FULL PAPER

BJC

British Journal of Cancer (2013) 108, 1771–1777 | doi: 10.1038/bjc.2013.183

Keywords: chemotherapy; endometrial cancer; everolimus; mTOR inhibition

Everolimus as second- or third-line treatment of advanced endometrial cancer: ENDORAD, a phase II trial of GINECO

I Ray-Coquard*[,1], L Favier[2], B Weber[3], C Roemer-Becuwe[4], P Bougnoux[5], M Fabbro[6], A Floquet[7], F Joly[8], A Plantade[9], D Paraiso[10] and E Pujade-Lauraine[11]

[1]Department of Medical Oncology, Centre Léon Bérard, 28 rue Laennec, Lyon Cedex 08, France; [2]Department of Medical Oncology, Centre Georges François Leclerc, 1 rue Professeur Marion – BP 77980, Dijon Cedex, France; [3]Department of Medical Oncology, Centre Alexis Vautrin-Brabois, 6 Avenue de Bourgogne Brabois, Vandoeuvre les Nancy Cedex, France; [4]Department of Medical Oncology, ORACLE – Centre d'Oncologie de Gentilly, 2 rue Marie Marvingt, Nancy, France; [5]Department of Medical Oncology, Centre Hospitalier Universitaire Bretonneau, 2 Boulevard Tonnellé, Tours, France; [6]Department of Medical Oncology, CRLC Val d'Aurelle, Parc Euromédecine – 208 Rue des Apothicaires, Montpellier Cedex, France; [7]Department of Medical Oncology, Institut Bergonié, 229 Cours de l'Argonne, Bordeaux Cedex, France; [8]Department of Medical Oncology, Centre François Baclesse, Avenue du Général Harris, Caen, France; [9]Medical Oncology Department, Hôpital des Diaconesses, 18 rue du Serget Bauchat, 75012 Paris, France; [10]Department of Medical Oncology, Centre Hospitalier de l'Agglomération Montargoise, 658 Rue des Bourgoins, Amilly Cedex, France and [11]Department of Medical Oncology, Université Paris Descartes, AP-HP, Hôpitaux Universitaires Paris Centre, Site Hôtel Dieu, 1 Place du Parvis Notre-Dame – Place Jean-Paul II, Paris Cedex 04, France

Background: Patients with recurrent/metastatic endometrial cancer that progresses after chemotherapy have limited treatment options and poor outcomes. Preclinical data suggest the oral mammalian target of rapamycin inhibitor everolimus may provide clinical benefit in these patients.

Methods: In this multicenter, open-label, phase 2 study, patients with advanced or metastatic endometrial cancer refractory to one or two previous chemotherapy regimens received everolimus 10 mg per day until progression or unacceptable toxicity. Primary end point was the non-progressive disease rate at 3 months. Secondary end points included duration of response, progression-free, and overall survival (OS), and safety.

Results: Forty-four patients were enrolled (median age, 65 years); 66% received one previous chemotherapy regimen. The 3-month non-progressive disease rate was 36% (95% confidence interval 22–52%), including two patients (5%) with partial response (PR). At 6 months, two additional patients experienced PR. Median duration of response was 3.1 months. Median progression-free and OS were 2.8 months and 8.1 months, respectively. The most common adverse events were anaemia (100%), fatigue (93%), hypercholesterolaemia (81%), and lymphopenia (81%).

Conclusion: Everolimus demonstrated efficacy and acceptable tolerability in patients with chemotherapy-refractory advanced or metastatic endometrial cancer. These results support the further development of phosphatidylinositol 3-kinase-targeted therapies in endometrial cancer.

*Correspondence: Dr I Ray-Coquard; E-mail: isabelle.ray-coquard@lyon.unicancer.fr

Received 17 December 2012; revised 11 March 2013; accepted 1 April 2013; published online 23 April 2013

Endometrial cancer accounts for ~5% of all cancers in women (Ferlay *et al*, 2010). In 2008, ~287 000 endometrial cancer cases were reported worldwide, making it the sixth most common cancer in women. Endometrial cancer is more common in developed *vs* undeveloped regions and is the fourth most common cancer in women in Europe and the United States (Ferlay *et al*, 2010; Jemal *et al*, 2010).

Early-stage endometrial cancer (International Federation of Gynaecology and Obstetrics stage I or II) can be effectively treated with surgery, with or without adjuvant radiotherapy or chemotherapy, and is associated with a 5-year survival rate of 80% to 90% (Creasman *et al*, 2006). Treatment of recurrent and/or metastatic endometrial cancer is limited to cytotoxic chemotherapy and, for patients with hormone receptor-positive disease, hormonal therapy (Colombo *et al*, 2011; National Comprehensive Cancer Network Inc., 2012). First-line chemotherapy for advanced disease typically includes a platinum salt, paclitaxel, and/or anthracyclines and is associated with a median progression-free survival (PFS) of <12 months and a median overall survival (OS) of <20 months (Humber *et al*, 2007; Sovak *et al*, 2007; Pectasides *et al*, 2008). Although there is no standard of care in second- and third-line settings, patients may receive anthracyclines if not used in the first-line setting, cyclophosphamide, 5-fluorouracil, topotecan, or progestational agents. However, many patients are not eligible for chemotherapy owing to its associated toxicity profile.

Therapies targeted to signal transduction pathways dysregulated in endometrial cancer may provide improved efficacy and safety for recurrent or metastatic endometrial cancer. The phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway is frequently overactivated in endometrial cancer, making it an attractive treatment target. Activating mutation or amplification of *PIK3CA* is observed in 27% to 52% of endometrial cancers, with mutations more common in endometrioid *vs* non-endometrioid tumours (Oda *et al*, 2005; Hayes *et al*, 2006; Catasus *et al*, 2009, 2010; Konopka *et al*, 2011; Rudd *et al*, 2011). Mutations in *PTEN*, a negative regulator of the PI3K/Akt/mTOR pathway, are observed in 11% to 79% of endometrial cancers depending on histological type, with mutations more common in endometrioid *vs* non-endometrioid tumours (Hayes *et al*, 2006; Catasus *et al*, 2009, 2010; Konopka *et al*, 2011; Rudd *et al*, 2011).

Everolimus is an oral mTOR inhibitor currently approved in various countries for treatment-refractory advanced renal cell carcinoma; progressive, unresectable, advanced pancreatic neuroendocrine tumours; and renal angiomyolipoma and subependymal giant-cell astrocytomas associated with tuberous sclerosis complex. Preclinical data suggest mTOR inhibition may provide benefit in advanced endometrial cancer (Podsypanina *et al*, 2001; Milam *et al*, 2007; Block *et al*, 2010). For example, in a mouse *Pten* heterozygote model, everolimus significantly reduced endometrial hyperplasia and the proliferation index, and significantly increased apoptosis compared with control (Milam *et al*, 2007).

The objective of the current study (ClinicalTrials.gov identifier NCT00870337) was to assess the efficacy and safety of everolimus monotherapy in women with advanced or metastatic endometrial cancer refractory to one or two previous chemotherapy regimens.

PATIENTS AND METHODS

Patients. Patients eligible for study inclusion were aged $\geqslant 18$ years and had histologically confirmed, metastatic or locally advanced endometrial adenocarcinoma not eligible for surgery that progressed after one or two lines of chemotherapy; at least one line of chemotherapy must have contained a platinum derivative. Additional inclusion criteria included a $\geqslant 3$-month interval since the last chemotherapy line; $\geqslant 1$ metastatic lesion located outside previously irradiated zones and measurable according to the Response Evaluation Criteria In Solid Tumours, version 1.0 (RECIST 1.0) (Therasse *et al*, 2000); Eastern Cooperative Oncology Group performance status $\leqslant 2$; negative pregnancy test within 7 days of first dose of study treatment and use of adequate contraception throughout the study (women of child-bearing potential only); and adequate bone marrow and hepatic and renal function. Exclusion criteria included uncontrolled cerebral metastases; other serious or uncontrolled medical conditions; history of other cancer, with the exception of adequately treated cervical carcinoma *in situ* or basal or squamous cell carcinoma; and previous mTOR inhibitor treatment. After enrolment of the first 22 patients, a protocol amendment was introduced that excluded patients who received treatment with other chemotherapeutic drugs, hormonal therapy, radiation, or other antitumor agent within 21 days of the first dose of study drug.

All patients provided written informed consent. The study was approved by a central ethics committee and conducted in accordance with international standards of good clinical practice and all local laws and regulations.

Procedures. In this French, multicenter, open-label, phase II trial, all patients received everolimus 10 mg once daily as two 5-mg pills taken with water on an empty stomach or after a light, low-fat meal. Treatment was administered continuously until disease progression or unacceptable toxicity. In the case of adverse events (AEs) or toxicity thought to be related to everolimus, everolimus dosing could be delayed or reduced according to an algorithm outlined in the study protocol. The first and second dose reductions were 5 mg per day and 5 mg every other day, respectively. If the AE or toxicity did not resolve within 21 days of treatment interruption or recurred after everolimus reintroduction, treatment was discontinued. Grade 3 hyperlipidemia was managed per local clinical practice; everolimus was withheld for grade 4 hyperlipidemia. Hyperglycaemia was managed by everolimus dose adjustment and/or the addition of metformin as investigator choice.

Tumour measurements included X-ray and/or computed tomography (CT) scan of the chest and abdominal and pelvic CT scan or magnetic resonance imaging. Measurements were performed at screening, every 3 months during treatment and follow-up, and at the time of treatment discontinuation. Safety assessment included monitoring and recording of all AEs, regular laboratory evaluations of haematology and clinical chemistry, regular measurement of vital signs, performance of physical examinations, and recording of all concomitant medications. Adverse events and laboratory abnormalities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (National Cancer Institute, 2006).

Statistical analysis. The primary study end point was the rate of non-progressive disease at 3 months, defined as the proportion of patients with a complete or partial response (CR or PR, respectively) or stable disease (SD) as assessed by local review according to RECIST 1.0. The choice of non-progressive disease at 3 months as the primary end point is consistent with other phase II studies of rare cancers, including sarcoma (Schoffski *et al*, 2011). Secondary end points included the rate of non-progressive disease at 6 months and best overall response according to RECIST 1.0; duration of response, defined as the time from the date of the first confirmed response to the date of disease progression or death due to cancer; PFS, defined as the time from enrolment to the date of disease progression or death due to any cause; OS, defined as the time from enrolment to the date of death due to any cause; and safety and toxicity. The potential predictive value of select biomarkers is reported separately.

This study was designed using a Simon two-stage mini–max design (Simon, 1989). To show a >15% success rate (i.e., >15% of patients without progressive disease at 3 months) with 90% power and $\alpha = 5\%$, 44 evaluable patients were required. In stage one of the study, if at least four of the first 19 evaluable patients demonstrated CR, PR, or SD, recruitment was continued until 44 evaluable patients were enrolled. In stage two, if at least 11 patients demonstrated CR, PR, or SD, everolimus was considered to have shown sufficient efficacy to warrant further study.

Kaplan–Meier methodology was used to estimate PFS and OS. Progression-free survival and OS equality in subgroups was assessed using the log-rank test. The protocol-specified population evaluable for non-progressive disease included all enrolled patients who had no protocol deviations and received everolimus for ⩾1 month according to the study protocol. The protocol-specified safety population and the population evaluable for clinical benefit included all patients who received ⩾1 dose of study drug.

RESULTS

Forty-four patients were enrolled at 18 French centres between April 2008 and October 2009. Between stages one and two, enrolment was stopped for 6 months. At the time of analysis, 43 patients had discontinued treatment owing to progressive disease (65%) or AEs (35%). Median age was 65 years (range, 52–77 years), and 64% of patients had endometrioid tumours (Table 1). Per protocol, all patients previously received one (66%) or two (34%) lines of chemotherapy. The treatment-free interval was ⩽6 months in 64% of patients. In addition to chemotherapy, a majority of patients were previously treated with surgery (89%) and radiotherapy (80%); 14% of patients received previous hormonal treatment.

Efficacy. At 3 months, 16 patients (36%) in the total population had non-progressive disease, including two (5%) with PR and 14 (32%) with SD (Table 2). The trial, therefore, met the prespecified criteria for efficacy of everolimus in patients with chemotherapy-refractory advanced endometrial cancer. At 6 months, the rate of non-progressive disease remained 36%, with an additional two patients experiencing PR (Table 2). At both 3 and 6 months, the rates of non-progressive disease in patients with endometrioid ($n = 28$), serous ($n = 11$), and other ($n = 5$) histology were 39%, 27%, and 40%, respectively ($P =$ not significant) (Table 2). The best overall response was PR in four patients (9%), SD in 12 patients (27%), and progressive disease in 25 patients (57%); three patients (7%) were not evaluable because they received <3 months of treatment or had their treatment discontinued owing to toxicity. Partial response was observed in three patients (11%) with endometrioid histology, one patient (9%) with serous histology, and no patients with other histology. The median (range) duration of response was 3.1 months (2.5 − 19.8+ months). The median (range) duration of SD was slightly longer at 4.3 months (2.1–14.9 months).

Median PFS in the overall population was 2·8 months (95% confidence interval (CI), 0.6–5.1) (Figure 1A). No difference in median PFS was noted between patients previously treated with one *vs* two chemotherapy regimens (3.0 months (95% CI, 0.0–6.1) *vs* 2.8 months (1.3–4.3); $P = 0.784$). Median OS was 8.1 months (95% CI, 5.1–11.1) in the overall population (Figure 1B). No difference in median OS was observed between patients previously treated with one *vs* two chemotherapy regimens (9.3 months (95% CI, 5.0–13.6) *vs* 7.7 months (95% CI, 6.6–8.9); $P = 0.735$). No effect of tumour type, histological grade, presence of abdominal, pelvic, lung, lymph node, liver, or bone/soft tissue metastases, or duration of treatment-free interval on PFS or OS was observed (data not shown).

Table 1. Baseline demographics and disease characteristics of the total population ($N = 44$)

Characteristics	$N = 44$
Age, years, median (range)	65 (52–77)
ECOG performance status	
0–1	26 (82)
2	8 (18)
Histological type	
Endometrioid	28 (64)
Serous	11 (25)
Other[a]	5 (11)
Histological grade	
1	9 (20)
2	16 (36)
3	17 (39)
Unknown	2 (5)
Metastatic sites	
Abdomen/pelvis	25 (57)
Lung	23 (52)
Lymph nodes	20 (45)
Liver	15 (34)
Treatment-free interval	
<3 Months	16 (36)
3–6 Months	12 (28)
>6 Months	16 (36)
Previous chemotherapy	44 (100)
1 Line	29 (66)
2 Lines	15 (34)

Abbreviation: ECOG = Eastern Cooperative Oncology Group. Note: Unless otherwise noted, all data are presented as *n* (%).
[a]Includes three clear-cell carcinomas, one mixed Müllerian tumour, and one undifferentiated tumour.

Safety. Median duration of everolimus exposure was 2.5 months (range, 12 days to >25.7 months). Dose reductions and interruptions occurred at 18 (13%) and 31 (23%) of 137 total study visits, respectively. The most common cause of dose reduction or interruption was mucositis, which accounted for 39% of reductions and 23% of interruptions. Other AEs that led to dose reduction and interruption were asthenia, fever, vomiting, hyperlipidemia, rash, thrombocytopenia, nausea, thromboembolism, and diarrhoea.

Although all patients enrolled in the study met the protocol-specified criteria for inclusion in the safety population, one female patient was excluded from analysis because she died of unknown causes prior to the 1-month visit, thus precluding the collection of safety data. Of the 43 patients included in the safety population, all experienced at least one AE, a majority of which were of grade 1 or 2 severity (Table 3). The most common non-haematologic AEs were fatigue (93%), nausea (51%), rash (49%), vomiting (49%), and mucositis (49%). The most common grade 3/4 AEs were fatigue (42%), anorexia (26%), and infection (16%). Pneumonitis was observed in five patients (12%; grade 3, 5%). Three patients who experienced SD developed pulmonary toxicities necessitating permanent everolimus discontinuation after 1.6 months, 2.5 months, and 7.0 months of treatment. In one patient, pulmonary toxicity resolved without supportive therapy. In the other two patients, pulmonary toxicity resolved after treatment with

Table 2. Disease response rates at 3 and 6 months in the total population ($N = 44$)

	Total Population ($N = 44$)		Endometrioid histology ($n = 28$)		Serous histology ($n = 11$)		Other histology ($n = 5$)	
Response, *n* (%)	**3 Months**	**6 Months**	**3 Months**	**6 Months**	**3 Months**	**6 Months**	**3 Months**	**6 Months**
Non-progressive disease	16 (36)	16 (36)	11 (39)	11 (39)	3 (27)	3 (27)	2 (40)	2 (40)
Complete response	—	—	—	—	—	—	—	—
Partial response	2 (5)	4 (9)	1 (4)	3 (11)	1 (9)	1 (9)	0	0
Stable disease	14 (32)	12 (27)	10 (36)	8 (29)	2 (18)	2 (18)	2 (40)	2 (40)
Progressive disease	25 (57)	25 (57)	15 (54)	15 (54)	8 (73)	8 (73)	2 (40)	2 (40)
Not evaluable	3 (6)	3 (6)	2 (7)	2 (7)	0	0	1 (20)	1 (20)

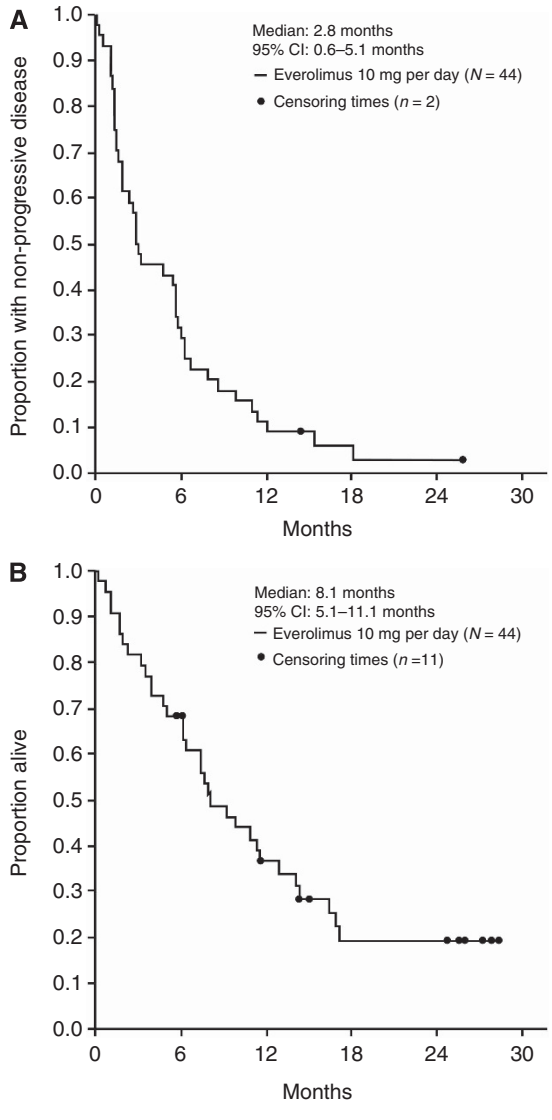

Figure 1. Efficacy results in the total population ($N = 44$). (**A**) progression-free survival; (**B**) OS

Table 3. Adverse events reported in ⩾10% of patients in the safety population ($N = 43$), regardless of relationship to study drug

Event, *n* (%)	Any grade	Grade 3/4
Non-haematologic		
Fatigue	40 (93)	18 (42)
Nausea	22 (51)	4 (9)
Cutaneous rash[a]	21 (49)	2 (5)
Mucositis	21 (49)	4 (9)
Vomiting	21 (49)	4 (9)
Anorexia	20 (47)	11 (26)
Diarrhoea	19 (44)	5 (12)
Infection	18 (42)	7 (16)
Constipation	14 (33)	1 (2)
Oedema	12 (28)	1 (2)
Dyspnoea	8 (19)	1 (2)
Haemorrhage	8 (19)	0
Thromboembolism	7 (16)	5 (12)
Pneumonitis	5 (12)[b]	2 (5)[c]
Haematologic		
Anaemia	43 (100)	6 (14)
Lymphopenia	35 (81)	10 (23)
Leucopenia	21 (49)	2 (5)
Neutropenia	15 (35)	1 (2)
Thrombocytopenia	9 (21)	2 (5)
Biochemical[d]		
Hypercholesterolaemia	30 (81)	3 (8)
Hypertriglyceridemia	27 (69)	—
Hyperglycaemia	25 (61)	4 (10)
Elevated ALT	20 (48)	—
Elevated AST	15 (36)	—
Hypercalcemia	6 (14)	—

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase.
[a]Includes rash, pruritus, erythema, and dry skin.
[b]All cases of pneumonitis were interstitial except for 1 case of infectious pneumonitis.
[c]One case each of interstitial and infectious pneumonitis.
[d]$n = 42$ for ALT, AST, and hypercalcemia; 41 for hyperglycaemia; 39 for hypertriglyceridemia; and 37 for hypercholesterolaemia.

ceftriaxone ($n = 1$) or ceftriaxone plus metronidazole followed by ceftriaxone plus piperacillin ($n = 1$). Thromboembolism occurred in seven patients (16%). Thromboembolic events included one pulmonary embolism (grade 4) and six venous thromboembolisms (one grade 4, three grade 3, and two grade 2). The most common haematological AEs were anaemia (100%), lymphopenia (81%), and leucopenia (49%) (Table 3). Thrombocytopenia (all grades) was observed in 21% of patients, with one patient each experiencing grade 3 and 4 events. Biochemical abnormalities included hypercholesterolaemia (81%), hypertriglyceridemia (69%), and hyperglycaemia (61%) (Table 3). Additional therapy included prophylactic (39%) and curative (32%) mouthwash,

antibiotics (36%), and corticosteroids (20%). Hypertension at baseline reduced the risk of haemorrhage compared with normal blood pressure at baseline ($P = 0.045$). No other relationships between comorbid conditions and risks of toxicity were observed.

A total of 56 serious AEs were experienced by 34 patients (77%). Of these serious AEs, 25 (45%) were considered to be related to study drug. The most common serious AEs were reduced general condition (nine events), thrombosis (six events), infection and interstitial lung disease (four events each), and hyperglycaemia and renal insufficiency (three events each). Eleven patients (25%) died during the study. Of these deaths, 10 were related to disease progression. One patient experienced sudden death considered unlikely to be related to study drug.

DISCUSSION

In this open-label, phase II study, everolimus enabled 36% of patients with advanced endometrial cancer refractory to one or two previous chemotherapy regimens to remain progression free at 3 months. Thus, the trial met the prespecified criteria for efficacy of everolimus in this patient population. The non-progressive disease rate remained 36% at 6 months. The rate of non-progressive was higher in patients with endometrioid *vs* serous histology (39% *vs* 27%), although this difference was statistically significant. Median PFS and OS in the total population were 2.8 months and 8.1 months, respectively, with similar results observed

Table 4. Studies of mTOR inhibitors in endometrial cancer

Study	Population (*N*)	Treatment	Best overall response (%)	Median duration of non-progressive disease (months)	Median PFS (months)	Median OS (months)	Disc. due to AEs (%)
Everolimus							
Current study	Recurrent/metastatic disease refractory to 1 or 2 chemotherapy regimens (44)	10 mg per day PO	CR: 0 PR: 9 SD: 27 PD: 57 NA: 6	Response: 3.1 SD: 4.3	2.8	8.1	35
Slomovitz *et al*, 2010	Progressive/recurrent disease treated with 1 or 2 chemotherapy regimens (35)	10 mg per day PO	CR: 0 PR: 0 SD: 43[a] PD: 57[a]	4.5	NA	NA	40
Temsirolimus							
NCIC IND160 (Oza *et al*, 2011a)	Metastatic or locally advanced chemotherapy-naive disease (33)	25 mg IV weekly	CR: 0 PR: 24/14[b] SD: 69 PD: 15	Response: 5.1 SD: 9.7	7.33	NA	27
	Metastatic or locally advanced disease treated with 1 chemotherapy regimen (27)	25 mg IV weekly	CR: 0 PR: 7/4[b] SD: 48 PD: 48	Response: 4.9 SD: 3.8	3.25	NA	
Fleming *et al*, 2011	Advanced, persistent, or recurrent disease previously treated with ⩽1 chemotherapy regimen (20)[c]	25 mg IV weekly	CR: 10 PR: 20 SD: 55 PD: 15	NA	NA	NA	18
Ridaforolimus							
NCIC IND 192 (Mackay *et al*, 2011)	Recurrent or metastatic disease; only adjuvant chemotherapy permitted (34)	40 mg per dayd PO 5 days per week	CR: 0 PR: 7[d] SD: 53 PD: 40	PR: 7.9 and 17.3[e] SD: 7.1	NA	NA	38
Oza *et al*, 2011b	Advanced or metastatic disease treated with 1 or 2 lines of chemotherapy (64)	40 mg per day PO 5 days per week	CR + PR: 8/0[b] SD: 56/35[b] PD: 23/25[b]	NA	5.6/3.6[b]	9.6	33
Colombo *et al*, 2007; ARIAD Pharmaceuticals Inc., 2012	Advanced disease with documented progression despite previous chemotherapy (45)	12.5 mg IV 5 consecutive days every other week	CR: 0 PR: 10 SD: 19	NA	NA	NA	NA

Abbreviations: AE, adverse event; CR = complete response; IV = intravenous; mTOR = mammalian target of rapamycin; NA = not available; NCIC = National Cancer Institut Canada; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PO = orally; PR = partial response; SD = stable disease.

[a] At 8 weeks.

[b] Presented as response as assessed by investigator/response as assessed by independent review.

[c] Includes only those patients treated with temsirolimus alone.

[d] Both patients who experienced PR were chemotherapy naive.

[e] Duration of response in the two patients who experienced PR.

for patients previously treated with one and two lines of systemic chemotherapy.

Our results are generally similar to those of other phase II studies of mTOR inhibitors in pretreated recurrent/metastatic endometrial cancer (Table 4) (Colombo *et al*, 2007; Slomovitz *et al*, 2010; Fleming *et al*, 2011; Mackay *et al*, 2011; Oza *et al*, 2011a, 2011b; ARIAD Pharmaceuticals Inc., 2012). In another trial of everolimus for patients with progressive or recurrent endometrioid endometrial cancer previously treated with one or two chemotherapy regimens, the non-progressive disease rate at 8 weeks was 43%, and the median duration of non-progressive disease was 4.5 months (Slomovitz *et al*, 2010). At 20 weeks, the confirmed clinical benefit rate, defined as CR or PR or SD of $\geqslant 8$ weeks in duration, was 21%. Interim results of trials of oral ridaforolimus for advanced endometrial cancer suggest ridaforolimus provides a response rate similar to that of everolimus but with a higher rate and a slightly longer duration of disease stabilisation (Table 4) (Colombo *et al*, 2007; Mackay *et al*, 2011; Oza *et al*, 2011b; ARIAD Pharmaceuticals Inc., 2012).

Although achieving disease remission while receiving everolimus monotherapy appears unlikely, limiting disease growth by interrupting this biological pathway is a reasonable approach for disease control. Evaluation of everolimus in combination with hormonal therapy or chemotherapy should be explored. For example, everolimus in combination with the non-steroidal aromatase inhibitor letrozole has shown promising clinical efficacy in patients with recurrent endometrial cancer (Slomovitz *et al* 2011). In addition, everolimus in combination with tamoxifen has been shown to restore hormonal sensitivity in advanced breast cancer and provide clinical benefit (Bachelot *et al*, 2012). Given the high rate of comorbid diabetes in patients with endometrial cancer, combination therapy with everolimus and metformin, which has demonstrated synergistic activity in preclinical models of cancer (Liu *et al*, 2012), is being explored in endometrial cancer (ClinicalTrials.gov identifier NCT01205672). Conversely, more profound inhibition of the PI3K/Akt/mTOR pathway may provide improved clinical efficacy in chemotherapy-refractory endometrial cancer. The novel oral agent BEZ235, which inhibits both PI3K and mTOR, has demonstrated promising preclinical activity in both *in vitro* and *in vivo* endometrial cancer models (Yang *et al*, 2011; Shoji *et al*, 2012). The pan–class I PI3K inhibitor BKM120, which has demonstrated promising activity in preclinical models of several cancers, is being assessed in phase II studies as second-line therapy for advanced endometrial cancer (ClinicalTrials.gov identifier NCT01289041) and as first-line therapy for advanced, metastatic, or recurrent endometrial cancer (ClinicalTrials.gov identifiers NCT01397877 and NCT01550380). Other PI3K/Akt/mTOR pathway inhibitors currently in development for endometrial cancer include the pan–class I PI3K inhibitor XL147 (SAR245408; ClinicalTrials.gov identifier NCT01013324), the dual PI3K/mTOR inhibitors PF-04691502 and PF-05212384 (ClinicalTrials.gov identifier NCT01420081) and GDC-0980 (ClinicalTrials.gov identifier NCT01455493), and the Akt inhibitor MK-2206 (ClinicalTrials.gov identifier NCT01307631). Of note, stratifying patient enrolment by *KRAS* mutation status may be of value in future studies exploring therapies targeted to the PI3K/Akt/mTOR pathway, as in a biomarker analysis based on the present study population, *KRAS* mutation was significantly associated with shorter PFS ($P<0.001$) and OS ($P=0.034$) (Trédan *et al*, 2012).

The safety profile of everolimus was acceptable in the context of this heavily pretreated population of patients with advanced endometrial cancer. Although all patients experienced at least one AE, most were of grade 1 or 2 severity. The most common grade 3/4 AEs of any cause were fatigue (42%), anorexia (26%), and infection (16%). The overall safety profile observed in this study was similar to those observed in other studies of everolimus in cancer (Motzer *et al*, 2010; Yao *et al*, 2011; Zhu *et al*, 2011), including endometrial cancer (Slomovitz *et al*, 2010). Three patients with SD experienced pulmonary toxicity requiring study withdrawal after 1.6, 2.5, and 7.0 months of treatment. After everolimus discontinuation, all cases of pulmonary toxicity resolved either spontaneously ($n=1$) or with treatment ($n=2$). Pulmonary-related toxicity needs to be further evaluated in patients receiving prolonged mTOR inhibitor therapy.

Specific to this highly comorbid population, we did not find any correlation between comorbidities (e.g., diabetes, obesity, hypertension) and specific toxicities, except for hypertension, which reduced the risk of haemorrhage compared with normal blood pressure at baseline ($P=0.045$). Of note, the percentage of patients who discontinued treatment due to AEs (35%) was higher in this study than in studies of everolimus monotherapy in patients with other cancers (8%–17%) (Motzer *et al*, 2010; Yao *et al*, 2011). However, it was consistent with the high rate of discontinuation observed in other phase II studies of mTOR inhibitors in heavily pretreated advanced endometrial cancer (Table 4) (Slomovitz *et al*, 2010; Mackay *et al*, 2011; Oza *et al*, 2011b).

In conclusion, everolimus demonstrated clinical efficacy according to the prespecified criteria, as well as acceptable tolerability, in patients with advanced or metastatic endometrial cancer that progressed after one or two lines of previous systemic chemotherapy, supporting the further development of therapies targeted to the PI3K/Akt/mTOR pathway in endometrial cancer.

ACKNOWLEDGEMENTS

We would like to thank all participating patients and centres, Nicolas Gane and Virginie Thouviot of the study office of the GINECO Group (Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens), and Khemaies Slimane of Novartis Pharmaceuticals. We would like to thank Melanie Leiby, PhD (ApotheCom, Yardley, PA, USA), for providing editorial support in the preparation of this manuscript. This support was funded by Novartis Pharmaceuticals. This work was supported by Novartis Pharmaceuticals Corporation.

CONFLICT OF INTEREST

F Joly has served as an advisory board member and a consultant for Janssen, Novartis, Pfizer, Roche, and Sanofi Aventis. All remaining authors have declared no conflicts of interest.

REFERENCES

ARIAD Pharmaceuticals Inc. ARIAD presents positive efficacy data on AP23573, novel mTOR inhibitor, in phase 2 metastatic endometrial cancer trial [press release]. Available http://phx.corporate-ir.net/phoenix.zhtml?c=118422&p=irol-newsArticle_print&ID=1010401&highlight= (accessed 16 February 2012).

Bachelot T, Bourgier C, Cropet C, Ray-Coquard I, Ferrero JM, Freyer G, Abadie-Lacourtoisie S, Eymard JC, Bebled M, Spaëth D, Legouffe E, Allouache D, El Khouri C, Pujade-Lauraine E (2012) Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth fact receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. *J Clin Oncol* **30**: 2718–2724.

Block M, Fister S, Emons G, Seeber S, Grundker C, Gunthert AR (2010) Antiproliferative effects of antiestrogens and inhibitors of growth factor receptor signaling on endometrial cancer cells. *Anticancer Res* **30**: 2025–2031.

Catasus L, D'Angelo E, Pons C, Espinosa I, Prat J (2010) Expression profiling of 22 genes involved in the PI3K-AKT pathway identifies two subgroups

of high-grade endometrial carcinomas with different molecular alterations. *Mod Pathol* **23**: 694–702.

Catasus L, Gallardo A, Cuatrecasas M, Prat J (2009) Concomitant PI3K-AKT and p53 alterations in endometrial carcinomas are associated with poor prognosis. *Mod Pathol* **22**: 522–529.

Colombo N, McMeekin S, Schwartz P, Kostka J, Sessa C, Gehrig P, Holloway R, Braly P, Matei D, Einstein M (2007) A phase II trial of the mTOR inhibitor AP23573 as a single agent in advanced endometrial cancer. *J Clin Oncol* **25**(Suppl): Abstr. 5516.

Colombo N, Preti E, Landoni F, Carinelli S, Colombo A, Marini C, Sessa C (2011) Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Ann Oncol* **22**(Suppl 6): vi35–vi39.

Creasman WT, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, Heintz AP, Ngan HY, Pecorelli S (2006) Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet* **95**(Suppl 1): S105–S143.

Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM (2010) Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* **127**: 2893–2917.

Fleming GF, Filiaci V L, Hanjani P, Burke II JJ, Davidson SA, Leslie KK, Zaino RJ (2011) Hormonal therapy plus temsirolimus for endometrial carcinoma (EC): Gynecologic Oncology Group Trial #248. *J Clin Oncol* **29**(Suppl): Abstr. 5014.

Hayes MP, Wang H, Espinal-Witter R, Douglas W, Solomon GJ, Baker SJ, Ellenson LH (2006) PIK3CA and PTEN mutations in uterine endometrioid carcinoma and complex atypical hyperplasia. *Clin Cancer Res* **12**: 5932–5935.

Humber CE, Tierney JF, Symonds RP, Collingwood M, Kirwan J, Williams C, Green JA (2007) Chemotherapy for advanced, recurrent or metastatic endometrial cancer: a systematic review of Cochrane collaboration. *Ann Oncol* **18**: 409–420.

Jemal A, Siegel R, Xu J, Ward E (2010) Cancer statistics, 2010. *CA Cancer J Clin* **60**: 277–300.

Konopka B, Janiec-Jankowska A, Kwiatkowska E, Najmola U, Bidzinski M, Olszewski W, Goluda C (2011) PIK3CA mutations and amplification in endometrioid endometrial carcinomas: relation to other genetic defects and clinicopathologic status of the tumors. *Hum Pathol* **42**: 1710–1719.

Liu H, Scholz C, Zang C, Schefe JH, Habbel P, Regierer AC, Schulz CO, Possinger K, Eucker J (2012) Metformin and the mTOR inhibitor everolimus (RAD001) sensitize breast cancer ceels to the cytotoxic effect of chemotherapeutic drugs *in vitro*. *Anticancer Res* **32**: 1627–1637.

Mackay H, Welch S, Tsao MS, Biagi JJ, Elit L, Ghatage P, Martin LA, Tonkin KS, Ellard S, Lau SK, McIntosh L, Eisenhauer EA, Oza AM (2011) Phase II study of oral ridaforolimus in patients with metastatic and/or locally advanced recurrent endometrial cancer. *J Clin Oncol* **29**(Suppl): Abstr. 5013.

Milam MR, Celestino J, Wu W, Broaddus RR, Schmeler KM, Slomovitz BM, Soliman PT, Gershenson DM, Wang H, Ellenson LH, Lu KH (2007) Reduced progression of endometrial hyperplasia with oral mTOR inhibition in the Pten heterozygote murine model. *Am J Obstet Gynecol* **196**: 247.e1–247.e5.

Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grunwald V, Thompson JA, Figlin RA, Hollaender N, Kay A, Ravaud A (2010) Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. *Cancer* **116**: 4256–4265.

National Cancer Institute (2006) Common terminology criteria for adverse events v3.0 (CTCAE). *National Cancer Institute Web site. http://ctep.cancer.gov/reporting/ctc_v30.html.*

National Comprehensive Cancer Network (2012) NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms. **V.3.2012** *National Comprehensive Cancer Network Web site*. http:/www.nccn.org.

Oda K, Stokoe D, Taketani Y, McCormick F (2005) High frequency of coexistent mutations of PIK3CA and PTEN genes in endometrial carcinoma. *Cancer Res* **65**: 10669–10673.

Oza AM, Elit L, Tsao MS, Kamel-Reid S, Biagi J, Provencher DM, Gotlieb WH, Hoskins PJ, Ghatage P, Tonkin KS, Mackay HJ, Mazurka J, Sederias J, Ivy P, Dancey JE, Eisenhauer EA (2011a) Phase II study of temsirolimus in women with recurrent or metastatic endometrial cancer: a trial of the NCIC Clinical Trials Group. *J Clin Oncol* **29**: 3278–3285.

Oza AM, Poveda A, Clamp AR, Pignata S, Scambia G, Del Campo JM, McCormack M, Sevcik L, Schwartz BM, Guan S, Lee R, Cheng JD, Haluska FG (2011b) A randomized phase II (RP2) trial of ridaforolimus (R) compared with progestin (P) or chemotherapy (P) in female adult patients with advanced endometrial carcinoma. *J Clin Oncol* **29**(Suppl): Abstr. 5009.

Pectasides D, Xiros N, Papaxoinis G, Pectasides E, Sykiotis C, Koumarianou A, Psyrri A, Gaglia A, Kassanos D, Gouveris P, Panayiotidis J, Fountzilas G, Economopoulos T (2008) Carboplatin and paclitaxel in advanced or metastatic endometrial cancer. *Gynecol Oncol* **109**: 250–254.

Podsypanina K, Lee RT, Politis C, Hennessy I, Crane A, Puc J, Neshat M, Wang H, Yang L, Gibbons J, Frost P, Dreisbach V, Blenis J, Gaciong Z, Fisher P, Sawyers C, Hedrick-Ellenson L, Parsons R (2001) An inhibitor of mTOR reduces neoplasia and normalizes p70/S6 kinase activity in Pten+/− mice. *Proc Natl Acad Sci USA* **98**: 10320–10325.

Rudd ML, Price JC, Fogoros S, Godwin AK, Sgroi DC, Merino MJ, Bell DW (2011) A unique spectrum of somatic PIK3CA (p110alpha) mutations within primary endometrial carcinomas. *Clin Cancer Res* **17**: 1331–1340.

Schoffski P, Ray-Coquard IL, Cioffi A, Bui NB, Bauer S, Hartmann JT, Krarup-Hansen A, Grunwald V, Sciot R, Dumez H, Blay JY, Le CA, Wanders J, Hayward C, Marreaud S, Ouali M, Hohenberger P (2011) Activity of eribulin mesylate in patients with soft-tissue sarcoma: a phase 2 study in four independent histological subtypes. *Lancet Oncology* **12**: 1045–1052.

Shoji K, Oda K, Kashiyama T, Ikeda Y, Nakagawa S, Sone K, Miyamoto Y, Hiraike H, Tanikawa M, Miyasaka A, Koso T, Matsumoto Y, Wada-Hiraike O, Kawana K, Kuramoto H, McCormick F, Aburatani H, Yano T, Kozuma S, Taketani Y (2012) Genotype-dependent efficacy of a dual PI3K/mTOR inhibitor, NVP-BEZ235, and an mTOR inhibitor, RAD001, in endometrial carcinomas. *PLoS ONE* **7**: e37431.

Simon R (1989) Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* **10**: 1–10.

Slomovitz BM, Brown J, Johnston TA, Mura D, Levenback C, Wolf J, Adler KR, Lu KH, Coleman RL (2011) A phase II study of everolimus and letrozole in patients with recurrent endometrial carcinoma. *J Clin Oncol* (2011) SupplAbstr. 5012.

Slomovitz BM, Lu KH, Johnston T, Coleman RL, Munsell M, Broaddus RR, Walker C, Ramondetta LM, Burke TW, Gershenson DM, Wolf J (2010) A phase 2 study of the oral mammalian target of rapamycin inhibitor, everolimus, in patients with recurrent endometrial carcinoma. *Cancer* **116**: 5415–5419.

Sovak MA, Dupont J, Hensley ML, Ishill N, Gerst S, Abu-Rustum N, Anderson S, Barakat R, Konner J, Poyner E, Sabbatini P, Spriggs DR, Aghajanian C (2007) Paclitaxel and carboplatin in the treatment of advanced or recurrent endometrial cancer: a large retrospective study. *Int J Gynecol Cancer* **17**: 197–203.

Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* **92**: 205–216.

Trédan O, Treilleux I, Wang Q, Gane N, Pissaloux D, Bonnin N, Petit T, Cretin J, Bonichon-Lamichhane N, Priou F, Lavau-Denes S, Mari V, Freyer G, Lebrun D, Alexandre J, Ray-Coquard I (2012) Predicting everolimus treatment efficacy in patients with advanced endometrial carcinoma: a GINECO study. *Target Oncol;* e-pub ahead of print 13 December 2012; doi:10.1007/s11523-012-0242-9.

Yang S, Xiao Z, Meng X, Leslie K (2011) Combination therapy with mTOR and PI3 kinase inhibitors is broadly synergistic in a wide variety of endometrial cancer cells. *Proc Obstet Gynecol* **2**: 6.

Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, Hobday TJ, Okusaka T, Capdevila J, de Vries EG, Tomassetti P, Pavel ME, Hoosen S, Haas T, Lincy J, Lebwohl D, Oberg K (2011) Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* **364**: 514–523.

Zhu AX, Abrams TA, Miksad R, Blaszkowsky LS, Meyerhardt JA, Zheng H, Muzikansky A, Clark JW, Kwak EL, Schrag D, Jors KR, Fuchs CS, Iafrate AJ, Borger DR, Ryan DP (2011) Phase 1/2 study of everolimus in advanced hepatocellular carcinoma. *Cancer* **117**: 5094–5102.