

Keywords: metastatic endometrial cancer; targeted therapy; PI3K inhibitor; buparlisib/BKM120

Phase II study of the PI3K inhibitor BKM120 in patients with advanced or recurrent endometrial carcinoma: a stratified type I–type II study from the GINECO group

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Background: Patients with metastatic endometrial carcinoma have a poor prognosis and PIK3CA mutations and amplifications are common in these cancers. This study evaluated the efficacy and safety of the pure PI3K inhibitor BKM120 in advanced or recurrent endometrial carcinoma.

Methods: This phase II, multicentre, single-arm, double strata (histological low grade (LG) or high grade (HG)) open-label study enrolled patients with histologically confirmed advanced or recurrent endometrial carcinoma who had received not more than one prior chemotherapy regimen. Patients received initially BKM120 100 mg tablets once daily. Primary end points were proportion of patients free of progression at 2 months (HG strata) or at 3 months (LG strata), objective response rate (ORR), and safety.

Results: A total of 40 patients were enrolled, of whom 16 patients had received BKM120 at 100 mg. Because of high toxicities (cutaneous rash (54%), depressive events (47%), and anxiety (40%)), the IDMC has proposed to stop recruitment at 100 mg and to continue the clinical trial with a lower dose of 60 mg per day. In addition, 24 patients (median age 67 years old) were newly enrolled (14 in the LG strata and 10 in the HG strata). Rate of nonprogression at 2 months in the HG strata was 70% and at 3 months was 60% in the LG strata. Median progression-free survival (PFS) for all patients is 4.5 months (CI 95% 2.8–6.1), and the median PFS for LG strata is 8.3 months compared with 3.8 months for the HG strata. No response was reported. At 60 mg per day, the most commonly reported treatment-related adverse events (AEs) were hyperglycaemia (58%), cognitive (31%), digestive (28%), hepatic liver functions (26%), and rash (23%). The most commonly reported treatment-related grade ≥ 3 AEs were HTA (17%), hyperglycaemia (17%), and increased alanine aminotransferase (24%). Five patients (21%) stopped BKM120 for toxicity.

Conclusions: The BKM120 was associated with an unfavourable safety profile and minimal antitumour activity in monotherapy in advanced or recurrent endometrial carcinoma. The clinical trial was stopped before end of recruitment for toxicity.

Endometrial cancer is the most common gynaecologic malignancy and the fourth most common cancer in European and North American women, accounting for ~6% of new cancer cases and 3% of cancer deaths per year (Ferlay *et al*, 2010). Approximately 75% of endometrial cancer cases are diagnosed with the tumour confined to the uterine corpus, but after primary surgery, 20% of these tumours recur and have limited response to systemic therapy.

The 5-year survival rate for women with advanced stage III or IV disease is 57–66% and 20–26%, respectively (Creasman *et al*, 2006). Endometrial cancers are commonly classified into 2 histologic subtypes: endometrioid (type I), accounting for 60–70% of endometrial cancers and nonendometrioid (type II; 30–40%). Several studies have correlated progression-free survival (PFS) to hormonal agents with tumour grade (Decruze and Green, 2007).

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Thigpen *et al* (1986) in a GOG study showed that median survival durations were also significantly longer for patients with grade 1 tumours than for those with grade 3 tumours (18.8 and 6.9 months, respectively). Type I endometrial cancers are oestrogen dependent with high expression of oestrogen (ER) and progesterone (PR) receptors, exhibit microsatellite instability, frequent loss-of-function mutations in the PTEN (phosphatase and tensin homologue) tumour suppressor gene (in up to 80% of endometrioid cancers), and mutational activation of the PI3K pathway (PIK3CA mutations: 36–52%; PIK3R1 mutations: 21–43%). Type II cancers more frequently show p53 mutations and HER2 amplification (27–44% of type II tumours) (Murali *et al*, 2014).

Therapies for advanced and recurrent disease are rarely curative, median overall survival being ~12 months. Cytotoxic chemotherapy (mostly anthracyclins, platinum salts and taxanes) is indicated as frontline treatment for the majority of women with metastatic or recurrent disease (Humber *et al*, 2007; Pectasides *et al*, 2008). Hormonal treatment is a particularly attractive option for the treatment of advanced endometrial cancer for patients with low-grade endometrial tumours, and those presenting with an asymptomatic indolent recurrence (Rose *et al*, 2000).

Targeted therapies, which specifically inhibit molecular abnormalities, have emerged as a novel approach and 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 (Rudd *et al*, 2011; Konopka *et al*, 2011). Importantly, low expression of the tumour suppressors PTEN, TSC2, and LKB1 has been associated with PI3K/mTOR pathway activation in endometrial cancer (Salvesen *et al*, 2004). There is increasing evidence suggesting that the PI3K/Akt pathway plays an important role in survival. A variety of pathway inhibitors have been demonstrated to interact with the PI3K signalling cascade, lacking or losing inhibition of this pathway in tumours with constitutive activation of the respective target receptors. Previous clinical trials reported activity with mTOR inhibitors in relapsed endometrial carcinoma (Slomovitz *et al*, 2012; Ray-Coquard *et al*, 2013). Constitutive activation of the PI3K pathway was found to be involved in this phenomenon, suggesting that PI3K inhibition could be a potentially useful strategy to overcome resistance towards certain receptor-targeted therapies. However, at this date, no direct correlation exists between PI3K/Akt activation and mTOR activity inhibitors in endometrial cancer as other cancers subtypes. BKM120 (buparlisib) is an oral pure PI3K inhibitor with broad antitumour activity in preclinical and in a phase I clinical study (Bendell *et al*, 2012).

The objective of this French multicentre phase II study (ClinicalTrials.gov identifier NCT01397877) was to assess the efficacy and safety of BKM120 (buparlisib) monotherapy in women with advanced or metastatic endometrial cancer.

MATERIALS AND METHODS

Patients. Patients eligible for study inclusion were aged >18 years with histologically confirmed, metastatic or locally advanced endometrial adenocarcinoma not amenable to potentially curative treatment with local surgery and/or radiation therapy who received no more than one prior chemotherapy regimen. Previous adjuvant phase with chemotherapy and radiotherapy was authorised, if interval-free survival was >12 months between the end of chemotherapy and relapse. Additional inclusion criteria included at least one 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 <2 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, except adequately treated cervical carcinoma *in situ* or basal or squamous cell carcinoma; and previous PI3K inhibitor treatment. 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.

Histological subgroups. Recently, new prognosis and predictive factors for efficacy of treatments and survival are published and defined histological type I vs type II (Llobet *et al*, 2009). This stratified analysis of endometrial carcinoma has major importance looking at targeted therapies involving ER, PR, or PI3K pathway (Ali, 2000). A centralised histological analysis was required to confirm diagnosis and to define tumour grade. According to this result, eligible patients were included in double strata; histological low grade in strata 1 (endometrioid grade I and II, mucinous) and high grade in strata 2 (serous, endometrioid grade III, clear cell, carcinosarcoma, and undifferentiated carcinoma).

Treatment. All patients received BKM120 (buparlisib) 100 mg daily (2 tablets of 50 mg) until progression or unacceptable toxicity. In the case of adverse events (AEs) or toxicity thought to be related to BKM120, buparlisib dosing could be delayed or reduced according to an algorithm outlined in the study protocol. For grade 3 and recurrent grade 2 toxicities, BKM120 could be reduced to 80 mg daily (first appearance of toxicities) and then 60 mg daily (second episode of toxicity).

Because of high rate of grade 3/4 toxicities, the Independent Data Monitoring Committee (IDMC) proposed to stop recruitment at 100 mg after recruitment of 16 patients (in July 2012) and to continue with a lower dose of 60 mg per day (from February 2013). Then, patients received BKM120 60 mg daily (1 tablet of 50 mg and 1 tablet of 10 mg) until progression or unacceptable toxicity. For grade 3 and recurrent grade 2 toxicities, BKM120 could be reduced to 50 mg daily (first appearance of toxicities) and then 40 mg daily (second episode of toxicity).

Methods. 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 for patients with low-grade tumours, and every 2 months for patients with high-grade tumours, 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. The AEs and laboratory abnormalities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Statistical analysis. The primary study end point was rate of nonprogression at 3 months (12 weeks) for patients with low-grade tumours (strata 1) and at 2 months (8 weeks) for patients with high-grade tumours (strata 2). Secondary end points included objective response rate (RECIST criteria) PFS at 6 months; clinical benefit, duration of clinical benefit, and time to second-line treatment (chemotherapy or hormonal therapy); overall survival (OS); safety and toxicity; surrogate markers of efficacy (biologic, pharmacokinetic); molecular analysis and correlation for response and PFS by strata. The duration of response was defined as the time from the date of the first confirmed response to the date of disease progression or death because of cancer; PFS was defined as

the time from enrolment to the date of disease progression or death because of any cause; and OS was defined as the time from enrolment to the date of death because of any cause.

This study was designed using a Simon two-stage mini-max design (Simon, 1989) To show a >70% success rate (i.e., >70% of patients without progressive disease at 3 months for strata 1 and 2 months for strata 2) with 90% power and $\alpha = 5\%$, 24 evaluable patients were required by strata. In stage one of the study and for each strata, if at least 5 of the first 10 evaluable patients demonstrated complete response (CR), partial response (PR), or stable disease (SD), recruitment was continued until 24 evaluable patients were enrolled. In stage two, if at least 14 patients demonstrated CR, PR, or SD, BKM120 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 BKM120 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

Between December 2011 and January 2014, 40 patients were enrolled at 13 French centres. At the time of analysis, 38 patients had discontinued treatment owing to adverse events (36.8%) and progressive disease (63.2%). Between stages BKM120 100 mg and BKM120 60 mg, enrolment was stopped during 7 months.

Results with BKM120 100 mg daily. A total of 16 patients were included at 100 mg daily. Because of high rate of grade 3/4 toxicities (cutaneous rash (54%), depressive events (47%), and anxiety (40%)), the IDMC proposed to stop recruitment at 100 mg but to continue the recruitment with a lower dose of 60 mg per day. At 100 mg per day, 9 patients (56%) stopped BKM120 for toxicity. Median time of toxicity apparition was 58.5 days (range 14–147 days). Median duration of BKM120 exposure was 34 days (9–753 days). Of the 16 included patients, 7 were evaluable for primary end point: 4 stable disease (2 at 3 months, and 2 at 2 months) 2 progressions, and 1 death.

Results for BKM120 60 mg daily. At this level dose, 24 patients were included. Patient characteristics are summarised in Table 1. Median age was 67.1 years (range 50–80 years) and 71% of patients had endometrioid carcinomas. In addition, 14 patients (58%) were included in strata I (low grade) and 10 patients (42%) in strata II (high grade). The treatment-free interval was 16.1 months (range 0.7–22.5 months) and a majority of patients were previously treated with surgery (83%). The median duration of treatment was 3.7 months (range 14 days to 12.2 months).

Efficacy. Concerning the primary study end point, the rate of nonprogression at 3 (arm 1) or 2 (arm 2) months was 65% (IC95 (44–86)) with 60% for strata I (low-grade tumour) and 70% for strata II (high-grade tumour). Median PFS and OS for all patients were 4.5 months (CI 95% 2.8–6.1) and 10.1 months (CI 95% not feasible) respectively; median PFS for LG strata was 8.3 months (CI 95% 5.8–10.8) compared with 3.8 months (CI 95% 3.0–4.6) for the HG strata (Figure 1). No objective response was reported. Six patients (25%) received <3 months of treatment because of a rapid progressive disease, whereas 4 patients were not evaluable for efficacy because of a very early medical withdrawal due to toxicity. In strata I, 6 patients experienced long-term stability disease (i.e., >6 months) (range 7–13.4 months). These six patients had an endometrioid grade I/II carcinoma and five patients had never

received chemotherapy. Median duration between initial therapeutic management and metastatic relapse was 27.4 months.

Safety. Median duration of BKM120 (60 mg daily) exposure was 3.7 months (range 14 days to 12.2 months). Of the patients, 87% experienced grade 3/4 toxicity. Five patients (21%) received <3 months of treatment owing to toxicity. Only 13 patients (54%) received BKM120 for >3 months, and 8 patients had their treatment discontinued to toxicity, and among them 6 patients continued treatment with dose reduction. The most common causes of dose reduction or interruption were hepatic cytolysis and hyperglycaemia. Median time for toxicity apparition was 69.5 days (range 14 days to 350 days).

Of the 24 patients included at this level dose, all experienced at least one AE, a majority of which were of grade 1 or 2 severity. The most common nonbiological all-grade AEs were fatigue (74%), cutaneous rash (55%), depression (42%) abdominal pain (41%), and diarrhoea (37%) (Table 2). The most common grade 3/4 AEs were hypertension (17%), cutaneous rash (13%), and fatigue (8%). The most common biological all-grade AEs were hepatic cytolysis defined by increased alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (86%), lymphopenia (47%), hyperglycaemia (67%), and hypercholesterolaemia (61%) (Table 3). A total of 259 AEs were experienced by 24 patients (100%) including 31 serious AEs for 18 patients (75%). 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 for each), and hyperglycaemia and renal insufficiency

Table 1. Patient characteristics

| Patient characteristics | Cohort 60 mg (n = 24) | | Cohort 100 mg (n = 16) | |
|---|--------------------------|----|---------------------------|----|
| | N | % | N | % |
| Median age, years (range) | 67.1 (50.0–79.7) | | 65.2 (53.6–79.5) | |
| Eastern Cooperative Oncology Group Performance Status | | | | |
| 0 | 10 | 42 | 7 | 44 |
| 1 | 14 | 58 | 6 | 38 |
| 2 | — | — | 2 | 12 |
| Missing | — | — | 1 | 6 |
| Histological type | | | | |
| Endometrioid | 17 | 71 | 13 | 81 |
| Serous | 2 | 8 | 1 | 6 |
| Carcinosarcoma | 5 | 21 | 2 | 13 |
| Strata | | | | |
| Strata I (endometrioid/ mucinous grade 1 or 2) | 14 | 58 | 7 | 44 |
| Strata II (high grade) | 10 | 42 | 9 | 56 |
| Disease | | | | |
| Initial metastatic disease | 9 | 38 | 9 | 56 |
| Relapse | 15 | 62 | 7 | 44 |
| Metastatic sites | | | | |
| Lung | 12 | 50 | 10 | 63 |
| Nodes | 11 | 47 | 11 | 69 |
| Peritoneal | 6 | 25 | 3 | 19 |
| Uterus | 5 | 21 | 4 | 25 |
| Pelvis | 7 | 29 | — | — |
| Liver | 2 | 8 | 5 | 31 |
| Other sites | 6 | 25 | 5 | 31 |
| Treatment-free interval | | | | |
| Months, range | 16.1 (0.7–22.5) | | 26.0 (14.6–51.6) | |
| Prior treatment | | | | |
| Surgery | 20 | 83 | 11 | 69 |
| Hormonal therapy | 1 | 4 | — | — |
| Radiation therapy | 8 | 33 | 5 | 31 |
| Chemotherapy first line | 8 | 33 | 3 | 19 |

(three events for each). Eleven patients (25%) died during the study. Of these deaths, 10 were related to disease progression.

DISCUSSION

In this French phase II of the GINECO group, multicentre, single-arm study, BKM120 was associated with an unfavourable safety profile for endometrial cancer patients and showed a minimal antitumour activity in monotherapy in this population, except for low-grade endometrioid tumours. The clinical trial was stopped before the end of recruitment for toxicity.

Interestingly, the safety profile of BKM120 is significantly different depending on the primary tumours sites and even histological types. For example, in lung cancers, the most common

grade 3/4 AEs related to BKM120 (100 mg by day) were hyperglycaemia (23.3%), asthenia, and fatigue (6.7% each) for patients with squamous carcinomas, and increased ALT (15.2%), increased aspartate AST, hyperglycaemia (12.1% each), asthenia, and rash (6.1% each) for nonsquamous carcinomas (Vansteenkiste *et al*, 2015). A phase Ib study of BKM120 (100 mg daily) with letrozole in ER-positive metastatic breast cancer has shown a safe combination with reversible toxicities. Grade 3 AEs, regardless of causality, were observed in 27% of patients. No grade 4 AE was observed. The most common grade 3 AEs were transaminase elevation (15%), fatigue (5%), rash (5%), and depression (5%) (Mayer *et al*, 2014). The BKM120 is associated with several potential toxicities, some of which are shared by the class of this agent. For example, the role of the PI3K/Akt/mTOR signalling pathway in regulating glucose metabolism can explain hyperglycaemia. Cutaneous rash have been attributed to cytokine

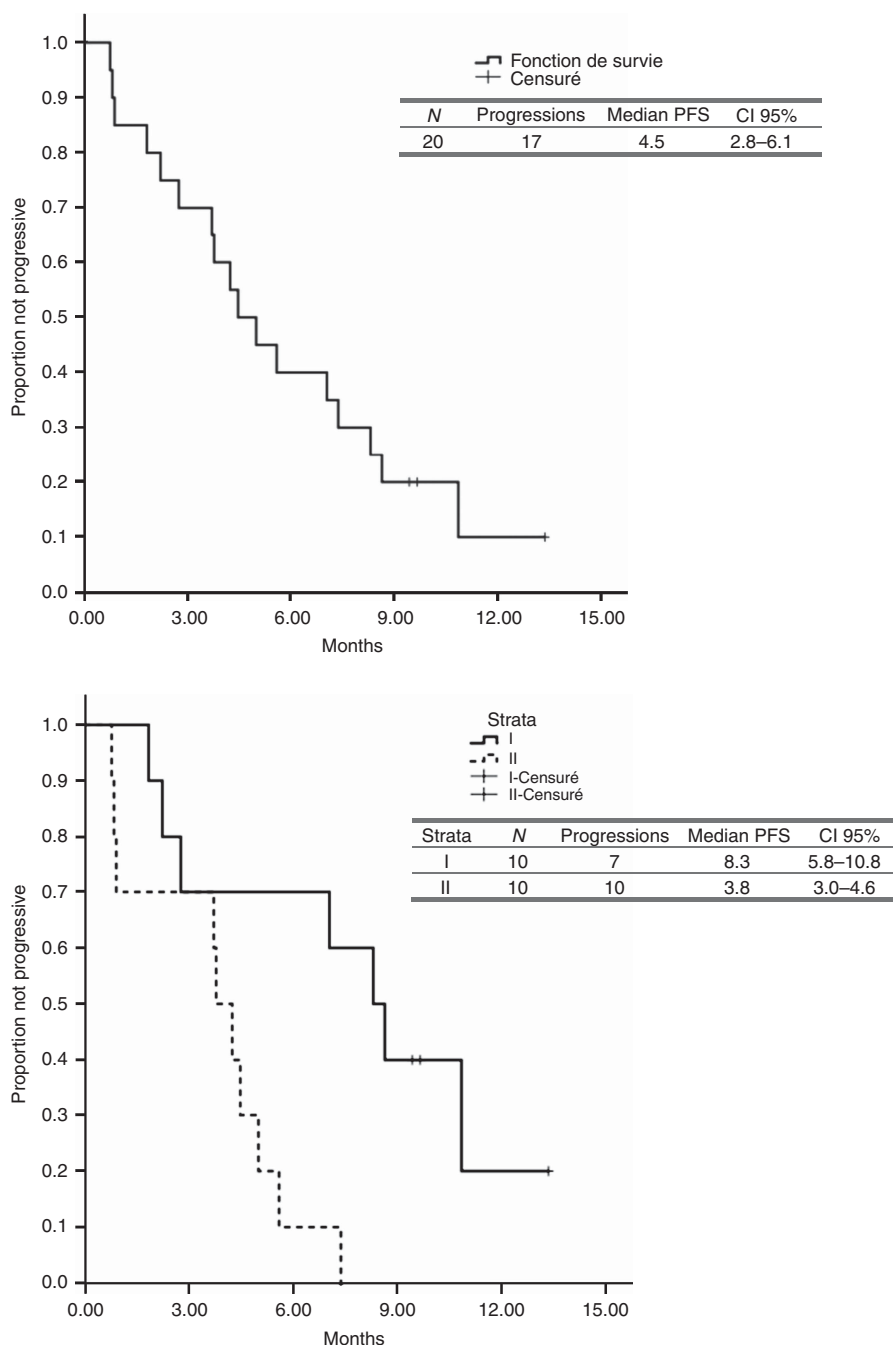


Figure 1. Overall and stratified progressive-free survival.

and chemokine deregulation resulting from pathway inhibition (Chia *et al*, 2015). Greater intensity and frequency of side effects in endometrial cancer may be explained by patients' physiological characteristics but also may be a different PI3K/AKT/mTOR pathway deregulation.

The PTEN is a tumour suppressor gene. Mutations or loss of function in PTEN plays a significant role in the pathogenesis of endometrial cancer (Ali, 2000). Loss of PTEN expression or increased PIK3CA expression activates AKT that leads to increased activity of mTOR, causing cell proliferation. The first generation of mTOR inhibitors that is currently being evaluated for clinical trials in patient with advanced or recurrent endometrial cancer included everolimus, temsirolimus, and ridaforolimus (Table 4). However, mTOR inhibitors have shown modest therapeutic efficacy in monotherapy, but interestingly, an interesting signal for low-grade endometrioid tumours as in the present study. Ray-Coquard *et al* (2013) showed partial response in three patients (11%) with low-grade tumour (Trédan *et al*, 2013) similar to Oza *et al* (2011) who observed 4 of 7 partial response (57%) for endometrioid low-grade tumours. Table 4 reported all data using mTOR inhibitor in endometrial carcinoma. As mTOR inhibitors represented the first generation of targeted therapies, exploring new compounds as PI3K inhibitors seemed an important issue on endometrial carcinoma. Moreover, Piliarisib, a PI3K inhibitor, was associated with a favourable safety profile and minimal antitumour activity (rate of PFS >6 months was 11.9%) in phase II, multicentre, single-arm study that enrolled patients with metastatic endometrial carcinomas (Matulonis *et al*, 2015).

The next step was to explore combination with hormonal therapies. In breast cancer, clinical data suggest that use of mTOR inhibitors can overcome acquired resistance to aromatase-inhibitor therapy (Bachelot *et al*, 2012). Specifically in endometrial cancer, there are *in vitro* data that mTOR inhibitors increase progesterone messenger RNA (mRNA) expression (Bae-Jump *et al*, 2010). Two phase II trials combining mTOR inhibitors with hormonal therapy have been completed in endometrial cancer. The GOG-0248 is a randomised phase II trial in women with hormone therapy-naïve

disease (only one prior chemotherapy regimen permitted). Patients received temsirolimus alone or concomitantly with MEGACE alternating with TAMOXIFENE. The arm with the combined regimen closed rapidly because of an unacceptable rate (32%) of venous thrombosis (7 in 22 patients) (Fleming *et al*, 2014). The second trial is an open-label, single-arm phase II study in patients with recurrent endometrial cancer who had received two or fewer prior chemotherapeutic regimens. Patients received the combination of letrozole and everolimus. Of the 35 patients, 11 (31%) had an objective response and 14 of 35 patients (40%) had a clinical benefit, defined as CR, PR, or SD for at least 8 weeks. None of the patients discontinued treatment as a result of toxicity (Slomovitz *et al*, 2015). All these data suggested clearly a potential effect targeting this pathway. However, monotherapy seems not to be the best strategy and combination might be an alternative.

Because of the data published on cross-talk between signal transduction pathways, particularly ER signalling and the PI3K/Akt/ mTOR pathway (Bachelot *et al*, 2012), combination with hormonal therapy needs to be also explored for endometrial carcinoma. In order to explore this hypothesis, a French multicentric randomised open-label phase I/II evaluating AZD2014 (dual mTORC1/mTORC2 inhibitor) in combination with anastrozole from the CLIP-GINECO group will open beginning in 2016 for the treatment of metastatic hormone receptor-positive endometrial adenocarcinoma.

Overall, results from this study demonstrate that BKM120 has an unfavourable risk-benefit ratio in women with advanced or metastatic refractory endometrial cancer. The positive signal for low-grade endometrioid tumours and results of previous clinical trials with mTOR inhibitors tend to show that inhibition of the PI3K/Akt/mTOR pathway may be a viable therapeutic target for a subset of patients with advanced endometrial cancer.

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Table 2. Nonbiological AEs (cohort 60 mg)

| Nonbiological grade (CTCAE v4.03) (n = 24) | Grade 1–2 | Grade 3–4 |
|--|-----------|-----------|
| Cutaneous rash | 10 (42%) | 3 (13%) |
| Mucositis | 5 (21%) | 1 (4%) |
| Nausea | 8 (33%) | — |
| Vomiting | 5 (21%) | — |
| Constipation | 9 (37%) | — |
| Diarrhoea | 9 (37%) | — |
| Abdominal pain | 8 (33%) | 2 (8%) |
| Anorexia | 8 (33%) | 1 (4%) |
| Intestinal perforation | — | 1 (4%) |
| Hypertension | 1 (4%) | 4 (17%) |
| Dyspnoea | 4 (17%) | 1 (4%) |
| Depression | 10 (42%) | — |
| Anxiety | 5 (21%) | — |
| Fatigue | 16 (66%) | 2 (8%) |
| Infection without neutropenia | 5 (21%) | 1 (4%) |
| Change of the general state | — | 2 (8%) |
| Pains | 11 (46%) | — |
| Lymphangitis | — | 1 (4%) |

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events.

Table 3. Biological AEs (cohort 60 mg)

| Biological grade (CTCAE v4.03) (n = 24) | Grade 1–2 | Grade 3–4 |
|--|-----------|-----------|
| Neutropenia | 2 (8%) | — |
| Anaemia | 6 (26%) | 1 (4%) |
| Lymphopenia | 10 (43%) | 1 (4%) |
| Hepatic cytolysis (increase in ALT and/or AST) | 11 (47%) | 4 (17%) |
| Increase in PAL | 11 (47%) | — |
| Increase in GGT | 10 (43%) | 3 (13%) |
| Hyperglycaemia | 12 (52%) | 4 (17%) |
| Hypokalaemia, hypomagnesaemia, hyponatraemia | — | 1 (4%) |
| Hypercholesterolaemia | 14 (61%) | — |
| Renal toxicity | 9 (38%) | 1 (4%) |

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; GGT = gamma-glutamyltransferase; PAL = Alkaline phosphatase.

Table 4. Studies of mTOR inhibitors in endometrial cancer

| | Admin. | Dose | n | Previous chemotherapy regimens | Stable disease | Partial response | PFS (months) |
|--|--------|------------------------------|----|--------------------------------|----------------|------------------|--------------|
| Temsirolimus Oza et al (2011) | IV | 25 mg per week | 33 | 0 | 69% | 14% | 9.7 |
| Temsirolimus Oza et al (2011) | IV | 25 mg per week | 25 | <2 | 48% | 4% | 3.7 |
| Temsirolimus Fleming et al (2014) | IV | 25 mg per week | 50 | 0-1 | 52% | 22% | 8 |
| Everolimus Slomovitz et al (2010) | PO | 10 mg per day | 35 | 1 or 2 | 43% | 0% | ND |
| Everolimus Ray-coquard et al (2013) | PO | 10 mg per day | 44 | 1 or 2 | 31% | 5% | 2.8 |
| Ridaforolimus Colombo et al (2013) | IV | 12.5 mg per day × 5 every 2w | 45 | >2 | 18% | 11% | <4 |
| Ridaforolimus Tsoref et al (2014) | PO | 40 mg per day × 5 every week | 34 | 0 | 52.9% | 8.8% | 6.6 |
| Ridaforolimus Oza et al (2015) | PO | 40 mg per day × 5 every week | 64 | 1 or 2 | 56.3% | 8.3% | 3.6 |

Abbreviations: Admin. = administration; IV = intravenous; mTOR = mammalian target of rapamycin; ND = not determined; PFS = progression-free survival; PO = per os.

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CONFLICT OF INTEREST

The authors declare no conflict of interest except F Joly who declares NOVARTIS board expert.

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