2. JACW Synopsis

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Clinical Study Report Synopsis: Study H8Z-MC-JACW

Title of Study: A Randomized Phase 2 Study of LY2181308 in Combination with Docetaxel versus Docetaxel in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer who Were Previously Treated with First Line Chemotherapy

Number of Investigators: This multicenter study included 35 principal investigators.

Study Centers: This study was conducted at 35 study centers in 6 countries.

Publication Based on the Study: None at this time

Length of Study:
Date of first patient visit/patient enrolled: 18 May 2010
Date of last patient visit/patient completed entire study: 29 June 2012

Phase of Development: 2

Objectives:

The primary objective of was to evaluate the anti-tumor activity of LY2181308 in combination with docetaxel therapy (experimental arm) compared to docetaxel alone (control or standard of care arm) in second-line non-small cell lung cancer (NSCLC) patients.

The secondary objectives of this study were:

- To characterize and compare the quantitative and qualitative toxicities of LY2181308 combined with docetaxel and docetaxel in this patient population.
- To compare efficacy variables of both therapies including:
  - Time-to-event variables:
    - Progression-free survival (PFS)
    - Overall survival (OS)
    - Time to worsening of symptoms (TWS)
    - Time to objective tumor response
    - Time to documented disease progression
  - Objective tumor response rate (RR)
  - Duration of response
- To evaluate the pharmacokinetics (PK) of LY2181308 and docetaxel alone and when combined together.
- To explore biomarkers relevant to tumor progression and/or survivin expression such as, but not limited to:
  - Survivin expression determined in the original diagnostic tumor tissues
  - Plasma survivin biomarker
  - Other survivin-associated biomarkers, if required.
  - Survivin expression in tumor tissues obtained prior to starting second-line chemotherapy (not mandatory)
- To compare changes in the individual item scores, the Average Symptom Burden Index (ASBI), and total score of the Lung Cancer Symptom Scale (LCSS).

Study Design: This was a randomized, controlled, open-label, multicenter, international Phase 2 study of LY2181308 in combination with docetaxel compared to docetaxel in patients with locally advanced or metastatic (Stage IIIB or IV) NSCLC who were previously treated with first line chemotherapy.

Number of Patients:

Planned: Approximately 120 (analysis of the primary endpoint was planned to occur after 120 patients received at least 2 cycles of therapy and had their tumors measured)

Randomized: LY2181308 + docetaxel (N=120), docetaxel alone (N=60)

Treated (at least 1 dose): LY2181308 + docetaxel (N=114), docetaxel alone (N=48)

Completed: All patients received a minimum of 1 cycle of study therapy.

Diagnosis and Main Criteria for Inclusion:

- NSCLC patients who were eligible for second-line chemotherapy treatment with docetaxel
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1
- Had previous first-line chemotherapy for advanced NSCLC
- Adequate organ function
- Had no pre-existing neuropathy equivalent to Common Terminology Criteria for Adverse Events (CTCAE) ≥Grade 2
- Had no symptomatic brain metastasis at the time of study entry

Test Product, Dose, and Mode of Administration:

Arm A

Pre-medication: Oral dexamethasone 16 mg per day (eg, 8 mg twice daily [BID]) was administered for 3 days starting 1 day prior to docetaxel administration (or with equivalent regimen), unless clinical contraindications existed.

Prior to Cycle 1 only (Day -1 and Day -2 of Lead-in): 2 loading doses of LY2181308 750 mg were administered by intravenous (IV) infusion over approximately 3 hours (eg, 3 hours ± 30 minutes) daily on Days -2 and -1.

Cycle 1 (Day 1 through Day 21): The third loading dose of LY2181308 750 mg was administered by IV infusion on Day 1 of Cycle 1, followed by docetaxel 75 mg/m^2 administered approximately 60 minutes after LY2181308 infusion. Two additional doses of LY2181308 (750 mg over 3-hour infusion) were administered in Cycle 1 on Days 6 and 14.

Cycle 2 – n (Day 1 through Day 21): LY2181308 750 mg was administered by IV infusion over approximately 3 hours (± 30 minutes) weekly on Days 1, 8, and 15 of each 21-day cycle until disease progression. Approximately 60 minutes after LY2181308 administration was completed, docetaxel 75 mg/m^2 was administered by IV infusion over approximately 1 hour (± 15 minutes) on Day 1 of each 21-day cycle.

Reference Therapy, Dose, and Mode of Administration:

Arm B

Pre-medication: Oral dexamethasone 16 mg per day (eg, 8 mg BID) was administered for 3 days starting 1 day prior to docetaxel administration (or with equivalent regimen), unless clinical contraindications existed.

Day 1 of each cycle: Docetaxel 75 mg/m^2 was administered by IV infusion over 1 hour (±15 minutes) on Day 1 of each 21-day cycle. Docetaxel was administered until disease progression was confirmed.

Duration of Treatment: 4 months

Lead-in period: 2 days; for Arm A only
Treatment period: 4 months
Wash-out period: none
Observation period: OS or study end (approximately 12 months)

Variables:

Efficacy: Primary: change in tumor size (CTS) after 2 cycles of therapy. Secondary: PFS, OS, TWS, time to objective tumor response, time to documented disease progression, objective tumor RR, duration of response.

Safety: Serious adverse events (SAEs), adverse events (AEs), laboratory parameters, vital signs, corrected QT interval prolongation.

Bioanalytical: PK, pharmacogenomics, urine, and serum markers.

Pharmacokinetic: Mean population plasma LY2181308 and docetaxel PK parameters (clearance, exposure, volume of distribution, half-lives); derived maximum plasma concentration (C_{max}) and time to maximum plasma concentration (t_{max}) for LY2181308 and docetaxel; partial area under the curve (AUC) for docetaxel.

Pharmacodynamic: Plasma survivin protein changes, survivin expression in tumor tissue.

Health Outcomes: TWS, ASBI, LCSS.

Statistical or Other Evaluation Methods:
Approximately 150 patients were to be randomized to Arm A or Arm B using a 2:1 ratio to randomize twice as many patients in Arm A compared to Arm B.
Efficacy: A t-test was used to analyze the CTS (log ratio of Cycle 2 tumor size over baseline tumor size). The CTS used tumor size measurements as a continuous rather than categorical variable. Tumor measurements were made according to Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1).
A log-rank test was used for time-to-event analyses. Tumor response was assessed by RECIST, version 1.1. A Pearson's chi-square test was used for tumor RRs. The influence of prognostic factors on efficacy endpoint was explored using appropriate modeling techniques.
Safety: CTCAE version 4.0.
Bioanalytical: Sparse PK sampling for population analysis. Docetaxel PK was investigated in the presence and the absence of LY2181308 (patient population comparison). LY2181308 was investigated in the absence and presence of docetaxel (within-patient comparison).
Pharmacokinetic: Mean population PK parameters were calculated using non-linear mixed effect modeling implemented in NONMEM. Classical non-compartmental analysis was carried out to derived C_{max} and t_{max} for LY2181308 and docetaxel, as well as partial area under curve (AUC) for docetaxel. Pharmacokinetic versus covariate (such as age, weight, body surface area, creatinine clearance, serum creatinine, alpha-1-acid glycoprotein) relationships were investigated.
Health Outcomes: Time to event analysis of worsening symptoms was performed. Descriptive statistics were summarized by treatment and time point, and linear mixed models of the individual items, the ASBI and total score; generalized linear model estimation of the AUCs of the ASBI and total scores.

Summary:

Patient Disposition, Baseline Demographics, and Characteristics

- Of the 207 patients who entered the study, 120 were randomly assigned to LY2181308/docetaxel and 60 were randomly assigned to docetaxel alone. One-hundred fourteen patients received at least 1 dose of LY2181308/docetaxel and 48 patients received at least 1 dose of docetaxel alone. The most common reasons for early discontinuation were progressive disease (n=64) and AEs (n=23) in the LY2181308/docetaxel arm and progressive disease (n=25) and AEs (n=3) in the docetaxel alone arm.
- Patient demographics were similar between the 2 treatment arms. The median age at baseline was 61.96 years in the LY2181308/docetaxel arm and 64.25 years in the docetaxel alone arm. Most patients were Caucasian in both arms (LY2181308/docetaxel, 96.5%; docetaxel alone, 93.8%). All patients had a baseline ECOG PS score of 0 (LY2181308/docetaxel, 32.5%; docetaxel alone, 27.1%) or 1 (LY2181308/docetaxel, 67.5%; docetaxel alone, 72.9%). No patients had a baseline ECOG PS score of 2.
- Most patients in both arms had a histopathological initial basis for their pathological diagnosis (LY2181308/docetaxel, 84.2%; docetaxel alone, 85.4%). Nearly half of all patients (48.1%) had an initial pathological diagnosis of adenocarcinoma of the lung (LY2181308/docetaxel, 50.9%; docetaxel alone, 41.7%). The second most frequently reported initial pathological diagnosis in both arms was squamous cell carcinoma of the lung (29.6%), which was reported by more patients in the docetaxel alone arm (47.9%) compared to the LY2181308/docetaxel arm (21.9%). Most patients in both arms had Stage IV disease at study entry (LY2181308/docetaxel, 91.2%; docetaxel alone, 87.5%).
- All treated patients (100%) received prior therapy. Prior surgery was reported by 27.2% of patients in the LY2181308/docetaxel arm and 25.0% of patients in the docetaxel alone arm. Prior radiotherapy was reported by 46.5% of patients in the LY2181308/docetaxel arm and 37.5% of patients in the docetaxel alone arm. Prior systemic therapy was reported by all (100%) patients in the LY2181308/docetaxel arm and all (100%) patients in the docetaxel alone arm.

Efficacy:

Primary Efficacy

- The mean tumor size ratio at Cycle 2 to that at baseline in the LY2181308/docetaxel arm was 1.07 (standard deviation [SD], 0.28) and in the docetaxel arm alone arm was 1.04 (SD, 0.28). There was no statistically significant difference in CTS from baseline after 2 cycles by treatment between the LY2181308/docetaxel and docetaxel alone arms (t-test p-value = 0.666).
- Cox regression models were fitted to the data independently to obtain a hazard ratio (HR) and its 90% confidence interval (CI) for each prognostic and baseline factor. Among the baseline factors assessed, age group (<65 vs. ≥65), lactate dehydrogenase (LDH) group (high vs. low), and CTS group (increase vs. decrease) had statistically significant effects on PFS.

Secondary Efficacy

- There was no statistically significant difference in PFS between the LY2181308/docetaxel and docetaxel alone arms. The median PFS was 2.83 (95% CI, 1.84 to 3.65) months with LY2181308/docetaxel and 3.35 (95% CI, 2.69 to 4.57) months with docetaxel alone (log-rank p-value = 0.191). The 6-month survival rate was 21% (95% CI, 14% to 29%) with LY2181308/docetaxel and 26% (95% CI, 14% to 40%) with docetaxel alone.
- No substantial change in treatment effect (that is, HR) on PFS was observed between LY2181308/docetaxel and docetaxel alone when adjusted for baseline age group (<65 vs. ≥65, [HR=1.81 (90% CI, 1.18 to 2.76)]), baseline LDH group (high vs. low, [HR=1.44 (90% CI, 0.97 to 2.15]); and CTS group (increase vs. decrease [HR=0.45 (90% CI, 0.30 to 0.68)]).
- The median OS was 7.9 (90% CI, 6.6 to 9.7) months with LY2181308/docetaxel and 8.8 (90% CI, 5.7 to 13.8) months with docetaxel alone (log-rank p-value = 0.481). The 12-month survival rate was 32% (90% CI, 20% to 40%) with LY2181308/docetaxel and 38% (90% CI, 20% to 50%) with docetaxel alone.
- The objective tumor progression rate was 69.3% (95% CI, 60.8% to 77.8%) with LY2181308/docetaxel and 68.8% (95% CI, 55.6% to 81.9%) with docetaxel alone. The overall symptomatic deterioration rate was 17.5% (95% CI, 10.6% to 24.5%) in the LY2181308/docetaxel arm and 10.4% (95% CI, 1.8% to 19.1%) in the docetaxel alone arm.
- The median time to objective tumor response was not reached with LY2181308/docetaxel or docetaxel alone (90% CI, not reached to not reached for both treatment arms (log rank p-value = 0.158).
- The median response duration was 2.8 (90% CI, 2.8 to not reached) months with LY2181308/docetaxel and 5.4 (90% CI, not reached to not reached) months with docetaxel alone (log rank p-value = 0.843).
- The median time to progression was 2.9 (90% CI, 2.0 to 3.7) months with LY2181308/docetaxel and 3.4 (90% CI, 2.8 to 5.6) months with docetaxel alone (Wald's p-value = 0.249).

Patient-reported Outcomes

- The median TWS (overall combined LCSS score) was 1.0 (90% CI, 0.7 to 1.0) months with LY2181308/docetaxel and 0.8 (90% CI, 0.5 to 1.1) months with docetaxel alone (log-rank p-value = 0.512; HR, 1.13; 90% CI, 0.82% to 1.57, Wald's p-value = 0.520).

Pharmacokinetics

- Pharmacokinetics data for LY2181308 was available from 86 patients. The data enabled the determination of parameters of a multi-compartment PK model. The PK analysis results indicated that LY2181308 PK characteristics in patients with NSCLC were similar to and consistent with the LY2181308 PK in the Phase 1 cancer patient population (Study JACP) and with the LY2181308 PK profile in the hormone-refractory prostate cancer (HRPC) patient population (Study JACR).
- LY2181308 PK data indicated that there was a significant relationship between elimination clearance of LY2181308 and creatinine clearance.
- The LY2181308 plasma exposure data in Study JACW are consistent with the data reported previously and the data reported in Study JACR.

- A population-to-population comparison can be made to conclude that LY2181308 area under the curve from 0 to 8 hour postdose (AUC_{0-8}) does not change with the administration of docetaxel on the same day (docetaxel infusion starting 30 minutes to 1 hour after LY2181308 end of infusion).
- In addition, no statistical differences in docetaxel exposure area under the curve from 0 to infinity (extrapolation to infinity) (AUC_{0-INF}) were observed between Arm A and Arm B. In Study JACR, docetaxel exposure (mean value and variability) was similar between the 2 treatment arms, suggesting that the presence of LY2181308 did not influence docetaxel PK. However, it is important to note that this was not a formal within-patient comparison of docetaxel PK in the presence and absence of LY2181308, but rather a population-to-population comparison using PK estimates from the 2 treatment arms.

Safety

- Ten on-therapy deaths occurred in the LY2181308/docetaxel arm and 3 on-therapy deaths occurred in the docetaxel alone arm.
- Overall, 42 (36.8%) patients in the LY2181308/docetaxel arm had ≥1 SAE assessed as possibly related to study drug. In the docetaxel alone arm, 20 (41.7%) patients had ≥1 SAE assessed as possibly related to study drug.
- Ten patients in the LY2181308/docetaxel arm and 3 patients in the docetaxel alone arm discontinued due to SAEs assessed as possibly related to study drug.
- Adverse events leading to discontinuation that occurred in >1 patient in either arm were (LY2181308/docetaxel vs. docetaxel alone): death (2.5% vs. 0%), dyspnea (1.7% vs. 0.0%), pleural effusion (1.7% vs. 0.0%), and thorombocytopenia (1.7% vs. 0.0%).

Conclusions:

- No statistically significant difference in the CTS from baseline after 2 cycles by treatment was observed between the LY2181308/docetaxel and docetaxel alone arms.
- There was no statistically significant difference in PFS between the LY2181308/docetaxel and docetaxel alone arms.
- Safety of LY2181308 in combination with docetaxel was consistent with their known safety profiles.
- The LY2181308 PK profile was consistent with previous studies.