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A phase II evaluation of selumetinib (AZD6244, ARRY-142886), a selective MEK-1/2 inhibitor in the treatment of recurrent or persistent endometrial cancer: An NRG Oncology/Gynecologic Oncology Group study

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Abstract

Background—Activation of the mitogen activated protein kinase pathway plays a pivotal role in cell proliferation and is frequently activated in endometrial cancer. We sought to evaluate the

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CONFLICTS OF INTEREST

All other co-authors have no conflicts of interest to declare.

This trial was registered at clinicaltrials.gov (NCT01011933)

efficacy/safety of selumetinib, a selective MEK-1/2 inhibitor in women with recurrent endometrial cancer.

Methods—This was a phase II, single-arm, open-label study evaluating response and 6-month event-free survival (EFS) as primary endpoints. Eligible patients had measurable disease, 1–2 prior cytotoxic regimens, and performance status 0–2. Selumetinib 75 mg PO BID was administered daily until progression or intolerance. One cycle was 28 days.

Results—Fifty-four patients were enrolled; 2 were excluded due to improper pre-study treatment (1) and never treated (1), leaving 52 evaluable for efficacy/safety. Median age was 62; histology included endometrioid (58%), serous (17%) and mixed (23%). Seventeen patients (33%) had 2 prior cytotoxic regimens. The median number of cycles administered was 2 (1–34). Three (6%) patients had objective response (1 CR, 2 PR); 13 had SD as best response. The proportion of patients with 6-month EFS was 12%. Median EFS, progression-free and overall survival was 2.1, 2.3, and 8.5 months, respectively. Drug-attributed grade 3/4 adverse events were observed (5%) were fatigue (15%), anemia (10%), pain (10%), extremity edema (8%), and dyspnea (6%). There was 1 grade 4 infection (renal), 1 grade 4 anemia, and 1 death due to hemorrhage (rectum).

Conclusions—Selumetinib was tolerable in this population but did not meet pre-trial specifications for clinical efficacy.

Keywords

Selumetinib; endometrial cancer; MEK inhibitor; toxicity; Phase II trial

INTRODUCTION

Uterine epithelial adenocarcinoma is the most common of all uterine malignancies and is the most common gynecologic malignancy in the United States [1]. Most cases are early stage at presentation where long-term survival is common. However, approximately 25% of early stage and more than 50% of advanced stage cancers will recur. Outside of local disease failures, limited options are available for the majority of patients with distant disease.

MEK is a critical kinase in the mitogen-activated protein (MAP) kinase signal transduction pathway for many growth factor receptors that provide growth signals to cancer cells, including epidermal growth factor (EGF) receptor, insulin-like growth factor (IGF)-1 receptor and platelet-derived growth factor (PDGF) receptor. Cell signaling through growth factor receptors and protein kinases plays an essential role in cell survival, proliferation, and differentiation. One of the most important and best understood MAP kinase pathways involved in normal and uncontrolled cell growth is the RAS/RAF kinase pathway. Active guanosine triphosphate (GTP)-bound RAS triggers the phosphorylation and activation of RAF kinase. RAF then phosphorylates MEK1 and MEK2 on 2 serine residues [2]. Activated MEK then phosphorylates its only known substrates, the MAP kinases, ERK1 and 2. pERK dimerizes and translocates to the nucleus where it is involved in several important cellular functions, including, but not limited to, nuclear transport, DNA repair, nucleosome assembly and translocation, and mRNA processing and translation [2,3].

Selumetinib is a potent, selective, orally-available, and non-ATP competitive small molecule inhibitor of the mitogen-activated protein (MAP) kinase, MEK-1/2 [4]. Pre-clinically and clinically, selumetinib has demonstrated good oral bioavailability, safety and efficacy and it being studied in a number of solid tumors including, low grade serous ovarian cancer where the pathway is known to be active.. A Phase II study of low-grade serous ovarian cancer patients reported objective responses in 16% in a tumor associated with limited response to chemotherapy, radiation or hormones [5]. Alterations in, and activation of MAPK signaling, have also been reported in epithelial endometrial cancers. For instance, activating mutations in IGF1-r/FGFR2 occur in 16–20% of cases, Ras (20%) and downstream phosphorylation of ERK is present in 60–70% of cases [6]. Given these findings, we sought to test the hypothesis that selumetinib monotherapy would have clinical activity in epithelial endometrial cancer. To our knowledge, this is the first report of selumetinib in endometrial cancer patients.

METHODS

Patients

All enrolled patients signed an approved informed consent in accordance with federal, state, and local requirements and authorization permitting release of personal health information. Eligible patients met the following criteria: histologic confirmation of primary endometrial cancer by central pathology review (executed by the GOG Pathology Committee); 1 or 2 prior cytotoxic regimens; GOG performance status of 0 to 2 (patients with 2 prior chemotherapy regimens were required to be performance status of 0 or 1); measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST v1.0) [7]; tumors within a previously irradiated field were designated as “non-target” unless progression was documented or biopsy confirmed as persistent disease; discontinuation of prior chemotherapy at least 3 weeks before registration and hormonal therapy at least 1 week before registration; recovery of the effects of recent surgery, radiotherapy, or chemotherapy; freedom from active infection requiring antibiotics; adequate hematologic (absolute neutrophil count 1,500/mcl and platelets 100,000/mcl), renal (serum creatinine 1.5 times the institutional upper limit of normal [ULN] and urine protein-to-creatinine ratio <1), hepatic (serum bilirubin 1.5 times ULN and AST and alkaline phosphatase 2.5 times ULN), and coagulation (prothrombin time such that international normalized ratio 1.5 or between 2 and 3 for patients receiving stable doses of therapeutic warfarin, and partial thromboplastin time 1.5 times ULN) laboratory values; left ventricular ejection fraction within institutional normal limits; negative serum pregnancy test before study entry.

Patients were ineligible if they met any of the following criteria: prior treatment with selumetinib or other MAPK pathway–targeted therapy; prior treatment with any non-cytotoxic therapy (other than hormonal therapy); other malignancies (except non-melanomatous skin cancer) evident within 5 years or prior cancer treatment that contradicts eligibility; non-healing wound, ulcer, or bone fracture; abdominal fistula, GI perforation, or intra-abdominal abscess within 28 days; active bleeding or pathologic condition that carries high risk of bleeding; known metastatic CNS disease; clinically significant cardiovascular disease; and major surgical procedure within 28 days of anticipated study treatment.

Treatment

Enrolled patients were to receive selumetinib 75 mg orally twice daily until disease progression or adverse events prohibited further therapy. One cycle equaled 28 days. Two dose reductions were allowed (50 mg BID and 50 mg daily) for severe adverse events. Patients were instructed to take selumetinib as close to 12 hours apart as possible. Dosing delays of 4 or more hours were to be skipped. Selumetinib was to be taken on an empty stomach with no food or drink other than water 1 hour before and 2 hours after dosing. Patients were cautioned to avoid food and medicine that interfere with CYP1A2 or CYP3A4 activity. A pill calendar was kept by the patient and was reviewed at each visit, as were concomitant medications. Potential drug-specific adverse effects such as pulmonary or lower extremity edema, visual disturbances and rash were to undergo specific investigation and, if available, prophylaxis for subsequent cycles.

Safety was monitored with history, physical examination, and laboratory assessment before each treatment cycle, with adverse events defined and graded according to Common Terminology Criteria for Adverse Events (version 3). Selumetinib was held for grade 3 or 4 hematological toxicity until recovery to grade 2 or less. If appropriate, treatment was resumed at a 1 dose level reduction. Similarly, grade 3 or 4 non-hematologic toxicity required dose interruption until recovery to grade 2 or lower, unless it was a toxicity of special interest (hypertension, cardiac, pulmonary, stomatitis, ocular). In this circumstance, dosing was held until recovery to grade 1 or less, and then restarted following a 1 level dose reduction. No dose re-escalations were permitted.

Evaluation Criteria

Activity of selumetinib was assessed according to RECIST (version 1.0) either by palpation before each cycle or by computed tomography or magnetic resonance imaging at baseline, every other cycle for the first 6 months, and every 3 months thereafter or as indicated clinically.

Statistical Methods

The primary objective of this study was to assess the efficacy and safety of selumetinib in patients with recurrent or persistent endometrial cancer. The primary measure of efficacy was an assessment of objective tumor responses and the proportion of women who were event-free for at least 6 months (EFS at 6 months; endpoints are progression, death, or beginning a subsequent therapy). The null hypothesis relating to uninteresting levels of activity was determined from an analysis of a historical data set based on a similar population of patients where the levels of activity were believed to be inactive to modestly active (see Table 1 of Aghajanian et al) [8]. The null hypothesis jointly specified the probability of a patient experiencing a tumor response to be 10% or less and the probability of a patient being EFS at 6 months to be 15% or less. Clinically significant differences were 15% or 20% increases in the probability of response and 6-month EFS, respectively (i.e., probabilities of 25% or 35%, respectively). Using a method by Sill et al. [9], a two-stage design was used with a goal of limiting patient exposure to inactive agents while restricting the probabilities of type I and type II errors to approximately 10%. The targeted accrual for the first stage was 26 patients but the number was allowed to deviate for administrative

purposes. If 26 patients were accrued, the maximum number of patients with responses was 2, and the maximum number with EFS at 6 months to reject the regimen was 5. If either endpoint exceeded its threshold, the study would open to stage 2. The cumulative targeted accrual for the second stage was 51 but was allowed to deviate. If 52 patients were accrued, the maximum number of patients with responses and EFS at 6 months to reject the regimen was 8 and 12, respectively. If either endpoint exceeded their respective critical value, the regimen was deemed interesting.

The realized sample sizes limited the probabilities of type I and II errors to no more than 10% under the null hypothesis. The probability of early termination was between 42% and 49%, depending on the likely range of association between the two variables.

Characteristics of interest included age, performance status, prior treatment, grade, response, progression-free survival (PFS), EFS, and the hazards of progression, death, or treatment failure and the hazard of death. Survival curves were generated by the method of Kaplan-Meier [10]. Some characteristics were examined as ordinal categorical variables (e.g., response with progressive disease < stable disease < response). Associations were examined with correlations (e.g. Spearman rank correlation coefficient), exact Chi-square tests, the Jonckheere-Terpstra test, and the Cox proportional hazards model [11–14]. Secondary objectives assessed in this study were to provide estimates of median duration of PFS, EFS, and overall survival (OS). If a p-value was less than or equal to 5%, an association was designated as suggestive. Given the small sample sizes, a lack of a suggestive association should not be interpreted as definitive.

RESULTS

Patient's characteristics

Fifty-four patients were enrolled from September 2009 through October of 2011; 2 were excluded, one for improper pre-study treatment and one never treated after enrollment. This left 52 evaluable patients for toxicity and response. Table 1 presents patient characteristics. Consistent with other trials conducted in this setting, the majority of the patients were over age 60, Caucasian, of good performance status and had high-grade endometrioid tumors. Of note, 42% were high-risk subtypes, such as, serous, clear cell and mixed epithelial histology, and over half had undergone radiotherapy, predominately to the pelvis and/or para-aortic nodal regions.

Adverse Events

Table 2 lists hematological and non-hematological toxicities. Overall, selumetinib was well tolerated with few hematological toxicities; one grade 4 anemia was recorded. The most common significant or grade 3 non-hematological toxicities were constitutional (fatigue/asthenia), rash, gastrointestinal (nausea/vomiting) and peripheral edema. Three events of dyspnea were attributed to selumetinib without further characterization. Laboratory abnormalities observed were transient rises in liver function tests, seen predominately in the first 2 cycles, which resolved expectantly. There were two fatalities on study. One patient presented with massive metastatic disease in the liver and experienced hepatic failure upon

disease progression. The event was attributed as “definitely” due to disease but “possibly” linked to selumetinib. Review of this case did not prompt or require alteration to the informed consent document. The other fatality occurred in a patient who had previously received pelvic radiation and died of a rectal hemorrhage. The cause of death was listed as “disease” but contribution of selumetinib could not be excluded.

Clinical Activity

Table 3 details further clinical efficacy parameters. Over 190 monthly cycles of selumetinib were administered to this cohort with the median number of cycles being 2 (InterQuartile Range (IQR): 2–4 cycles). There were 1 complete and 2 partial responses producing an overall response rate of 6% (90% Confidence Interval (CI): 2%–14%). Stable disease was observed in 13 other patients (25%), and includes 8 patients on study treatment for more than 5 cycles. The most common reason for treatment discontinuation was disease progression, occurring in 34 (65%) of participants. Eleven patients were progression-free at six months (PFS: 21%; 90% CI: 12%–33%), however, EFS was 12% (90% CI: 5%–22%) [6]. Figure 1 presents the Kaplan-Meier survival curves for PFS, EFS and overall survival (OS) for evaluable patients; median PFS is 2.3 months, EFS 2.1 months and median OS is 8.5 months.

DISCUSSION

In this multicenter, open label phase II clinical trial, we demonstrate that selumetinib at this dose and schedule is well tolerated in patients with recurrent or persistent measurable epithelial endometrial cancer, but has limited single-agent activity and did not meet our pre-specified efficacy parameters for objective response and proportion of patients without treatment progression at 6 months. Despite these findings, there is intense interest to evaluate the MAPK pathway due to its roles in proliferation, metastasis and tumor cell survival.

Recently, The Cancer Genome Atlas (TCGA) performed an integrated genomic, transcriptomic and proteomic characterization of tumor and germline DNA from 373 predominately endometrioid adenocarcinomas [6]. Frequent alternations in MAPK, PI3K and beta-catenin pathways were reported and analysis of the mutation spectra demonstrated frequent KRAS mutation in the POLE (ultramutated) and MSI high (hypermutated) cohorts. In addition, KRAS was amplified in 20% of the copy-number low cohort. However, in these cohorts, several alternative driving pathways coexist and downstream activation can occur even in the absence of KRAS mutation. Indeed, WNT signaling can occur via KRAS, SOX17 or CTNNB1 mutations, which appear to be mutually exclusive in the copy-number low group. The objective responses (1 CR and 2 PRs in this trial), while low and not unexpected given the multiple activating pathways in endometrial cancer, do suggest a potential identifiable cohort in whom targeting might be of value [15–19]. Unfortunately, at this time it is not clear that identifiable MAPK alterations (e.g. Ras/Raf mutation) are sufficient or necessary for clinical response with MEK inhibitors in endometrial cancer. An ongoing randomized trial of MEK versus MEK/Akt inhibition is stratifying by Kras mutation status. (NCT01935973)

Nevertheless, pathway activation analysis suggest that single agent targeted approaches are unlikely to realize the full potential of therapy. Prior experience with single agent PI3K/Akt/mTOR targeting has also met disappointing results in endometrial cancer patients. (reviewed in Reference [20]) The most widely studied, TORC1 inhibitors, have demonstrated response rates from 0–22% in previously treated endometrial cancer patients; some trials have demonstrated higher response rates among chemo-naïve patients including a randomized phase II (ridaforolimus) compared to chemotherapy or endocrine therapy [21]. An exception to this observation was observed in a randomized clinical trial of temsirolimus vs temsirolimus plus megestrol acetate in patients with recurrent endometrial cancer. The combination arm was terminated due to unacceptable rates of venous thromboembolism. However, response rates to temsirolimus were 24% and 19% among untreated and previous chemotherapy exposures [22]. Similarly, PI3K and Akt inhibitors have demonstrated limited objective response as single agents, including a recently reported trial of MK-2206 (an allosteric Akt inhibitor) in uterine cancer [23].

Based on emerging genomic characterization of these tumors a more strategic investigative approach is being devised and conducted. Since PI3K pathway alterations commonly co-exist with MAPK activation, dual targeted approaches are now underway, particularly with MEK and Akt or PI3K/mTOR inhibitors. One study, GOG-2290 is randomizing patients (with similar eligibility to the current trial) to trametinib (a MEKi) versus trametinib plus an Akt inhibitor (GSK2141795) (NCT01935973). The cohorts are stratified by KRAS mutation status and crossover from trametinib to the combination is allowed upon progression. Another trial is enrolling only patients with a PIK3CA or Akt mutation onto a single-agent Akt inhibitor (NCT01226316). Similarly, preclinical data have demonstrated that synthetic lethality may be induced by use of a PARP inhibitor in combination with PI3K pathway alteration, particularly with PTEN loss [24–25]. This has prompted a multi- arm phase I trial of olaparib in combination with an Akt or PI3K/mTOR inhibitor (NCT02208375). Further development strategies may also incorporate other modalities, such as chemotherapy and radiation as are being investigated in other tumor sites (NCT02041481, NCT01828034, NCT01146756).

While there is excitement in developing rational targeting strategies in this disease, a major limitation is toxicity. Indeed, heretofore MEK/Akt combination trials have been difficult to administer due to overlapping toxicities (such as rash, transaminitis, pneumonitis, gastrointestinal intolerance) [26]. In addition, patients with endometrial cancer are typically older, have frequent and more chronic comorbidities, and are often of poorer performance status, which add to the observance of drug-related and unrelated toxicities. Indeed, in the current study, 7 (13%) patients voluntarily discontinued treatment prior to progression. In addition, prior exposure to pelvic and/or para-aortic radiation can limit marrow tolerance and increase gastrointestinal toxicity, a frequent adverse event of MAPK and PI3K pathway targeting. Close observation, prophylactic and early treatment of adverse events, as well as, careful dose modification will be necessary mitigating strategies.

In light of the frequent and prolific genomic alterations observed in endometrial cancer, pathway targeting represents an exciting and promising new direction of therapy. As observed in the current trial, single agent therapy, without a validated biomarker

demonstrating target addiction, is unlikely to make a measurable difference in outcome. Indeed, nearly all trials performed in an unselected population of endometrial cancer patients where biomarkers have been evaluated retrospectively, have failed to correlate with observed response. However, integrated and integral biomarker based trials represent the most likely strategy to fully realize the potential therapeutic efficacy of targeted therapy.

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RESEARCH HIGHLIGHTS

- Selumetinib, a MEK inhibitor was tolerable in recurrent endometrial cancer patients
- Objective responses were observed in 6% of patients
- The most significant drug-related severe adverse events were fatigue, anemia and pain.

—	PFS	52	23	15	9	6	4	3	1
- - -	EFS	52	21	11	4	3	2	1	1
.....	OS	52	15	37	19	3	12	5	2

Figure 1. A comparison of the Kaplan-Meier (KM) estimates of the survival function for event-free survival (EFS), progression-free survival (PFS) and overall survival (OS) for patients on this study (N=52). Median PFS is 2.3 months (interquartile range: 1.7 to 5.6 months); EFS is 2.1 months (interquartile range: 1.7 to 3.9 months); and Median OS is 8.5 months (interquartile range 3.5 to 15.5 months). Almost twice as many patients were progression-free at 6 months (21.2%) as were event-free at 6 months (11.5%). Five of the eleven patients who experienced progression more than 6 months after starting study treatment began another therapy within 6 months of study entry and were censored for the KM estimates. Most of these therapies involved a taxane and/or carboplatin. The reasons for discontinuing the study therapy were toxicities (3 with rash, itching, fatigue, SOB, and abdominal pain), patient refusal (1), and interactions with other drugs (1).

Figure 2.

Efficacy assessment in the Gynecologic Oncology Group's 229 queue. The shaded region in the lower left corner represents uninteresting effectiveness by response and EFS at 6 months. The white area encompasses a region of uncertain effectiveness between the null and alternative hypothesis. The shaded areas in the upper and right regions of the plot contain proportions of response and EFS at 6 months that are clearly interesting.

Selumetinib at this dose and schedule was associated with a rate of non-progression in line with target parameters, but with limited objective response. Other agents evaluated in this queue are provided for reference as they were assessed under the same eligibility criteria and similar statistical plans.

Gefitinib, lapatinib, and thalidomide had EFS at 6 months estimated with PFS at 6 months.

Abbreviations: PFS: progression-free survival; RR: response rate; bev/tem: bevacizumab and temsirolimus combination

Table 1

Patient Demographics (N=52)

Characteristics	Category	n	%	Total
Age group	40–49	4	7.7	4
	50–59	16	30.8	16
	60–69	19	36.5	19
	70–79	11	21.2	11
	>=80	2	3.8	2
Ethnicity	Hispanic	1	1.9	1
	Non-Hispanic	49	94.2	49
	Unknown/Unsp.	2	3.8	2
Race	White	42	80.8	42
	Black/African-American	6	11.5	6
	Asian	2	3.8	2
	American Indian/Alaskan	2	3.8	2
Performance Status	0	29	55.8	29
	1	22	42.3	22
	2	1	1.9	1
Cell Type	Clear Cell Carcinoma	1	1.9	1
	Endometrioid	30	57.7	30
	Mixed Epithelial Carcinoma	12	23.1	12
	Serous Adenocarcinoma	9	17.3	9
Histologic Grade	1	7	13.5	7
	2	13	25.0	13
	3	23	44.2	23
	Not Graded	9	17.3	9
Histology/Grade	Endometrioid, grade 1	5	9.6	5
	Endometrioid, grade 2	13	25.0	13
	Endometrioid, grade 3	11	21.2	11
	Endometrioid, not	1	1.9	1
	Serous	9	17.3	9
	Clear Cell	1	1.9	1
	Mixed Epithelial	12	23.1	12
Prior	1 Prior Regimen	35	67.3	35
	2 Prior Regimens	17	32.7	17
Prior Radiation	No	24	46.2	24
	Yes	28	53.8	28

Table 2

Maximum Grade Adverse Events Attributed to Selumetinib (N=50)

AE Category	0	1	2	3	4	5	Total
Leukopenia	39	11	2	0	0	0	52
Thrombocytopenia	48	4	0	0	0	0	52
Neutropenia	45	3	2	2	0	0	52
Anemia	21	10	16	4	1	0	52
Auditory/Ear	51	0	1	0	0	0	52
Cardiac	45	2	2	3	0	0	52
Coagulation	51	0	0	1	0	0	52
Constitutional	16	18	10	8	0	0	52
Dermatologic	16	13	18	5	0	0	52
Gastrointestinal	9	18	19	6	0	0	52
Genitourinary/Renal	50	0	1	1	0	0	52
Hemorrhage	47	4	0	0	0	1	52
Hepatobiliary	51	0	0	0	0	1	52
Infection	51	0	0	0	1	0	52
Lymphatics	31	10	7	4	0	0	52
Metabolic	34	9	3	6	0	0	52
Neuropathy	49	2	0	1	0	0	52
Other Neurological	44	5	0	3	0	0	52
Ocular/Visual	48	1	2	1	0	0	52
Pain	33	8	6	5	0	0	52
Pulmonary	40	6	3	3	0	0	52
Sexual/Reproductive	51	0	1	0	0	0	52
Vascular	51	0	1	0	0	0	52

Table 3

Treatment Outcome Parameters (N=50)

Characteristic	Category	n	%	Total
Off Study Therapy	Yes	52	100.0	52
Cycles of Treatment	1	12	23.1	12
	2	22	42.3	22
	3	4	7.7	4
	4	5	9.6	5
	5	1	1.9	1
	6	3	5.8	3
	9+	5	9.6	5
Reason Off Therapy	Disease Progression	34	65.4	34
	Refusal	4	7.7	4
	Adverse Events	9	17.3	9
	Death	2	3.8	2
	Other Reason	3	5.8	3
RECIST Response	Complete response	1	1.9	1
	Partial response	2	3.8	2
	Stable disease	13	25.0	13
	Increasing disease	24	46.2	24
	Indeterminate	12	23.1	12
PFS > 6 Months	No	41	78.8	41
	Yes	11	21.2	11
EFS > 6 Months	No	46	88.5	46
	Yes	6	11.5	6
Survival Status	Alive	4	7.7	4
	Dead - Disease-related	42	80.8	42
	Dead - Rx & Disease	2	3.8	2
	Dead - Neither Rx/Dis	1	1.9	1
	Dead - Undetermined	2	3.8	2
	Dead - Reason Pending	1	1.9	1