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Phase II study of oral ridaforolimus in women with recurrent or metastatic endometrial cancer☆,☆☆

Daliah Tsoref [a], Stephen Welch [b], Susie Lau [c], James Biagi [d], Katia Tonkin [e], Lee Ann Martin [f], Susan Ellard [g], Prafull Ghatage [h], Laurie Elit [i], Helen J. Mackay [a], Ghassan Allo [a], Ming-Sound Tsao [a], Suzanne Kamel-Reid [a], Elizabeth A. Eisenhauer [j], Amit M. Oza [a,*]

[a] Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto ON Canada
[b] London Regional Cancer Program, London ON Canada
[c] McGill University, Dept. Oncology, Montréal, QC, Canada
[d] Cancer Centre of Southeastern Ontario, Kingston, ON, Canada
[e] Cross Cancer Institute, Edmonton, AB, Canada
[f] BCCA, Fraser Valley Cancer Centre, Surrey, BC, Canada
[g] BCCA, Cancer Centre for the Southern Interior, Kelowna, BC, Canada
[h] Tom Baker Cancer Centre, Calgary, AB, Canada
[i] Juravinski Cancer Centre at Hamilton Health Sciences, Hamilton, ON, Canada
[j] NCIC Clinical Trials Group, Queen's University, Kingston, ON, Canada

HIGHLIGHTS

- Ridaforolimus is a reasonably tolerated oral mTOR inhibitor with encouraging clinical benefit response in endometrial cancer.
- Durable disease stabilization constitutes a significant proportion of responses observed.
- Factors predictive of response are still to be elucidated.

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ABSTRACT

Objective. The phosphatidylinositol-3 kinase/serine–threonine kinase PI3K/AKT pathway is postulated to be central to cancer cell development. Activation of this pathway is believed to promote angiogenesis, protein translation and cell cycle progression. A large percentage of endometrial carcinomas have demonstrated mutations within this regulation pathway which result in constitutional activation. The downstream effector protein mammalian target of rapamycin (mTOR) acts as a critical checkpoint in cancer cell cycling and is a logical target for drug development. The efficacy and tolerability of the oral mTOR inhibitor ridaforolimus were evaluated in this study.

Methods. This phase II study evaluated the single agent tolerability and activity of oral ridaforolimus administered at a dose of 40 mg for 5 consecutive days followed by a 2 day break, in women with recurrent or metastatic endometrial carcinoma who had received no chemotherapy in the metastatic setting.

Results. 31 of 34 patients were evaluable. Three partial responses (8.8%) were observed with response duration ranging between 7.9 and 26.5 months. An additional 18 patients showed disease stabilization (52.9%) for a median duration of 6.6 months. Response rates were not affected by previous chemotherapy exposure. No correlation was found between response and mutation status.

Conclusion. Oral ridaforolimus was reasonably tolerated and demonstrated modest activity in women with recurrent or metastatic endometrial cancers. Potential synergy between mTOR inhibition, angiogenesis and hormonal pathways warrants ongoing evaluation.

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* Corresponding author at: Princess Margaret Hospital, University Health Network, Bras Family Drug Development Program, 610 University Avenue, Suite 5-700, Toronto, Ontario M5G 2M9, Canada. Fax: +1 416 946 4467.
E-mail address: amit.oza@uhn.ca (A.M. Oza).

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Introduction

Endometrial cancer remains the most common gynecologic malignancy in the developed world with over 40,000 new cases annually [1]. Standard treatment options in the recurrent setting are limited and consist of chemotherapy and hormonal therapies. Hormonal therapy options include progestins, selective estrogen modulators and aromatase inhibitors. Responses are unpredictable, modest and short lived producing average progression free survival (PFS) of 4 months and overall survival rates (OS) of 10 months [2]. Chemotherapy response rates range between 20 and 40% for initial monotherapy, increasing with the use of doublet regimens [3,4]. Upon treatment failure, second-line chemotherapy options are challenging and of limited efficacy [5] and additional treatments are urgently needed. The identification of effective targeted agents would be of huge significance for this population.

An important central pathway in molecular regulation of cancer cells is the phosphatidylinositol-3 kinase/serine–threonine kinase (PI3K/AKT) pathway, which upon dysregulation promotes tumorigenesis [6]. Components of this pathway have been shown to be constitutively activated or mutated in a high percentage of endometrial cancers, particularly those referred to as type I/endometrioid tumors [7]. Activation mutations in the oncogenes PI3K and AKT have been reported [8,9] as have a loss of function mutations in the tumor suppressor gene encoding phosphatase and tensin homology (PTEN) [10]. The effector protein mammalian target of rapamycin (mTOR) ultimately acts as a critical checkpoint in the progression of cells from the G1 to the S-phase.

As a downstream effector protein within the PI3K/AKT pathway, mTOR is a logical target for the development of agents capable of inhibiting the protein thereby arresting cell cycling. Rapamycin and its derivatives inhibit the function of mTOR with tumor growth arrest dramatically observed in a large range of tumors in the preclinical experimental setting [11]. This includes endometrial cancer cell lines where rapamycin has demonstrated a growth inhibitory effect [12] and mTOR inhibition has resulted in reduced development and progression of hyperplastic lesions [13].

The scientific rationale described above has spurred the development of multiple mTOR inhibitors or rapalogs over recent years. To date, six single agent phase II trials evaluating rapalogs in recurrent endometrial cancer have been published [14]. This group of drugs has consistently demonstrated single agent anti-tumor activity in women with recurrent endometrial cancer with a generally predictable and acceptable toxicity profile. While objective response rates to mTOR inhibition are low (0–25%), clinical benefit secondary to prolonged disease stabilization is significant.

Hormonal exposure is known to be significant in the development of endometrial cancer and drugs manipulating hormonal growth stimulation have long been in use in endometrial cancer patients. Preclinical data suggesting that mTOR inhibition reverses hormonal resistance has led to increased interest in clinical trials combining rapalogs and hormonal therapies. Encouraging potential for this strategy was noted by Slomovitz et al. when a clinical benefit response of 42% was observed for letrozole and everolimus in combination [15].

Ridaforolimus (deforolimus; AP23573; MK8669) is an analog of sirolimus and a small molecule inhibitor of mTOR. It is postulated that it exerts its inhibitory effects via interaction with the hydrophobic surface of FKBP in the context of the FKBP-ridaforolimus-mTOR ternary complex resulting in high-affinity inhibitory binding. Encouraging preclinical data has led to the clinical development of ridaforolimus and evaluation of its efficacy in a wide range of malignancies. Previous studies have demonstrated encouraging single agent activity in women with recurrent/metastatic disease with intravenous ridaforolimus [16].

This trial (NCIC Clinical Trials Group [NCIC CTG] IND 192) assessed the activity of oral ridaforolimus in women with recurrent or metastatic endometrial cancer. Correlative studies were incorporated into the study design in an attempt to identify predictive biomarkers of activity.

Patients and methods

This was a nonrandomized, open-label, multicenter, single arm, phase II study investigating the efficacy of ridaforolimus in patients with locally advanced, recurrent and/or metastatic carcinoma of the endometrium conducted by the NCIC CTG. Trial procedure and protocol were in accordance with Good Clinical Practice guidelines and gained full research ethics board approval at each of the participating institutions. All patients provided written informed consent prior to enrolment on study.

Eligibility

Women with pathologically confirmed recurrent or metastatic endometrial cancer, with ECOG performance status 0–2 and evidence of radiologically measurable disease were eligible to participate in the trial. Availability of archival primary tumor tissue was mandatory. Patients were permitted to have received prior hormonal therapy as part of either adjuvant therapy or for the treatment of metastatic disease. Prior chemotherapy however, was only permitted if administered in an adjuvant setting. No previous exposure to mTOR inhibitors was allowed.

Study design and treatment plan

Patients self-administered ridaforolimus continuously at a dose of 40 mg daily for 5 consecutive days followed by a two day break. One cycle was defined as 28 days and cycle length was not altered for missed doses with instructions regarding toxicity related dose-adjustments clearly defined. Treatment was continued until disease progression, inter-current toxicities, unacceptable adverse events, patient withdrawal of consent or inability to continue treatment.

Management of toxicity

Temporary dose reductions were recommended for grade 2 or 3 toxicities with dose escalation upon resolution of toxicity to a severity of grade 1 or less. The length of time until resolution of toxicity as well as the number of episodes of experienced toxicity was incorporated into an algorithm determining whether permanent dose reductions were implemented. Three levels of dose reduction were permitted of 30 mg, 20 mg and 10 mg respectively, prior to ultimate discontinuation of drug. Evidence of grade 3 or 4 interstitial pneumonitis warranted drug discontinuation whereas in instances of grade 2 pneumonitis drug was withheld with the potential for repeat administration at a level one dose reduction (30 mg) if toxicity resolved to grade 1 or less severity within a 4 week period.

On-study evaluation

Chest X-ray and computed tomography were performed at baseline and after every two cycles at 8 weeks or at any time there was clinical suspicion of progressive disease (PD). Tumor response was evaluated by using Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) criteria [17]. All radiologic responses were reviewed by independent radiologists, and only those responses confirmed by radiology review were included in the final analysis of results. Hematology and biochemistry were evaluated on days 1 and 15 of each cycle and patient review including evaluation of adverse events occurred on day 1 of each cycle. Grading of toxicities was in accordance with the National Cancer institute Common Terminology Criteria for Adverse Events, Version 3.0.

All patients were reviewed 4 weeks after the completion of therapy. Additional follow-up was not required for patients who discontinued treatment as a result of progressive disease other than for the documentation of ongoing toxicities. Follow-up continued once every 3 months until relapse, progression of disease or death.