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CLINICAL STUDY REPORT C14006 SYNOPSIS

Study Title: A Phase 2 Study of MLN8237, a Novel Aurora A Kinase Inhibitor, in the Treatment of Patients with Platinum-Refractory or Platinum-Resistant Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Carcinoma

Investigator(s): PPD

Study Center(s): 17 study centers in the United States, France, and Poland

Publication (reference): Matulonis U, Sharma S, Ghamande S, Gordon M, Del Prete S, Ray-Coquard I, et al. Single-agent activity and safety of the investigational Aurora A kinase inhibitor MLN8237 in patients with platinum-treated epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. In: European Society for Medical Oncology (ESMO); 2010 8-12 October; Milan, Italy.

Phase: 2

Initiation Date (first subject enrolled): 25 March 2009

Completion Date (last subject completed): 27 January 2011

Study Objectives: The primary objective was to estimate the objective antitumor response rate of alisertib (MLN8237) using the Response Evaluation Criteria in Solid Tumors (RECIST) or CA 125 criteria in patients with platinum-refractory or platinum resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma

The secondary objectives included the following:

- To estimate the progression-free survival (PFS), duration of response (DOR), time to disease progression (TTP), and clinical benefit (response and stable disease [SD]) associated with alisertib.
- To further characterize the adverse event (AE) profile associated with alisertib.

METHODS

Design: This was an open-label, multicenter, single-arm, phase 2 study of alisertib in the treatment of patients with platinum-refractory or platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinomas.

This study used a Simon optimal 2-stage design. In the first stage of the study, 21 response-evaluable patients were to be enrolled. If 3 or more patients experienced a response, then an additional 29 evaluable patients were to be enrolled. The hypothesis was that if 8 patients out of the total of 50 evaluable patients experienced a response, then alisertib would be considered to be of interest in the treatment of platinum-refractory or platinum resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. In the first stage of the study, up to 5 evaluable patients who were primary platinum refractory were allowed; in the second stage up to 7 evaluable patients who were primary platinum-refractory were allowed.

All patients were treated with alisertib 50 mg twice daily (BID) on Days 1 through 7 of each treatment cycle followed by a 14-day period with no treatment. Treatment cycles were repeated every 21 days. The dose of alisertib could be reduced for toxicities. Dose delays or toxicity requiring dose reduction below 30 mg BID resulted in removal from the trial. A patient who required a treatment delay of greater than 3 weeks past Day 1 of the next scheduled treatment cycle was removed from the study.

Patients continued to receive repeated cycles of alisertib treatment for a maximum of 12 months, or until there was evidence of disease progression or unacceptable treatment-related toxicity. Therapy was continued beyond 12 months if after discussion between the investigator and the sponsor it was determined that a patient would derive benefit from continued therapy. Patients whose disease had not progressed will be followed off treatment every 12 weeks for up to 12 months, until progressive disease (PD) was documented, or treatment with another anticancer therapy was started.

Number of Patients (planned and analyzed): Approximately 56 patients were planned for enrollment (to obtain 50 patients evaluable for response); however, the study was stopped after 31 patients were enrolled after results of the interim analysis failed to show the expected overall response rate in the first 21 evaluable patients.

Diagnosis and Main Criteria for Inclusion: Patients were 18 years of age or older, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and had a diagnosis of histologically or cytologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. Patients had platinum-refractory or platinum-resistant malignant disease and had measurable neoplastic disease according to the RECIST criteria, or a CA 125 level of > 40 units/mL AND clinical evidence of neoplastic disease.

Test Product, Dose and Mode of Administration, Batch Number: Alisertib powder-in-capsule (PIC) formulation was given by mouth (PO) in a dosage of 50 mg twice daily (BID) for 7 days (Days 1–7) of each 21 day treatment cycle. Lot numbers were: 18C029, 18C030, and 18C031.

Duration of Treatment: The maximum duration of therapy was 12 months, unless after discussion between the investigator and sponsor it was determined that a patient would derive benefit from continued therapy beyond 12 months.

Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable.

Efficacy Assessments: The primary endpoint was the combined objective response rate, defined as complete response plus partial response (CR + PR) by RECIST criteria or response by CA 125 criteria. The secondary endpoints included PFS, DOR, TTP, and the clinical benefit rate.

Safety Assessments: AEs, serious adverse events (SAEs), assessments of clinical laboratory values, and vital signs measurements.

Pharmacokinetic Assessments: Pharmacokinetic (PK) data to contribute to subsequent population PK analyses. Blood samples (3 mL) for the determination of plasma concentrations of alisertib were collected only during Cycles 1 and 2 of the study. Alisertib plasma concentration-time data were summarized descriptively using the PK evaluable population.

Pharmacogenetic Assessments: One peripheral blood sample was obtained prior to alisertib dosing for the purpose of genotyping each patient for polymorphisms in CCI [redacted] that could influence tumorigenesis.

Banked tumor tissue, if available, was collected and evaluated for Aurora A kinase protein expression and gene amplification and additional candidate biomarkers of response to MLN8237 and Aurora A pathway signaling.

Blood samples also were obtained at Cycle 1, Day 1 before the first dose of alisertib and at the scheduled visit at Cycle 1, Day 8 for assessment of full-length and caspase-cleaved fragments of CK18 as markers of tumor cell death in serum.

Statistical Methods: Summary tabulations were presented that display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent (of non-missing values) per category for categorical data.

The primary efficacy analysis was based on the response-evaluable population. The number and percentage of patients in each response category of the combined objective response rate (CR, PR, SD, and PD) was tabulated, and the estimate of the response rate (rate of the sum of CR, PR) was presented with 2-sided 95% exact binomial confidence intervals for platinum refractory patients, platinum resistant patients, and overall.

Separate by-patient listings of the response at each cycle by RECIST 1.1 criteria and CA 125 citeria were also presented.

Secondary efficacy analyses: PFS was analyzed based on the Safety Population and response-evaluable population respectively using the Kaplan-Meier method, for platinum refractory patients, platinum resistant patients, and overall. Results are summarized by 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CI), as well as the percentage of censored observations.

RESULTS

Demographic Results: A total of 31 patients (6 platinum-refractory and 25 platinum-resistant) were enrolled and received study drug.

Twenty-two (71%) patients experienced PD, and 2 (6%) patients experienced symptomatic deterioration. The other primary reasons for discontinuation from study treatment were: adverse event (3 [10%] patients, 1 [17%] platinum-refractory and 2 [8%] platinum-resistant); withdrawal by patient (3 [10%] patients, 1 [17%] platinum-refractory and 2 [8%] platinum-resistant); and other (investigator decision) for 1 (3%) patient (platinum-resistant). Four patients (2 [33%] platinum-refractory and 2 [8%] platinum-resistant) experienced TEAE(s) that led to treatment discontinuation; however, only 3 of the 4 patients had "adverse event" listed as the primary reason off treatment.

All patients were female, and 97% of patients were white. The mean age was 57.0 years (range 25-80 years); 21 (68%) patients were < 65 years of age. Mean weight was 67.63 kg (range 48-129 kg), and mean baseline body surface area (BSA) was 1.72 m^2 (range 1.4-2.4 m^2). Twenty-five (81%) patients had a primary diagnosis of epithelial ovarian cancer, and the mean overall time since the initial diagnosis was 2.13 years (range 0.7-5.9 years). All patients had a baseline ECOG performance status of 0 or 1. The platinum-refractory group had a shorter mean time since initial diagnosis (1.59 years) than the platinum-resistant group (2.26 years); otherwise, demographic and baseline characteristic were similar between groups.

All 31 patients had prior therapy before entering the study. Thirty out of 31 patients (97%) had prior systemic therapy, and more than half (53%) had 3 or more lines of prior systemic therapy. Of the 30 patients who had prior systemic therapy, best response to the last therapy was CR in 3 (10%) patients, PR in 4 (13%) patients, SD in 7 (23%) patients, and PD in 12 (40%) patients; in 4 (13%) patients, the best response was not assessable. There was a better response to the last therapy in the platinum-resistant group than in the platinum-refractory group, where over half (55%) of the former had achieved SD or better, while 67% of platinum-refractory patients had experienced PD. The most common regimens of prior systemic therapy were carboplatin (90% of all patients), paclitaxel (87% of all patients), and doxorubicin (39% of all patients and 48% of platinum-resistant patients [no platinum-refractory patients received this prior therapy]). Doxorubicin HCl (liposome injection) was coded to doxorubicin in the management of study data. All other prior systemic therapy regimens were in < 30% of patients. There had been a mean of 1.1 months (range 0-3 months) since progression from the last line of systemic therapy. Seven (23%) patients had undergone prior intraperitoneal chemotherapy, all of whom had received a single line of treatment. Of these, 4 (57%) patients had achieved CR or PR on this previous therapy, while 1 (14%) patient experienced PD (results were unavailable for 2 patients). Prior intraperitoneal chemotherapy regimens included

cisplatin, paclitaxel, carboplatin, and cyclophosphamide. There was a mean of 8.1 months (range 0-19 months) since progression from the last line of intraperitoneal chemotherapy.

The most common (≥ 20% of all patients) concomitant medications included stomatologicals, mouth preparations, loperamide, sodium chloride, paracetamol, granulocyte colony stimulating factor, lorazepam, docusate, morphine, omeprazole, pegfilgrastim, diphenhydramine, and ciprofloxacin.

Efficacy Results: The combined objective response rate (CR + PR + response) for the Response-Evaluable Population based on investigator assessments was 10% overall (95% CI 0.020, 0.258). No platinum-refractory patients met the combined objective response criteria. The clinical benefit rate, which was defined as the rate of the sum of CR, PR, Response, and SD, where for SD to qualify as having clinical benefit, there must be no progression of neoplastic disease for at least 4 treatment cycles, was 26% overall, and was comprised of 8 patients in the platinum-resistant group. Kaplan-Meier estimates of progression-free survival, ie, the estimated probabilities that a patient will live with a disease that does not get worse, are 80.65% at 30 days, 49.66% at 60 days, 41.38% at 90 days, and 33.10% at 120 days from starting the medication.

Safety Results: A total of 31 patients received at least 1 dose of alisertib and were included in the Safety Population. The mean number of treatment cycles completed was 4.7 (min 1, max 26), with a median of 2 cycles overall. Mean total dose taken was 2939 mg (min 100, max 18250) at a mean relative dose intensity of 90.12% (min 14%, max 100%). Of the 31 patients treated overall, 4 (13%) patients had the dose held for an AE, 11 (35%) patients had the dose reduced due to an AE, and 1 (3%) patient had the dose discontinued for an AE.

Of the 31 patients in the Safety Population, 30 patients (97%) experienced a treatment-emergent adverse event (TEAE); all 30 of these patients experienced at least 1 drug-related TEAE. Neutropenia was the most commonly reported AE overall (65% overall; platinum refractory, 50%; platinum resistant, 68%). Other common AEs included fatigue (58% overall, platinum refractory 50%, platinum resistant 60%), diarrhea (55% overall; platinum refractory, 50%; platinum resistant, 56%), and anemia (52% overall; platinum refractory, 33%; platinum resistant, 56%).

The most common (≥ 10% of overall patients) drug-related TEAEs included neutropenia, fatigue, diarrhea, alopecia, stomatitis, anemia, leukopenia, nausea, thrombocytopenia, and vomiting.

The most common (≥ 10% of overall patients) Grade 3 or higher TEAEs were neutropenia, leukopenia, thrombocytopenia, stomatitis, fatigue, anemia, and febrile neutropenia. The most common Grade 3 or higher drug-related TEAEs also included neutropenia, leukopenia, thrombocytopenia, stomatitis, and fatigue.

No patients died during the study up to the cutoff date used for safety evaluation.

Overall, a total of 11 (35%) patients experienced SAEs, of whom 6 (19%) had SAEs that were considered to be drug related. Related SAEs included febrile neutropenia, neutropenia, leukopenia, stomatitis, thrombocytopenia, pyrexia, anemia, abdominal pain, bacteremia, hypokalemia, and shock. Of the drug-related serious adverse events, each occurred with low frequency, affecting 1 or 2 patients as a related SAE in this study.

Overall, 4 (13%) patients experienced TEAEs that led to discontinuation (platinum refractory, 2 [33%] patients; platinum resistant, 2 [8%] patients). Of the 4 patients who discontinued treatment due to an AE, 1 patient discontinued during the 7 days of treatment and the other patients discontinued during the rest period. In addition, of the 4 patients who discontinued treatment due to an AE, 3 patients were withdrawn due to Grade 3 or 4 blood disorders (neutropenia, febrile neutropenia, leukopenia, anemia, and thrombocytopenia), and 1 patient was withdrawn due to shock. Among patients who were administered 3 or more cycles (n = 13), none were reported to have discontinued due to an AE.

There were no unexpected trends over the course of the study for changes in any hematology or chemistry laboratory parameter. Overall, the most commonly reported hematology laboratory abnormality reported as a TEAE was neutropenia, which was reported in 20 (65%) patients. Anemia was reported in 16 (52%) patients, leukopenia in 12 (39%) patients, and thrombocytopenia in 9 (29%) patients. The anemia may have been multi-factorial in etiology, including possible association with frequent blood tests required for safety evaluation in this trial. While thrombocytopenia was frequently observed as a laboratory finding, the clinical significance was not clearly defined and few patients reported bleeding events. A high proportion of patients experiencing the laboratory abnormalities of neutropenia, leukopenia, and thrombocytopenia presented with Grade 3 or higher events. Of all 31 patients in the Safety Population, 13 (42%) patients were diagnosed with grade ≥ 3 neutropenia, 7 (23%) patients with grade ≥ 3 leukopenia, and 6 (19%) patients with grade ≥ 3 thrombocytopenia.

Prophylactic myeloid growth factors were not required in cycle 1, but were allowed to manage severe neutropenia according to ASCO guidelines. While frequent CBC monitoring was employed and the Grade 3 or higher neutropenia was observed in 13 (42%) patients, these frequencies included laboratory findings with unclear clinical significance, and the frequency of Grade 3 or higher febrile neutropenia was 10%.

The incidence of hematology laboratory abnormalities reported as AEs was higher in the platinum-resistant group for the most common laboratory abnormalities reported as AEs. The incidence of serum chemistry abnormalities reported as TEAEs was generally low (≤ 20%) for all parameters.

Vital sign changes from baseline to end of treatment were generally small and similar between the platinum-refractory and platinum-resistant groups.

Pharmacokinetic Results: The geometric mean of alisertib steady-state trough concentration was 1.4 μM (CV = 56%, N = 23), which was above the 1 μM steady-state plasma concentrations associated with saturating levels of pharmacodynamics and antitumor activity in a mouse xenograft model.

Pharmacogenetic Results: CCI genotype data will be formally evaluated as a potential covariate in the final cross-study population PK analysis to confirm understanding of the contribution of CCI genotype to the variability in alisertib PK. The results of the population PK analysis will be reported separately.

CONCLUSIONS: This open-label, phase 2 study was designed with primary endpoint to investigate clinical antitumor activity of alisertib, an orally active small-molecule Aurora A kinase inhibitor, in patients with relapsed and refractory cancer of the ovary, fallopian tube and peritoneum. Subjects enrolled with histologically confirmed ovarian cancer after treatment failure of standard platinum and other systemic therapies. Thirty of 31 patients (97%) had undergone prior systemic therapy before entering the study. Over half (53%) had 3 or more lines of prior systemic therapy. Seven patients (23%) had undergone prior intraperitoneal chemotherapy, all of whom had received a single line of treatment. The study was conducted at 17 centers in the US, France and Poland. The starting dose was 50 mg BID for 7 days, followed by a 14-day recovery period in 21 day cycles, corresponding to the Recommended Phase 2 Dose and schedule, determined from prior Phase 1 studies.

In this population with advanced, pre-treated solid tumors, toxicities were frequently observed, but were largely Grade 1 to 2 severity. Neutropenia was the most commonly reported AE overall (65% overall; platinum refractory, 50%; platinum resistant, 68%). Other common AEs included fatigue (58% overall; platinum refractory, 50%; platinum resistant, 60%), diarrhea (55% overall; platinum refractory, 50%; platinum resistant, 56%), and anemia (52% overall; platinum refractory, 33%; platinum resistant, 56%). Many of the hematologic toxicities were asymptomatic with unclear

clinical significance. For example, although neutropenia was reported in a large majority percentage (65%) of treated patients, febrile neutropenia was reported in a smaller proportion (10%). The most common drug-related TEAEs included neutropenia, fatigue, diarrhea, alopecia, stomatitis, anemia, leukopenia, nausea, thrombocytopenia, and vomiting.

In general, toxicities could be monitored by routine clinical assessments and were generally manageable by supportive care or dose reduction. Of the 31 patients treated overall, 4 (13%) patients had the dose held for an AE, 11 (35%) patients had the dose reduced due to an AE, and 1 (3%) patient had the dose discontinued for an AE during the 7 days of treatment (For the 3 other patients in which AE resulting in discontinuation was observed, the discontinuation occurred during the rest period). Of the 4 patients who discontinued treatment due to an AE, 3 patients were withdrawn due to Grade 3 or 4 blood disorders (neutropenia, febrile neutropenia, leukopenia, anemia, and thrombocytopenia), and 1 patient was withdrawn due to shock . Among patients who were administered 3 or more cycles (n=13), none were reported to have discontinued due to an AE.

Common toxicities affected the bone marrow and gastrointestinal mucosa, as well as alopecia. These are likely to represent on-target toxicities related to the mechanism of action of the drug in inhibiting Aurora A kinase activity in highly proliferative tissues, and are consistent with those reported in studies with the first-generation Aurora A kinase inhibitor, MLN8054.[1, 2] With the exception of alopecia, major cumulative toxicities were not observed, and the most frequently occurring toxicities (except alopecia) were generally reversible in the recovery period between cycles.

Alisertib pharmacokinetics was evaluated with limited sampling in the first cycle. The steady state plasma concentrations achieved at trough were similar to the plasma levels associated with antitumor activity, estimated from in vivo preclinical models (approximately 1 micromolar.[3]

Conclusions are as follows:

- The most commonly reported toxicities were neutropenia, stomatitis, and alopecia, and the most frequent reason for discontinuation were neutropenia and stomatitis, likely reflecting the alisertib pharmacologic mechanism to inhibit AAK and interfere with mitotic function of cells in proliferative tissues.
- Toxicities were frequent but generally manageable with supportive care and modifications of the dose or schedule as required. Overall, 4 (13%) patients experienced TEAEs that led to discontinuation (platinum refractory, 2 [33%] patients; platinum resistant, 2 [8%] patients). Of the 4 patients who discontinued treatment due to an AE, 1 patient discontinued during the 7 days of treatment and the other patients discontinued during the rest period. In addition, of the 4 patients who discontinued treatment due to an AE, 3 patients were withdrawn due to Grade 3 or 4 blood disorders (neutropenia, febrile neutropenia, leukopenia, anemia, and thrombocytopenia), and 1 patient was withdrawn due to shock. Central nervous system (CNS) effects such as somnolence, associated with the benzodiazepine structure, were not a major dose-limiting toxicity, but were observed in some patients. Among patients who were administered 3 or more cycles (n = 13), none discontinued due to an AE. Given the durable, but low frequency responses observed in some patients who continued multiple treatment cycles, the data provides support for the approaches used in this study for clinical monitoring, dose reduction, and supportive care especially during the initial weeks of drug administration.
- At the dose of 50 mg BID for 7 days, the mean steady state average trough concentration exceeded the plasma concentration associated with saturating levels of pharmacodynamics and efficacy in mouse xenograft studies (1 micromolar).
- Anti-tumor activity was observed, including partial responses and stable disease. The overall combined response rate was 10% overall (95% CI 0.020, 0.258) and the clinical benefit rate was 26% (95% CI 0.119, 0.446). Responses were not observed in the subset of patients with platinum-refractory disease.

In summary, this first multicenter and multi-regional phase 2 protocol to enroll adult patients with solid tumors demonstrated clinical safety findings consistent with prior Phase 1 clinical experiences, observed in adults with diverse solid tumors enrolled to protocols C14001 and C14002. As an oral outpatient treatment, AEs were generally predictable and could be monitored and managed by dose modification or conventional approaches to supportive care. Alisertib administration did lead to toxicities, including effects on bone marrow and gastrointestinal systems, which were serious and required hospitalization in some patients. The efficacy results did not satisfy the protocol-defined criterion of ≥ 3 CR + PR responses in the first 21 evaluable patients, analyzed after the first stage of enrollment in a 2-stage design. However, the study did demonstrate some single agent antitumor activity of alisertib in this population, including a) 10% response rate in the overall population enrolled (N = 31); b) sustained responses in some patients, durable for periods extending beyond 1 year with continued treatment cycles; and c) clinical benefit rate of 26%. For treatment of patients with advanced ovarian cancer, the results of this study support potential development strategies in a more defined sub-population and/or in combination with other agents to improve clinical utility and disease control.

References

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