Gynecologic Oncology 144 (2017) 96–100

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

A phase 2 study of alisertib (MLN8237) in recurrent or persistent uterine leiomyosarcoma: An NRG Oncology/Gynecologic Oncology Group study 0231D☆

David M Hyman, MD [a,*], Michael W Sill, PhD [b], Heather A Lankes, PhD [b], Richard Piekarz, MD, PhD [c], Mark S Shahin, MD [d], Mildred R Ridgway, MD [e], Floor Backes, MD [f], Meaghen E Tenney, MD [g], Cara A. Mathews, MD [h], James S Hoffman, MD [i,1], Carol Aghajanian, MD, PhD [a,j], Martee L Hensley, MD [a,j]

[a] Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
[b] NRG Oncology Statistics and Data Management Center, Buffalo, NY 14263, USA
[c] Cancer Therapy Evaluation Program, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA
[d] Abington Hospital, Jefferson Health, Abington, PA 19001, USA
[e] University of Mississippi Medical Center, Jackson, MS 39216, USA
[f] Ohio State University, Wexner Medical Center, Hilliard, OH 43026, USA
[g] Gynecologic Oncology, The University of Chicago Medicine & Biological Sciences, Chicago, IL 60637, USA
[h] Women & Infants Hospital, Providence, RI 02905, USA
[i] Hospital of Central Connecticut, New Britain, CT 06050, USA
[j] Weill Cornell Medical College, New York, NY 10065, USA

HIGHLIGHTS

- Uterine leiomyosarcomas are poor prognosis tumors with few effective treatments.
- Aurora-A kinase deregulations are common in uterine leiomyosarcoma.
- Alisertib monotherapy was not active in advanced/recurrent uterine leiomyosarcoma.

ARTICLE INFO

Article history:
Received 17 August 2016
Received in revised form 13 October 2016
Accepted 21 October 2016
Available online 27 October 2016

Keywords:
Alisertib
Aurora kinase
Uterine leiomyosarcoma

ABSTRACT

Objective. This two-stage Phase II study assessed the activity of single agent alisertib in patients with recurrent/persistent uterine leiomyosarcoma (uLMS).

Methods. Eligibility criteria included histologically-confirmed, recurrent or persistent uLMS, age ≥ 18, 1–2 prior cytotoxic regimens, and RECIST version 1.1 measurable disease. The primary objective of the study was to evaluate the efficacy of alisertib through the frequency of patients with objective tumor responses and the frequency who survived event-free for at least 6 months (EFS6). The endpoints for EFS were RECIST progression, death, or beginning a subsequent therapy. The null hypothesis jointly specified the probability of a patient experiencing a tumor response to less than or equal to 5% and the probability of a patient surviving event-free for at least 6 months to less than or equal to 20%. A two-stage design was used with a target accrual of 23 patients for stage 1 and 47 pts. cumulative for stage 2. Confidence intervals do not correct for multiplicity.

Results. Twenty-three patients were enrolled with two patients excluded on central histology review, yielding 21 eligible patients. Median age was 61 years. Prior treatment was either 1 cytotoxic regimen (71.4%) or 2 (28.6%). The most common treatment related AEs (grade 3 or worse) were anemia Hensley et al. (2008a) , leukopenia Hensley et al. (2008b) , neutropenia Maki et al. (2007) , thrombocytopenia Huang et al. (2012) , mucositis Hensley et al. (2008a) , diarrhea Huang et al. (2012) , and palmer-planter syndrome Zivanovic et al. (2012) . There were no objective responses (0%; 90% CI: 0–10.4%). Best response was stable disease (38.1%); 12 patients

☆ Parts of this study were presented in abstract form at the ASCO annual meeting held in Chicago, Illinois on 5/29 to 6/2/2015.

* Corresponding author at: Memorial Sloan Kettering Cancer Center, 300 East 60th Street, New York, NY 10065, USA.
E-mail addresses: hymand@mskcc.org (D.M. Hyman), msill@gogstats.org (M.W. Sill), hlankes@gogstats.org (H.A. Lankes), rpiekarz@nih.gov (R. Piekarz), mshahin@abingtonhealth.org (M.S. Shahin), mridgway@umc.edu (M.R. Ridgway), Floor.Backes@osumc.edu (F. Backes), mtenney@bsd.uchicago.edu (M.E. Tenney), cmathews@wihri.org (C.A. Mathews), James.HoffmanMD@baystatehealth.org (J.S. Hoffman), aghajanc@mskcc.org (C. Aghajanian), hensleym@mskcc.org (M.L. Hensley).
[1] Dr. Hoffman's current affiliation is Baystate Medical, Springfield, MA.

http://dx.doi.org/10.1016/j.ygyno.2016.10.036

had progressive disease (57.1%). EFS6 was 0% (90% CI: 0–10.4%). Median PFS and OS were 1.7 (90% CI: 1.4–3.2) and 14.5 months (90% CI: 7.6 - NA), respectively.

Conclusion. Alisertib did not demonstrate clinically meaningful single agent activity in previously treated uLMS.

1. Introduction

Uterine leiomyosarcoma (uLMS) is a rare and highly aggressive malignancy that accounts for approximately 60% of all uterine sarcomas [1]. Although patients are often diagnosed with FIGO stage 1 (uterine confined) disease, recurrence rates are estimated to be between 50 and 70% [2,3]. To date, the mainstay of treatment for patients who develop unresectable metastatic disease is cytotoxic chemotherapy with response rates to first-line multidrug chemotherapy ranging from 27 to 53% [4–9]. The efficacy of second-line chemotherapy drops significantly with most regimens offering response rates of 10–15% [10–15]. As a result, the overall survival of metastatic uLMS remains poor.

Developing treatment for advanced uLMS has been hampered by a limited understanding of the genomic and epigenetic mechanisms underlying the aggressive clinical phenotype of uLMS. Characterization of benign uterine leiomyomas by whole-genome sequencing has revealed that even these benign precursor lesions demonstrate remarkable genomic complexity consistent with chromosome shattering and reassembly resembling chromothripsis [16]. These studies have also revealed frequent mutation of *MED12* in benign leiomyomas but much lower rates in uLMS suggesting that many of these tumors may arise *de novo* rather than transforming from leiomyomas [17–19]. To date there has been no large scale unbiased sequencing study reported in uLMS. As a result of the absence of clearly actionable genomic alterations in uLMS, the role of targeted therapy has remained limited. Pazopanib, a small molecule inhibitor of multiple tyrosine kinases including VEGF-1, -2, and -3, is currently the only approved targeted therapy for advanced soft tissue sarcoma (including LMS) although the overall degree of clinical benefit is modest and other VEGF targeted therapies have failed to demonstrate activity [20–23].

Previous genome-wide transcriptional profiling of uLMS compared to benign myometrium and leiomyoma found that the majority of the most overexpressed gene products involve genes that regulate mitotic centrosome and spindle functions [24]. Among the most highly overexpressed genes include Aurora A and B kinase. In aggregate, the aurora family of kinases play a central role in mitosis, specifically centrosome maturation and separation, bipolar spindle assembly, chromosome alignments, and cytokinesis [25]. Overexpression of Aurora A has been shown to induce transformation in certain cell lines by disrupting the G2 checkpoint [26]. Finally, aurora A kinase inhibition has demonstrated antiproliferative effects in multiple preclinical models of uLMS [27]. Alisertib is a highly potent, Aurora kinase A selective inhibitor [28]. Based on these data, as well as the ongoing and unmet need for effective therapies for this disease, a Phase II study of alisertib in advanced recurrent or persistent uLMS was undertaken. The primary objective was to evaluate the efficacy of the alisertib as defined by objective tumor responses and the frequency who survived event-free for at least 6 months.

2. Methods

2.1. Patient selection

Histologic confirmation of the original primary tumor by the GOG Pathology Committee central review process was required. To be eligible, patients had to be ≥18 years of age and have had incurable recurrent or persistent uLMS. Patients were required to have had at least one prior chemotherapeutic regimen for management of leiomyosarcoma and were allowed to receive, but not required to receive, one additional cytotoxic regimen for recurrent or persistent disease. Biologic, small molecule and hormonal therapies were not counted towards prior therapy. GOG performance status of 0 to 2 was required; and had to be 1 or less if patients had received two prior cytotoxic regimens. All patients were required to have measurable disease by Response Criteria in Solid Tumors (RECIST 1.1). Patients must have had adequate hematologic parameters (absolute neutrophil count ≥1500/mcl, leukocytes ≥3000/mcl, and platelets ≥100,000/mcl), renal function (serum creatinine ≤1.5 × the institutional upper limit of normal [ULN] OR creatinine clearance ≥60 ml/min/1.73m^2), and hepatic function (serum bilirubin ≤1.5 ULN, AST and ALT ≤3 × ULN, and alkaline phosphatase ≤2.5 × ULN). A signed approved informed consent in accordance with federal, state and local requirements and an authorization permitting release of personal health information were required for all patients. Participation in this trial required protocol approval by institutional review boards.

Patients were ineligible if they met any of the following criteria: prior therapy with an aurora kinase pathway inhibitor; prior malignancies (other than non-melanomatous skin cancer) evident within three years of prior cancer treatment; known CNS disease; clinically significant cardiovascular disease; history of hepatitis B, C or HIV; patients who were pregnant or nursing; patients unable to take oral medication and to maintain a fast for 2 h before and 1 h after alisertib administration; and patients unable to discontinue agents that effect gastric pH including proton pump inhibitors and histamine-2 antagonists.

2.2. Treatment

Enrolled patients received alisertib 50 mg twice daily by mouth on days 1–7 of each 21 day cycle. Treatment was continued until disease progression or adverse events prohibited further therapy. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Patients were required to have had an absolute neutrophil count ≥1000/mcl, platelets ≥100,000/mcl, AST and ALT ≤3 × ULN, and bilirubin ≤ ULN prior to initiating treatment on day 1 of each subsequent cycle. Dose reductions for neutropenia and thrombocytopenia occurring during a cycle were managed per protocol based on timing, depth and duration of the specific cytopenia. Unless otherwise specified, alisertib was held for grade 2 non-hematologic adverse events, resuming treatment at the same dose with resolution of toxicity to grade 1 or less, and held, then resumed with a one-level dose reduction for grade 3 non-hematologic adverse events after resolution of toxicity to grade 1 or less. A maximum of two dose reductions for management of adverse events were permitted. Treatment interruptions of up to 2 weeks are permitted for resolution of treatment-related toxicities. Failure of resolution of a treatment-related toxicity within 2 weeks required discontinuation of study treatment.

2.3. Evaluation criteria

Activity of alisertib was assessed according to the RECIST version 1.1 guidelines by computed tomography or magnetic resonance imaging at baseline, every two cycles (or equivalent time frame for patients off treatment prior to disease progression) for the first 6 months, and then every 3 months thereafter until disease progression was