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Original Research

Actionable molecular alterations in advanced gynaecologic malignancies: updated results from the ProfiLER programme

Romain Varnier [a,b], Olivia Le Saux [c], Sylvie Chabaud [d], Gwenaëlle Garin [d], Emilie Sohier [e,f], Qing Wang [e], Sandrine Paindavoine [f], David Pérol [d], Christian Baudet [e,f], Valéry Attignon [e], Daniel Pissaloux [b,g], Pierre Heudel [c], Benoit You [b,h], Cécile Leyronnas [i], Olivier Collard [j], Olivier Trédan [c], Nathalie Bonnin [h], Jérôme Long [i], Jean-Philippe Jacquin [j], Philippe A. Cassier [c], Olfa Derbel [c,k], Gilles Freyer [b,h], Alain Viari [f,l], Jean-Yves Blay [b,c], Isabelle Ray-Coquard [a,b,c,*]

[a] *Medical Practices Evaluation Team – HESPER EA7425, Centre Léon Bérard, Lyon, France*
[b] *Université Claude Bernard Lyon 1, Lyon, France*
[c] *Department of Medical Oncology, Centre Léon Bérard, Lyon, France*
[d] *Department of Clinical Research, Centre Léon Bérard, Lyon, France*
[e] *Department of Translational Research, Centre Léon Bérard, Lyon, France*
[f] *Synergie Lyon Cancer, Plateforme de Bioinformatique 'Gilles Thomas', Centre Léon Bérard, Lyon, France*
[g] *Department of Biopathology, Centre Léon Bérard, Lyon, France*
[h] *CITOHL, IC-HCL, Hospices Civils de Lyon, Université Claude Bernard Lyon 1, Lyon, France*
[i] *Department of Medical Oncology, Institut Daniel Hollard, Grenoble, France*
[j] *Department of Medical Oncology, Institut Lucien Neuwirth, Saint-Priest-En-Jarez, France*
[k] *Department of Medical Oncology, Hôpital Privé Jean Mermoz, Lyon, France*
[l] *INRIA Grenoble Rhône-Alpes, Montbonnot Saint-Martin, France*

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Abstract ***Objectives:*** The objectives of this study were to identify actionable genomic alterations in the gynaecological subpopulation of the ProfiLER programme and to report clinical efficacy of recommended targeted treatment (RTT).

* *Corresponding author*: Department of Medical Oncology, Centre Léon Bérard, 28 rue Laennec, 69008, Lyon, France. Fax: +33478782716.
E-mail address: isabelle.ray-coquard@lyon.unicancer.fr (I. Ray-Coquard).

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Molecular targeted agents;
Next-generation sequencing;
aCGH

Methods: The ProfiLER programme (NCT01774409) is a multicentric prospective trial aiming to implement molecular profiling in patients with advanced refractory cancers. In this programme, tumour DNA is analysed by targeted next-generation sequencing (69 genes) and by whole genome array comparative genomic hybridisation. Clinical cases and genomic profiles are presented in a dedicated molecular tumour board to guide treatment strategies. We report here an analysis of patients with gynaecological cancers included in this trial.
Results: From February 2013 to February 2017, 309 patients with gynaecologic cancer were included; 279 (90%) had sufficient quality, and 131 patients (42.4%) had at least one actionable genomic alteration in cancer cells. Four alterations were shared by at least 3% of the patients: 27 (9.7%) *PIK3CA* mutations, 15 (5.4%) *KRAS* mutations, 11 (3.9%) *ERBB2* amplifications and 9 (3.2%) *CDKN2A* deletions. Forty-one treatments were initiated among 39 patients (12.6% of the screened population): 8 (20%) had a partial response, and other 10 (24%) had a stable disease. The median progression-free survival was 2.7 months. The median overall survival was 15.6 months for patients who received a RTT.
Conclusion: Molecular profiling identified actionable alterations in 42.4% of patients with advanced refractory gynaecologic cancer, but only 12.6% were treated with a RTT. Among them, 46% derived clinical benefit (5.8% of the screened population).
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1. Introduction

Gynaecologic malignancies affect more than 1 million women each year and cause the death of 494 000 of them worldwide [1]. The first-line strategy for patients with ovarian, endometrial and cervical cancer is based on tumour histopathology [2–4]. Recently, better knowledge of carcinogenesis and progress in molecular biology has led to the development of targeted treatments such as tyrosine kinase inhibitors or monoclonal antibodies [5]. Today, in gynaecologic cancers, only bevacizumab and poly(ADP-ribose) polymerase (PARP) inhibitors are approved for ovarian cancer in different settings [6–10], and bevacizumab is approved for metastatic cervical cancer in first-line treatment [11].

Precision medicine tests the hypothesis that genomic characterisation of tumours provides genomic biomarkers that may guide decisions of treatment with targeted oncogene treatment [12]. Gynaecologic cancers are heterogeneous, and genomic analysis of these tumours has already been interrogated by The Cancer Genome Atlas (TCGA) [13–15]. Feasibility and interest of precision medicine programmes have been reported [16–24], but clinical data are still lacking in gynaecologic oncology. ProfiLER is a French multicentric clinical trial (NCT01774409) aiming to identify 'actionable alterations' in patients with advanced solid tumours [25]. The main objective of this study was to analyse the results of this programme in patients with advanced refractory gynaecologic malignancies.

2. Patients and methods

2.1. Study design

The ProfiLER programme is a non-randomised, prospective, multicentric cohort study, combined with a biological sample collection and a clinical data collection, dedicated to patients with cancer after the standard of care. The study was approved by the French National Agency for Medicines and Health Products Safety and by a national ethics committee (CPP Sud-Est IV). This study is registered in ClinicalTrials.gov, number NCT01774409.

2.2. Inclusion criteria

Patients were older than 18 years, and available tumour (fresh or archival) sample was required. After written consent, a blood sampling was conducted, and archival tumour samples (from initial diagnosis or relapse) were used. The patients were recruited during their medical care, either during standard management or in the case of therapeutic failure.

This study includes the subpopulation of female patients with locally advanced, relapsed or metastatic gynaecologic malignancies of all histology types. Rare gynaecologic tumours (defined as non–high-grade ovarian carcinomas, non-endometrioid endometrial carcinomas, non-squamous cervical carcinomas and other primary tumours) could also be recruited, with a specific focus. Indeed, the promoting centre is the French national reference centre for rare gynaecological tumours (TMRO network).

2.3. Tumour sample management

After central quality control by a pathologist, each tumour sample underwent molecular analyses in the promoting centre. Sixty-one genes and 8 hot spot regions of cancer-related genes (Supplementary Table 1) were sequenced by targeted next-generation sequencing (NGS; Ion Torrent PGM Sequencer, Life Technologies) to assess mutations, insertions and deletions. Copy-

number variations of the whole genome were studied by array comparative genomic hybridisation (aCGH; Agilent platform or Affymetrix platform). The minimal DNA input amount needed was 200 ng for NGS and 1.5 μg for aCGH.

2.4. Multidisciplinary molecular board

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

2.5. End-points

The main objective was to describe actionable molecular alterations in patients with gynaecologic cancer of the ProfiLER programme. Secondary objectives were to evaluate access to RTTs, identify limitations to their implementation and to assess efficacy of RTT in this setting.

2.6. Assessments

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

Patients with a treatment recommendation were followed up according to the study protocol if included in a clinical trial or according to the routine practice for off-label use. Response to RTT was evaluated according to Response Evaluation Criteria in Solid Tumours 1.1 [26] using best response rates. The clinical benefit rate (CBR) was defined as the percentage of patients achieving a complete response (CR), a partial response (PR) or stable disease (SD).

2.7. Statistical analysis

As inclusion in the study could occur throughout the course of the disease, overall survival (OS) was defined as time from the molecular tumour board until death (any cause) or latest news. OS was estimated using the Kaplan–Meier method, and survival curves were generated. The reverse Kaplan–Meier method was used

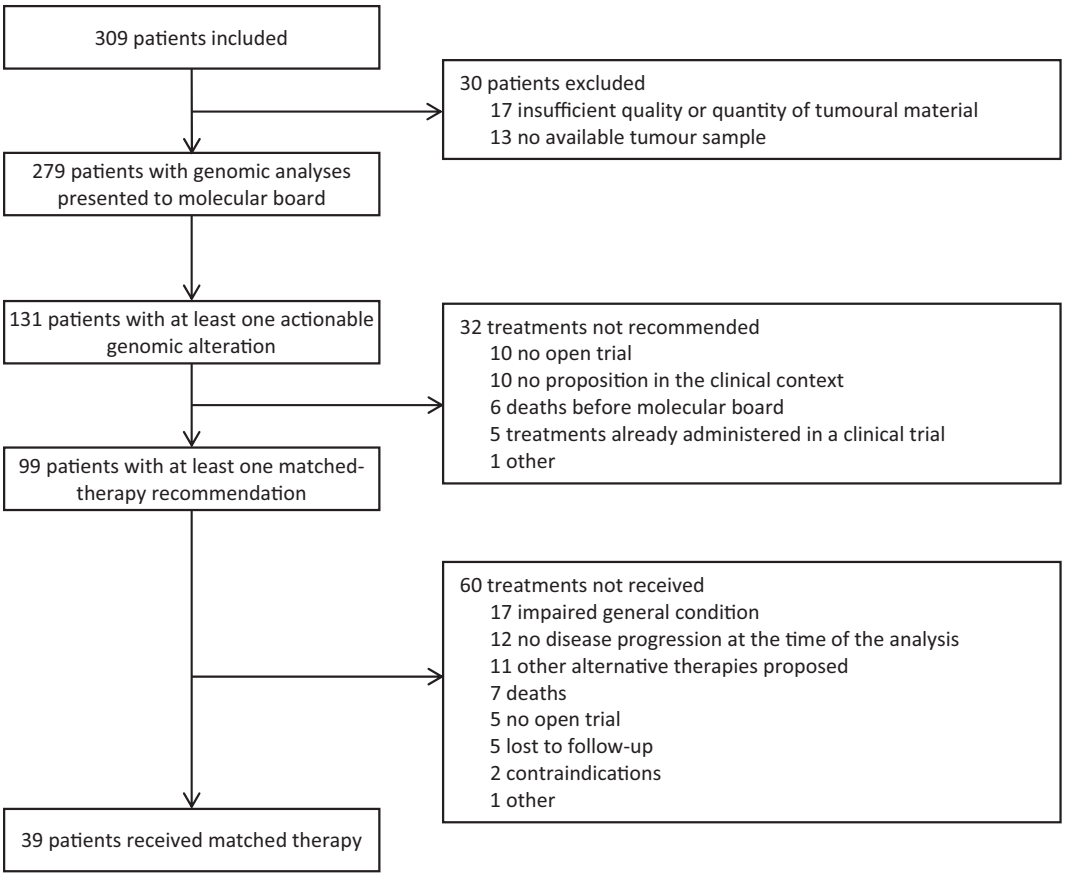

Fig. 1. Flow chart.

to estimate the median follow-up durations. All analyses were performed using SAS version 9.4.

3. Results

3.1. Population

From February 2013 to February 2017, of the first 2579 patients included in the ProfiLER programme, 309 had advanced gynaecologic cancers (12%) (Fig. 1). Thirty patients (9.7%) were excluded owing to insufficient quality or quantity of tumour material, and 279 tumour samples with a median cellularity of 70% were available: 188 (67.4%) were primary tumours, while 72 (25.8%) were metastatic samples and 10 (3.6%) were relapsed tumour samples (missing data for 9 samples). Finally, 279 patients (90.3%) were presented to the molecular board with at least one genomic analysis: NGS analysis for 263 patients (94.3%), aCGH for 248 patients (88.8%) and both for 234 (83.9%) patients. The median time between inclusion in the ProfiLER programme and decision by the molecular board was 2.9 months (range from 0.4 to 10.6).

The patients' characteristics are reported in Table 1. Ovarian malignant tumours were the most frequent cancers (n = 176, 63%), followed by uterine tumours (n = 61, 22%), cervical tumours (n = 32, 11%) and other localisations (n = 10, 4%). Altogether, 118 (42.3%) patients had a rare histological form of gynaecologic cancer. Detailed histological subtypes are described in Table 2.

3.2. Genomic alterations

Among 309 screened patients, 131 patients (42.4% of the screened population and 47% of the patients with molecular analysis) had at least one actionable genomic alteration, including 48 patients (15.5%) who presented several actionable alterations (Table 3). The actionable alteration rate was similar for patients with rare tumours (n = 56, 47.5% of analysed patients). Overall, 209 actionable genomic alterations were reported (Fig. 2 and Supplementary Table 2).

Genomic alterations were mainly missense mutations (at least one identified in 77 patients; 28% of patients with molecular analysis) and gene amplifications (n = 57; 20%). Twenty-two (8%) homozygous deletions were also identified. Four genomic alterations were shared by at least 3% of the patients: 27 (9.7%) *PIK3CA* hot spot mutations, 15 (5.4%) *KRAS* hot spot

Table 1
Patient characteristics.

Characteristics	Localisation							All analysed 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 localisations 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)

ECOG, Eastern Cooperative Oncology Group.; FIGO, International Federation of Gynecology and Obstetrics; PS, Performance Status.

Table 2
Localisation and histology of tumours.

Ovarian, fallopian and peritoneal cancer	n = 176 (63.1%)
Epithelial	160 (57.3%)
Serous adenocarcinoma	133 (47.7%)
Endometrioid adenocarcinoma	4 (1.4%)
Malignant mixed Mullerian tumour	9 (3.2%)
Mucinous adenocarcinoma	4 (1.4%)
Clear cell tumour	8 (2.9%)
Other	2 (0.01%)
Germ cell tumours	8 (2.9%)
Sex cord-stromal tumours	7 (2.5%)
Sarcoma, leiomyosarcoma	1 (0.003%)
Uterine cancer	n = 61 (21.9%)
Epithelial carcinoma	39 (14.0%)
Adenocarcinoma	26 (9.3%)
Malignant mixed Mullerian tumour	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	n = 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	n = 10 (3.6%)
Epithelial tumours	6 (2.2%)
Adenocarcinoma	5 (0.02%)
Squamous cell carcinoma	1 (0.003%)
Sarcoma	3 (0.01%)
Other	1 (0.003%)

mutations, 11 (3.9%) *ERBB2* amplifications and 9 (3.2%) *CDKN2A* (P16/INK4) homozygous deletions (Fig. 2). Genes encoding for proteins in the *PI3K-AKT-mTOR* pathway, *RAS-RAF-MEK-ERK* pathway, cell cycle and *ERBB* family were frequently altered, with 52 (18.6%), 31 (11.1%), 25 (9.0%) and 14 (5%) patients, respectively.

3.3. Recommended treatments and access to RTTs

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

3.4. Efficacy of RTTs

Forty-one RTT lines were initiated among 39 patients. Two patients died, and one patient stopped the clinical trial owing to toxicity before any tumour evaluation. Among the 38 evaluable treatment lines, 8 patients (20%) had a PR to everolimus (n = 3), LY2780301, pazopanib, sorafenib, trastuzumab and vemurafenib, and 10 (24%) had a SD. The CBR was 5.8% (18/309) for the entire screened population. Twenty patients (49%) had progressive disease at the time of the first evaluation. The median progression-free survival (PFS) was 2.7 months (95% confidence interval [CI]: 2.3–4.7) for patients receiving RTT (Fig. 3A).

Forty patients died before the molecular board and were not included in the OS analysis. The median OS was 15.6 months (95% CI = 6.6–33) for the 39 patients who initiated a RTT and 14.2 months (95% CI = 11–17.4) for the 200 patients who did not receive RTT (p = 0.44) (Fig. 3B). The OS of patients with at least one actionable alteration was not significantly different to that of patients with no detectable molecular alteration with the ProfiLER panel (Fig. 3C).

4. Discussion

The objective of this study was to describe the landscape of actionable genomic alterations in tumours in the gynaecologic subpopulation of the ProfiLER programme and their impact on the patient outcome. At the time of the analysis, 90% of the eligible patients had an aCGH and/or a targeted NGS performed on their tumour sample, within a median time of 2.9 months after inclusion. Therefore, analysis of somatic genomic alterations was shown to be feasible in routine practice.

Actionable genomic alterations were identified in 42.4% of patients with advanced refractory gynaecologic malignancies, a proportion which is similar to that of other tumour sites already reported in the global population of the ProfiLER programme [25]. This result is also consistent with the findings by Takenaka *et al.* [16] on 72 ovarian cancers (49%), with the study by Spreafico *et al.* [17] about 55 ovarian cancers (64%) and with the results by Muller *et al.* [18] about 29 cervical tumours (59%). Freixinos *et al.* [19] and Rodriguez *et al.* [20] identified a higher number of actionable alterations (72% and 93%, respectively) in patients with

Table 3
Conclusions of the molecular tumour board.

Conclusions	Localisation							All analysed 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%)
Recommended treatments								
PI3K-AKT-mTOR inhibitor	16 (12%)	5 (11%)	8 (62%)	14 (29%)	5 (28%)	6 (43%)	2 (20%)	56 (20%)
Sorafenib (multitarget 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 (multitarget 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%)

gynaecologic cancer using a bigger gene panel (more than 250 genes compared with only 69). Whether larger panels can provide a larger proportion of patients with actionable alteration is being explored currently, including in the PROFILER-02 randomised clinical trial (NCT03163732).

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

Rare histological subtypes of gynaecologic tumours were over-represented (42.4%) in our study. The actionability rate was 47.5% for them, leading to treatment recommendations to 41 patients (34.7%)

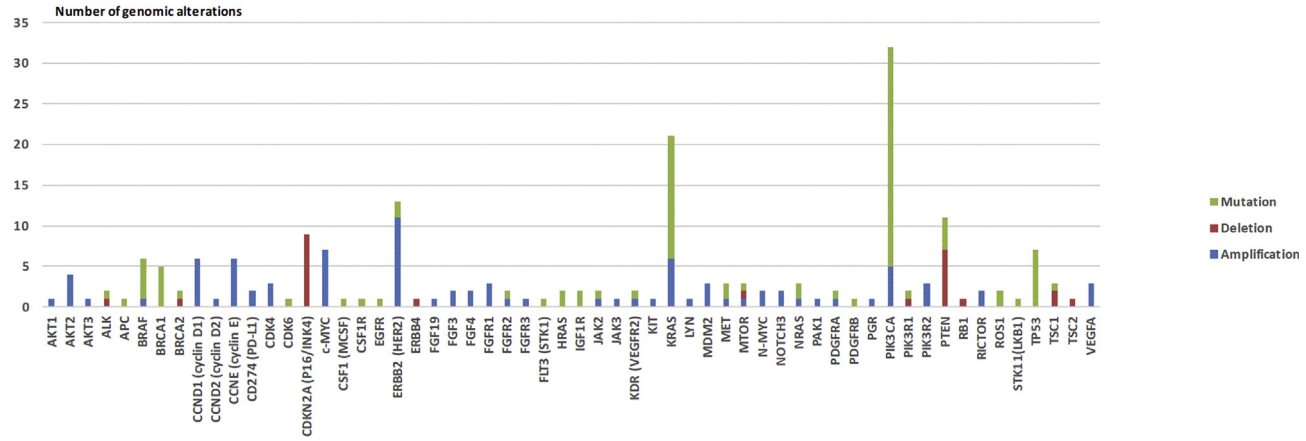

Fig. 2. Actionable genomic alterations.

contrasting with the usual lack of therapeutic possibilities for these patients.

PIK3CA, *KRAS* and *ERBB2* alterations are known to be shared by ovarian [13,28], endometrial [14] and cervical [15] tumours. In the present population of gynaecological cancers, these three genes were indeed the most frequently altered genes in 11.5%, 7.5% and 4.7% of the 279 patients, respectively, with genomic analyses presented to the molecular board.

BRCA1/2 mutations were identified specifically in the panel in only 2.8% of patients with ovarian cancer, compared with 22% in the TCGA programme [13]. This results from a selection bias towards rare histologic subtypes of the present series. In addition, high-grade ovarian serous adenocarcinomas already benefited from systematic *BRCA* testing in clinical practice [29] and previously identified *BRCA* mutations were not re-explored.

Only 39 of our 99 patients (39.3%) with a RTT actually initiated the treatment, which represents 12.6% of the screened population. As already described [30], access to RTT was limited not only by the lack of open trials evaluating these drugs but also by impaired general status of our patients. However, the present access rate was relatively high compared with the global population of the ProfiLER programme (163/699: 23%) [25] and with similar studies (19% in the study by Freixinos *et al.* [19], 43% in the study by Spreafico *et al.* [17] and 36% in the study by Rodriguez *et al.* [20]).

This trial was not designed to evaluate clinical efficacy. Nevertheless, the CBR to RTT in advanced refractory gynaecologic cancer was interesting with 18 PRs or SDs of 41 RTT lines initiated (44%). Yet only 5.8% of the whole screened population benefited from RTT. In another setting, in patients with metastatic breast cancer, the SAFIR01 study reported a CBR of 30% [23].

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

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

In 67% of the patients, molecular analyses were performed on tumour samples from initial surgery of the primary tumour. In the future, liquid biopsy may help overcome this problem [32]. The present screening strategy enables reduction of the empirical approach used in the past to select second- or later-line treatments in many cancers. Still, it will be important to develop tools to better characterise key molecular cancer drivers in given patients for the development of precision oncology [33].

To our knowledge, this study is one of the largest programmes of precision medicine in gynaecologic oncology reported so far. There are however limitations to this study. The patients included in the ProfiLER programme were selected late and heavily pre-treated. Molecular analyses were performed using technologies that have largely improved (while being less costly) since the initiation of this programme. Similarly, interpretation by the molecular board may have evolved with

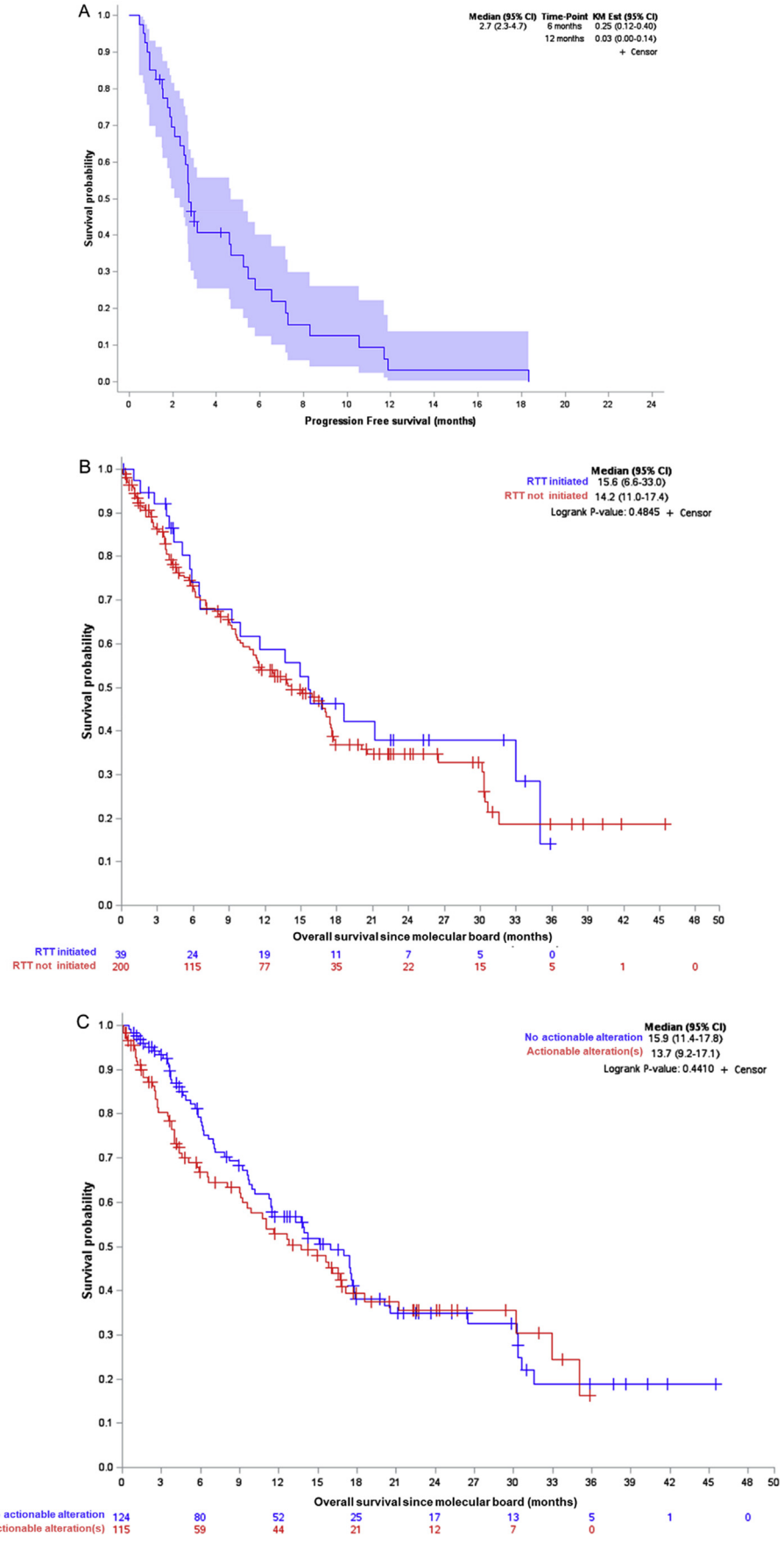

Fig. 3. (A) Progression-free survival of patients receiving a recommended targeted treatment. (B) Overall survival of patients receiving a recommended targeted treatment and of patients treated with conventional systemic treatment in the gynaecologic population. (C) Overall survival of patients with actionable alteration(s) and without any actionable alteration. RTT, recommended targeted treatment; CI, confidence interval.

science knowledge and experience of the participants during the four years.

5. Conclusion

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

Conflict of interest statement

Dr. Trédan reports personal fees from Roche, Novartis, Lilly, AstraZeneca and Pfizer during the conduct of the study. Dr. Pérol reports personal fees from Roche, Lilly and AstraZeneca during the conduct of the study. Dr. Blay reports grants from Roche, Novartis, Bayer and GSK during the conduct of the study. All other authors have nothing to disclose.

Author contributions

S.C., G.G., D.Pe., O.T., P.A.C., J.-Y.B. and I.R.-C. designed the study. E.S., C.B. and A.V. realised bioinformatic analyses. Q.W., S.P., V.A. and D.Pi. performed molecular analyses. P.H., B.Y., C.L., O.C., O.T., N.B., J.L., J.-P.J., P.A.C., O.D., G.F., J.-Y.B. and I.R.-C. recruited and followed up patients. R.V. and O.L.S. collected data. S.C. realised statistical analysis. R.V., O.L.S., S.C. and I.R.-C. interpreted data. R.V. and O.L.S. wrote the manuscript draft. I.R.-C. reviewed the manuscript. All authors read and accepted the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.06.017.

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