An open-label, single-arm, prospective, multi-center, tandem two-stage designed phase II study to evaluate the efficacy of fulvestrant in women with recurrent/metastatic estrogen receptor-positive gynecological malignancies (FUCHSia study)

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► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/ijgc-2023-005229).

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Received 21 December 2023
Accepted 10 April 2024

To cite: Trozzi R, Tuyaerts S, Annibali D, *et al. Int J Gynecol Cancer* Published Online First: [please include Day Month Year]. doi:10.1136/ijgc-2023-005229

ABSTRACT

Objective This study aimed to evaluate fulvestrant efficacy in women with estrogen receptor-positive low-grade gynecological cancers. The primary objective was to determine the response rate. Secondary objectives were progression-free survival, clinical benefit, duration of response, safety, tolerability, and quality of life.

Methods FUCHSia is an open-label, single-arm, prospective, multi-center phase II study. The study population included patients with recurrent/metastatic low-grade gynecological malignancies with estrogen receptor positivity who received a maximum of two lines of previous hormonal therapy. Patients received fulvestrant (FASLODEX, AstraZeneca) via two intramuscular injections (250 mg/5 mL each) in the gluteal muscle on day 1, day 15, day 29, and then every 28 days thereafter until disease progression, withdrawal from the trial due to any unacceptable adverse event, or withdrawal of patient consent.

Results A total of 15 patients (uterine sarcoma n=4; sex cord-stromal ovarian tumors n=3; endometrial carcinoma n=4; serous ovarian cancer n=4) were enrolled. Median follow-up was 48 weeks (interquartile range (IQR) 26–122) in the uterine sarcoma cohort, 63 weeks (IQR 28–77) for sex cord-stromal tumors, 19 weeks (IQR 17–21) for endometrial carcinoma, and 60 weeks (IQR 40–119) for serous ovarian cancer. One partial response according to Response Evaluation Criteria in Solid Tumors v1.1 was observed in one uterine sarcoma patient. No responses were observed in the other cohorts. However, stable disease was observed in three uterine sarcomas (median duration 12 weeks), three sex cord-stromal tumors (median duration 32 weeks), and four low-grade serous ovarian cancer patients (median duration 20 weeks), leading to a disease control rate of 100% for these tumor types. All patients with endometrial carcinoma showed progressive disease.

Conclusion Fulvestrant may control tumor growth in recurrent/metastatic estrogen receptor-positive low-grade gynecological malignancies of specific histology. Further studies are needed to confirm these results.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Estrogens play an important role in gynecological malignancies, and hormonal therapies are part of the therapeutic options. In particular, although the use of fulvestrant seems promising, results are still controversial.

WHAT THIS STUDY ADDS

⇒ This study demonstrated that fulvestrant has a disease control rate of 100% in the treatment of patients with recurrent uterine sarcomas, sex cord-stromal tumors, and low-grade serous ovarian cancer.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Fulvestrant showed disease control in some relapses of gynecological malignancies. Further studies are needed to confirm our results.

INTRODUCTION

Hormonal treatment for gynecological cancers is emerging as a strategy to reduce hormone levels or inhibit their biological activity, thereby stopping or slowing cancer growth.[1] Fulvestrant is a steroidal molecule acting as an estrogen high-affinity competitive antagonist. It lacks agonistic effects on any type of tissue, and upon binding to estrogen receptors it can accelerate their degradation by denaturing their structure. Estrogens are a group of steroid compounds exerting pleiotropic effects in different physiological processes. They have been also related to oncological processes, and some malignancies such as breast,[2] prostate,[3] and gynecological cancers are indeed characterized by expression of estrogen receptors.[4]

Fulvestrant appears potentially promising for patients with estrogen/progesterone receptors-positive tumors, and it is used in estrogen

receptor-positive, metastatic breast cancers in post-menopausal women.[5] However, its role in the treatment of gynecological cancer has been poorly investigated and only a few clinical trials have been performed, showing contrasting results.[6–11] Overall, modest results were reported, except for sporadic case reports that described durable responses.[10 11] However, the absence of high-quality randomized trials does not allow for definitive conclusions about fulvestrant's role in gynecological cancers.

We investigated the efficacy of fulvestrant administration in patients with recurrent/metastatic low-grade gynecological malignancies: endometrial stromal sarcomas, adenosarcomas without sarcomatous overgrowth, leiomyosarcomas, endometrial carcinomas, sex cord-stromal tumors, and serous ovarian cancers.

METHODS

Study Design

FUCHSia was an investigator-initiated, open-label, single-arm, prospective, multi-center, tandem, two-stage designed phase II study enrolling patients with recurrent/metastatic estrogen receptor-positive gynecological malignancies. The study is registered on ClinicalTrials.gov (NCT03926936) and EudraCT registry (2017-005018-76 BE). Study protocol and amendments were approved by the UZ Leuven Ethics Committee Research (ID number: S60857) and by independent ethics committees or review boards at each participating institution. All patients provided written informed consent. The study was conducted in compliance with local and national regulations and following the Declaration of Helsinki and the International Council for Harmonization Guidelines for Good Clinical Practice.

Patients

The study population included patients with recurrent/metastatic low-grade gynecological malignancies; these malignancies were endometrial stromal sarcomas, adenosarcomas without sarcomatous overgrowth, leiomyosarcomas, endometrial carcinomas, sex cord-stromal tumors, and serous ovarian cancers. Patients needed to have measurable disease, according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and estrogen receptor positivity based on immunohistochemistry. Only a maximum of two lines of previous hormonal therapy (tamoxifen, progestins, and/or aromatase inhibitors) were allowed. Post-menopausal patients with adequate organ functions were enrolled (platelets $>100\times10^9$/l, serum total bilirubin <1.5 xULN, alanine transaminase or aspartate transaminase <2.5 xULN, or <5 xULN in the presence of liver metastases).

Patients with an Eastern Cooperative Oncology Group (ECOG) score ≥2, active malignancy, currently receiving (and unwilling to discontinue) any estrogen replacement therapy, participating in another study with an investigational agent, or who received prior chemotherapy or targeted therapy within 4 weeks before study day 1 were excluded.

Treatment Schedule

Patients received two intramuscular injections (250 mg/5 mL each) of fulvestrant (FASLODEX, AstraZeneca) in the gluteal muscle on day 1, day 15, day 29, and then every 28 days thereafter until disease progression, unacceptable adverse event, or withdrawal of patient consent. In case of complete response, patients continued treatment for up to 2 years in case of no measurable disease. In case of partial response or stable disease, patients were evaluated based on tolerability, and eventually treated for up to 3 years or until progression. If disease progression occurred after treatment stopped due to partial response/stable disease, treatment could be restarted and continued until disease progression.

Efficacy and Safety Evaluations

The study's primary objective was to determine the response rate on fulvestrant treatment in each tumor type group, comprising either partial or complete response, as determined by RECIST v1.1 and assessed by CT scans. The secondary endpoints were progression-free survival, clinical benefit (comprising complete response, partial response, and stable disease of any duration), duration of response in each tumor type group, safety, tolerability of fulvestrant, and quality of life. Patients were evaluated per tumor type group. Radiologic imaging analyses included contrast-enhanced CT and FDG PET/CT scans, and were performed at screening and every 3 months thereafter.

For safety assessment, patients were monitored for clinical/laboratory values (hemoglobin, white blood cell count, platelets, absolute neutrophil count, creatinine, total bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, calcium, magnesium, albumin, sodium, and potassium), and adverse events at each visit until 56 days following the last administration of treatment. Adverse events were graded according to Common Terminology Criteria for Adverse Events version 5.0.

For the assessment of the quality of life, patients were requested to complete two questionnaires; the EuroQol-5D and the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, at screening and every 3 months thereafter. The EuroQol-5D essentially consists of the EQ-5D descriptive system and the EQ visual analog scale (EQ VAS). The EuroQol-5D descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ VAS records the respondent's self-rated health on a vertical, visual analog scale where the endpoints are labeled 'Best imaginable health state' and 'Worst imaginable health state'.[12] The QLQ-C30 is composed of five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status/quality-of-life scale, and six single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, and diarrhea) and perceived financial impact of the disease.[13]

Testing for Estrogen Receptor Positivity

Archival tumor samples were assessed locally at each participating center for estrogen receptors status using immunohistochemistry. A centralized pathological review was not performed. At least 10% of tumor cells needed to be estrogen receptor-positive for inclusion in the trial. Furthermore, tumors were scored according to the Allred method. This is a scoring system based both on staining intensity (0=none, 1=weak, 2=moderate, 3=strong) and the proportion of cells stained (0=0%, 1=<1%, 2=1–10%, 3=11–33%, 4=34–66%, 5=>66%).[14]

Statistical Plan

The trial had a tandem two-stage design. In stage 1, a maximum of 20 patients per tumor type group were planned to be enrolled in the trial. The interim analysis would assess the efficacy of fulvestrant administration when the first 15 evaluable patients in each tumor type group completed 24 weeks of treatment, but all enrolled subjects were analysed at interim analysis.

Based on the results of interim analysis, for each tumor type group, either the trial would be stopped for futility or continued to stage 2, according to the stopping criteria described by Pusztai et al.[15] Assuming an expected target level of activity of 25% response rate in each tumor type group for patients included in stage 1, and using a non-informative prior distribution of β (1, 1) for benefit rate, the trial would need to stop if <1 response would be achieved in 15 evaluated patients (meaning that there is <7.5% probability that the expected level of activity will be reached, as reported by Pusztai et al.[15] The sample size for stage 2 would follow the criteria reported by Pusztai et al, and is set to a maximum of 30 patients in stage 2 (resulting in a total of 50 patients per tumor type cohort).

The trial enrolled its first patient in July 2019. Based on an estimation of the number of patients for each tumor type that was expected to be recruited per year and the planned number of centers that would join, the recruitment of 200 patients (50 per tumor type) was expected to be completed in 48 months. However, in case of complete response, patients could continue the treatment for up to 2 years, while in case of partial response or stable disease, patients could be treated for up to 3 years or until progression. Since patient accrual was slower than anticipated in all groups, it was decided to prematurely close the trial after 22 months, with 16 patients enrolled.

We experienced several problems that made the enrollment lower than expected. In Belgium, some centers that were supposed to join the trial experienced logistic problems. In the Netherlands, fulvestrant is freely available; thus, patients who could have entered the study received the drug outside the study. There was also competition with other trials investigating novel drugs in the same patient population.

According to the study protocol, patients still in treatment could continue receiving treatment until disease progression or toxicities. At the time of the analysis, even if the trial was closed, one patient affected by low-grade endometrial stromal sarcoma was still in treatment. Descriptive statistics were used to assess safety and to summarize adverse events' frequencies. For quality of life, mean changes from baseline scores were evaluated.

RESULTS

Patient Characteristics

Between July 2019 and March 2021, 16 patients were enrolled at three sites in Belgium and Netherlands. Only 15 were eligible and included in this analysis (uterine sarcomas n=4; sex cord-stromal tumors n=3; low-grade endometrial carcinomas n=4; low-grade serous ovarian cancers n=4). All patients, except for one low-grade endometrial carcinoma case, had at least one measurable tumor lesion at baseline. The patient without measurable disease was initially considered to be in relapse owing to increased tumor markers, and was wrongly included. However, during the entire duration of the study, the disease remained unmeasurable and she was excluded from the final analysis.

All patients were previously treated with hormonal therapies. Moreover, seven out of 15 patients received previous chemotherapy (median previous lines 3.5, interquartile range (IQR) 3–7). One patient had previous therapy with bevacizumab, while one received a WEE-1 inhibitor in the context of a clinical trial (online supplemental table 1). Median follow-up was 48 weeks (IQR 26–122) in the uterine sarcoma cohort, 63 weeks (IQR 28–77) for sex cord-stromal tumors, 19 weeks (IQR, 17–21) for low-grade endometrial carcinoma, and 60 weeks (IQR 40–119) for low-grade serous ovarian cancers. The median number of fulvestrant administration cycles was 12 (IQR 8–30) for uterine sarcomas, 14 (IQR 7–14) for sex cord-stromal tumors, 5 (IQR 4–5) for low-grade endometrial carcinomas, and 11 (IQR 8–13) for low-grade serous ovarian cancers.

Ten of 15 patients (66.7%) patients had an ECOG status of 0; the remaining five (33.3%) patients had an ECOG status of 1. The most represented histological subtype was low-grade endometrial stromal sarcomas (n=3, 75%) for uterine sarcomas, granulosa cell tumor (n=3, 100%) for sex cord-stromal tumors, and endometrioid (n=4, 100%) for low-grade endometrial carcinomas. All patients received prior hormonal treatment, while six patients (40%) also received a second line of hormonal therapy. The median Allred score was 5 (IQR 4.25–5) for uterine sarcoma, 4 (IQR 3–5) for sex cord-stromal tumors, 5 (IQR 4–5) for endometrial carcinoma, and 5.5 (IQR 5–7.5) for low-grade serous ovarian cancers. Baseline patients' characteristics are summarized in Table 1.

Efficacy

One partial response according to RECIST v1.1 was observed in one case of low-grade adenosarcoma without sarcomatous overgrowth out of four uterine sarcomas. No responses were observed in other cohorts. However, stable disease was noted in three patients with low-grade endometrial stromal sarcomas (median duration 12 weeks), three patients with sex cord-stromal tumors (median duration 32 weeks), and four patients with low-grade serous ovarian cancer patients (median duration 20 weeks), leading to a disease control rate of 100% for these tumor types. For low-grade endometrial carcinomas, all patients had progressive disease. A detailed breakdown of the responses per cohort is shown in Table 2. Figure 1 shows tumor burden evolution in all patients.

Median progression-free survival was 79, 49, 36, and 14 weeks for uterine sarcomas, sex cord-stromal tumors, low-grade serous ovarian cancers, and low-grade endometrial carcinomas, respectively (Online supplemental figure S1). Median overall survival has not been reached yet, since only three patients have died (two uterine sarcomas and one low-grade endometrial carcinomas). Efficacy data (progression-free survival, best overall response) per patient, concerning the Allred score and prior hormonal treatments, are reported in Figure 2. No correlation was observed between Allred score and progression-free survival or the best overall response. An increased progression-free survival in patients who received two prior lines of hormonal treatment (online supplemental figure S2) was, however, not reflected in the best overall response.

Table 1 Disease characteristics of the patients at baseline per disease cohort

Disease characteristics	Uterine sarcoma (n=4)	Sex cord-stromal tumors (n=3)	Endometrial carcinoma (n=4)	Serous ovarian cancer (n=4)
Histology				
Adenosarcoma	1			
Endometrial stromal sarcoma	2			
Unknown	1			
Granulosa cell tumor		3		
Endometrial carcinoma			4	
Low-grade serous ovarian cancer				4
FIGO stage at diagnosis				
I	1	2	2	0
II	1	1	0	0
III	0	0	1	3
IV	1	0	1	1
Unknown	1	0	0	0
Grade				
1	3	0	2	1
2	0	0	2	0
3	0	0	0	0
NA	1	3	0	3
ECOG performance status				
0	2	2	4	2
1	2	1	0	2
Prior surgery				
Yes	4	3	4	4
No	0	0	0	0
Prior radiation				
Yes	1	1	4	0
No	3	2	0	4
Prior chemotherapy lines				
0	4	3	1	0
1	0	0	2	3
≥2	0	0	1	1
Prior targeted therapy				
Yes	0	0	1	1
No	4	3	3	3
Allred score				
1	0	0	0	0
2	0	0	0	0
3	0	1	0	0
4	1	1	1	0
5	3	1	3	2
6	0	0	0	1
7	0	0	0	0
8	0	0	0	1
Number of prior hormone therapies				

Continued

Table 1 Continued

Disease characteristics	Uterine sarcoma (n=4)	Sex cord-stromal tumors (n=3)	Endometrial carcinoma (n=4)	Serous ovarian cancer (n=4)
1	2	1	4	2
2	2	2	0	2
Prior type of hormone therapy				
Anti-estrogen	1	1	0	4
Aromatase inhibitor	2	2	1	2
Progestin	3	2	3	0
GnRH analog	0	0	0	0

ECOG, Eastern Cooperative Oncology Group ; FIGO, Federation of Gynecology and Obstetrics; GnRH, gonadotropin-releasing hormone agonist; NA, not available.

Safety

Fulvestrant treatment was well tolerated, and no patients discontinued treatment nor reduced the dose due to adverse events. In total, 46 adverse events of any grade occurred in 12 patients. Most adverse events were mild (n=20) or moderate (n=21). Five adverse events were considered treatment-related, but all of them were mild. There were five serious adverse events, of which four were severe; however, none of them could be related to the study treatment. Three patients died due to disease progression.

Health-Related Quality of Life

For quality of life assessment, patients were requested to complete the EORTC QLQ-C30 and the EuroQol-5D questionnaires at screening (n=13), week 4 (n=6), month 3 (n=11), month 6 (n=3), month 9 (n=5), month 15 (n=1), month 18 (n=1), and month 21 (n=1). Global health status was consistent in time for all groups for both tests (Figure 3), ranging from 60–80 out of 100 in most cases. Of note, low-grade endometrial carcinoma patients progressed quickly (median progression-free survival 14 weeks), resulting in the discontinuation of the treatment and a drop in the quality of life of the only patient assessed at 3 months after the start of the treatment: from 70 out of 100 on average at baseline (n=4) to 16 out of 100 at month 3 (n=1)

EORTC QLQ-C30 functional scales revealed that physical and cognitive functioning were the most affected functional aspects (online supplemental figure S2). Most patients reported problems with fatigue, pain, insomnia, and appetite loss that did not correlate clearly with time (online supplemental figure S3). In line with the results obtained in the EORTC QLQ-C30 questionnaire, EuroQol-5D evidenced that most patients had problems with usual activities, pain or discomfort, and anxiety or depression that evolved differently in each subgroup over time (online supplemental figure S4).

DISCUSSION

Summary of Main Results

Our study shows that fulvestrant may show efficacy in disease control in some gynecological malignancies. Indeed, for low-grade endometrial stromal sarcomas, sex cord-stromal tumors, and low-grade serous ovarian cancers, a 100% disease control rate was obtained. Some patients obtained a long progression-free survival despite a modest tumor dimension increase, as in two out of four low-grade serous ovarian cancers (mean progression free survival 24 months). The best overall responses have been obtained in the uterine sarcomas group. Overall, fulvestrant was well tolerated in most patients.

The health-related quality of life remained constant for all groups, except for a low-grade endometrial carcinoma patient, according to the EORTC QLQ-C30 questionnaire. Most patients reported physical and cognitive limitations before the start of the treatment that did not improve on treatment. Fatigue, pain, insomnia, and appetite loss were the most frequently reported symptoms. EuroQol-5D questions revealed that most patients experienced issues with

Table 2 Responses (RECIST v1.1) by disease cohort

Outcome	Uterine sarcoma (n=4)	Sex cord-stromal tumors (n=3)	Endometrial carcinoma (n=4)	Serous ovarian cancer
Response rate	1 (25 (2.6 to 64.4))	0 (0 (0 to 47.4))	0 (0 (0 to 35.1))	0 (0 (0 to 40.3))
Complete response	0 (0 (0 to 40.3))	0 (0 (0 to 47.4))	0 (0 (0 to 35.1))	0 (0 (0 to 40.3))
Partial response	1 (25 (2.6 to 64.4))	0 (0 (0 to 47.4))	0 (0 (0 to 35.1))	0 (0 (0 to 40.3))
Stable disease	3 (75 (35.6 to 97.4))	3 (100 (52.6 to 100))	0 (0 (0 to 35.1))	4 (100 (59.7 to 100))
Progressive disease	0 (0 (0 to 40.3))	0 (0 (0 to 47.4))	4 (80 (43.5 to 97.9))	0 (0 (0 to 40.3))
Disease control rate	4 (100 (59.7 to 100))	3 (100 (52.6 to 100))	0 (0 (0 to 35.1))	4 (100 (59.7 to 100))

Data are number of patients (% (90% CI)), unless otherwise indicated.
RECIST, Response Evaluation Criteria in Solid Tumors.

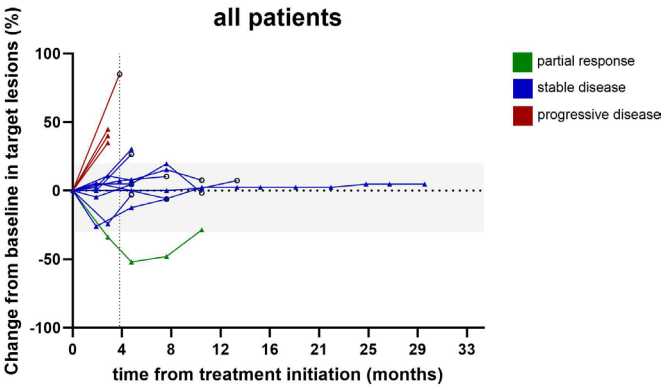

Figure 1 Spider plot. Dynamics of response according to best response (Response Evaluation Criteria in Solid Tumors v1.1). The dotted lines at –30% and +20% indicate thresholds for partial response and progressive disease, respectively, per RECIST v1.1. Circles indicate patients with new lesions or growth in non-target lesions (ie, progressive disease, even with a <20% change in the target lesions).

usual activities, pain, discomfort, anxiety, or depression that do not seem to correlate with therapy.

Results in the Context of Published Literature

Low-grade serous ovarian cancer is characterized by estrogen receptor positivity.[5] The use of fulvestrant has been evaluated only in a phase II study on 26 patients. According to modified RECIST, 50% of the enrolled patients achieved stable disease at 90 days. The median progression-free survival was 62 days. Toxicity was low, with no grade 3 or 4 toxicities. These results are in line with our findings. However, the increased follow-up reveal a longer median progression-free survival in our cohort (36 weeks vs 62 days).[6] This could be explained by the different treatment schedules, suggesting that higher doses could be more effective without increasing toxicity.

Even though sex cord-stromal tumors, and in particular granulosa cells tumors, usually overexpress estrogen receptors, to the best of our knowledge, this is the first study investigating the administration of fulvestrant in recurrent granulosa cell tumor patients. The results showed an encouraging 100% disease control rate (4 of 4 patients). Other hormonal therapies have been investigated in this setting, a recent phase II trial investigated the administration of anastrozole in 41 post-menopausal recurrent granulosa cell tumor patients with estrogen receptor-positive disease obtaining only modest objective responses (overall RECIST v1.1 objective response rate 10.5%).[16]

Treatment with fulvestrant in the treatment of relapsed low-grade endometrial stromal sarcomas with estrogen/progesterone receptor positivity has been previously reported in a single case report. In line with our results, after 6 months of treatment, the patient achieved stable disease.[7] Other hormonal treatments like aromatase inhibitor as first-line treatment have been investigated. In one retrospective cohort of 48 patients with low-grade endometrial stromal sarcoma, the objective response rate was modest (8%), but the disease control rate at 12 months was 79%, and the median progression-free survival was 161 months.[17]

For endometrial cancer cases, results are controversial. Emons et al[8] investigated the use of fulvestrant in 35 patients with advanced/recurrent endometrial cancers, finding some partial responses and stable diseases. The response rate in intention to treat group was 11.4% and the overall survival was 13.2 months. In the protocol population the efficacy was higher, with a response rate of 15.4% and an overall survival of 16.7 months.[8] In a Gynecologic Oncology Group study, 53 patients with advanced/recurrent endometrial

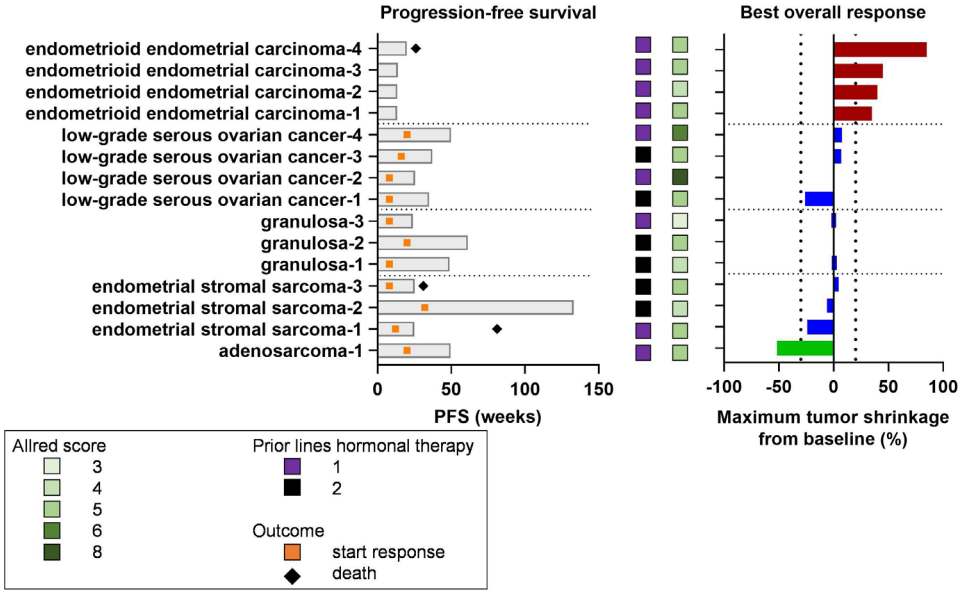

Figure 2 Overview of treatment efficacy per patient. The graph on the left shows the progression-free survival per individual patient according to histological subtype. Orange squares indicate the timepoint at which the response started and black diamonds indicate the time of death. The graph on the right shows the best percentage change from baseline in the sum of diameters of the target lesions; best overall response is indicated by color-coding of bars and includes assessment of target, non-target, and new lesions. The dotted lines at –30% and +20% indicate thresholds for partial response and progressive disease, respectively, per RECIST v1.1. Colored squares between both graphs indicate the expression level of estrogen receptors (Allred score) and the prior line of hormonal therapy.

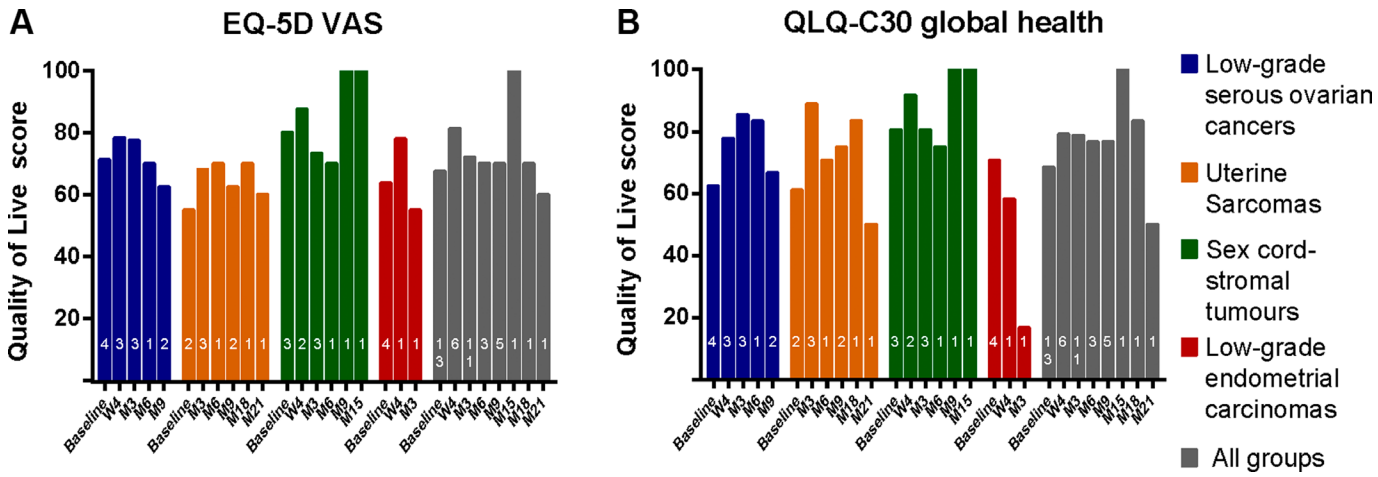

Figure 3 Quality of life as assessed by the EuroQol-5D visual analog scale (EuroQol-5DVAS) (a) and the EORTC quality of life questionnaire (b). Patients completed both questionnaires at screening, week 4, and every 3 or 6 months thereafter. Every bar represents the median score obtained at every time point. A high score for the question represents a high quality of life. The number in the bar represents the number of patients that answered. EEC, endometrial cancer; LGSOC, low-grade serous ovarian cancer; SCST, sex cord-stromal tumors; US, uterine sarcomas.

cancer (estrogen receptor-positive and estrogen receptor-negative) were treated with fulvestrant in a dose of 250 mg for two cycles. Authors reported that among 31 estrogen receptor-positive patients, 1 (3%) patient developed a complete response, 4 (13%) had a partial response, and 9 (29%) had stable disease.[9] These results contrast with two different case reports describing durable responses (>25 and >36 months) to fulvestrant.[10 11] In our series, no low-grade endometrial carcinoma patients responded to the treatment, and all of them progressed.

Unexpectedly, patients who received a higher number of previous hormonal treatments had a better response. A possible explanation has been provided recently by Gaillard et al, who reported that mutations in the ESR1 gene can induce resistance to endocrine therapy in breast and gynecological malignancies since they result in constitutive activation of estrogen receptor α even in the absence of estrogen. As a result, a selective estrogen receptor degrader like fulvestrant could be particularly effective in this setting.[18]

Strengths and Weaknesses

Before the FUCHSia study, there were only anecdotal reports about efficacy of fulvestrant in low-grade estrogen receptor-positive gynecological malignancies. A larger scale, prospective trial to assess the clinical benefit of fulvestrant in these patients was lacking. With the FUCHSia trial, we aimed to test its clinical benefit on different low-grade estrogen receptor-positive gynecological cancer patients who were already resistant to other endocrine therapies and who had no other therapeutic option available.

Our study has a number of limitations, including the premature closure impacting the number of patients enrolled, and the sample size is therefore small. Furthermore, the different tumor types did not allow us to perform a statistical analysis and obtain definitive conclusions. Another possible limitation is that we included low-grade tumors, and the long progression-free survival that we obtained could be related to their indolent biological behavior instead of the efficacy of the drug. Of note, the number of patients that filled the questionnaires varied from one time point to another and decreased quickly in time due to patient progression or dropout, difficulties for the patient to fill in the form, or any other reason. Thus, and given the limited number of patients, especially at the latest timepoints, no firm conclusions could be drawn.

Implications for Practice and Future Research

In recent years, the interest in hormonal therapies has been increasing in gynecological oncology. In particular, because of its high expression of estrogen receptor, some ovarian cancer histotype has become the ideal target for hormonal treatment, and several phase II–III trials are ongoing to evaluate the benefit of hormonal treatment, even without chemotherapy.[19 20] Moreover, recent evidence has shown that molecular features could boost the efficacy of hormonal treatment, such as the association between aromatase inhibitors and cyclin-dependent kinase inhibitors in patients with relapsed estrogen receptor-positive low-grade serous ovarian cancer and endometrial cancer.[21 22] Similarly, the use of fulvestrant combined with targeted drugs is currently under investigations in three phase II trials, evaluating the association with cyclin-dependent kinase inhibitors[23] or PI3K inhibitors.[24 25]

CONCLUSIONS

In this explorative study, only low-grade endometrial carcinomas showed no clinical benefit. Given the limited treatment options, in combination with poor sensitivity to cytotoxic drugs, these observations allow us to consider the use of fulvestrant in some recurrent estrogen receptor-positive gynecological tumors. Importantly, quality of life was only minimally affected by fulvestrant. The fact that the study was prematurely closed underscores the need for larger collaborative initiatives for rare cancers.

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Acknowledgements We thank all patients for participating in the trial and all investigators and site personnel. AstraZeneca provided the study drug fulvestrant.

Contributors FA,ST,DA contributed to study design, data interpretation; RT, AHP contributed to literature search, and writing of the manuscript; LB,PVD,KL,CD,HT contributed to data collection; ST,AHP contributed to data analysis and generation of figures; FA,DA,ST,LB,PVD,KL,CD,HT contributed in revision of the manuscript. All authors read and approved the final paper. FA act as guarantor.

Funding The study was financially supported by Kom Op Tegen Kanker (Stand up to Cancer, the Flemish Cancer Society) and by the Research Foundation Flanders (FWO-TBM program).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Universitaire Ziekenhuizen Leuven (UZ Leuven) ID number: S60857. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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