 initial status^c				
IA	0 (0.0%)	3 (10.7%)	3 (5.4%)	Fisher Exact P = 0.526
IIB	1 (3.6%)	1 (3.6%)	2 (3.6%)	
IIIA/B	2 (7.1%)	3 (10.7%)	5 (8.9%)	
IIIC	18 (64.3%)	16 (57.1%)	34 (60.7%)	
IV	7 (25.0%)	5 (17.9%)	12 (21.4%)	
Origin of the cancer				
Ovary	33 (94.3%)	30 (90.9%)	63 (92.6%)	Fisher Exact P = 0.478
Fallopian tubes	0 (0.0%)	2 (6.1%)	2 (2.9%)	
Peritoneum	1 (2.9%)	1 (3.0%)	2 (2.9%)	
Not determined	1 (2.9%)	0 (0.0%)	1 (1.5%)	
Histological type				
Serous / Sero-papillary	33 (94.3%)	28 (84.8%)	61 (89.7%)	Fisher Exact P = 0.361
Clear cell	0 (0.0%)	1 (3.0%)	1 (1.5%)	
Endometrioid	0 (0.0%)	1 (3.0%)	1 (1.5%)	
Mucinous	0 (0.0%)	1 (3.0%)	1 (1.5%)	
Undifferentiated	0 (0.0%)	1 (3.0%)	1 (1.5%)	
Other	2 (5.7%)	1 (3.0%)	3 (4.4%)	
Histological grade^d				
High grade	31 (88.6%)	25 (78.1%)	56 (83.6%)	Fisher Exact P = 0.581
Low grade	2 (5.7%)	2 (6.3%)	4 (6.0%)	
NA	2 (5.7%)	3 (9.4%)	5 (7.5%)	
Other	0 (0.0%)	2 (6.3%)	2 (3.0%)	
Tumor biomarkers				
CA 125 (UI/mL)^e: median (min; max)	127.0 (39.0; 896.0)	166.3 (51.4; 3206.0)	161.7 (39.0; 3206.0)	Wilcoxon P = 0.226
BRCA Status				
Non mutated	16 (45.7%)	18 (54.5%)	34 (50.0%)	Fisher Exact P = 0.303
Mutated BRCA1	2 (5.7%)	5 (15.2%)	7 (10.3%)	
Mutated BRCA2	1 (2.9%)	1 (3.0%)	2 (2.9%)	
Unknown	16 (45.7%)	9 (27.3%)	25 (36.8%)	
Hormonal receptor status^f				
Negative	3 (15.0%)	3 (20.0%)	6 (17.1%)	Fisher Exact P = 1.000
Positive	17 (85.0%)	12 (80.0%)	29 (82.9%)	
Previous treatment				
Patients included after one line	27 (77.1%)	27 (81.8%)	54 (79.4%)	
Patients included after two lines	8 (22.9%)	6 (18.2%)	14 (20.6%)	
1st line characteristics				
Carboplatin	2 (5.7%)	1 (3.0%)	3 (4.4%)	Fisher Exact P = 1.000
Platinum + Taxane	32 (91.4%)	31 (93.9%)	63 (92.6%)	
Carboplatin + Taxane + Doxorubicin	1 (2.9%)	1 (3.0%)	2 (2.9%)	
2nd line characteristics				
Carboplatin + Taxane	1 (12.5%)	2 (33.3%)	3 (21.4%)	Fisher Exact P = 0.501
Carboplatin + Doxorubicin	4 (50.0%)	1 (16.7%)	5 (35.7%)	
Carboplatin + Gemcitabine	3 (37.5%)	3 (50.0%)	6 (42.9%)	
At least one occurrence of Bevacizumab or other anti-angiogenics maintenance treatment	23	25	48 (70.6%)	
At least one occurrence of PARP-inhibitor as maintenance treatment	1	1	2 (2.9%)	

a Missing data for 2 patients of arm 1 and 1 patient of arm 2; b Missing data for 1 patient of arm 2; c Missing data for 7 patients of arm 1 and 5 patients of arm 2; d Missing data for 1 patient of arm 2; e Missing data for 1 patient of arm 1; f Missing data for 18 patients of arm 1 and 15 patients of arm 2

Table 2: Grade 3/4 adverse events with frequency \geq 5% in any arm

	Tamoxifen n=35		Regorafenib n=33		All patients n=68	
	n	%	n	%	n	%
Digestive toxicity						
Gastrointestinal obstruction	4	11.4	5	15.2	9	13.2
Abdominal pain	2	5.7	2	6.1	4	5.9
Diarrhea	0	0.0	4	12.1	4	5.9
Vomiting	0	0.0	2	6.1	2	2.9
Cutaneous toxicity						
Hand-foot skin reactions	0	0.0	12	36.4	12	17.6
Cutaneous rash	0	0.0	6	18.2	6	8.8
Stomatitis / mucositis	0	0.0	5	15.2	5	7.4
Biological abnormalities						
Neutropenia	6	17.1	4	12.1	10	14.7
Anemia	5	14.3	3	9.1	8	11.8
Lymphopenia	3	8.6	4	12.1	7	10.3
Thrombocytopenia	2	5.7	5	15.2	7	10.3
Gamma GT increased	5	14.3	2	6.1	7	10.3
Leukopenia	3	8.6	2	6.1	5	7.4
AST increased	3	8.6	1	3.0	4	5.9
ALT increased	2	5.7	1	3.0	3	4.4
Creatinin increased	2	5.7	0	0.0	2	2.9
PAL increased	2	5.7	0	0.0	2	2.9
Other						
Arterial hypertension	7	20.0	7	21.2	14	20.6
Fatigue	3	8.6	5	15.2	8	11.8
Pain	2	5.7	2	6.1	4	5.9
General physical health deterioration	2	5.7	1	3.0	3	4.4
Infection without neutropenia	0	0.0	3	9.1	3	4.4
Dyspnea	0	0.0	2	6.1	2	2.9

Table 3: Treatment exposure and outcomes for patients of the tamoxifen and regorafenib arms

	Randomization Arm		All patients n = 68	Test
	Arm 1: Tamoxifen n = 35	Arm 2: Regorafenib n = 33		
Duration of treatment, months Median (min; max)	3.7 (0.1; 25.7)	3.6 (0.0; 14.9)	3.7 (0.0; 25.7)	Wilcoxon P = 0.208
At least one dose reduction	1 (2.9%)	20 (60.6%)	21 (30.9%)	Fisher Exact P = <0.001
Reason for permanent discontinuation^a				
Tumor progression	27 (81.8%)	20 (62.5%)	47 (72.3%)	Fisher Exact P = 0.015
Toxicity	3 (9.1%)	8 (25.0%)	11 (16.9%)	
Patient choice	0 (0.0%)	4 (12.5%)	4 (6.2%)	
Investigator decision	1 (3.0%)	0 (0.0%)	1 (1.5%)	
Deterioration of general status/non-response	2 (6.1%)	0 (0.0%)	2 (3.1%)	
Outcomes				
Progression	31 (88.6%)	29 (87.9%)	60 (88.2%)	Fisher Exact P = 1.000
Increased CA-125	23 (74.2%)	23 (79.3%)	46 (76.7%)	Fisher Exact P = 0.763
Symptomatic deterioration related to the disease	5 (16.1%)	9 (31.0%)	14 (23.3%)	Fisher Exact P = 0.227
Death	15 (42.9%)	15 (45.5%)	30 (44.1%)	Fisher Exact P = 1.000
Efficacy				
Best response^b				
CR	4 (12.1%)	0 (0.0%)	4 (6.2%)	Fisher Exact P = 0.124
PR	1 (3.0%)	2 (6.3%)	3 (4.6%)	
SD	22 (66.7%)	19 (59.4%)	41 (63.1%)	
PD	6 (18.2%)	10 (31.3%)	16 (24.6%)	
NE	0 (0.0%)	1 (3.1%)	1 (1.5%)	
Objective response rate^c [90% confidence interval]	5 (15.2%) [6.2%; 29.3%]	2 (6.5%) [1.2%; 18.9%]	7 (10.9%) [5.2%; 19.6%]	Chi-2 p = 0.265
Response rate on CA-125 [90% confidence interval]	9 (26.5%) [14.6%; 41.6%]	11 (34.4%) [20.6%; 50.4%]	20 (30.3%) [21.1%; 40.9%]	Chi-2 p = 0.485

a Missing data for 2 patients of arm 1 and 1 patient of arm 2; b Missing data for 2 patients of arm 1 and 1 patient of arm 2; c Missing data for 2 patients of arm 1 and 2 patients of arm 2