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1 **Submission to the *European Journal of Cancer***

2 Title: Actionable molecular alterations in advanced gynecologic malignancies: updated results from
3 the ProfiLER program

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49

50 **Key words:** precision medicine; gynecologic cancer; molecular targeted agents; next generation
51 sequencing; aCGH.

52 Abstract:

53 Objectives: The objectives of this study were to identify actionable genomic alterations in the
54 gynecological subpopulation of the ProfiLER program and to report clinical efficacy of recommended
55 targeted therapies (RTT).

56 Methods: The ProfiLER program (NCT01774409) is a multicentric prospective trial aiming to
57 implement molecular profiling in patients with advanced refractory cancers. In this program, tumor
58 DNA is analyzed by targeted next-generation sequencing (69 genes) and by whole genome array
59 comparative genomic hybridization. Clinical cases and genomic profiles are presented in a dedicated
60 molecular tumor board to guide treatment strategies. We report here an analysis of patients with
61 gynecological cancers included in this trial.

62 Results: From February 2013 to February 2017, 309 gynecologic cancer patients were included; 279
63 (90%) had sufficient quality and 131 patients (42.4%) had at least one actionable genomic alteration in
64 cancer cells. Four alterations were shared by at least 3% of the patients: 27 (9.7%) *PIK3CA* mutations,
65 15 (5.4%) *KRAS* mutations, 11 (3.9%) *ERBB2* amplifications and 9 (3.2%) *CDKN2A* deletions. Forty-
66 one treatments were initiated among 39 patients (12.6% of the screened population): 8 (20%) had a
67 partial response and other 10 (24%) had a stable disease. Median progression-free survival was 2.7
68 months. Median overall survival was 15.6 months for patients who received a RTT.

69 Conclusion: Molecular profiling identified actionable alterations in 42.4% of patients with advanced
70 refractory gynecologic cancer but only 12.6% were treated with a RTT. Among them, 46% derived
71 clinical benefit (5.8% of the screened population).

72 **Introduction**

73 Gynecologic malignancies affect more than 1 million women each year and cause the death of 494 000
74 of them worldwide (1). First-line strategy for patients with ovarian, endometrial and cervical cancer is
75 based on tumor histopathology (2–4). Recently, better knowledge of carcinogenesis and progress in
76 molecular biology has led to the development of targeted treatments such as tyrosine-kinase inhibitors
77 or monoclonal antibodies (5). Today, in gynecologic cancers, only bevacizumab and PARP inhibitors
78 are approved for ovarian cancer in different settings (6–10) and bevacizumab for metastatic cervical
79 cancer in first-line (11).

80 Precision medicine tests the hypothesis that genomic characterization of tumors provides genomic
81 biomarkers that may guide decisions of treatment with targeted oncogene treatment (12). Gynecologic
82 cancers are heterogeneous and genomic analysis of these tumors has already been interrogated by The
83 Cancer Genomic Atlas (TCGA) (13–15). Feasibility and interest of precision medicine programs have
84 been reported (16–24), but clinical data are still lacking in gynecologic oncology. ProfiLER is a
85 French multicentric clinical trial (NCT01774409) aiming to identify “actionable alterations” in
86 patients with advanced solid tumors (25). The main objective of this study was to analyze the results
87 of this program in patients with advanced refractory gynecologic malignancies.

88

89 **Patients and methods**

90 **Study design**

91 The ProfiLER program is a non-randomized, prospective, multicentric cohort study, combined with a
92 biological sample collection and a clinical data collection, dedicated to cancer patients after standard
93 of care. The study was approved by the French National Agency for Medication Security (ANSM) and
94 by a national ethics committee (CPP Sud-Est IV). This study is registered in ClinicalTrials.gov,
95 number NCT01774409.

96 **Inclusion criteria**

97 Patients were aged over 18 and available tumor (fresh or archival) sample was required. After written
98 consent, a blood sampling was done and archival tumor samples (from initial diagnosis or relapse)
99 were used. Patients were recruited during their medical care, either during standard management or in
100 the case of therapeutic failure.

101 This study includes the subpopulation of female patients with locally advanced, relapsed or metastatic
102 gynecologic malignancies of all histology types. Rare gynecologic tumors (defined as non-high-grade
103 ovarian carcinomas, non-endometrioid endometrial carcinomas, non-squamous cervical carcinomas
104 and other primary tumors) could also be recruited, with a specific focus. Indeed, the promoting center
105 is the French national reference center for rare gynecological tumors (TMRO network).

106 **Tumor sample management**

107 After central quality control by a pathologist, each tumor sample underwent molecular analyses in the
108 promoting center. Sixty-one genes and 8 hot-spot regions of cancer-related genes (*Supplementary*
109 *table 1*) were sequenced by targeted Next Generation Sequencing (Ion Torrent PGM Sequencer, Life
110 Technologies) to assess mutations, insertions and deletions. Copy number variations of whole genome
111 were studied by array Comparative Genomic Hybridization (Agilent platform or Affymetrix platform).
112 The minimal DNA input amount needed was of 200ng for NGS and 1.5µg for aCGH.

113 Multidisciplinary Molecular Board

114 A dedicated panel of clinicians and scientists reviewed tumor genomic profiles in order to determine
115 the relevance of identified genomic alterations and recommended targeted treatment, matching one (or
116 more) actionable alterations when it was clinically relevant. This molecular board was held on a
117 weekly basis. Recommended targeted treatment (RTT) had to be approved by national authorities or
118 available through a clinical trial. Results and conclusions of this meeting were reported in the medical
119 record of the patient and sent to the investigator.

120 Endpoints

121 The main objective was to describe actionable molecular alterations in the gynecologic cancer patients
122 of the ProfiLER program. Secondary objectives were to evaluate access to recommended targeted
123 treatments and identify limitations to their implementation, and to assess efficacy of RTT in this
124 setting.

125 Assessments

126 Characteristics of patients and disease history since diagnosis were retrospectively collected after
127 inclusion. All data were updated until July 31, 2017.

128 Patients with a treatment recommendation were followed according to the study protocol if included in
129 a clinical trial, or according to the routine practice for off-label use. Response to RTT was evaluated
130 according to RECIST 1.1 (26) using best response rates. Clinical benefit rate (CBR) was defined as the
131 percentage of patients achieving either a complete response (CR), or a partial response (PR) or stable
132 disease (SD).

133 Statistical analysis

134 As inclusion in the study could occur throughout the course of the disease, overall survival (OS) was
135 defined as time from the molecular tumor board until death (any cause) or latest news. OS was
136 estimated using the Kaplan–Meier method and survival curves were generated. The reverse Kaplan–
137 Meier method was used to estimate the median follow-up durations. All analyses were performed
138 using SAS version 9.4.

139 Results

140 Population

141 From February 2013 to February 2017, out of the first 2579 patients included in the ProfILER
142 program, 309 had advanced gynecologic cancers (12%) (*Figure 1*). Thirty patients (9.7%) were
143 excluded due to insufficient quality or quantity of tumor material and 279 tumor samples with a
144 median cellularity of 70% were available: 188 (67.4%) were primary tumors, while 72 (25.8%) were
145 metastatic samples and 10 (3.6%) were relapsed tumor samples (missing data for 9 samples). Finally,
146 279 patients (90.3%) were presented to the molecular board with at least one genomic analysis: NGS
147 analysis for 263 patients (94.3%), aCGH for 248 patients (88.8%) and both for 234 (83.9%) patients.
148 Median time between inclusion in the ProfILER program and decision by the molecular board was 2.9
149 months (range from 0.4 to 10.6).

150 Patient's characteristics are reported in *Table 1*. Ovarian malignant tumors were the most frequent
151 cancers ($n=176$, 63%), followed by uterine tumors ($n=61$, 22%), cervical tumors ($n=32$, 11%) and
152 other localizations ($n=10$, 4%). Altogether, 118 (42.3%) patients had a rare histological form
153 gynecologic cancer. Detailed histological subtypes are described in *Table 2*.

154 Genomic alterations

155 Among 309 screened patients, 131 patients (42.4% of the screened population and 47% of the patients
156 with molecular analysis) had at least one actionable genomic alteration, including 48 patients (15.5%)
157 who presented several actionable alterations (*Table 3*). The actionable alteration rate was similar for
158 patients with rare tumors ($n=56$, 47.5% of analyzed patients). Overall, 209 actionable genomic
159 alterations were reported (*Figure 2* and *Supplementary Table 2*).

160 Genomic alterations were mainly missense mutations (at least one identified in 77 patients; 28% of
161 patients with molecular analysis) and gene amplifications ($n=57$; 20%). Twenty-two (8%)
162 homozygous deletions were also identified. Four genomic alterations were shared by at least 3% of the
163 patients: 27 (9.7%) *PIK3CA* hot-spot mutations, 15 (5.4%) *KRAS* hot-spot mutations, 11 (3.9%)
164 *ERBB2* amplifications and 9 (3.2%) *CDKN2A* (P16/INK4) homozygous deletions (*Figure 2*). Genes

165 encoding for proteins in the *PI3K-AKT-mTOR* pathway, *RAS-RAF-MEK-ERK* pathway, cell cycle and
166 *ERBB* family were frequently altered, with 52 (18.6%), 31 (11.1%), 25 (9.0%) and 14 (5%) patients
167 respectively.

168 Recommended treatments and access to recommended targeted treatments

169 A targeted treatment was recommended for 99 patients (32%). Median number of previous lines of
170 chemotherapy was 3 (range from 1 to 9). The most frequently recommended treatments were
171 everolimus ($n=32$), sorafenib ($n=26$), *PI3K-AKT/mTOR* inhibitors ($n=19$) and anti-*HER2* targeted
172 therapy ($n=9$) (Table 3). With a median follow-up of 17.9 months since the molecular tumor board
173 decision, 39 out of 99 patients with a recommended therapy (39%, 12.6% of the screened population)
174 initiated a RTT (Figure 1 and Supplementary Table 3). Sixty patients (19.4%) could not get access to a
175 recommended targeted treatment despite actionable alterations: 17 patients (5.5%) had impaired
176 general status ($PS > 2$), 12 patients (3.9%) had no progressive disease at the time of the analysis, 11
177 (3.6%) were proposed for other treatment, 7 died (2.3%), 5 (1.6%) of them had no access to adequate
178 clinical trial, 5 (1.6%) were lost to follow-up and 2 patients (0.6%) had a contraindication. Two
179 patients began two lines of treatment by RTT. Four RTT were prescribed “off-label” and the 37 others
180 were administered within specific clinical trials, such as the “MOST Plus” (NCT02029001) basket-
181 trial promoted by the Centre Leon Bérard.

182 Efficacy of recommended targeted treatments

183 Forty-one RTT lines were initiated among 39 patients. Two patients died, and one patient stopped the
184 clinical trial due to toxicity before any tumor evaluation. Among the 38 evaluable treatment lines, 8
185 patients (20%) had a partial response to everolimus ($n=3$), LY2780301, pazopanib, sorafenib,
186 trastuzumab and vemurafenib, and 10 (24%) had a stable disease. Clinical benefit rate was 5.8%
187 (18/309) for the entire screened population. Twenty patients (49%) had progressive disease at the time
188 of the first evaluation. Median PFS was 2.7 months (95% CI 2.3-4.7) for patients receiving RTT
189 (Figure 3A).

190 Forty patients died before the molecular board and were not included in the overall survival analysis.
191 Median OS was 15.6 months (95% CI = 6.6-33) for the 39 patients who initiated a RTT and 14.2
192 months (95% CI = 11-17.4) for the 200 patients who did not receive RTT ($p=0.44$) (*Figure 3B*). The
193 OS of patients with at least one actionable alteration was not significantly different to that of patients
194 with no detectable molecular alteration with the ProfiLER panel (*Figure 3C*).

195

196 Discussion

197 The objective of this study was to describe the landscape of actionable genomic alterations in tumors
198 in the gynecologic subpopulation of the ProfILER program, and their impact on patient outcome. At
199 the time of the analysis, 90% of the eligible patients had an aCGH and/or a targeted NGS performed
200 on their tumor sample, within a median time of 2.9 months after inclusion. Therefore, analysis of
201 somatic genomic alterations was shown to be feasible in routine practice.

202 Actionable genomic alterations were identified in 42.4% of patients with advanced refractory
203 gynecologic malignancies, a proportion which is similar to that of other tumor sites already reported in
204 the global population of the ProfILER program (25). This result is also consistent with Takenaka et al.
205 (16) findings on 72 ovarian cancers (49%), with Spreafico et al. (17) study about 55 ovarian cancers
206 (64%) and with Muller et al. (18) results about 29 cervical tumors (59%). Freixinos et al. (19) and
207 Rodriguez et al. (20) identified a greater number of actionable alterations (respectively 72% and 93%)
208 in gynecologic cancers patients using a bigger gene panel (more than 250 genes compared to only 69).
209 Whether larger panels can provide a larger proportion of patients with actionable alteration is being
210 explored currently including in the PROFILER-02 randomized clinical trial (NCT03163732).

211 In the present study, identification of an alteration led to a treatment recommendation in 99 patients
212 (32%). At the time of interim analysis of the NCI-MATCH trial, about one in five gynecologic cancer
213 patients tested (23%) had a gene abnormality that paired with a study drug (22). Comparisons must be
214 done cautiously due to the lack of common criteria to define 'actionable' alterations. The ESMO Scale
215 for Clinical Actionability of molecular Targets (ESCAT) (27) should avoid this issue for future
216 studies.

217 Rare histological subtypes of gynecologic tumors were over-represented (42.4%) in our study.
218 Actionability rate was 47.5% for them, leading to treatment recommendations to 41 patients (34.7%)
219 contrasting with the usual lack of therapeutic possibilities for these patients.

220 *PIK3CA*, *KRAS* and *ERBB2* alterations are known to be shared by ovarian (13,28), endometrial (14)
221 and cervical (15) tumors. In the present population of gynecological cancers, these three genes were

222 indeed the most frequent altered genes in respectively 11.5%, 7.5% and 4.7% of the 279 patients with
223 genomic analyses presented to the molecular board.

224 *BRCA1/2* mutations were identified specifically in the panel in only 2.8% of ovarian cancers patients,
225 compared to 22% in the TCGA program (13). This results from a selection bias towards rare histologic
226 subtypes of the present series. Also high-grade ovarian serous adenocarcinomas already benefited
227 from systematic *BRCA* testing in clinical practice (29) and previously identified *BRCA* mutations were
228 not re-explored.

229 Only 39 of our 99 patients (39.3%) with a RTT actually initiated the treatment which represents 12.6%
230 of the screened population. As already described (30), access to RTT was limited by the lack of open
231 trials evaluating these drugs, but also by impaired general status of our patients. However the present
232 access rate was relatively high compared to the global population of the ProfiLER program (163/699:
233 23%) (25) and to similar studies (19% in Freixinos et al. (19), 43% in Spreafico et al. (17) and 36% in
234 Rodriguez et al. (20)).

235 This trial was not designed to evaluate clinical efficacy. Nevertheless, clinical benefit rate (CBR) to
236 RTT in advanced refractory gynecologic cancer was interesting with 18 partial responses or stable
237 disease out of 41 RTT lines initiated (44%). Yet only 5.8% of the whole screened population benefited
238 from RTT. In another setting, in metastatic breast cancer patients, the SAFIR01 study reported a CBR
239 of 30% (23).

240 Responses to RTT were variable and the range of PFS was wide (from 1.5 to 18.3 months, the longest
241 for a patient treated with everolimus for a squamous cell carcinoma of the cervix). The survival of
242 patients treated with RTT was not significantly different to that of the other patients: of course, this
243 analysis is considerably biased and cannot serve to establish the value of the strategy used in this
244 research program. Randomized trials comparing RTT vs conventional care will need to be
245 implemented. Pairwise comparison with the results of the previous and following treatment lines may
246 also be informative (31). Several patients with *PIK3CA* mutations showed promising responses to
247 LY2780301 and everolimus, needing to be confirmed.

248 The limited response rate results from different phenomenons: 1) the absence of efficient models to
249 predict for the biological role of a given molecular alteration in a given patient, 2) from the clonal
250 heterogeneity of metastatic cancers, 3) the limited sequencing panel 4) the lack of availability of
251 appropriate RTT, 5) the significant drop-off of patients from MTB to initiation of RTT.

252 In 67% of the patients, molecular analyses were performed on tumor samples from initial surgery of
253 the primary tumor. In the future, liquid biopsy may help overcome this problem (32). The present
254 screening strategy enables to reduce the empirical approach used in the past to select second or latter
255 line treatments in many cancers. Still, it will be important to develop tools to better characterize key
256 molecular cancer drivers in given patients for the development of precision oncology (33).

257 To our knowledge, this study is one of the largest programs of precision medicine in gynecologic
258 oncology reported so far. There are however limitations to this study. Patients included in the
259 ProfiLER program were selected late and heavily pre-treated. Molecular analyses were performed
260 using technologies which have largely improved (while being less costly) since the initiation of this
261 program. Similarly, interpretation by the molecular board may have evolved with science knowledge
262 and experience of the participants during the four years.

263 **Conclusion**

264 This study helped to better characterize the genomic profile of gynecologic malignancies. Nearly half
265 of the patients had actionable molecular alterations, using a small gene panel testing (less than 100
266 genes), but one third of patients actually received the recommended RTT. Future trials will have to
267 explore broader gene panels and ensure that a larger proportion of patients have access to the
268 recommended treatment in order to determine more precisely the value of this strategy. General
269 genomic screening of cancers cells to guide the treatment of advanced gynecological cancer patients
270 refractory to standard treatment remains a topic of research, to be evaluated in future clinical trials.
271 Proposal of such molecular analysis for metastatic patients needs to be anticipated and not to be
272 reserved for patients after several lines of systemic treatments.

273 **Conflict of interest statement**

274 Dr. Tredan reports personal fees from Roche, personal fees from Novartis, personal fees from Lilly,
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279 **Author contribution**

280 SC, GG, DPe, OT, PC, JYB and IRC designed the study. ES, CB and AV realized bioinformatics
281 analyzes. QW, SP, VA and DPi performed molecular analyzes. PH, BY, CL, OC, OT, NB, JL, JPI,
282 PC, OD, GF, JYB and IRC recruited and followed-up patients. RV and OLS collected data. SC
283 realized statistical analysis. RV, OLS, SC and IRC interpreted data. RV and OLS wrote the manuscript
284 draft. IRC reviewed the manuscript. All authors read and accepted the final version of the manuscript.

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399

400 **Table and figures legends**

401 *Supplementary table 1: sequenced genes*

402 * Only hot-spot mutation regions were sequenced for these 8 genes

403 *Figure 1: Flow chart*

404 *Table 1: Patients characteristics*

405 *Table 2: Localization and histology of tumors*

406 *Table 3: Conclusions of the molecular tumor board*

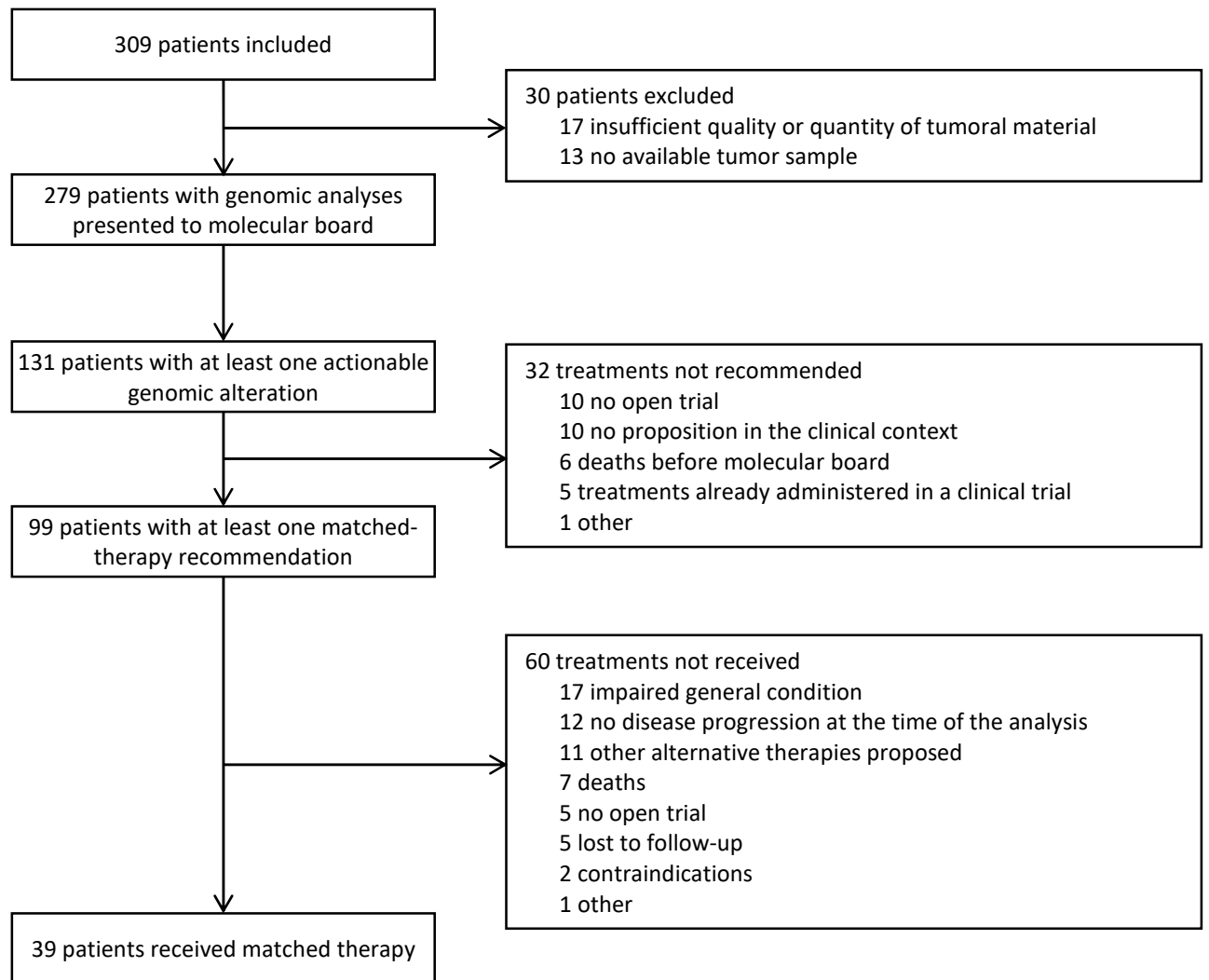
407 *Figure 2: Actionable genomic alterations*

408 *Supplementary Table 2: Classification of the actionable genomic alterations by type of tumor*
409 (percentages; background color from red to green by decreasing frequency)

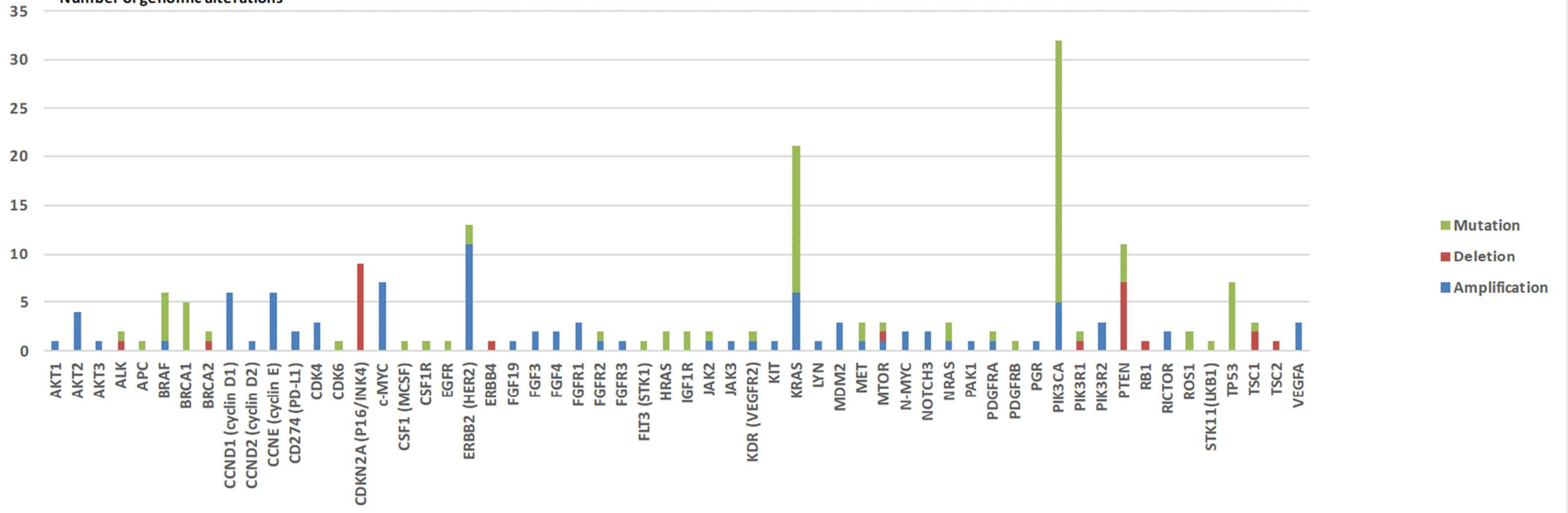
410 *Figure 3: A) Progression free survival of patients receiving a recommended targeted treatment B)*
411 *Overall survival of patients receiving a recommended targeted treatment and of patients treated with*
412 *conventional systemic treatment in the gynecologic population C) Overall survival of patients with*
413 *actionable alteration(s) and patients without any actionable alteration*

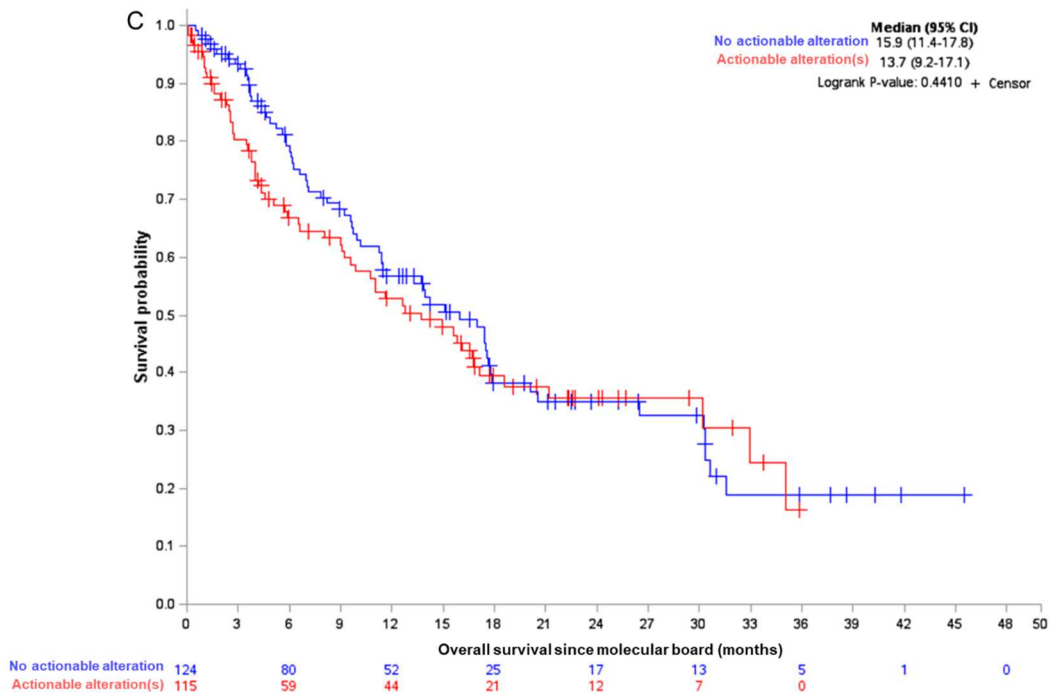
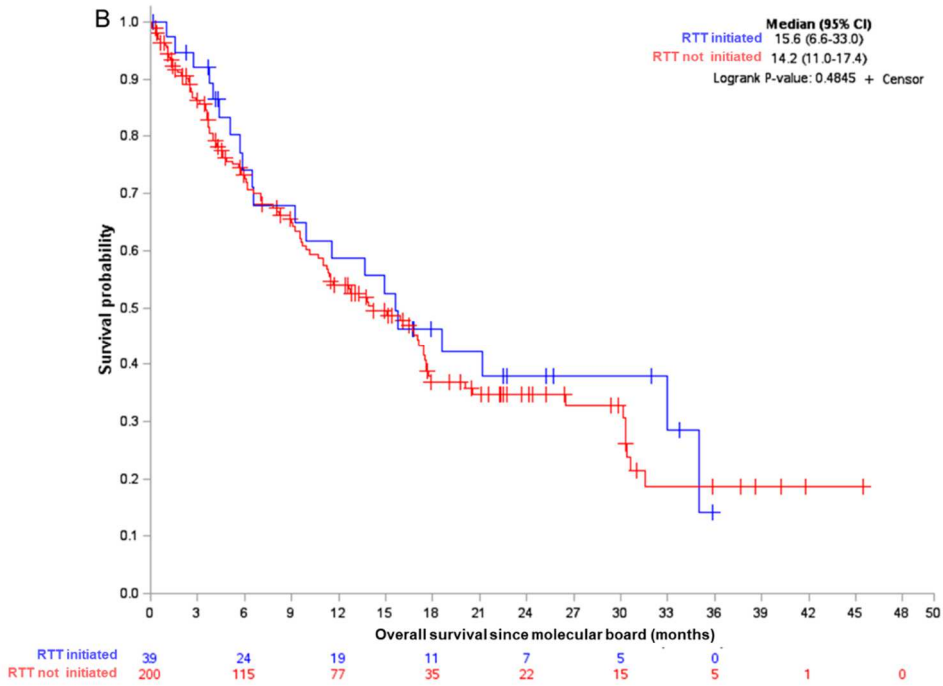
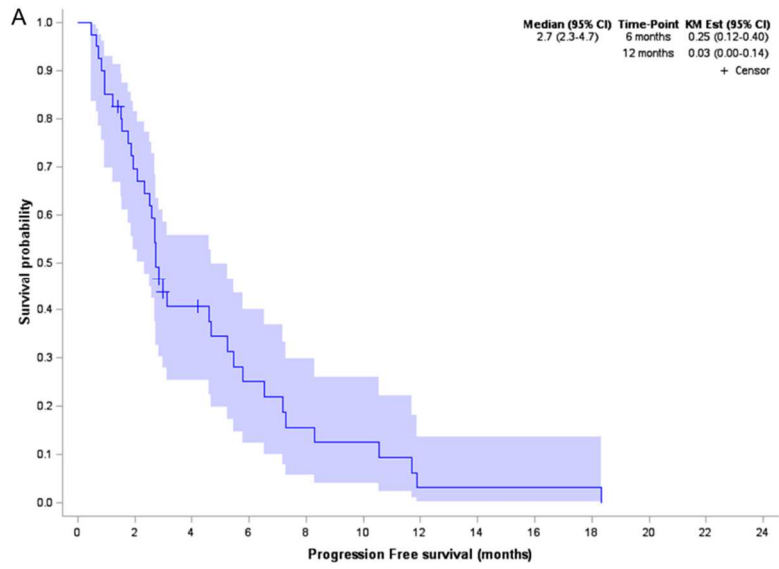
414 *Supplementary Table 3: initiated RTT*

415 PD: progressive disease, SD: stable disease, PR: partial response, NA: not available



Number of genomic alterations





	Localization													All analyzed patients (n = 279)		
	Ovarian cancer				Uterine cancer				Cervical cancer				Other (n = 10)			
	Common (n = 130)		Rare (n = 46)		Common (n = 13)		Rare (n = 48)		Common (n = 18)		Rare (n = 14)					
Age at inclusion																
Median (Min-Max)	61 (21-81)		60 (22-84)		63 (35-75)		61 (31-84)		45 (31-71)		44 (30-75)		58 (38-74)		60 (21-84)	
PS ECOG																
Missing data	12		5		0		6		1		0		0		24	
0	25	(21%)	11	(27%)	6	(46%)	13	(31%)	6	(35%)	2	(14%)	0	(0%)	63	(25%)
1	85	(72%)	28	(68%)	7	(54%)	23	(55%)	9	(53%)	11	(79%)	8	(80%)	171	(67%)
2	8	(7%)	2	(5%)	0	(0%)	4	(10%)	2	(12%)	1	(7%)	1	(10%)	18	(7%)
3	0	(0%)	0	(0%)	0	(0%)	2	(5%)	0	(0%)	0	(0%)	1	(10%)	3	(1%)
Grade																
Missing data	9		16		0		5		4		8		1		43	
1	26	(22%)	2	(7%)	2	(15%)	6	(14%)	3	(21%)	1	(17%)	1	(11%)	41	(17%)
2	22	(18%)	5	(17%)	7	(54%)	5	(12%)	6	(43%)	0	(0%)	0	(0%)	45	(19%)
3	73	(60%)	23	(77%)	4	(31%)	32	(74%)	5	(36%)	5	(83%)	8	(89%)	150	(64%)
FIGO stage at diagnosis																
Missing data	1		0		0		2		0		1		1		5	
Stage I or II	8	(6%)	20	(44%)	5	(39%)	24	(52%)	13	(72%)	8	(62%)	0	(0%)	78	(29%)
Stage III or IV	121	(94%)	26	(57%)	8	(62%)	22	(48%)	5	(28%)	5	(39%)	9	(100%)	196	(72%)
Number of metastatic localizations at inclusion																
Missing data	0		1		0		0		0		0		0		1	
0	40	(31%)	13	(29%)	1	(8%)	3	(6%)	0	(0%)	1	(7%)	1	(10%)	59	(21%)
1	40	(31%)	9	(20%)	7	(54%)	27	(56%)	6	(33%)	1	(7%)	2	(20%)	92	(33%)
2	21	(16%)	12	(27%)	2	(15%)	10	(21%)	8	(44%)	8	(57%)	4	(40%)	65	(23%)
>= 3	29	(22%)	11	(24%)	3	(23%)	8	(17%)	4	(22%)	4	(29%)	3	(30%)	62	(22%)
Previous lines of systemic treatment																
Median (Min-Max)	4 (0-20)		3 (0-20)		2 (0-14)		2 (0-14)		4 (0-7)		3 (0-8)		3.5 (0-11)		3 (0-20)	

Ovarian, Fallopian and Peritoneal Cancer	<i>n</i> = 176 (63.1%)
Epithelial –	160 (57.3%)
Serous Adenocarcinoma	133 (47.7%)
Endometrioid adenocarcinoma	4 (1.4%)
Malignant mixed Mullerian tumor	9 (3.2%)
Mucinous adenocarcinoma	4 (1.4%)
Clear cell tumor	8 (2.9%)
Other	2 (0.01%)
Germ cell tumors	8 (2.9%)
Sex cord stromal tumors	7 (2.5%)
Sarcoma Leiomyosarcoma	1 (0.003%)
Uterine Cancer	<i>n</i> = 61 (21.9%)
Epithelial carcinoma	39 (14.0%)
Adenocarcinoma	26 (9.3%)
Malignant mixed Mullerian tumor	11 (3.9%)
Other	2 (0.01%)
Sarcoma	22 (7.9%)
Leiomyosarcoma	13 (4.7%)
Stromal sarcoma	8 (2.9%)
Other	1 (0.003%)
Cervix cancer	<i>n</i> = 32 (11.5%)
Epithelial carcinoma	29 (10.4%)
Adenocarcinoma	11 (4.0%)
Squamous cell carcinoma	18 (6.5%)
Other	3 (0.01%)
Vulvar and Vaginal Cancer	<i>n</i> = 10 (3.6%)
Epithelial tumors	6 (2.2%)
Adenocarcinoma	5 (0.02%)
Squamous cell carcinoma	1 (0.003%)
Sarcoma	3 (0.01%)
Other	1 (0.003%)

	Localization														All analyzed patients (n = 279)	
	Ovarian cancer				Uterine cancer				Cervical cancer				Other (n = 10)			
	Common (n = 130)		Rare (n = 46)		Common (n = 13)		Rare (n = 48)		Common (n = 18)		Rare (n = 14)					
Length between inclusion and molecular board (months)																
Median (Min-Max)	2.8 (1-11)	2.8 (1-8)	2.3 (1-5)	2.7 (0.4-9)	3.4 (2-6)	2.6 (1-8)	3.2 (2-6)	2.9 (0.4-11)								
Number of actionable alterations																
0	73	(56%)	26	(57%)	5	(39%)	24	(50%)	8	(44%)	6	(43%)	6	(60%)	148	(53%)
1	32	(25%)	16	(35%)	2	(15%)	17	(35%)	8	(44%)	4	(29%)	4	(40%)	83	(30%)
2	18	(14%)	3	(7%)	5	(39%)	2	(4%)	2	(11%)	3	(21%)	0	(0%)	33	(12%)
3	5	(4%)	1	(2%)	1	(8%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	7	(3%)
4	0	(0%)	0	(0%)	0	(0%)	3	(6%)	0	(0%)	1	(7%)	0	(0%)	4	(1%)
5	1	(1%)	0	(0%)	0	(0%)	1	(2%)	0	(0%)	0	(0%)	0	(0%)	2	(1%)
6	1	(1%)	0	(0%)	0	(0%)	1	(2%)	0	(0%)	0	(0%)	0	(0%)	2	(1%)
Class of actionable alterations																
Mutation(s)	33	(25%)	14	(30%)	8	(62%)	10	(21%)	5	(28%)	5	(36%)	1	(10%)	77	(28%)
Amplification(s)	27	(21%)	6	(13%)	0	(0%)	12	(25%)	5	(28%)	4	(29%)	3	(30%)	57	(20%)
Deletion(s)	9	(7%)	3	(7%)	0	(0%)	7	(15%)	0	(0%)	3	(21%)	0	(0%)	22	(8%)
Treatment recommendation																
Yes	44	(34%)	12	(26%)	7	(54%)	19	(40%)	7	(39%)	7	(50%)	3	(30%)	99	(36%)
No	86	(66%)	34	(74%)	6	(46%)	29	(60%)	11	(61%)	7	(50%)	7	(70%)	180	(65%)
Number of recommended treatments																
0	86	(66%)	34	(74%)	6	(46%)	29	(60%)	11	(61%)	7	(50%)	7	(70%)	180	(65%)
1	32	(25%)	9	(20%)	3	(23%)	16	(33%)	7	(39%)	4	(29%)	3	(30%)	74	(27%)
2	9	(7%)	3	(7%)	4	(31%)	2	(4%)	0	(0%)	3	(21%)	0	(0%)	21	(8%)
3	1	(1%)	0	(0%)	0	(0%)	1	(2%)	0	(0%)	0	(0%)	0	(0%)	2	(1%)
4	2	(2%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(1%)
Previous lines of systemic treatment																
PI3K-AKT-mTOR inhibitor	16	(12%)	5	(11%)	8	(62%)	14	(29%)	5	(28%)	6	(43%)	2	(20%)	56	(20%)
Sorafenib (multi target inhibitor)	17	(13%)	3	(7%)	2	(15%)	1	(2%)	0	(0%)	3	(21%)	0	(0%)	26	(9%)
HER2 inhibitor	3	(2%)	1	(2%)	0	(0%)	3	(6%)	0	(0%)	1	(7%)	1	(10%)	9	(3%)
FGF inhibitor	3	(2%)	0	(0%)	2	(15%)	0	(0%)	2	(11%)	0	(0%)	0	(0%)	7	(3%)
BRAF inhibitor	3	(2%)	1	(2%)	0	(0%)	1	(2%)	0	(0%)	0	(0%)	0	(0%)	5	(2%)
BET inhibitor	2	(2%)	1	(2%)	0	(0%)	2	(4%)	0	(0%)	0	(0%)	0	(0%)	5	(2%)
CDK inhibitor	4	(3%)	1	(2%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	5	(2%)
MDM2 inhibitor	0	(0%)	0	(0%)	0	(0%)	5	(10%)	0	(0%)	0	(0%)	0	(0%)	5	(2%)
ALK inhibitor	3	(2%)	1	(2%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	4	(1%)
MAP kinase inhibitor	4	(3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	4	(1%)
Bcr-Abl inhibitor	1	(1%)	1	(2%)	0	(0%)	0	(0%)	1	(6%)	0	(0%)	0	(0%)	3	(1%)
Pazopanib (multi target inhibitor)	0	(0%)	2	(4%)	0	(0%)	0	(0%)	0	(0%)	1	(7%)	0	(0%)	3	(1%)
PARP inhibitor	1	(1%)	0	(0%)	0	(0%)	1	(2%)	0	(0%)	0	(0%)	0	(0%)	2	(1%)
RAK / MEK inhibitors	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(0%)
JAK inhibitor	0	(0%)	1	(2%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(0%)
RAF-MEK inhibitor	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(0%)
NOCH inhibitor	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(0%)
Endocrine therapy	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(6%)	0	(0%)	0	(0%)	1	(0%)
PDL1-PD1 inhibitor	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(0%)
VEGF inhibitor	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(0%)