

Research Report

Evaluating the role of aromatase inhibitors in the treatment of low-grade endometrial stromal sarcomas

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ABSTRACT

Objectives: Endometrial stromal sarcomas (ESS) are rare, accounting for < 1% of all uterine malignancies. Treatment has been guided by small case series and retrospective studies. Endocrine therapy is used in both adjuvant and metastatic settings. Aromatase inhibitors (AIs) are widely used in clinical practice. We sought to evaluate clinical outcomes of AI use in the largest cohort of patients with LGESS to date.

Methods: We performed a retrospective study of patients with LGESS treated with an AI at our institution from 1/1998–12/2020. Response was evaluated using RECIST 1.1. The Kaplan-Meier method was used to estimate median progression-free (PFS) and overall (OS) survival.

Results: Forty patients were identified. Treatment was well tolerated, with 57.5% experiencing adverse effects. The most common were arthralgias (12 patients, 30%) and hot flashes (9, 22.5%). Two of 11 patients with RECIST-evaluable imaging experienced a partial response to treatment. Median PFS for the entire cohort was 79.2 months (95% CI 39.7 months to NE); the 5-year PFS rate was 59.6% (95% CI 41.8% to 73.6, $p = 0.065$). Median follow-up for the 29 survivors was 97.9 months (range: 12.6–226.7). The 5-year OS rate was 81.5% (95% CI 64.9–90.7%). One patient who discontinued AI after 10 years of treatment recurred 1 year later.

Conclusion: AIs were well tolerated and offered periods of prolonged disease stability, even in the metastatic setting. Our study suggests, however, that response rates may be lower than previously reported. Data on optimal duration of treatment is needed, but the rarity of LGESS is an obstacle to conducting large clinical trials.

1. Introduction

Endometrial stromal sarcomas (ESS) are rare, representing <1% of all malignancies arising from the uterus and accounting for 7–25% of all uterine mesenchymal tumors (Hoang et al., 2018; Hosh et al., 2016; Amant et al., 2014; Abeler et al., 2009). ESS is a genetically heterogeneous group of uterine sarcomas that are classified as low-grade (LGESS) or high-grade (HGESS) based on morphological and immunohistochemical characteristics (Lee et al., 2012). LGESS are generally slow-

growing malignancies, with an indolent clinical course, but they can recur even after many years. HGESS often harboring *YWHAE* and *BCOR* genetic abnormalities exhibit high-grade morphology and may be associated with more aggressive clinical behavior compared to LGESS that frequently harbor *JAZF1* rearrangements (Lee et al., 2012).

Optimal therapy for these rare tumors has not been well established (Seagle et al., 2017). First-line treatment generally consists of surgery with total abdominal hysterectomy and bilateral salpingo-oophorectomy. The role of adjuvant treatment is unclear; current

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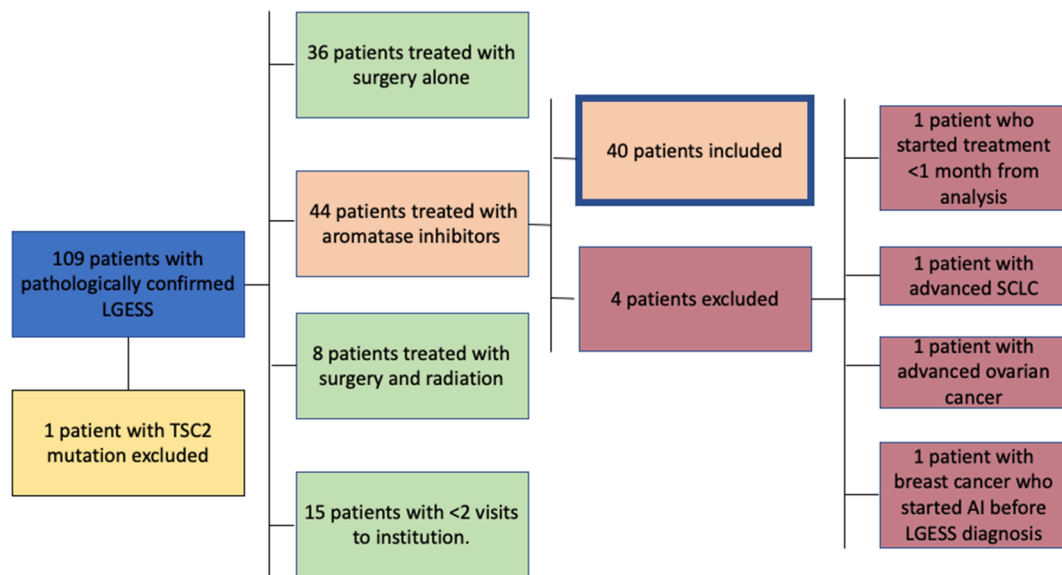


Fig. 1. Inclusion criteria. LGESS, low-grade endometrial stromal sarcoma; SCLC, small cell lung cancer.

practice is guided by small retrospective studies (Ferrandina et al., 2020). Due to high rates of estrogen receptor (ER)/progesterone receptor (PR) positivity in LGESS, endocrine therapy has been investigated as adjuvant treatment for both early and advanced disease (Amant et al., 2014; Chu et al., 2003). The use of progesterone derivatives (megestrol acetate or medroxyprogesterone), aromatase inhibitors (AIs) (letrozole, anastrozole, exemestane), gonadotrophin-releasing hormone (GnRH) analogs (leuprolide) and estrogen receptor antagonists (fulvestrant) have been described. A historic study of 22 patients with LGESS found that 31% (4/13) who received adjuvant progestins recurred, compared with 67% (6/9) who did not receive endocrine therapy (Chu et al., 2003). Another adjuvant study of LGESS found that the median overall survival (OS) of patients receiving endocrine therapy (most commonly megestrol acetate or medroxyprogesterone) was 94 months [95% CI, 90–96] versus observation (72 months) [95% CI, 71–78] ($p = 0.07$) (Leath et al., 2007). While progesterone is an effective treatment for LGESS, it has a number of adverse effects, including weight gain, water retention, hot flashes, and increased risk of thromboembolic disease (Reich and Regauer, 2006). AIs work by interfering with estrogen production from androgens by suppressing aromatase enzyme activity (Fabian, 2007). They are generally well tolerated and are a mainstay in postmenopausal hormone-sensitive breast cancer management. A pooled analysis of small retrospective studies of AI use in LGESS reported a response rate of 67% (Altman et al., 2012). A study of 13 patients with metastatic or recurrent LGESS included 11 patients treated with AI and 2 patients treated with progestins. A response rate of 46.2% was reported for the group, but it is unclear how many of these responders were treated with an AI (Thanopoulou et al., 2015). Due to the rarity of this tumor, prospective data are limited. A phase 2, single-arm clinical trial of 15 patients with hormone-naïve measurable LGESS (60% with distant metastases) treated with anastrozole was reported by Friedlander et al (Friedlander et al., 2021). The response rate was 26.7%, with a durable clinical benefit rate of 66% at 18 months (Friedlander et al., 2021).

Our study is one of the largest retrospective studies to evaluate the clinical outcomes associated with use of AI in LGESS.

2. Methods

We performed a retrospective study of patients with LGESS treated with an AI at Memorial Sloan Kettering Cancer Center (MSK) from January 1998 to December 2020. The study was approved by the Institutional Review Board. An institutional database was used to identify patients, and electronic medical records (EMRs) were reviewed for demographics, stage, sites of metastases, volume of metastatic disease, tumor grade, hormone receptor status, performance status, prior treatments, type and dose of AI used, and toxicities. In addition, we recorded the presence or absence of several comorbidities and concurrent cancers. Patients with synchronous metastatic cancer were excluded. Toxicities were recorded based on provider notes from the EMRs. All pathology reports and available hematoxylin-and-eosin and immunohistochemical slides were reviewed by a gynecologic pathologist. ER and PR stains had been previously performed as part of the clinical work-up, and results were recorded. Results of MSK-IMPACT and MSK-Fusion, which were completed as part of separate studies, were also reviewed. MSK-IMPACT is a hybridization capture based next-generation sequencing assay that interrogates all exons and select introns of 468 genes to identify mutations, copy number changes, microsatellite instability status, and select structural variants (Zehir et al., 2017). The MSK-Fusion panel is a custom RNA sequencing panel via a next-generation sequencing platform that uses anchored multiplex PCR (via the Archer platform) (Zheng et al., 2014).

We used descriptive statistics to report on this cohort of patients. Progression-free survival (PFS) was defined as time from the start of AI until disease progression or death. Patients who had reached neither endpoint were censored at the date of last follow-up. Overall survival (OS) was defined as time from the start of AI until death or last follow-up. The Kaplan-Meier method was used to estimate the median PFS/OS and survival rate. The p value was used to test association between pertinent variables. Survival outcomes were obtained using the log-rank test for PFS and permutation log-rank test for OS (this was due to the small event number in OS) (Heller and Venkatraman, 1996). All analyses were performed using R version 4.1.1 (Mathematics Tifsa. The comprehensive R archive Network, 2021). Objective response in the first

Table 1
Demographics.

Age	
Median, years	55 (Range, 23–61)
Race	
Black	4 (10%)
White	31 (77.5%)
Asian	1 (2.5%)
Indian	3 (7.5%)
Unknown	1 (2.5%)
Weight (BMI mg/m²)	
Normal weight (BMI 18.5 to < 25)	13 (32.5%)
Overweight (BMI 25 to < 30)	16 (40%)
Obesity Class 1 (BMI 30 to < 35)	4 (10%)
Obesity Class 2 (BMI 35 to < 40)	2 (5%)
Obesity Class 3 (BMI > 40)	3 (7.5%)
Unknown	2 (5%)
Smoking status	
Never smoker	28 (70%)
Ex-smoker	7 (17.5%)
Current smoker	2 (5%)
Unknown	3 (7.5%)
Comorbidities	
Diabetes	3 (7.5%)
Hypertension	14(35%)
Hypothyroidism	7 (17.5%)
Renal failure	5(12.5%)
Prior cerebral vascular accident	2(5%)
Thromboembolic disease	10(25%)
Other malignancies	
Breast cancer	3(7.5%)
Renal cancer	2 (5%)
Urothelial cancer	1 (2.5%)
Skin cancer	1 (2.5%)
Leukemia	1 (2.5%)
Other sarcoma	1 (2.5%)
Thyroid cancer	2 (5%)
Lung cancer	1 (2.5%)
Colon cancer	1 (2.5%)
Neuroblastoma	1 (2.5%)
Documented use of hormone replacement therapy	
Documented use of oral contraceptive	10 (25%)
Prior fertility treatments	
Parity	
0	9 (22.5%)
1	2 (5%)
2	20 (50%)
3	6 (15%)
4	2 (5%)
Unknown	1 (2.5%)
Menopausal status at initial diagnosis	
Pre-menopausal at diagnosis	24 (60%)
Menopause at diagnosis	14 (35%)
Unknown	2 (5%)
Menopausal status at recurrence	
Pre-menopausal at recurrence	2 (5%)
Menopause at recurrence	27 (67.5%)
No recurrence to date	11 (27.5%)

six months of treatment was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1 for patients who had measurable disease and suitable imaging available at the time of data analysis.

3. Results

One hundred -nine patients with pathologically confirmed LGESS were evaluated at our institution over the study period. On re-review of pathology and available genomic results, one TSC2mutant LGESS was removed. Forty-four patients were treated with an AI; 4 of these patients

were later excluded from the analysis, including 2 patients with a concurrent metastatic cancer (reasons for exclusion are shown in Fig. 1). The median age at initiation of AI was 55 (range, 23–84) years. The majority (77.5%) were white. Twenty-five patients had elevated body mass indices (BMI); 9 of these patients had obesity (BMI > 30 mg/m²) and 3 (7.1%) had class 3 obesity (BMI > 40 mg/m²). Hypertension (35%) was the most common comorbidity. Ten (25%) patients had a history of another cancer (early-stage or in remission). Three (7.5%) had early-stage breast cancer; 2 of those patients presented with LGESS after treatment with tamoxifen (1 of the 2 patients had been treated with tamoxifen for 3 weeks, the other for 5 months). Of the patients with available data on prior hormonal use preceding their diagnosis of ESS, 6 had a history of hormone replacement therapy use, 10 had documented oral contraceptive use, and 3 had previous in vitro fertilization treatments. Median parity was 2 (range, 0–4). Only 14 patients (35%) were menopausal at the time of their initial diagnosis. Additional demographic information is shown in Table 1.

Thirty-two patients (80%) had tumor hormone receptor status available for review; all were ER positive. Four patients included underwent targeted massively parallel sequencing of their tumors with MSK-IMPACT, and 2 had further analysis using MSK-Fusion, a targeted multiplex RNA sequencing assay. One tumor had copy number alterations in *PMS2* and *AKT1* in addition to a *JAZF1-SUZ12* fusion. A second tumor had a *JAZF1-PHF1* fusion. No alterations were identified in the two remaining tumors.

The majority of patients (45%, n = 18) had stage 1 disease at initial diagnosis, with a median disease-free interval to first recurrence of 5 years (range, 5 months–22 years). Ten patients (25%) have not recurred. All patients underwent surgery as first-line treatment. Two patients (one who presented at 25 years of age and the other at 26 years) deferred bilateral salpingo-oophorectomy at initial presentation; one of these patients had a supracervical hysterectomy with right salpingo-oophorectomy and left salpingectomy; the other had a total abdominal hysterectomy with right ovarian cystectomy. As shown in Fig. 2, 24 (65%) patients received adjuvant endocrine therapy after initial surgery; 11 (27.5%) were treated with megestrol acetate and 13 (32.5%) with AI. Five (12.5%) patients were treated with adjuvant AI after surgical debulking. Fifteen (37.5%) patients had metastatic or stage IV disease at the time of AI initiation, and 20 (50%) had pelvic or abdominal recurrence. AI was the only endocrine therapy used in 14 (35%) patients. AI was the first endocrine therapy in 21 (52.5%) patients. Prior endocrine therapies and other prior treatments are included in Table 2. Seventeen (42.5%) patients received more than one AI during their treatment course. As shown in Table 2, letrozole was the AI most often used. At the time of AI initiation, 13 patients (32.5%) had visceral metastases: six (15%) with lung metastases only; three (7.5%) had liver metastases only; two patients had both liver and lung metastases (5%); one patient had lung and cardiac atrium metastases (2.5%); and one patient had bone and lung metastases (2.5%). Two additional patients had stage IV disease due to T4 tumors.

AI treatment was relatively well tolerated, with just over half of the patients (57.5%) experiencing adverse effects. Arthralgias (12 patients, 30%), hot flashes (9 patients, 22.5%) and fatigue (6 patients, 15%) were the most commonly reported. All documented adverse events are outlined in Supplementary Table 1. Nine patients switched AIs due to intolerable adverse events, and for 6 (66.7%) patients this led to better tolerance. The most common transition was from a non-steroidal AI such as letrozole or anastrozole to the steroidal AI exemestane. Seven (17.5%) patients discontinued treatment due to side effects.

Eighteen patients had measurable disease on imaging at the time of

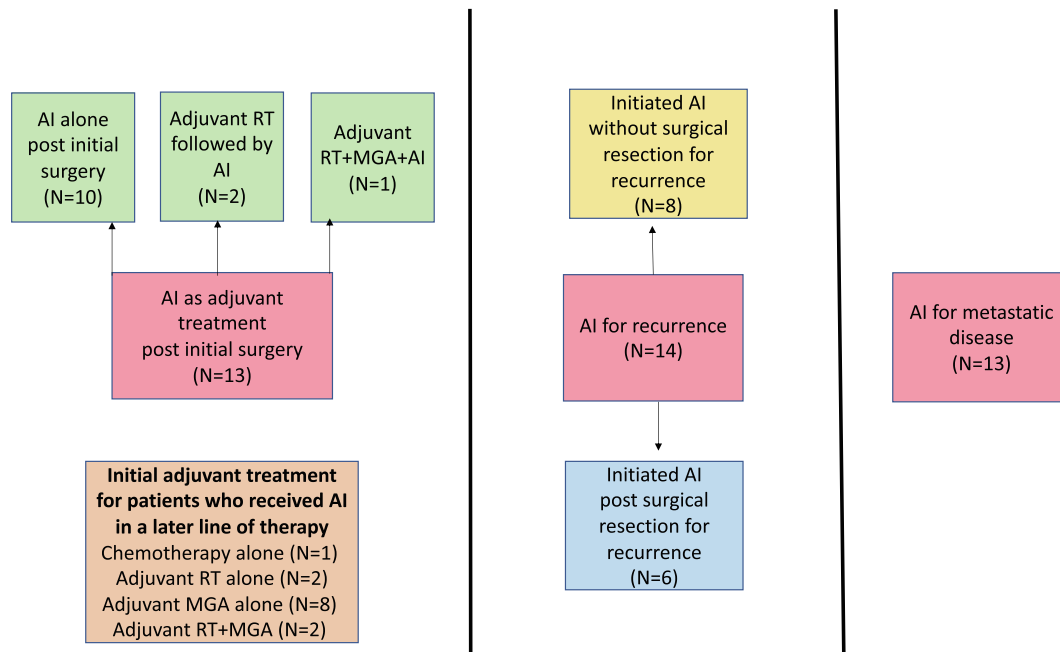


Fig. 2. Summary of aromatase inhibitor use. AI, aromatase inhibitor; BSO, bilateral salpingo-oophorectomy; MGA, Megestrol acetate; RT, radiotherapy.

AI initiation. Five patients did not have baseline scans available for review, because their AI was initiated at an outside institution. Two patients had PET scans as their initial imaging study, precluding optimal RECIST 1.1 assessment. Of the 11 patients for whom RECIST 1.1 could be assessed, there were 2 documented partial responses at six months. Both patients had lung metastases, and 1 also had a pericapsular hepatic implant. Eight patients had stable disease, and 1 had progressive disease. Among the entire cohort of 40 patients, 19 had progressed. No patients died without progression. The median follow-up for the 21 progression-free survivors was 89.4 months (range: 12.6–226.7 months). The median PFS for the entire cohort was 79.2 months (95% CI 39.7 months to NE), with a 5-year PFS rate of 59.6% (95% CI 41.8 to 73.6%, $p = 0.065$). PFS in the metastatic setting was 39 months (95% CI 4.8 to 132 months), with a 5-year PFS rate of 44% (95% CI 16.8–68.4%). PFS survival results for other cohorts are included in [Table 3](#). Seven patients were changed to another AI after progression; 5 of these patients (71.4%) subsequently had a stable 3-month scan (disease stability range, 3–64 months).

Among the entire cohort of 40 patients, there were 11 deaths. All deaths were disease-related. The median follow-up for the 29 survivors was 97.9 months (range: 12.6–226.7 months). The median OS for the entire cohort was not reached ([Fig. 3](#)), with a 5-year OS rate of 81.5% (95% CI 64.9–90.7%). The 5-year OS rate for the metastatic cohort was 67.3% (95% CI 34–86.5%). Survival results for all cohorts are shown in [Table 3](#). Two patients (5%) stopped AI after 5 years without recurrence. Five additional patients (12.5%) stopped AI after 10 years; one of these patients, who had stage 4 disease at initial diagnosis, recurred 1 year after discontinuation of AI.

4. Discussion

LGESS is a rare malignancy, and there is no large prospective trial data available to guide optimal adjuvant therapy. The response rates to

endocrine therapy in other retrospective studies have been reported to be as high as 67% ([Altman et al., 2012](#)). In the current study, despite only two partial responses, we demonstrate that patients treated with AIs generally experience a prolonged period of disease stability, with a median PFS of 79.2 months (95% CI 39.7 months to NE) and a 5-year PFS rate of 59.6% (95% CI 41.8 to 73.6%, $p = 0.065$). Disease stability can be achieved even in a metastatic setting, with a median PFS of 39 months (95% CI 4.8 to 132 months) and a 5-year OS rate [for the metastatic cohort] of 67.3% (95% CI 34–86.5%). Our 5-year OS rate for patients who received AI as adjuvant treatment after primary surgery was 91.7% (95% CI 53.9–98.8%). A retrospective study comparing survival in patients who received adjuvant radiation versus surgery alone in ESS reported 5-year OS rates of 72.2% and 90.7%, respectively ([Barney et al., 2009](#)). Our results, demonstrating lower response rates but durable clinical benefit in patients with recurrent and metastatic disease, are in line with results of the recently published phase 2 clinical trial in a similar albeit hormone-naïve population ([Friedlander et al., 2021](#)).

Our study provides important information that should be included when counseling patients and managing their expectations for treatment. We show that changing from one AI to another after progression may offer additional benefit with respect to disease stability. Five of 7 (71.4%) patients who changed from one AI to another after progression demonstrated stable disease on subsequent 3-month follow-up scan. We found that AIs are generally very well-tolerated, but a significant minority of patients ($n = 7$, 17.5%) discontinued due to adverse effects. As an alternative to discontinuation of AI, some patients transitioned from non-steroidal to steroidal AIs with improvement in adverse symptomatology. In a systematic review and meta-analysis of toxicity in extended adjuvant therapy with AI in early breast cancer, discontinuation due to adverse events occurred in 17% of patients in the prolonged treatment group and 13.4% in the control group ([Goldvaser et al., 2018](#)). Our discontinuation rate was similar at 17.5%. In the anastrozole alone or in

Table 2
Cancer and treatment.

Hormone receptor status	No. patients
ER/PR+	30 (75%)
ER+/PR status unknown	2 (5%)
Unknown	8 (20%)
Stage at initial diagnosis	
1	18 (45%)
2	8 (20%)
3	6 (15%)
4	6 (15%)
Unknown	2 (5%)
Surgery as first-line treatment	40 (100%)
Hysterectomy and bilateral salpingo-oophorectomy	38 (95%)
Supracervical hysterectomy with right salpingo-oophorectomy and left salpingectomy	1 (2.5%)
Total abdominal hysterectomy with right ovarian cystectomy	1 (2.5%)
Radiation therapy	
Adjuvant radiation initial surgery	6 (15%)
Radiation for local recurrence	3 (7.5%)
Radiation of distant metastases	2 (5%)
Number of prior systemic therapies	
0	20 (50%)
1	13 (32.5%)
2	3 (7.5%)
3	3 (7.5%)
4	1 (2.5%)
Number of prior endocrine therapies	
0	22 (55%)
1	13 (32.5%)
2	4 (10%)
3	1 (2.5%)
Prior Treatments	
Tamoxifen	5 (12.5%)
Megestrol acetate	18 (45%)
Leuprolide	1 (2.5%)
Chemotherapy	5 (12.5%)
Concomitant endocrine therapy with aromatase inhibitor	
Megestrol acetate	1 (2.5%)
Leuprolide	4 (10%)
Adjuvant endocrine therapy after initial surgery	24 (60%)
Adjuvant megestrol acetate	11 (27.5%)
Adjuvant aromatase inhibitor	13 (32.5%)
Adjuvant endocrine therapy after debulking surgery	9 (22.5%)
Adjuvant megestrol acetate	4 (10%)
Adjuvant aromatase inhibitor	5 (12.5%)
Aromatase inhibitor use	
Letrozole	28 (70%)
Anastrozole	18 (45%)
Exemestane	15 (37.5%)
One aromatase inhibitor	23 (57.5%)
Two aromatase inhibitors	13 (32.5%)
Three aromatase inhibitors	4 (10%)
Disease status at initiation of aromatase inhibitor	
Confined to uterus	5 (12.5%)
Confined to pelvis	7 (17.5%)
Localized spread	13 (32.5%)
Distant/visceral metastases/Stage 4 disease	15 (37.5%)
Site of distant metastases at initiation of aromatase inhibitor (n = 13)	
Lung only	6 (15%)
Liver only	3 (7.5%)
Lung and liver	2 (5%)
Lung and cardiac	1 (2.5%)
Lung and bone	1 (2.5%)
Subsequent treatment after progression/intolerance of aromatase inhibitors	
Fulvestrant	7 (17.5%)
Megestrol acetate	9 (22.5%)
Leuprolide	7 (17.5%)
Chemotherapy	4 (10%)
Clinical trial	1 (2.5%)

ER, estrogen receptor; PR, progesterone receptor.

combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early stage breast cancer (ATAC) trial, hot flashes (35% of patients) and musculoskeletal disorders (30.3% of patients) were the AEs most commonly experienced (The ATG, 2003). Our study showed a similar toxicity profile.

While the current study is one of the largest retrospective studies to focus on AI use in LGEES, the results are limited by the retrospective nature of the study, the heterogenous population, as well as the small sample size. The absence of baseline scans for radiology review meant that 7 patients in our cohort did not have their responses assessed by RECIST. Regarding toxicity, we were also limited to information documented by providers.

The optimal duration of treatment with AIs in the adjuvant and metastatic settings remains unclear. In our study, two patients did not recur after 5 years of AI treatment, but another patient did recur after 10 years of AI treatment. A phase 2 study examining the clinical impact of interruption versus maintenance of AI in locally advanced/metastatic LGEES is currently underway (NCT03624244) (NCT03624244). This study aims to determine the feasibility of interrupting AI in patients with locally advanced or metastatic LGEES after long-term stabilization or response. The investigators also aim to identify predictive factors of prolonged response or late resistance to endocrine therapy.

5. Conclusion

AIs are well-tolerated and offer periods of prolonged disease stability in LGEES, even in the metastatic setting. Our study suggests that response rates may be lower than previously reported in the literature. If a patient has progressed on one AI, it may be reasonable to try an alternative AI. The optimal duration of AI treatment in both the adjuvant and the metastatic setting is currently unclear, and we await the results of ongoing prospective trials.

CRediT authorship contribution statement

Fionnuala Crowley: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Karen A. Cadoo:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing. **Sarah Chiang:** Formal analysis, Writing – original draft, Writing – review & editing. **Diana L. Mandelker:** Formal analysis, Writing – original draft, Writing – review & editing. **Raazi Bajwa:** Formal analysis, Writing – original draft, Writing – review & editing. **Alexia Iasonos:** Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Qin C. Zhou:** Data curation, Writing – original draft, Writing – review & editing. **Kathryn M. Miller:** Writing – original draft, Writing – review & editing. **Martee L. Hensley:** Writing – original draft, Writing – review & editing. **Roisin E. O’Cearbhaill:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 3
Survival.

Variable	N	# Progressed	mPFS (mo, 95% CI)	3-yr PFS rate (95% CI)	5-yr PFS rate (5% CI)	Log-rank PV
All	40	19	79.2 (39.7-NE)	72% (55.1–83.4%)	59.6% (41.8–73.6%)	0.065
Metastatic setting	13	9	39 (4.8–132)	52.7% (23.4–75.5%)	44% (16.8–68.4%)	
Adjuvant initial surgery	13	3	Not Reached	84.6% (51.2–95.9%)	84.6% (51.2–95.9%)	
Recurrent/ Adjuvant debulking	14	7	51.4(9.4-NE)	78.6% (47.2–92.5%)	49.9% (19.7–74.2%)	
Variable	N	# Dead	mOS (mo, 95% CI)	3-yr OS rate (95% CI)	5-yr OS rate (5% CI)	Log-rank PV (p)
All	40	11	Not Reached	87.2% (72–94.5%)	81.5% (64.9–90.7%)	0.607
Metastatic setting	13	4	Not Reached	76.9% (44.2–91.9%)	67.3% (34–86.5%)	
Adjuvant initial surgery	13	2	Not Reached	100%	91.7% (53.9–98.8%)	
Recurrent/ Adjuvant debulking	14	5	132(84.2-NE)	85.1% (52.3–96.1%)	85.1% (52.3–96.1%)	

mPFS, median progression-free survival; mOS, median overall survival; yr, year; mo, months; CI, confidence interval; NE, not estimable; (p), permutation. Due to small p value for certain level of the variables (event # < 3), p-value is obtained by applying permutation Log-rank test with 5000 permutation times.

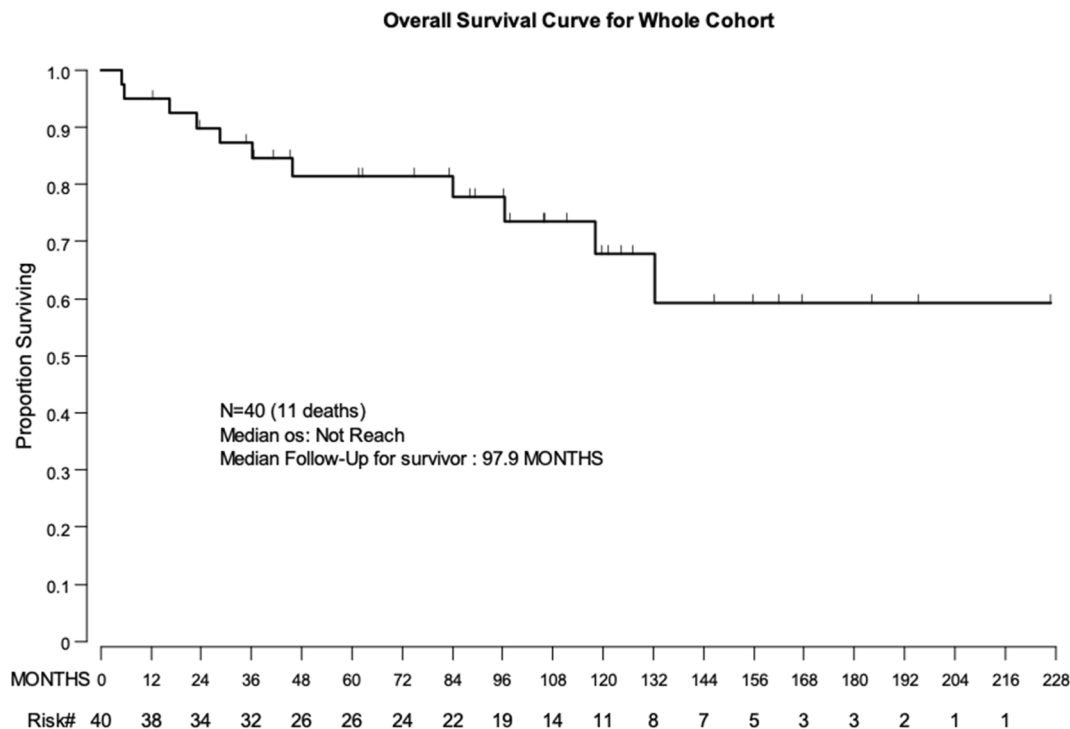


Fig. 3. Overall survival curve for entire cohort.

Disclosures

Dr. Cadoo reports the following, outside the submitted work: other from Astra Zeneca (travel, accommodation, meal; institutional support for therapeutic trial); other from Syndax Pharmaceuticals (institutional support for therapeutic trial). **Dr. Chiang** reports personal fees from AstraZeneca, outside the submitted work. **Dr. Hensley** reports the following, outside the submitted work: Spouse is an employee of Sanofi; GSK (Strategic Advisory Board); personal fees, Research to Practice (CME Faculty, Faculty speaker); royalties, Up to Date (author, chapters); Bayer (received an ASCO publication); personal fees, GOG (Symposium Chair and speaker); personal fees and travel expenses, Tesaro (Advisory Board); personal fees, Lilly Oncology (Advisory Board); personal fees, Merck (consulting); personal fees, Janssen (Advisory Board). **Dr. Iasonos** reports the following, outside the submitted work: Mylan (consultant; personal fees). **Dr. O’Cearbhaill** reports the following, outside the submitted work: Dr. O’Cearbhaill reports personal fees from Tesaro/GSK, personal fees from Regeneron , personal fees from Seattle Genetics,

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.gore.2022.100980>.

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