A Phase 2, Randomized, Open-Label Study of Irosustat Versus Megestrol Acetate in Advanced Endometrial Cancer

Patricia Pautier, MD, Ignace Vergote, MD, PhD,† Florence Joly, MD,‡ Bohuslav Melichar, MD,§ Elzbieta Kutarska, MD,‖ Geoffrey Hall, MD,¶ Anna Lisyanskaya, MD,# Nicholas Reed, MD,** Ana Oaknin, MD,†† Valerijus Ostapenko, MD,‡‡ Zanete Zvirbule, MD,§§ Eric Chetaille, MD,‖‖ Agnès Geniaux, PhD,‖‖ Muhammad Shoaib, MD,‖‖ and John A. Green, MD¶¶*

Objective: Advanced/metastatic or recurrent endometrial cancer has a poor prognosis. Malignant endometrial tissue has high steroid sulphatase (STS) activity. The aim of this study was to evaluate STS as a therapeutic target in patients with endometrial cancer.

Methods: This was a phase 2, multicenter, international, open-label, randomized (1:1), 2-arm study of the STS inhibitor oral irosustat 40 mg/d versus oral megestrol acetate 160 mg/d in women with advanced/metastatic or recurrent estrogen receptor–positive endometrial cancer. The primary end point was the proportion of patients without progression or death 6 months after start of treatment. Secondary end points included progression-free survival, time to progression, overall survival, and safety.

Results: Seventy-one patients were treated (36 with irosustat, 35 with megestrol acetate). The study was prematurely stopped after futility analysis. Overall, 36.1% and 54.1% of patients receiving irosustat or megestrol acetate had not progressed or died at 6 months, respectively. There were no statistically significant differences between irosustat and megestrol acetate in response and overall survival rates. Irosustat patients had a median progression-free survival of 16 weeks (90% confidence interval, 9.0–31.4) versus 40 weeks (90% confidence interval, 16.3–64.0) in megestrol acetate patients. Treatment-related adverse events occurred in 20 (55.6%) and 13 (37.1%) patients receiving irosustat or megestrol, respectively. Most adverse events in both groups were grade 1 or 2.

Conclusions: Although irosustat monotherapy did not attain a level of activity sufficient for further development in patients with advanced/recurrent endometrial cancer, this study confirms the activity of hormonal treatment (megestrol acetate) for this indication.

Key Words: Advanced/recurrent endometrial cancer, Hormone therapy, Irosustat, Megestrol acetate, Overall survival, Progression-free survival

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*Gustave Roussy Cancer Campus, Villejuif, France; †Leuven Cancer Institute, Leuven, Belgium; ‡Centre François Baclesse, Caen, France; §Palacky University Medical School and Teaching Hospital, Olomouc, Czech Republic; ‖Centrum Onkologii Ziemi Lubelskiej, Lublin, Poland; ¶Leeds Cancer Centre, St James University Hospital, Leeds, United Kingdom; #City Clinical Oncology Dispensary, St Petersburg, Russia; **Gartnavel General Hospital, Glasgow, United Kingdom; ††Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; ‡‡Vilnius University Institute of Oncology, Vilnius, Lithuania; §§Oncology Centre of Latvia, Riga East University Hospital, Riga, Latvia; ‖‖Ipsen Innovation, Les Ulis, France; and ¶¶Clatterbridge Cancer Centre, University of Liverpool, Bebington, Merseyside, United Kingdom.

Address correspondence and reprint requests to Patricia Pautier, MD, Gustave Roussy Cancer Campus, 114 Rue Édouard Vaillant, 94805 Villejuif, France. E-mail: patricia.pautier@gustaveroussy.fr.

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Despite progress in the therapy of early endometrial cancer, advanced or recurrent endometrial cancer has a poor prognosis. The treatment of advanced metastatic endometrial cancer relies on systemic therapy.[1] The activity of cytotoxic drugs in advanced disease is limited (up to 40% response rate in chemotherapy-naïve patients[2]), and the administration of cytotoxic drugs is accompanied by high toxicity[1] in this older population who are likely to have comorbidities.

Estrogens play a central role in the development of endometrial cancer.[3,4] The overproduction of estradiol (E2), estrone (E1), and testosterone in endometrial tissue is associated with the development of endometrial cancer.[5–7]

Hormonal therapy for recurrent endometrial cancer relies on the expression of hormone receptors, which act as nuclear transcription factors. For example, the expression of estrogen receptor (ER)-α in metastatic endometrial carcinoma tissue is statistically significantly related to clinical response to medroxyprogesterone acetate,[8] the hormonal agent used most commonly in patients with advanced/metastatic endometrial cancer. Another common hormonal therapy used is the antiprogesterone agent, megestrol acetate, which, when administered as monotherapy, results in a response rate of 15% to 30% in this setting.[9,10]

Tamoxifen, aromatase inhibitors, and luteinising hormone–releasing hormone agonists have also been used to treat endometrial cancer.[11–14] However, these agents have only a limited activity in advanced/metastatic endometrial cancer (9% to 33% response rate[15]). Nevertheless, in a recently published study of exemestane, 35% of patients with ER-positive disease had not progressed after 6 months.[16] Another study combining letrozole with everolimus reported clinical benefit in 40% of 35 enrolled patients with recurrent endometrial cancer.[17] Collectively, evidence suggests that a new generation of agents suitable for use in combination therapy and with higher specificity and fewer adverse effects is required, possibly targeting different mechanisms of action.

Steroid sulphatase (STS) is an enzyme that plays a pivotal role in the formation of E2 and androstenediol.[6,18] Malignant endometrial tissue possesses significantly higher STS activity and STS mRNA expression compared with normal endometrium,[19,20] providing a rationale for targeting the STS enzyme to treat endometrial cancer. Irosustat, a potent inhibitor of STS, has been shown to inhibit endometrial cancer growth in nude mice and has demonstrated activity in phase 1 clinical studies of patients with hormone-dependent breast cancer in whom the agent was well tolerated.[6,21–23]

The high in vitro specificity against STS and safety and tolerability in clinical studies of breast cancer[6,21–23] served as a basis for evaluation of irosustat in endometrial cancer. This study aimed to determine the antitumor efficacy, tolerability, and safety of irosustat compared with megestrol acetate in women with advanced/metastatic or recurrent ER-positive endometrial cancer.

MATERIALS AND METHODS

The study was conducted in 34 centers in 12 countries (Belgium, Czech Republic, France, Hungary, Latvia, Lithuania, Poland, Republic of Moldova, Russian Federation, Spain, Ukraine, and United Kingdom) between November 2009 and July 2013 (ClinicalTrials.gov clinical trial number: NCT00910091).

Seventy-three of the planned 80 patients were randomized. On June 6, 2011, the results of a futility analysis indicated that the probability of demonstrating superiority of irosustat over megestrol acetate in terms of progression-free survival (PFS) was very low. Consequently, the study sponsor decided to discontinue enrolment into the study. Patients already enrolled were informed of the decision and were offered the option to continue receiving the study treatment. They were also informed of the potential impact if they wished to remain in the study.

The trial was conducted according to the Declaration of Helsinki and International Harmonisation of Good Clinical Practice. All applicable local independent ethical committee and institutional review board approvals were obtained before starting the trial. All patients gave written informed consent.

Patients

Postmenopausal women with histologically confirmed, advanced, or recurrent endometrial carcinoma not eligible for treatment with surgery or radiotherapy alone; documented ER positivity (defined by at least 10% of positive cells in the primary tumor or in the metastatic tissue, if the primary tumor is unavailable); at least 1 measurable disease lesion, according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0; minimum indicator lesion size 20 mm (conventional techniques) or 10 mm (spiral computed tomography scan); target lesions not situated in the irradiated area; no history of other malignant disease except treated basal cell or high-grade cervical intraepithelial neoplasia in the previous 5 years; life expectancy of 6 months or more; and Eastern Cooperative Oncology Group performance status of 2 or less were enrolled in the present study.

Key exclusion criteria included previous systemic treatment for endometrial cancer with the exception of adjuvant chemotherapy; known central nervous system metastases; ongoing cardiac dysrhythmias or atrial fibrillation; concomitant use of carbonic anhydrase-II inhibitors; contraindications to megestrol acetate including hypersensitivity to one of the components of the drug product; any active arterial or venous thromboembolic event, or uncontrolled hypertension; and abnormal baseline findings that might jeopardize patient safety.

Study Design

This was a phase 2, multicenter, international, open-label, randomized, 2-arm study of oral irosustat 40 mg/d (ie, the dose that was previously established in a phase 1, dose-escalation study[21]) versus oral megestrol acetate 160 mg/d. Participants were randomized 1:1 to receive either treatment until objective tumor progression, 2 years after the last patient was randomized (June 3, 2011), withdrawal, or death. A computer-generated master randomization list generated in blocks according to a balance ratio was prepared and managed by a statistician independent from the study. The randomization number and associated treatment was allocated by an interactive voice/web response system service that was available to study investigators around the clock. Both drugs were taken once a day in the morning and under fasting conditions. Crossover into

the other arm on progression on 1 treatment was not predefined within the study design.

The primary end point was the proportion of patients who had neither progressed nor died 6 months after the start of treatment. Secondary end points included PFS (time from randomization until objective tumor progression or death from any cause), clinical benefit (defined as complete response [CR] + partial response [PR] + stable disease [SD] ≥12 weeks; as measured using RECIST version 1.0), the overall response (defined as CR + PR), the time to progression, the duration of response, the overall survival (OS) after 2 years, and the safety and tolerability of irosustat. Disease control (defined as PR + SD) formed a post hoc end point of the study.

Assessments

Tumor response was evaluated using computed tomography or magnetic resonance imaging, and RECIST version 1.0[24] at baseline and every 8 weeks with a subsequent radiological central review. The intensity of staining was not taken into account — only the proportion of stained cells; there was no central review of slides. The study centers provided survival status every 6 months until the end of the study (2 years after the randomization of the last patient). Adverse events (AEs) were monitored from the time of study entry to the end of the study. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events.[25]

Statistical Analysis

The primary population for the analyses was the intention-to-treat (ITT) population (all randomized patients), although sensitivity analyses of the primary end point and PFS were performed in the modified ITT (mITT) population (all randomized patients who received at least 1 treatment dose and had at least 1 measurable lesion according to RECIST criteria at baseline). The proportion of patients who had neither progressed nor died 6 months after the start of treatment was expected to be 50% in the irosustat arm and 25% in the megestrol acetate arm.[10,26] Using a 1-stage Fleming design[27] and assuming a 1-sided alpha of 0.05, the study was planned to have 91% power to reject the null hypothesis with a sample size of 32 evaluable patients per group. Assuming a withdrawal rate of 20%, the aim was to randomize 40 patients to each treatment arm to ensure 32 evaluable patients per arm, for a total sample size of 80.

Descriptive statistical analyses were carried out on the ITT population and percentage changes from baseline were also calculated. All statistical analyses were performed as 2-sided tests with a type 1 error rate set at 10%. The primary end point was calculated for each treatment group using normal binomial distribution together with 90% confidence intervals (CI). Secondary end point time event data were analyzed using Cox proportional hazards model and Kaplan-Meier plots.

RESULTS

Patients

Patient disposition is shown in Figure 1; 73 of the planned 80 patients were randomized before the study was terminated (36 in the irosustat arm and 37 in the megestrol acetate arm; ITT population), and 71 patients were treated (36 in the irosustat group and 35 in the megestrol acetate group; safety population; mITT population consisted of 35 in the irosustat arm and 34 in the megestrol acetate arm). Thus, the number of patients needed for statistical analyses was achieved.

Baseline characteristics and disease history were well balanced between treatment arms (Table 1). All patients enrolled in the study had ER-positive endometrial cancer and therefore were deemed to have type 1 or 2 endometrial cancer.

Efficacy

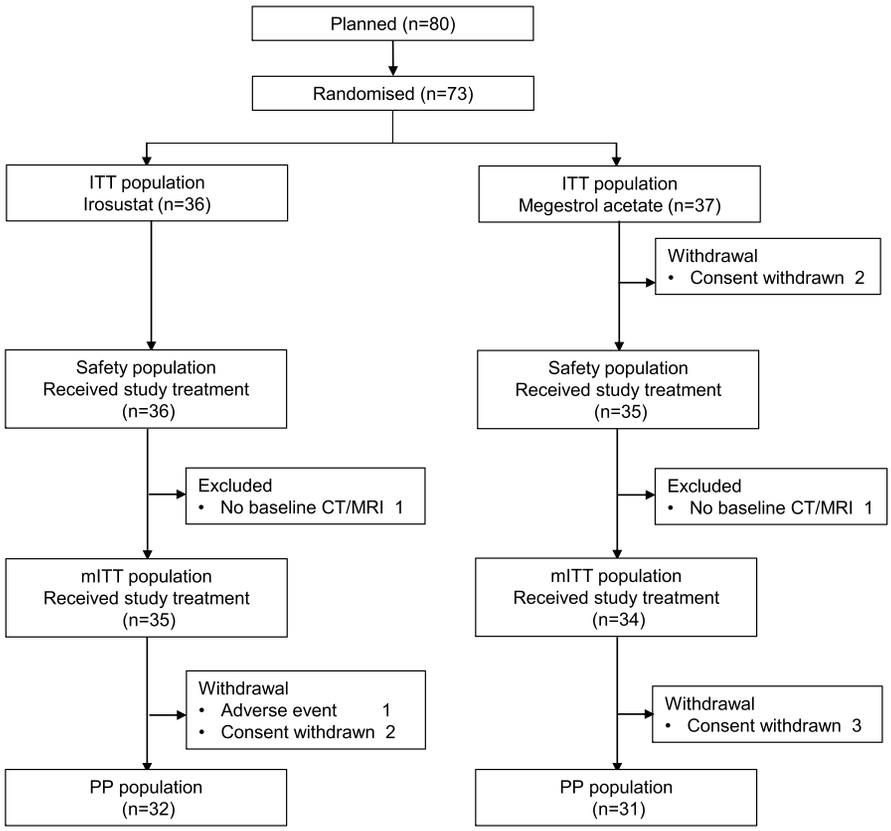
Overall, 36.1% (90% CI, 24.3–49.8) of patients receiving irosustat had not progressed or died at 6 months compared with 54.1% (90% CI, 40.8–66.8; P = NS) of patients in the megestrol acetate arm (Table 2). The median PFS was 16.1 weeks (90% CI, 9.0–31.4) versus 40.1 weeks (90% CI, 16.3–64.0; P = NS) for patients receiving irosustat and megestrol acetate, respectively (Fig. 2a). The median time to progression in the ITT population was 16.3 weeks (90% CI, 9.0–31.4) versus 40.1 weeks (90% CI, 24.1–64.0; P = 0.04) for patients receiving irosustat and megestrol acetate, respectively. The median duration of response was 105.1 weeks in the megestrol acetate arm, but was not calculable in the irosustat arm. Clinical benefit was achieved in 57.1% of irosustat-treated patients and 70.6% of megestrol acetate-treated patients (Table 2). The overall response rate (35.3% and 8.6%) and disease control rate (64.7% and 57.1%) were higher in the megestrol acetate arm compared with the irosustat arm (Table 2). Median OS was not reached in the megestrol acetate arm and was 63.4 weeks in the irosustat arm (Fig. 2b).

Adverse Events

Patients were exposed to irosustat and megestrol acetate for a median of 16.2 (range, 2.0–136.1) and 40.0 (range, 2.3–160.0) weeks, respectively.

Overall, 179 treatment-emergent AEs (TEAEs) were observed in 32 (88.9%) patients in the irosustat arm, and 186 TEAEs were observed in 29 (82.9%) patients in the megestrol acetate arm. Most TEAEs were grade 1 or 2 (mild to moderate; 154/179 [86%] with irosustat and 169/186 [91%] with megestrol acetate; 18 [10.1%], 2 [1.1%], and 1 [0.6%] grade 3, 4, and 5 TEAEs, respectively, in the irosustat arm and 16 [8.6%], 0 [0%], and 1 [0.5%] grade 3, 4, and 5 TEAEs, respectively, in the megestrol acetate arm). Treatment-related AEs (TRAEs) occurred in 20 (55.6%) patients in the irosustat arm and 13 (37.1%) patients in the megestrol acetate arm (Table 3). The most frequent TRAE in both study arms was dry skin. Grade 3 or higher TRAEs in the irosustat arm included dry skin, asthenia, hyponatremia, and hypertension (all n = 1), and grade 3 or higher TRAEs in the megestrol acetate arm included pulmonary embolism (n = 2) and hyperglycemia (n = 1; Table 3).

Study drug was permanently discontinued in 4 patients because of 5 TEAEs (3 patients in the irosustat arm, including 1 patient with grade 3 acute myocardial infarction considered not related to study drug, 1 patient with grade 3 hyponatremia considered related to study drug, and 1 patient with a grade 2 tumor hemorrhage considered not related to study drug as



ITT=intention to treat; PP=per protocol; mITT=modified intention to treat; CT=computed tomography; MRI=magnetic resonance imaging

FIGURE 1. Patient flow/disposition.

well as 1 patient with grade 3 dyspnea and grade 3 pleural effusion considered not related to study drug in the megestrol acetate arm).

Serious AEs (SAEs) were reported in 9 patients in the irosustat arm and 6 patients in the megestrol acetate arm. Among the SAEs, there were 2 deaths reported during the study — 1 patient in the irosustat group with lower respiratory tract infection and lung metastases from endometrial cancer, assessed as not related to study drug, and 1 patient in the megestrol acetate group with a pulmonary embolism assessed as related to study drug. The SAEs in the irosustat arm, each occurring in a different patient, included grade 3 inadequate control of diabetes; grade 3 acute renal failure; grade 3 vomiting and grade 2 asthenia; grade 2 hematuria; grade 2 anemia; grade 3 upper abdominal pain; grade 4 anemia; grade 2 nephrolithiasis; and grade 2 renal colic. None of these SAEs were considered related to study drug, but 1 patient had grade 3 asthenia, grade 3 hyponatremia, grade 2 decreased appetite, and grade 2 constipation, which were all considered related to study drug. The SAEs in the megestrol acetate arm, each occurring in a different patient, included grade 3 urinary retention; grade 3 dyspnea and grade 3 pleural effusion; grade 2 urinary retention; grade 3 vomiting; and grade 3 myocardial infarction. None of these SAEs were considered related to study drug, but 1 patient had a grade 3 pulmonary embolism considered related to study drug and 1 patient had a grade 4 pulmonary embolism leading to death that was considered related to study drug.

A clinically significant grade 4 hematological abnormality (anemia) judged unrelated to treatment and a nonclinically significant grade 4 abnormal potassium value were reported in 1 patient each in the irosustat group. Four patients in the irosustat group and 4 patients in the megestrol acetate group experienced grade 4 hematological values. Among these patients, decreased lymphocyte counts in 2 patients (1 in each treatment group) were judged by the investigator as clinically significant. In addition, 3 of 10 grade 4 biochemistry values in irosustat-treated patients and 6 of 13 in the megestrol acetate group were considered to be clinically significant.

DISCUSSION

In this randomized phase 2 trial, the investigational hormonal agent irosustat, evaluated as a single agent in patients with advanced/metastatic or recurrent endometrial cancer, failed to demonstrate the preplanned efficacy (the proportion of patients who had neither progressed or died after 6 months of treatment) compared with the reference hormonal treatment (megestrol acetate) because only one third of patients did not progress or die after 6 months. The disease control rate (PR + SD)

TABLE 1. Patient and disease characteristics at baseline (ITT population)

	Irosustat (N = 36) n (%)	Megestrol Acetate (N = 37) n (%)
Age, mean (SD), y	68.1 (11.4)	67.4 (8.6)
BMI, kg/m^2	—	—
<18.5	1 (2.8)	0
18.5–25	10 (27.8)	10 (27.0)
>25–30	10 (27.8)	8 (21.6)
>30	12 (33.3)	17 (45.9)
Missing	3 (8.3)	2 (5.4)
Time since diagnosis, median (range), y	2.7 (0.1–15.5)	1.8 (0.1–20.3)
Prior treatment with radiotherapy	—	—
Yes	24 (66.7)	22 (59.5)
No	12 (33.3)	15 (40.5)
Prior surgery		
Yes	30 (83.3)	29 (78.4)
No	6 (16.7)	8 (21.6)
ECOG performance status — score	—	—
0	13 (36.1)	15 (40.5)
1	19 (52.8)	16 (43.2)
2	4 (11.1)	4 (10.8)
Missing	0	2 (5.4)
FIGO stage at diagnosis	—	—
I	13 (36.1)	10 (27.0)
II	7 (19.4)	7 (18.9)
III	9 (25.0)	12 (32.4)
IV	7 (19.4)	8 (21.6)
Histological type	—	—
Endometrioid	22 (61.1)	24 (64.9)
Endometrial	10 (27.8)	12 (32.4)
Uterine papillary	2 (5.6)	1 (2.7)
Mucinous	1 (2.8)	0
Mixed	1 (2.8)	0
Histological grade	—	—
G1	8 (22.2)	10 (27.0)
G2	17 (47.2)	18 (48.6)
G3	9 (25.0)	8 (21.6)
Missing	2 (5.6)	1 (2.7)
No. metastatic disease	—	—
1	7 (19.4)	16 (44.4)
2–3	22 (61.1)	13 (36.1)
>3	4 (11.1)	5 (13.9)
ER status	—	—
Positive	36 (100)	37 (100)
Negative	0	0
Unknown	0	0
Progesterone receptor status	—	—
Positive	25 (69.4)	32 (86.5)
Negative	9 (25.0)	4 (10.8)
Unknown	0	0
Missing	2 (5.6)	1 (2.7)

Values are n (%) unless otherwise stated.

BMI indicates body mass index; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; and SD, standard deviation.

of 55.6% in the irosustat arm was also numerically inferior compared with the disease control rate of 59.4% with megestrol acetate.

Nevertheless, these results demonstrate long-term disease control with hormonal therapy in a subgroup of patients. More than 50% of patients were alive and 31% progression-free 2 years after the start of treatment with megestrol acetate. This response rate is higher than previously reported in other studies for patients with advanced/metastatic endometrial cancer treated with megestrol acetate,[9,10] indicating that hormone therapy remains a treatment option in this patient population with ER-positive tumors.

Most of the hormonal therapy studies in metastatic endometrial carcinoma were conducted more than a decade ago in a nonselected population of patients (in relation to ER expression), and the therapeutic approach in this setting has evolved since that time. Taxane-platin–based combination chemotherapy has become established, and supportive care of the comorbid conditions has improved. The present prospective trial confirms the activity of megestrol acetate in the current era characterized by the advent of targeted therapy and wide use of taxanes and platinum. A 3-year survival rate of more than 50% of patients with long-term disease control suggests that megestrol acetate may be considered for the treatment of systemic treatment-naive patients with metastatic ER-positive endometrial cancer.[9,28–30]

Many endometrial carcinomas express estrogen and progesterone receptors, and positivity for these receptors is associated with better treatment outcome.[5,6] Receptor-positive tumors also tend to be more differentiated (lower grades) than those without hormone receptors,[6] and it has been suggested that receptor-positive, well-differentiated tumors reflect the subset of responding tumors in hormonal therapy trials. In this study, such subsets of responsive tumors may have existed and contributed to the observed findings. For example, although all patients enrolled had ER-positive tumors, there were between-group differences in the proportion of tumors that tested positive for progesterone receptor. It

TABLE 2. Response to treatment with irosustat or megestrol acetate (ITT population)

	Irosustat 40 mg (N = 36)	Megestrol Acetate 160 mg (N = 37)
Patients who have not progressed or died at 6 m, % (90% CI)	36.1 (24.3–49.8)	54.1 (40.8–66.8)
Response*	—	—
Complete response	0	2 (5.4)
Partial response	3 (8.3)	10 (27.0)
SD ≥12 w	17 (47.2)	12 (32.4)
Progressive disease	14 (38.9)	8 (21.6)
Not evaluable	1 (2.8)	2 (5.4)

Values are n (%) unless otherwise stated.
*mITT population.

is possible that the higher proportion of progesterone receptor–positive tumors, at baseline, in patients treated with megestrol acetate, when compared with irosustat, may have influenced the higher than expected response to megestrol acetate. Moreover, most tumors in both treatment groups were of grade 1 or 2 histology. Response was not evaluated by histology grade, but evidence from existing treatments suggests that grade 1 or 2 tumors may be more responsive to treatment than higher grade tumors.

A large study of medroxyprogesterone acetate showed the overall response rate was higher in grade 1 and 2 tumors compared with grade 3 tumors.[26] Other hormonal monotherapies for endometrial cancer include the luteinising hormone-releasing hormone agonist triptorelin. The overall response rate to triptorelin in the phase 2 multicenter study in 24 patients with advanced or recurrent endometrial cancer was low (1 patient with a CR, 1 patient with a PR, and 5 patients with SD).[31] The aromatase inhibitors letrozole and anastrozole have also been evaluated but were found to have very little activity against endometrial cancer, although the studies included patients with grade 2 or 3 tumors, which are less sensitive to hormonal treatment.[12,32] Tamoxifen has also been studied as first-line therapy for patients with recurrent or metastatic endometrial cancer.[14] A Gynecologic Oncology Group study in 68 patients with unselected advanced/recurrent endometrial cancer reported a response rate of only 10% (3 patients with a CR and 4 patients with a PR) with a median PFS of 1.9 months and a median OS of 8.8 months.[14] However, a higher overall response rate to tamoxifen was observed among patients with grade 1 or 2 histology compared with grade 3 histology (response rates were 24% for grade 1, 14% for grade 2, and 3% for grade 3). These

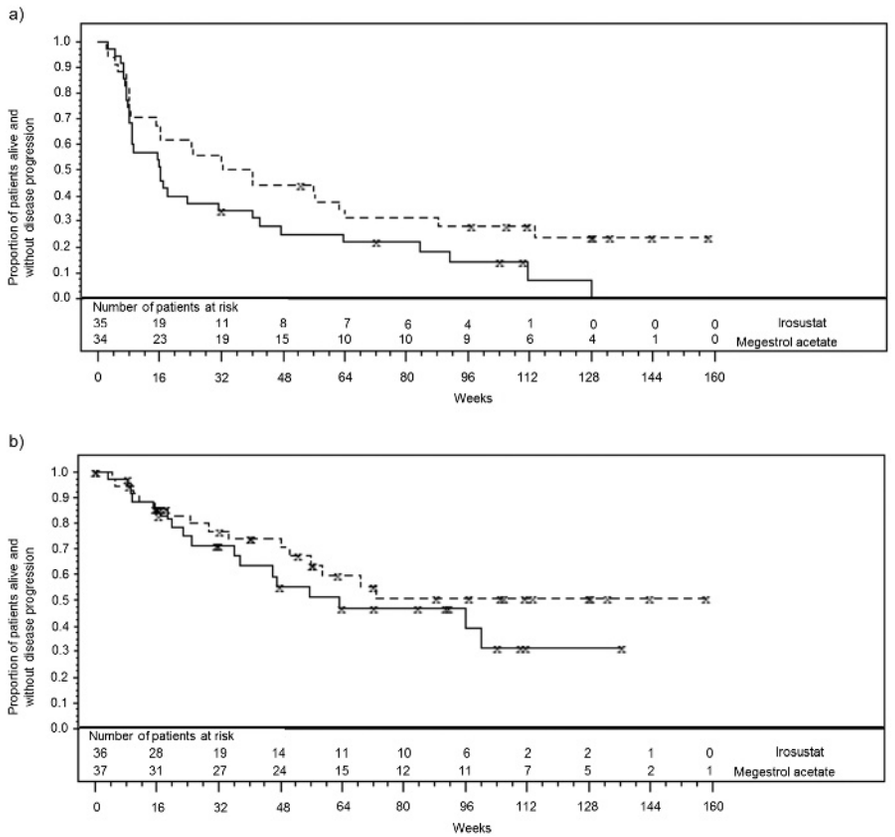


FIGURE 2. Kaplan-Meier plot of (A) PFS (mITT population) and (B) OS (ITT population) for patients receiving irosustat (solid line) and megestrol acetate (dashed line).

TABLE 3. Summary of TRAEs occurring in more than 1 patient by treatment group (safety population)*

	Irosustat 40 mg (N = 36) n (%)			Megestrol Acetate 160 mg (N = 35) n (%)		
	Total	Mild/Moderate†	Severe†	Total	Mild/Moderate†	Severe†
Patients experiencing any TRAEs	20 (55.6)	17 (47.2)	3 (8.3)	13 (37.1)	10 (28.6)	3 (8.6)
Dry skin	14 (38.9)	13 (36.1)	1 (2.8)	3 (8.6)	3 (8.6)	0
Asthenia	4 (11.1)	3 (8.3)	1 (2.8)	2 (5.7)	1 (2.9)	0
Fatigue	3 (8.3)	3 (8.3)	0	1 (2.9)	1 (2.9)	0
Constipation	3 (8.3)‡	2 (5.6)	0	0	0	0
Nausea	2 (5.6)	2 (5.6)	0	1 (2.9)	1 (2.9)	0
Vomiting	2 (5.6)	2 (5.6)	0	0	0	0
Muscle spasms	2 (5.6)	2 (5.6)	0	0	0	0
Headache	2 (5.6)	2 (5.6)	0	0	0	0
Hyponatremia	1 (2.8)	0	1 (2.8)	0	0	0
Hypertension	1 (2.8)	0	1 (2.8)	0	0	0
Hot flush	0	0	0	2 (5.7)	2 (5.7)	0
Dyspnea	0	0	0	2 (5.7)	2 (5.7)	0
Pulmonary embolism	0	0	0	2 (5.7)	0	2 (5.7)
Hyperglycemia	0	0	0	1 (2.9)	0	1 (2.9)

*All severe TRAEs reported.
†Mild/moderate defined as grade 1 or 2, severe defined as grade 3 or higher.
‡Severity of 1 result missing.

results suggest that ER/PR expression and not subjective assessment of tumor differentiation should be the principal selection criterion for hormone therapy.

Studies of hormone or combination chemotherapy regimens have reported median OS in the range of 7.0 to 38 months in patients with advanced or recurrent endometrial cancer.[14,15,33,34] The median OS, although not reached in the megestrol acetate arm, was 63.4 weeks (15 months) in the irosustat arm of the current study. This finding is within the range seen with existing treatments in the advanced/recurrent population, and is similar to survival (median OS of 13.3 months) recently achieved with the aromatase inhibitor, exemestane, in a patient population broadly similar to that enrolled in the current study (ie, ER-positive patients with advanced or recurrent endometrial cancer).[17]

There are also marked and clinically significant differences in the adverse-effect profiles of hormonal treatments compared with chemotherapy in the advanced/recurrent setting. Although, in the current study, 1 patient in the megestrol acetate group died from pulmonary embolism assessed as related to study drug, most other life-threatening toxicities of a combination regimen of cytotoxic drugs are not generally encountered in patients treated with hormonal agents. In the current study, the overall frequency of AEs was higher with irosustat than with megestrol acetate. However, only 1 patient in the irosustat group experienced SAEs considered related to the drug compared with 2 patients in the megestrol acetate group (who experienced thromboembolic AEs typical of megestrol acetate treatment). Therefore, irosustat may have a favorable safety profile in this population of patients with advanced endometrial cancer. Moreover, the nonoverlapping adverse-effect profiles of irosustat and megestrol acetate offer the potential for a regimen combining these 2 drugs.

Given the poor response rates of women with advanced endometrial cancer and the need for more potent treatments, combination with progestogens should be investigated. Further studies should explore combining STS inhibitors with other hormonal agents such as aromatase inhibitors, which may provide some additional benefit for patients with ER-positive tumors. This is being investigated in an ongoing clinical trial in patients with breast cancer (ClinicalTrials.gov; NCT01785992).

As with studies of this design, some methodological issues may have affected the interpretation of data from this study. Given ethical considerations in cancer trials, a placebo was not used in this study; however, use of a placebo may have enabled establishment of a background response rate in this population of patients with ER-positive, advanced/recurrent endometrial cancer. Other aspects of study design may have masked the true treatment effect of irosustat versus megestrol acetate. Specifically, tumors within the enrolled study population varied with respect to PR expression and thus potentially contributed to variability in response. In addition, the study design did not incorporate serial quantification of hormone receptor positivity during treatment to ascertain whether loss of expression contributed to response status.

In conclusion, the results of this study suggest that hormonal therapy has a different safety profile to chemotherapy for ER-positive endometrial cancer, with approximately one third of patients experiencing long-term disease

control. The results also suggest that the use of irosustat as a monotherapy is not efficacious enough and should be investigated in combination with other hormonal or targeted agents. Classical hormonal therapy with progesterone agents is still considered the standard treatment for postmenopausal women with hormone receptor-positive endometrial carcinoma. It is possible that the association of different pathways of hormonal therapies may increase the efficacy of different hormonal agents in endometrial cancer.

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