2. JZAG Synopsis

Clinical Study Report Synopsis: Study H8K-MC-JZAG

Title of Study: A Phase 2 Study of LY573636 Sodium as Treatment for Patients with Platinum-Resistant Ovarian Cancer

Number of Investigators: This multicenter study included 9 principal investigators.

Study Centers: This study was conducted at 9 study centers in 3 countries.

Publication Based on the Study: Gordon M, McMeekin S, Temkin S, Teww W, Streltsova O, Pecorilli S, Scambia G, Yapp S, Kaiser C, Ilaria R, Look K. Phase II, single-arm study of tasisulam-sodium (LY573636-sodium) as 2nd-4th line therapy for platinum resistant ovarian cancer. Cancer Ther. 2009;(8S). Abstract B197.

Length of Study:
Date of first patient enrolled: 15 February 2007
Data cutoff date: 07 February 2011
Date of last patient completed: at the time of database lock for this report (05 April 2011), 2 patients were still on therapy

Phase of Development: 2

Objectives:

The **primary** objective of this study was to determine the objective response rate (complete response [CR] and partial response [PR]) for LY573636 sodium in patients with epithelial ovarian cancer who had received no more than 2 prior systemic treatment regimens for platinum-resistant disease.

The **secondary** objectives of this study included: progression-free survival distribution, clinical benefit rate (CR+PR+stable disease), pharmacokinetics (PK) of LY573636 sodium, time-to-event variables (which included overall survival time, duration of overall objective response, and duration of stable disease), and safety of LY573636 sodium when given to this patient population.

Study Design: A nonrandomized, open-label, single-arm, multicenter Phase 2 investigation of LY573636 administered to patients with epithelial ovarian cancer who have received no more than 2 prior systemic treatment regimens for platinum-resistant disease.

Number of Patients:

Planned: Approximately 60 patients were planned to be enrolled in the original JZAG protocol.

Treated (at least 1 dose): 118 patients entered the study; 103 patients were enrolled; 103 patients received at least 1 dose of study drug.

Completed: Of the 103 enrolled patients, 101 completed the study. The primary reasons for study discontinuation among enrolled patients were progressive disease (76 patients, 73.8%), death (10 patients, 9.7%), and adverse events (AEs) (7 patients, 6.8%).

Diagnosis and Main Criteria for Inclusion:

Patient eligibility was based on the results of screening medical history, physical examination, clinical laboratory tests, and other procedures which are fully described in the JZAG Protocol.

The key criteria for inclusion in the study were:

- Women at least 18 years of age with a diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal cancer that is platinum-refractory or platinum-resistant.
- At least 1, but no more than 2, prior platinum-based chemotherapeutic regimens (containing carboplatin, cisplatin, or another organoplatinum compound). At least 1 of the prior platinum regimens must have contained a taxane.
- ECOG Performance Status of 0 or 1, life expectancy of ≥3 months, serum albumin level of at least 30 g/L, and adequate organ function.
- Measureable disease as defined by RECIST guidelines (Therasse et al. 2000), or CA-125 ≥2× upper limit of normal (Rustin 2003) if they had otherwise nonmeasurable disease as defined by the RECIST guidelines.

Key reasons for ineligibility in the study included:

- Women who were pregnant or lactating.
- More than 2 lines of systemic therapy for platinum-refrectory/resistant disease (not including neoadjuvant therapy).
- Patients requiring regular, periodic paracentesis.
- Patients who were receiving therapy with warfarin (Coumadin®).
- Electrocardiogram (ECG) abnormalities (e.g., QTC >470 msec).

Study Drug, Dose, and Mode of Administration:

Patients enrolled into the original protocol received an initial loading dose in Cycle 1 of LY573636, targeting a C_{max} of 420 μg/mL, followed by a chronic dose (which was 75% of the loading dose) in subsequent cycles, administered as an intravenous (IV) infusion given over approximately 2 hours, on Day 1 of a 21-day treatment cycle. Patients enrolled into protocol JZAG(a) received a loading dose of LY573636 targeting a C_{max} of 360 μg/mL, followed by a 90% chronic dose in subsequent cycles. Patients enrolled into protocol JZAG(b) and (c) received a loading dose and chronic doses of LY573636 on Day 1 of a 28-day treatment cycle. Doses were calculated using a dosing calculator targeting a tasisulam dose according to the patient's lean body weight and the precycle albumin level.

Patients continued on the respective dosing regimen as prescribed at the time of their enrollment, even when a new protocol amendment was intiated, as the observed hematologic toxicity which led to adjustments of the dosing regimen predominantly occurred in the early treatment cycles.

Duration of Treatment:

Patients received treatment until disease progression or any other reason requiring treatment discontinuation. The study was designed to end 12 months after the last enrolled patient received the first dose of LY573636. However, patients who were benefitting from study treatment were allowed to continue treatment until clinical or objective disease progression, with the agreement of the investigator and the Lilly clinical research physician.

Variables:

Efficacy: The **primary** efficacy objective for this study was to estimate objective response rate and 90% confidence limits. Lesion measurements were collected during the study using RECIST guidelines; or, for patients without measurable disease, CA-125 levels were used to determine response. **Secondary** efficacy endpoints of the study were to characterize the progression-free survival distribution, clinical benefit rate, time-to-progressive disease, overall survival time, duration of overall response (CR or PR), and duration of stable disease.

Safety: Safety was assessed by physical examinations, monitoring of AEs, clinical laboratory tests, electrocardiograms, vital signs, and dose adjustments.

Variables (continued):

Bioanalytical:

Study drug concentration and metabolism and/or protein binding of LY573636 were measured using bioanalytical samples.

Pharmacokinetic:

A population PK model for total drug was developed in nonlinear mixed effect modeling (NONMEM). The base model (2-compartmental PK models following zero-order infusion) was parameterized in terms of CL, initial volume of distribution (V_1), peripheral volume of distribution (V_2), and intercompartmental clearance (Q). The first order conditional with interaction estimation method was used in both models. Intersubject variability with exponential error structure was present on each of the PK parameters. Area under the concentration-time curve (AUC) above an albumin-corrected threshold (AUC_{alb}) was derived from the individual fitted PK from the population PK model.

Statistical Evaluation Methods:

Approximately 60 patients were planned to be enrolled in the original JZAG protocol to allow for at least 50 patients to complete the first on-study imaging evaluation at the end of Cycle 2. Protocol amendment (a) planned for the addition of approximately 25 more patients to the study (18 patients were actually added), and amendment (b) planned for the addition of approximately 25 additional patients (32 patients were actually added). An interim analysis was done to check for futility and determine if the trial should move forward. Results of the interim analysis after 21 patients were enrolled met the goal of $\geq$2 responses, with 2 confirmed and 2 unconfirmed responses.

Efficacy:

Data from all patients who received at least 1 dose of study drug were used for efficacy analyses. Only confirmed CR and PR was used to estimate the objective response rate. The objective response rate and the 90% confidence interval (CI) were estimated using an unadjusted normal approximation for binomial proportions (*z* approximation). The objective response rate goal of this study was at least 15%. Kaplan-Meier analyses (Kaplan and Meier 1958) were performed on the observed distributions of progression-free survival,overall survival, duration of overall response, and duration of stable disease. The clinical benefit rate and the 90% CIs were estimated using an unadjusted normal approximation for binomial proportions (*z* approximation).

Safety:

Safety analyses were carried out for the 3 subgroups (i.e., patients enrolled under the original protocol, patients enrolled under amendment (a), and patients enrolled under amendments [b] and [c]). All patients who received at least 1 dose of LY573636 were evaluated for safety and toxicity.

Safety information that was summarized and listed in MedDRA preferred terms included: all AEs (pre-existing and treatment-emergent); treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) including deaths; and discontinuations because of AEs. CTCAE grades for laboratory and non-laboratory adverse events (by preferred term) were also summarized. Adverse events were coded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) scale, Version 3.0.

Bioanalytical:

Blood samples were analyzed to determine the total LY573636 plasma concentrations in all patients receiving study drug.

Pharmacokinetic:

Pharmacokinetic (PK) analyses were conducted on all patients who received at least 1 dose of the study drug and who had samples collected. The population PK dataset was analyzed using the NONMEM program (Version 6) with PREDPP (Version V). The final 2-compartment total drug model developed from the Phase 1 study, JZAA, was used for the PK analysis. Covariate analysis was carried out to identify which factors contributed to the variability in PK parameters. Potential relationships between total drug PK parameters and clinical toxicities, such as hematologic metrics, were explored.

Summary:

- Tasisulam was administered to female patients at least 18 years of age with platinum-resistant ovarian cancer as a second- or third-line treatment regimen. Changes to the original study design of the protocol were made in amendment (a) and amendment (b) to explore alternative dosing regimens to decrease the risk of Grade 4 hematologic toxicity. Of the 103 patients who were enrolled in the study, 53 patients received a target C_{max} of 420 µg/mL, 18 patients received a target C_{max} of 360 µg/mL, and 32 patients were dosed targeting an AUC_{alb} range hypothesized to offer the best balance of efficacy and safety.
- The mean age of the study population was 57.4 years. All patients (N=103) who participated in this study had received at least 1 type of prior systemic cancer therapy. Sixty-seven patients (65.0%) had an ECOG performance status of 0, and 36 patients (35.0%) had an ECOG performance status of 1 at study entry. The majority of patients had Stage IIIC disease (51 patients, 50.5%) and were platinum-resistant (79 patients, 76.7%) at study entry.
- The objective response rate was 7.5% in the C_{max} 420 µg/mL group, 0% in the C_{max} 360 µg/mL group, and 3.1% in the albumin-tailored dose group. The overall objective response rate for this study was 4.9% (90% CI, 1.4 to 8.3), which did not achieve the objective response rate goal. Factors contributing to the low objective response rate may have been the study population's advanced disease stage, the extent of prior treatment, and the stringent response evaluation criteria.
- The Kaplan-Meier estimates for time to event distributions for the secondary efficacy endpoints for the C_{max} 420 µg/mL group, the C_{max} 360 µg/mL group, and the albumin-tailored dose group were: median progression-free survival was 1.87 months, 2.40 months, and 2.10 months, respectively; median overall survival time was 13.08 months, 10.09 months, and 11.63 months, respectively; and duration of stable disease was 3.71 months, 3.27 months, and 3.78 months, respectively. Duration of overall response was 5.03 months in the C_{max} 420 µg/mL group and was 12.68 months in the albumin-tailored dose group (there were no responses in the C_{max} 360 µg/mL group). The clinical benefit rate was 45.3% in the C_{max} 420 µg/mL group, 61.1% in the C_{max} 360 µg/mL group, and 34.4% in the albumin-tailored dosing group.
- Of the 103 patients who received at least 1 dose of study drug, 10 patients (9.71%) died during the study (6 of these deaths were due to AEs considered possibly related to the study drug), and 8 patients (7.77%) died within 30 days of discontinuation from study treatment (2 of these deaths were due to AEs considered possibly related to the study drug). The most common cause of death during the study or within 30 days of discontinuation was due to AEs. There were 23 patients (22.3%) who experienced at least 1 SAE that was considered possibly related to the study drug. Five patients (4.9%) were discontinued from the study due to AEs that were considered possibly related to the study drug. There were 87 patients (84.5%) with at least one TEAE considered possibly related to the study drug.
- The exposure-toxicity relationship in both Cycle 1 and Cycle 2 of the study is consistent with what has been observed in previous analyses, in which a higher AUCalb has been associated with a greater risk of Grade 4 hematologic toxicity.

Conclusions:

- The overall objective response rate for this study was 4.9% (90% CI, 1.4 to 8.3). The objective response rate goal of 15% was not achieved in this study.
- For the secondary efficacy endpoints, overall survival was the only event in which there was a notable difference among all patients, platinum-refractory patients, and platinum-resistant patients (11.63 months, 8.02 months, and 12.85 months, respectively). Since platinum-refractory patients typically have lower overall survival rates, this finding is as expected.
- The most common SAEs and CTCAEs possibly related to tasisulam were thrombocytopenia, neutropenia, and anemia. This is expected based on tasisulam's safety profile. Prior treatment with myelosuppressive agents, such as carboplatin and the taxanes, may also have contributed to these events, as 86% of the patients in the study received this combination as prior treatment.

- Although lowering the target C_{max} from 420 μg/mL to 360 μg/mL lowered the rate of Grade 4 hematologic toxicity in Cycle 1, a relatively low percentage of patients achieved the intended therapeutic AUC_{alb} range in either Cycle 1 (12%) or Cycle 2 (25%), and no patients achieved an objective response. This suggests that fixed C_{max} reduction did not provide the optimal benefit/risk.
- The relatively higher rate of Grade 4 hematologic toxicity in Cycle 2 compared with Cycle 1, associated with a higher AUC_{alb} range, suggests a possible role for slower drug clearance. This and other possible covariables, such as concomitant medications and comorbid illnesses, will be explored further in ongoing studies.
- Interpatient PK variability, especially in Cycle 2 or later, was relatively high despite albumin-tailored dosing; this posed challenges for this study population, who had been extensively pretreated with highly marrow-suppressive chemotherapy.