Hormone Therapy plus mTOR Inhibitors in the Treatment of Endometrial Carcinoma

Erica M Stringer¹ and Gini F Fleming²

1. Fellow, 2. Professor of Medicine, Department of Medicine, Section of Hematology Oncology, University of Chicago Medical Center, Chicago, IL, US.

Abstract

Hormonal therapies such as progestins have only modest activity in the treatment of advanced endometrial cancer. Mechanisms of resistance to progestin therapy are not well understood. However, activation of the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway has been associated with resistance to hormonal therapy and alterations in components of the PI3K/AKT/mTOR pathway, including inactivating mutations in PTEN, activating mutations in PIK3CA and mutations in PIK3R1, are very common in endometrial carcinomas. mTOR inhibitors, including temsirolimus, everolimus and ridaforolimus, are also known to be active against endometrial cancer, and interest has been stimulated in combinations of hormonal treatment with mTOR inhibitors, as both therapies have single-agent activity, and it is hypothesised that mTOR inhibition would enhance sensitivity to hormonal therapy.

Keywords

Endometrial cancer, hormone therapy, progestin, mTOR inhibitor, temsirolimus, everolimus, ridaforolimus, letrozole

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Correspondence: Gini F Fleming, University of Chicago Medical Center, 5841 South Maryland Ave MC2115, Chicago, IL 60637, US. E: gfleming@medicine.bsd.uchicago.edu

Endometrial Carcinoma

Endometrial cancer is the most common gynecologic malignancy in developed countries.¹ According to Surveillance, Epidemiology and End Results (SEER) statistics the estimated incidence of cancers of the uterine corpus for US women in 2011 is 46,470 women. The age-adjusted mortality rate is 4.2 deaths per 100,000 women per year, with an estimated 8,100 deaths in 2011. Median survival for women with recurrent or metastatic disease is only 12 to 15 months. The most commonly used systemic treatment for advanced disease at this time is platinum/taxane-based chemotherapy, which has produced higher response rates and longer median progression-free survivals than hormonal therapy, but progestins remain useful, and occasionally produce prolonged disease control. Mammalian target of rapamycin (mTOR) inhibitors have also recently been shown to have modest single-agent activity.

Type I and Type II Endometrial Carcinoma

Endometrial cancers are often divided into two conceptual categories: type I and type II.² About 80 % of endometrial carcinomas are type I, i.e. of endometrioid histology with low or intermediate grade. These cancers can arise in the setting of persistent unopposed oestrogen stimulation, and tend to occur in perimenopausal women.³ They are generally preceded by endometrial hyperplasia and are usually oestrogen and progesterone receptor (ER/PR) positive. Molecular alterations associated with type I tumours include deletions/inactivating mutations of the PTEN tumour suppressor gene (36–83 %), microsatellite instability (20–40 %), mutations of K-ras (15–30 %) and gain of function mutations in β -catenin (25–40 %).^{4–6} By contrast, type II tumours are histologically nonendometrioid e.g. serous or clear cell, and have no association with excess endogenous or exogenous oestrogen. They tend to occur in older women, and are aggressive with a proclivity for lymphovascular invasion, distant spread and deep tissue invasion; they account for nearly half of endometrial cancer deaths.⁷ The

genetic alterations associated with type II tumours include aneuploidy, p53 mutations (80–90 %), p16 inactivation (40 %), overexpression of human epidermal growth factor receptor 2 (HER-2)/neu (40–80 %) and E-cadherin alterations (80–90 %).^{4–6} Mutations in PIK3CA (gene encoding the catalytic subunit of PI3K) and PIK3R (which encodes the regulatory subunit of PI3K) can occur in both subtypes, although they appear to be more common in type I cancers.^{8,9} Increased signalling of the PI3K/AKT/mTOR pathway is associated with a poor prognosis in both type I and type II carcinomas.¹⁰

Hormone Therapy in the Treatment of Advanced Endometrial Cancer (see Table 1)

Since the early studies by Kelly and Baker in 1965, progestin-based therapy has played a role in the treatment of advanced endometrial carcinoma.^{11,12} Trials in chemotherapy-naïve advanced endometrial carcinoma patients have demonstrated response rates of 18–34 % to progestins with median overall survivals of 6–14 months.¹³ Commonly used regimens in the US include megestrol acetate (MA) 160 mg/day, or MA for three weeks alternating with tamoxifen (TAM) for 3 weeks. The addition of TAM was hypothesised to increase the percentage of endometrial cells that contain PRs, as well as the concentration of surface receptors.¹⁴ While this alternating regimen has not been compared with single-agent megestrol therapy in a randomised trial, the 27 % response rate reported is as high as or higher than that reported with any other hormonal regimen, and TAM causes less weight gain than MA. Dose escalations of MA to 1,000 mg/day did not improve overall survival or progression-free survival.¹⁵ In general, the highest response rates are found in patients with well-differentiated hormone receptor positive tumours.¹¹ However, objective response rates as high as 17 % have reported in PR-negative tumours, making ER/PR expression an inadequate predictor of benefit from hormone therapy in clinical practice. This may be partly related to heterogeneity

of receptor distribution within an individual tumour. The most common side effects of progestin-based therapy are weight gain in about 26 % and venous thrombosis in about 5 % of patients;¹⁶ oedema can also occur. Selective oestrogen modulators, such as TAM or arzoxifene, have also produced modest response rates, although lower than those seen with progestins.¹³ Aromatase inhibitors including letrozole and anastrozole have shown response rates of less than 10 %.^{17–19} Of note, patients on the trials of aromatase inhibitors were permitted to have had prior hormonal therapy, although not prior chemotherapy. A small multicentre phase II study of the National Cancer Institute of Canada (NCIC) Clinical Trials Group testing the use of letrozole found a 9.4 % response rate and no correlation between response and expression of the following biomarkers: PR (86 %), oestrogen receptor (OR) (86 %), PTEN (82 %), phosphorylated PKB/Akt (59 %), bcl-2 (49 %), p53 (32 %) and HER-2 (0 %).

mTOR Inhibitor Therapy in Endometrial Cancer

The mTOR is a protein downstream of PI3Kinase that is activated by oncogenic alterations of the pathway. mTOR regulates numerous cell functions, including protein translation, cell growth and apoptosis. There are two mTOR complexes, mTORC1 and mTORC2, both of which have downstream effects.²⁰ The rapamycin-analogue mTOR inhibitors currently available (temsirolimus, everolimus and ridaforolimus) all act via binding to the cytosolic protein, FK binding-protein 12 (FKBP12) and primarily inhibit mTORC1. As early *in vitro* work suggested that genetic abnormalities resulting in activation of the PI3K/AKT/mTOR pathway, including loss of PTEN function, were associated with anti-tumour efficacy of mTOR inhibitors, these agents were tested fairly early in endometrial cancer. Bae-Jump et al. demonstrated *in vitro* activity of rapamycin in both type I and type II endometrial cancer tumour explants²¹ and, indeed, clinical responses have been observed in both type I and type II endometrial cancers.

The NCIC Clinical Trials Group performed two phase II studies evaluating single-agent temsirolimus, the first in women with recurrent or metastatic chemotherapy-naïve disease, and the second in women who had prior chemotherapy. Temsirolimus 25 mg intravenously (IV) was administered weekly. In the chemotherapy-naïve group, four of 29 evaluable patients (14 %) had a partial response with a median response duration of 5.1 months and 20 (69 %) had stable disease with a median duration of 9.7 months. In the group with prior chemotherapy, only one of 25 evaluable patients (4 %) responded; 12 patients (48%) had stable disease with a median duration of 3.7 months.²² Neither absence of PTEN by immunohistochemical staining, PTEN mutation nor molecular markers of PI3K/Akt/mTOR pathway correlated with clinical outcomes.²³ Toxicities were typical of those seen with mTOR-inhibitor therapy, and included fatigue, rash, nausea, diarrhoea, mucositis and pneumonitis. Asymptomatic mucositis was particularly common in this study (42 %) with five patients (8 %) having grade 3 pneumonitis. Low levels of activity were also seen in phase II trials of ridaforolimus and everolimus in women with pretreated disease (see Table 2).

More recently a randomised phase II trial compared ridaforolimus with progestin-based therapy and standard chemotherapy in 130 women with advanced disease who had received one or two prior chemotherapy regimens. Almost one-third of patients had tumours of serous histology, and more than 50 % had grade 3 tumours. Ridaforolimus met the primary endpoint of the study by demonstrating a progression-free survival of 3.6 versus 1.9 months with progestins.²⁴ Toxicities with ridaforolimus included hyperglycaemia, fatigue,

Table 1: Hormone Therapy in Advanced Endometrial Cancer

Author	Drug	RR (%)	Median Overall Survival (mos)
Thigpen, 1986 ⁴⁰	MPA 150 mg/day	18	10.5
Lentz, 1996 ¹⁵	MA 800 mg/day	24	7.6
Thigpen, 1999 ¹³	MPA 200 mg/day	25	11.1
	MPA 1000 mg/day	15	7.0
Thigpen, 2001 ⁴¹	TAM 40 mg/day	10	8.8
Whitney, 2004 ⁴²	MPA 200 mg/day every other week and TAM 40 mg daily	33	13
Fiorica, 2004 ⁴³	MA 160 mg/day x 3 weeks followed by TAM 40 mg/day x 3 weeks	27	14
Pandya, 2001 ⁴⁴	MA 160 mg/day	20	12.6
	MA mg/160 mg/day + TAM 20 mg/day	19	8.6
Covens, 1997 ⁴⁵	Leuprolide 7.5 mg q 28 days	0	6
Lhomme, 1999 ⁴⁶	Triptorelin 3.75 mg q 28	8.7	7.2
Asbury, 2002 ⁴⁷	Goserelin 3.6 mg q day	11	7.3
Rose, 2000 ¹⁷	Anastrozole 1 mg/day	9	6
Ma, 2004 ¹⁹	Letrozole 2.5 mg/day	9.4	6.7

MA= megestrol acetate; MPA= medroxyprogesterone acetate; RR = response rate; TAM= tamoxifen.

diarrhoea, anemia and mucositis, but no grade 3 pneumonitis.²⁵ Given the toxicities with mTOR-inhibitor therapy, a biologic indicator of which patients are most likely to benefit is clearly needed, but no good predictive marker has emerged to date.

Rationale for Combination of mTOR Inhibitors with Hormone Therapy

The PI3K/AKT/mTOR signalling cascade has been widely implicated in resistance to chemotherapy agents, molecularly targeted agents, such as trastuzumab or gefitinib, radiotherapy and hormonal therapy.^{26–28} In breast cancer, clinical data have begun to suggest that use of mTOR-inhibitor therapy can overcome acquired resistance to trastuzumab and to aromatase-inhibitor therapy. A phase I/II study reported a 15 % response rate and a 34 % clinical benefit rate with the combination of trastuzumab plus everolimus in women with HER2 positive tumours that had progressed on trastuzumab therapy.²⁹ More definitive evidence is in the setting of the combination of an mTOR inhibitor with hormonal therapy. A randomised, double-blind, placebo-controlled phase III clinical trial (BOLERO-2) randomly assigned 724 hormone receptor positive advanced breast cancer patients who had recurrence or progression on a nonsteroidal aromatase inhibitor to exemestane (a steroidal aromatase inhibitor) plus everolimus or placebo. The combination therapy showed a superior progression-free survival of 10.6 months versus 4.1 months with exemestane alone.³⁰ The most common grade 3 or 4 adverse events with the combination were stomatitis, anaemia, dyspnoea, hyperglycaemia, fatigue and pneumonitis (3 %).

Specifically in endometrial cancer, there are *in vitro* data that mTOR inhibitors increase progesterone messenger RNA (mRNA) expression.^{21,31} In addition, *in vitro* and *in vivo* xenograft mouse models suggest that

Table 2: Phase II Trials of Mammalian Target of Rapamycin Inhibitors in Endometrial Carcinoma

Type of Trial	Drug	Mechanism	Patient Population	Response Rates	Prior Therapy
Phase II single agent ⁴⁸	R 40 mg x five days per week	mTORi	Recurrent/metastatic	PR 7.7 % (2 patients chemo-naïve) SD 58 % MD 6.6 months	Yes, adjuvant only
Randomised open-label phase II ²⁴	R 40 mg x five days per week (experimental arm) Progestin * or chemotherapy (control arm)	mTORi, PBT, chemo	Advanced/metastatic	PFS: 3.6 months for R vs 1.9 months for PBT by IRR (HR=0.53; p=0.008) Control: PR/SD 4.3 %/17 % by IRR Experimental: PR/SD 0 %/35 % by IRR	Yes
Randomised phase II ²²	TEM 25 mg weekly	mTORi	Recurrent/metastatic	Chemo-naïve PR 14 %, SD 69 % (MD 5.1 vs 9.7 months) Chemo-treated PR 4 % **, SD 48 % (MD 4.3 vs 3.7 months)	Yes
Randomised phase II ³⁵	TEM 25 mg weekly TEM 25 mg weekly + (MA 80 mg bid x three weeks alternating with TAM 20 mg bid x three weeks)	mTORi, PBT SERM	Advanced/recurrent	14% objective responses reported in combination arm Combined arm closed due to venous thrombosis	Yes
Single-institution, open-label, single-arm, phase II ⁴⁹	Everolimus 10 mg/day	mTORi	Recurrent disease	CBR 43 % at eight weeks CBR 21 % at 20 weeks	Yes
Two-institution, open-label, single-arm, phase II ³³	Everolimus 10 mg/day + letrozole 2.5 mg/day	mTORi, AI	Recurrent disease	CBR 42 % Objective RR 21 %	Yes

AI = aromatase inhibitor; CBR = Clinical Benefit Response (CR, PR, or SD); IRR = independent radiology review; MA = megestrol acetate; MD = median duration; MPA = medroxyprogesterone acetate, mTORi = mammalian target of rapamycin inhibitors; PR = partial response; PBT = progestin-based therapy; R = ridaforolimus; SERM = selective oestrogen modulator; TAM = tamoxifen; TEM = temsirolimus. *Progestin (MPA 200 mg/day or MA 60 mg/day); **Independently confirmed.

MPA activates the PI3K/AKT pathway in progestin-resistant cells, and that inhibiting this pathway reverses progestin resistance in these cell lines.³² Two phase II trials combining mTOR inhibitors with hormonal therapy have been completed in endometrial cancer, and both have been reported in abstract form (see Table 2). The Gynecologic Oncology Group (GOG) has completed GOG-0248, a randomised phase II trial in women with hormone therapy-naïve disease; one prior chemotherapy regimen was permitted (in the setting of stage I, II or III disease, or as radiation sensitiser for pelvic recurrence, or in setting of stage IV disease if patient was without evidence of disease at end of chemotherapy and at least six months elapsed prior to progression). Patients received either single-agent temsirolimus 25 mg IV weekly and or the temsirolimus given concomitantly with MA 80 mg bid for three weeks alternating with TAM 20 mg bid for three weeks. Unfortunately, the arm with the combined regimen closed after the first stage due to an unacceptable rate of venous thrombosis (seven events in 22 patients).^{34,35} Three of 21 patients (14 %) had a partial response at the time of the preliminary report. Results for the single agent are pending. A two-institution, open-label, single-arm phase II study in patients with recurrent endometrial cancer who had received two or fewer prior chemotherapeutic regimens received the combination of letrozole 2.5 mg daily and everolimus 10 mg daily. Four of 19 patients (21 %) had an objective response and eight of 19 (42 %) had clinical benefit, defined as complete response (CR), partial response (PR) or stable disease (SD) for at least eight weeks. This response rate appears better than the historic controls with hormone

therapy in a chemotherapy pretreated population, as well as better than results obtained by the same authors in a single agent trial of everolimus in a similarly pretreated population (no objective responses), although the rate of stable disease at eight weeks (43 %) was similar. The most common drug toxicities were fatigue, stomatitis, hypertriglyceridaemia, nausea and hyperglycaemia.³³ Given that response rates of over 10 % with any agent in the setting of chemotherapy pretreated endometrial cancer are unusual, further development of hormone therapy and PI3K pathway inhibitor combinations is clearly warranted.

Other Potential Combinations with mTOR Inhibitors in Endometrial Carcinoma

As described above, activation of the PI3K/AKT/mTOR pathway has been implicated as a mechanism of resistance to both trastuzumab and standard cytotoxic chemotherapy, and combining trastuzumab or chemotherapeutic agents with inhibitors of the pathway has overcome resistance in numerous reports.^{36,37} Trials combining chemotherapy with mTOR inhibitors have been slow to emerge, in part because the toxicities of the combinations are not always easy to manage.³⁸ However Kollmannsberger et al. successfully developed a regimen combining carboplatin/paclitaxel with temsirolimus on a two out of three week schedule³⁹ and a trial testing this regimen in the GOG has been completed; results should be available soon. Another opportunity might be combinations with trastuzumab. Endometrial carcinomas can both overexpress and amplify HER2; a phase II GOG trial of single-agent

trastuzumab in HER2-positive endometrial cancer found an overall rate of 11.5 % amplification, with highest rates of amplifications in serous carcinomas (seven of 25; 25 %), clear cell carcinomas (three of eight; 38 %) and mixed carcinomas (three of 11, 27 %). The trial, which permitted unlimited prior chemotherapy regimens, reported no

objective responses. However, given the preclinical data suggesting that PI3K/AKT pathway activation is associated with resistance to trastuzumab, and the encouraging clinical results of the everolimus/trastuzumab combination in breast cancer (described above), trials testing a similar combination in endometrial cancer are of interest. ■

- Jemal A, Siegel R, Ward E, et al., Cancer Statistics, *CA Cancer J Clin*, 2006 Mar-Apr;56(2):106–30.
- Bokhman JV, Two pathogenetic types of endometrial carcinoma, *Gynecol Oncol*, 1983;15(1):10–17.
- Creasman WT, Odicino F, Maisonneuve P, et al., Carcinoma of the corpus uteri, *Int J Gynaecol Obstet*, 2003;83 (Suppl. 1):79–118.
- Abal M, Planaguma J, Gil-Moreno A, et al., Molecular pathology of endometrial carcinoma: transcriptional signature in endometrioid tumours, *Histol Histopathol*, 2006;21(2):197–204.
- Hecht JL, Mutter GL, Molecular and pathologic aspects of endometrial carcinogenesis, *J Clin Oncol*, 2006;24(29): 4783–91.
- Lax SF, Molecular genetic pathways in various types of endometrial carcinoma: from a phenotypic to a molecular-based classification, *Virchows Arch*, 2004;444(3):213–23.
- Hamilton CA, Cheung MK, Osann K, et al., Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers, *Br J Cancer*, 2006;94(5):642–6.
- Rudd ML, Price JC, Fogoros S, et al., A unique spectrum of somatic PIK3CA (p110alpha) mutations within primary endometrial carcinomas, *Clin Cancer Res*, 2011;17(6): 1331–40.
- Urick ME, Rudd ML, Godwin AK, et al., PIK3R1 (p85alpha) is somatically mutated at high frequency in primary endometrial cancer, *Cancer Res*, 2011;71(12):4061–7.
- Salvesen HB, Carter SL, Mannelqvist M, et al., Integrated genomic profiling of endometrial carcinoma associates aggressive tumours with indicators of PI3 kinase activation, *Proc Natl Acad Sci U S A*, 2009;106(12):4834–9.
- Singh M, Zaino RJ, Filiaci VJ, Leslie KK, Relationship of oestrogen and progesterone receptors to clinical outcome in metastatic endometrial carcinoma: a Gynecologic Oncology Group Study, *Gynecol Oncol*, 2007;106(2):325–33.
- Chaudhry P, Asselin E, Resistance to chemotherapy and hormone therapy in endometrial cancer, *Endocr Relat Cancer*, 2009;16(2):363–80.
- Thigpen JT, Brady MF, Alvarez RD, et al., Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group, *J Clin Oncol*, 1999;17(6):1736–44.
- Markman M, Hormonal therapy of endometrial cancer, *Eur J Cancer*, 2005;41(5):673–5.
- Lentz SS, Brady MF, Major FJ, et al., High-dose megestrol acetate in advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study, *J Clin Oncol*, 1996;14(2):357–61.
- Bender, D, et al., Hormones and Receptors in Endometrial Cancer. *Proc Obstet Gynecol*, 2011. 1(July):25.
- Rose PG, Brunetto VL, VanLe L, et al., A phase II trial of anastrozole in advanced recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study, *Gynecol Oncol*, 2000;78(2):212–16.
- Burnett AF, Bahador A, Amezcua C, Anastrozole, an aromatase inhibitor, and medroxyprogesterone acetate therapy in premenopausal obese women with endometrial cancer: a report of two cases successfully treated without hysterectomy, *Gynecol Oncol*, 2004;94(3):832–4.
- Ma BB, Oza A, Eisenhauer E, et al., The activity of letrozole in patients with advanced or recurrent endometrial cancer and correlation with biological markers – a study of the National Cancer Institute of Canada Clinical Trials Group, *Int J Gynecol Cancer*, 2004;14(4):650–58.
- Watanabe R, Wei L, Huang J, mTOR signaling, function, novel inhibitors, and therapeutic targets, *J Nucl Med*, 2011;52(4):497–500.
- Bae-Jump VL, Zhou C, Boggess JF, et al., Rapamycin inhibits cell proliferation in type I and type II endometrial carcinomas: a search for biomarkers of sensitivity to treatment, *Gynecol Oncol*, 2010;119(3):579–85.
- Oza AM, Elit L, Tsao MS, et al., Phase II study of temsirolimus in women with recurrent or metastatic endometrial cancer: a trial of the NCIC Clinical Trials Group, *J Clin Oncol*, 2011;29(24):3278–85.
- Westin SN, Broadbudd RR, Personalized therapy in endometrial cancer: Challenges and opportunities, *Cancer Biol Ther*, 2012;13(1):1–13.
- Oza AM, Poveda A, Clamp AR, et al., A randomized Phase II (RP2) trial of ridaforolimus (R) compared with progestin (P) or chemotherapy (C) in female adult patients with advanced endometrial carcinoma, *J Clin Oncol*, 2011;29(24):3278–85.
- Diaz-Padilla I, Duran I, Clarke BA, Oza AM, Biologic rationale and clinical activity of mTOR inhibitors in gynecological cancer, *Cancer Treat Rev*, 2012;38(6):767–75.
- Lee S, Choi EJ, Jin C, Kim DH, Activation of PI3K/Akt pathway by PTEN reduction and PIK3CA mRNA amplification contributes to cisplatin resistance in an ovarian cancer cell line, *Gynecol Oncol*, 2005;97(1):26–34.
- Steelman LS, Navolanic P, Chappell WH, et al., Involvement of Akt and mTOR in chemotherapeutic- and hormonal-based drug resistance and response to radiation in breast cancer cells, *Cell Cycle*, 2011;10(17):3003–15.
- Sokolosky ML, Stadelman KM, Chappell WH, et al., Involvement of Akt-1 and mTOR in sensitivity of breast cancer to targeted therapy, *Oncotarget*, 2011;2(7):538–50.
- Morrow PK, Wulf GM, Ensor J, et al., Phase I/II study of trastuzumab in combination with everolimus (RAD001) in patients with HER2-overexpressing metastatic breast cancer who progressed on trastuzumab-based therapy, *J Clin Oncol*, 2011;29(23):3126–32.
- Baselga J, Campone M, Piccart M, et al., Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer, *N Engl J Med*, 2012;366(6):520–29.
- Temkin SM, Fleming G, Current treatment of metastatic endometrial cancer, *Cancer Control*, 2009;16(1):38–45.
- Gu C, Zhang Z, Yu Y, et al., Inhibiting the PI3K/Akt pathway reversed progestin resistance in endometrial cancer, *Cancer Sci*, 2011;102(3):557–64.
- Slomovitz BM, Brown J, Johnston TA, et al., Phase II study of everolimus and letrozole in patients with recurrent endometrial carcinoma, *J Clin Oncol*, 2011;29(24):3278–85.
- Tewari KKS, Monk BJ, American Society of Clinical Oncology 2011 Annual Meeting update: summary of selected gynecologic cancer abstracts, *Gynecol Oncol*, 2011;122(2):209–12.
- Fleming GF, Filiaci VL, Hanjani P, Hormone Therapy plus temsirolimus for endometrial carcinoma (EC): Gynecologic Oncology Group trial #248, *J Clin Oncol*, 2011 (suppl; abstr 5014).
- Fung AS, Wu L, Tannock IF, Concurrent and sequential administration of chemotherapy and the Mammalian target of rapamycin inhibitor temsirolimus in human cancer cells and xenografts, *Clin Cancer Res*, 2009;15(17):5389–95.
- Piguet AC, Semela D, Keogh A, et al., Inhibition of mTOR in combination with doxorubicin in an experimental model of hepatocellular carcinoma, *J Hepatol*, 2008;49(1):78–87.
- Temkin SM, Yamada SD, Fleming GF, A phase I study of weekly temsirolimus and topotecan in the treatment of advanced and/or recurrent gynecologic malignancies, *Gynecol Oncol*, 2010;117(3):473–6.
- Kollmannsberger C, Hirte H, Siu LL, et al., Temsirolimus in combination with carboplatin and paclitaxel in patients with advanced solid tumours: a NCIC-CTG, phase I, open-label dose-escalation study (IND 179), *Ann Oncol*, 2012;23(1):238–44.
- Thigpen JT, Brady MF, Alvarez RD, et al., Oral medroxyprogesterone acetate in advanced endometrial carcinoma, *Anticancer Research*, 1986;6(3):355.
- Thigpen T, Brady MF, Homesley HD, et al., Tamoxifen in the treatment of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study, *J Clin Oncol*, 2001; 19(2):364–7.
- Whitney CW, Brunetto VL, Zaino RJ, et al., Phase II study of medroxyprogesterone acetate plus tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study, *Gynecol Oncol*, 2004;92(1):4–9.
- Floricic JV, Brunetto VL, Hanjani P, et al., Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study, *Gynecol Oncol*, 2004;92(1):10–14.
- Pandya KJ, Yeap BY, Weiner LM, et al., Megestrol and tamoxifen in patients with advanced endometrial cancer: an Eastern Cooperative Oncology Group Study (E4882), *Am J Clin Oncol*, 2001;24(1):43–6.
- Covens A, Thomas G, Shaw P, et al., A phase II study of leuprolide in advanced/recurrent endometrial cancer, *Gynecol Oncol*, 1997;64(1):126–9.
- Lhomme C, Vennin P, Callet N, et al., A multicenter phase II study with triptorelin (sustained-release LHRH agonist) in advanced or recurrent endometrial carcinoma: a French anticancer federation study, *Gynecol Oncol*, 1999;75(2): 187–93.
- Asbury RF, Brunetto VL, Lee RB, et al., Goserelin acetate as treatment for recurrent endometrial carcinoma: a Gynecologic Oncology Group study, *Am J Clin Oncol*, 2002;25(6):557–60.
- Mackay H, Welch S, Tsao MS, Phase II Study of oral Ridaforolimus in patients with metastatic and/or locally advanced recurrent endometrial cancer: NCIC CTG IND 192, *J Clin Oncol*, 2011 (suppl; abstr 5013).
- Slomovitz B, et al., A phase 2 study of the oral mammalian target of rapamycin inhibitor, everolimus, in patients with recurrent endometrial carcinoma. *Cancer*, 2010. 116(23):5415-9.