2. JACR Synopsis

Clinical Study Report Synopsis: Study H8Z-MC-JACR

Title of Study: A Randomized Phase 2 Study of LY2181308 sodium in Combination with Docetaxel Versus Docetaxel in Hormone Refractory Prostate Cancer	
Number of Investigators: This multicenter study included 20 principal investigators.	
Study Center(s): This study was conducted at 20 study centers in 4 countries.	
Publication Based on the Study: Wiechno P, Chlosta PL, Smok-Kalwat J, Pikilel J, Henry DH, Christianson DF, Somer BG, Mellado B, Duran I, Castellano DE, Callies S, Andre V, Hurt K, Lahn MMF, Stockle M, Reuter C, Heinrich B. Interim results of a randomized phase 2 study with window-design to evaluate anti-tumor activity of the surviving antisense oligonucleotide (ASO) LY2181308 in combination with docetaxel for first-line treatment of castrate-resistant prostate cancer (CRPC) [poster]. Presented at the 47th Annual Meeting of the American Society of Clinical Oncology. June 3-7, 2011. Chicago, IL. Abstract 4592.	
Length of Study: Approximately 3 years, 8.5 months Date of first patient enrolled: 02 April 2008 Date of last patient completed therapy: 13 December 2011	**Phase of Development:** 2

Objectives:

Primary objective: To estimate progression-free survival (PFS) in patients with hormone refractory prostate cancer (HRPC) administered LY2181308 in combination with docetaxel compared to docetaxel alone.

Secondary objectives: a) To assess the safety and adverse event (AE) profile of the combination; b) to evaluate the pharmacokinetics (PK) of LY2181308 and docetaxel alone and in combination; c) to characterize prostate-specific antigen (PSA) kinetics and estimate PSA-derived endpoints; d) to estimate time-to-event variables, such as overall survival (OS), duration of overall response, and duration of stable disease; e) to document overall objective response rate (complete response and partial response); f) to assess biomarker responses associated with LY2181308 and docetaxel combination; g) to evaluate patient-reported outcomes (PROs) with the Functional Assessment of Cancer Therapy- Prostate Cancer (FACT-P) and the Brief Pain Inventory (BPI) to assess physical, social/family, emotional, and functional wellbeing domains, as well as symptoms commonly experienced by prostate cancer patients; and h) to evaluate clinical symptoms.

Pharmacogenetics (PGx) primary objective: To descriptively evaluate the distribution of genotypes by treatment arm for genetic polymorphisms in the candidate single nucleotide polymorphism (SNP) panel.

Pharmacogenetics exploratory objectives: a) To test for potential association between genetic variation and docetaxel PK outcomes at each SNP in the candidate gene panel that passed quality control through exploration of exposure as measured by area under the concentration time curve (log AUC0->inf [ng.hr/mL]) and concentration at maximum (log Cmax) ; b) to characterize the ABCB1 3-SNP haplotype (1236T-2677T-3435T) in the major ethnicity subgroup and, depending on the representative frequency of this haplotype, to test for association between the ABCB1 haplotype and docetaxel PK AUC and Cmax; and c) to test for potential association between genetic variation and PFS. Exploratory PGx safety objectives were proposed but not performed because the rates of the events of interest (ie, Grade 3/4 leukopenia/neutropenia and peripheral neuropathy, whether or not docetaxel induced) were too low for exploratory analysis.

Study Design: Study H8Z-MC-JACR (JACR) was an open-label, randomized, Phase 2 study of LY2181308 in combination with docetaxel versus docetaxel alone in patients with HRPC. Patients were randomized to LY2181308/docetaxel or docetaxel alone in a 2:1 ratio in favor of LY2181308/docetaxel. In Cycle 1 and beyond, patients randomized to docetaxel alone received 75 mg/m^2 docetaxel (1-hour intravenous [IV] infusion) every 3 weeks (1 administration per treatment cycle; the length of 1 treatment cycle was 3 weeks). In Cycle 1, patients randomized to LY2181308/docetaxel received a 750-mg loading dose (3-hour IV infusion) of LY2181308 as monotherapy administered daily on Days 1 through 3, followed by a maintenance dosing regimen of 750 mg (3-hour IV infusion) on Day 8 and Day 15. In Cycle 2 and beyond, LY2181308/docetaxel patients received a 750 mg LY2181308 dose (3-hour IV infusion) on Days 1, 8, and 15 in combination with docetaxel given at 75 mg/m^2 (1-hour IV infusion) on Day 1 of the specific cycle. All patients received prednisone (5 mg orally) twice daily continuously while taking docetaxel. Patients could have continued on study therapy after completion of 10 cycles in the absence of disease progression, or if the patient benefitted from therapy. Two interim analyses were performed; the first, for safety and pharmacokinetic (PK) assessment after 20 patients completed 2 cycles of therapy; and the second, for safety of the combination therapy and early efficacy assessment of PSA kinetics. Final analysis was based on PFS. This was an outpatient study.

Number of Patients:

Planned: 150

Randomized: 102 LY2181308/docetaxel; 52 docetaxel

Treated (at least 1 dose): 98 LY2181308/docetaxel; 51 docetaxel

Completed: 23 LY2181308/docetaxel; 24 docetaxel

Diagnosis and Main Criteria for Inclusion: Males ≥18 years of age with progressive HRPC defined by 2 consecutive increases in PSA values over a previous reference value; histologically or cytologically confirmed adenocarcinoma of the prostate that was metastatic and unresectable; adequate hematological, liver, and renal function; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.

Study Drug, Dose, and Mode of Administration:

For Cycle 1 only, a loading dose of 750 mg of LY2181308 was administered IV daily on Days 1, 2, and 3 to achieve a steady state. LY2181308 was then administered IV on Days 8 and 15, thus completing Cycle 1 therapy. LY2181308 750 mg/m^2 IV was then given weekly with docetaxel 75 mg/m^2 IV every 3 weeks. Prednisone (5 mg orally) twice daily (BID) was taken continuously while the patient received docetaxel therapy. Cycles were 3 weeks (21 days).

Reference Therapy, Dose, and Mode of Administration: Docetaxel 75 mg/m^2 was administered IV every 3 weeks. Prednisone (5 mg orally BID) was taken continuously while the patient received docetaxel therapy. Cycles were 3 weeks (21 days).

Duration of Treatment: The duration of treatment was up to at least 30 weeks (10 cycles). In the absence of disease progression, and if clinically beneficial, patients could continue treatment beyond 10 cycles for 2 additional cycles. A decision to continue further was made at the end of every additional 2-cycle treatment period.

Pre-treatment period: 21 to 28 days.

Treatment period: At least 10 cycles or 30 weeks.

Short-term follow-up period (postdiscontinuation): 30 days.

Long-term follow-up period (postdiscontinuation): until death.

LY2181308/docetaxel Arm: Frequency: For Cycle 1, a daily loading dose of LY2181308 for 3 days in Week 1, followed by a weekly dose of LY2181308 in Weeks 2 and 3. For Cycle 2 and beyond, a weekly dose of LY2181308 for Weeks 1-3. Docetaxel was given once every 3 weeks for Cycle 2 and beyond.

Docetaxel alone Arm: Frequency: Docetaxel was give once every 3 weeks for Cycle 1 and beyond.

Variables:

Efficacy: The primary efficacy measure was PFS. Progressive disease was defined by clinical symptoms, by a bone scan at a protocol-specified treatment time point showing a total of 2 or more new lesions consistent with progressive disease from baseline scan beginning with the second scheduled scan after initiating treatment (after completion of Cycle 6; approximately at 6 months, or by radiographic evidence of target lesions per Response Evaluation Criteria in Solid Tumors guidelines.

Secondary efficacy measures included multiple predefined PSA-derived endpoints, overall response rate, and OS.

Safety: Safety was assessed by physical examinations, monitoring of AEs, imaging studies, serum PSAs, clinical laboratory tests, and vital signs.

Patient-reported Outcomes: FACT-P (version 4) was used to evaluate differences in well being and common symptoms between treatment groups. The BPI was used to evaluate differences in patient-reported pain between treatment groups.

Pharmacokinetic/Pharmacodynamic: Plasma samples were collected from patients in the LY2181308/docetaxel arm and the docetaxel alone arm at prespecified treatment time points to determine LY2181308 and docetaxel concentrations and other PK parameters, alone and in combination.

Pharmacogenetics: Whole blood DNA samples were collected from patients in both treatment arms for analysis of a panel of drug enzyme metabolism and transporter (DMET) genes to determine the influence of genetic variants on treatment response, metabolism, or adverse events. The primary PGx measure was genotype frequency of specific SNPs. Exploratory measures included association analyses between PK parameters (docetaxel AUC or Cmax) and PFS and SNP genotypes and haplotypes .

Statistical Evaluation Methods:

Efficacy: Kaplan-Meier analyses were performed on the observed distributions of PFS. Parameter estimates of the PFS median and quartiles were reported for each treatment group. The log-rank test was performed to assess the treatment difference between the 2 groups. For secondary efficacy objectives, Kaplan-Meier analyses were performed on the observed distributions of OS; Pearson's chi-squared test was used to evaluate tumor response rates between treatments, and a model of the repeated measures of PSA was used to determine statistical significance of the treatment effect.

Safety: All patients who received at least 1 dose of LY2181308 or docetaxel were evaluated for safety and toxicity. Safety analyses included summaries of Common Terminology Criteria for Adverse Events (CTCAE) grades for laboratory and nonlaboratory parameters, treatment-emergent AEs, and dose adjustments.

Patient-reported Outcomes: Data from FACT-P and BPI were used to assess trends in PROs to generate hypotheses to be tested in future trials. The scores, and changes from baseline mean scores, were summarized at baseline and for each visit and compared between treatment arms.

Pharmacokinetic/Pharmacodynamic: Mean population plasma LY2181308 and mean population plasma docetaxel PK parameters (clearance, exposure, volume of distribution, half-lives) and subject variability were computed using non-linear mixed effect modeling (implemented in NONMEM).

Pharmacogenetics: The PGx population included all patients who received at least 1 dose of study drug and had genotyping. Single nucleotide polymorphism allele frequencies were analyzed for the PGx population and descriptive statistics applied. A Cox proportional hazards model, including genotype main effect, treatment effect, and genotype by treatment interaction on PFS, was applied to the PGx population . SNP-PK associations were analyzed for docetaxel AUCand Cmax in all patients in the PGx population that had both genotyping and PK data. Linear models were used to test for association between log-transformed docetaxel AUC and Cmax and genetic variation under a genotypic model with covariates of age, alpha-1 acid glycoprotein and body surface area.

Summary:

Patient Disposition, Baseline Demographics, and Characteristics

- A total of 20 sites participated in this study. Of the 194 patients who entered the study, 102 were randomly assigned to LY2181308/docetaxel and 52 were assigned to docetaxel alone. Ninety-eight patients received at least 1 dose of LY2181308/docetaxel and 51 patients received at least 1 dose of docetaxel alone. Twenty-three patients on the LY2181308/docetaxel arm and 24 patients on the docetaxel alone arm completed the study, defined in this study as completing 10 cycles of treatment with docetaxel. The most common reasons for early discontinuation were AEs (n=36) in the LY2181308/docetaxel arm and progressive disease (n=13) in the docetaxel alone arm. The most common AE in the LY2181308/docetaxel arm was thrombocytopenia (Common Terminology Criteria for Adverse Events term platelets) (n=10; 10.2%) and in the docetaxel alone arm was sensory neuropathy (n=3; 5.9%).
- The median age at consent was 69.07 years in the LY2181308/docetaxel arm and 69.97 years in the docetaxel alone arm. Caucasians were the most common ethnic group in both treatment arms (LY2181308/docetaxel, 95.9%; docetaxel alone, 96.1%). The most common baseline ECOG PS score was 0 or 1 (LY2181308/docetaxel, 94.9%; docetaxel alone, 98.0%). Importantly, 52.3% of patients in this study had an ECOG PS of 0.
- Most patients in both arms had Stage IV disease at initial diagnosis (LY2181308/docetaxel, 36.7%; docetaxel alone, 45.1%). However, at time of initial diagnosis, patients with Stage II disease were more common in the LY2181308/docetaxel arm (28/98 [28.6%]) compared with the docetaxel alone arm (10/51 [19.6%]). These patients may have failed in the original curative treatment and presented at enrollment with metastatic disease. Based on the tumor node metastasis classification, this appears to be confirmed because a higher percentage of patients in the LY2181308/docetaxel arm than the docetaxel alone arm had lymph node N1 metastasis (16/98 [16.3%] versus 6/51 [11.8%], respectively).
- The majority of treated patients (98%) received prior therapy. Prior systemic therapy was reported by 92.9% of patients in the LY2181308/docetaxel arm and 90.2% of patients in the docetaxel alone arm. Radiotherapy was reported by 59.2% of patients in the LY2181308/docetaxel arm and 49.0% of patients in the docetaxel alone arm. Prior surgery was reported by 45.9% of patients in the LY2181308/docetaxel arm and 37.3% of patients in the docetaxel alone arm.

Efficacy:

Primary Efficacy

- The median PFS was 8.64 (90% confidence interval [CI], 7.39 to 10.45) months in the LY2181308/docetaxel arm and 9.00 (90% CI, 7.00 to 10.09) months in the docetaxel alone arm. The difference between treatments was not statistically significant (log rank p-value = 0.755).
- Among the baseline factors assessed, circulating tumor cell (CTC; high vs. low), disease stage group (1 and 2 vs. 3 and 4), and PSA (high vs. low) had statistically significant effects on PFS.

Secondary Efficacy

- The median OS was 27.04 (90% CI, 19.94 to 33.41) months with LY2181308/docetaxel and 29.04 (90% CI, 20.11 to 39.26) months with docetaxel alone (log-rank p-value = 0.838). The 12-month survival rate was 79% (90% CI, 71% to 85%) with LY2181308/docetaxel and 82% (90% CI, 70% to 89%) with docetaxel alone.
- The objective tumor response rate was 10.2% (90% CI, 6% to 17%) for LY2181308/docetaxel and 21.6% (90% CI, 13% to 33%) for docetaxel alone (Fisher's exact test p-value = 0.081). There were no complete responses in either arm.
- The median time to objective tumor response was 4.40 (90% CI, 4.17 to no upper limit) months for LY2181308/docetaxel and 5.52 (90% CI, 2.92 to 5.65) months for docetaxel alone (log rank p-value = 0.716).
- The median response duration was 9.66 (90% CI, 6.93 to 11.07) months for LY2181308/docetaxel and 10.81 (90% CI, 7.49 to 14.29) months for docetaxel alone (log rank p-value = 0.712).
- Prostate-specific antigen responses (that is, ≥50% reduction) were observed in both treatment arms and rates were comparable between arms. No statistically significant difference (p=0.856) was observed in PSA response rates between treatment arms, per Fisher's exact test.

Patient-reported Outcomes

- The BPI "pain at its worst in the last 24 hours" item scores and the 7 interference items were found to be generally consistent and comparable between treatment arms.
- Of the subgroup of patients whose baseline BPI "pain at its worst in the last 24 hours" score was between 3 and 6 (inclusive), a pain improvement was seen in both arms, with the percentage of patients achieving at least a 20% improvement from baseline peaking at a higher percentage for the docetaxel alone arm compared to the LY2181308/docetaxel arm (approximately 80% vs. 60%, respectively). However, the percentage of patients achieving at least a 30% improvement peaked at a similar percentage (around 60%) in both treatment arms.
- The FACT-P score and its related scores were also generally consistent and comparable between treatment arms at baseline and throughout the active period.

Pharmacokinetics

- LY2181308 PK data indicated that based on the different clearance pathways, LY2181308 PK was not influenced by docetaxel co-administration. The PK data supported the fact that serum creatinine and/or creatinine clearance was a statistically significant covariate on LY2181308 clearance.
- Docetaxel exposure (mean value and variability) was similar between the 2 arms, suggesting that the presence of LY2181308 did not influence docetaxel PK.

Pharmacodynamics

- Circulating tumor cells were correlated with the administration with docetaxel, but not with LY2181308 monotherapy.
- The CTC baseline levels were highly predictive of PFS; patients with high CTC values at baseline had a median PFS of 6.97 (90% CI: 5.95, 8.51) months, whereas patients with low CTC values at baseline had a median PFS of 11.40 (90% CI: 9.00, 12.45) months. However, the effect of CTC at baseline was similar in both treatment arms, and was not a confounding factor in the evaluation of PFS.

Pharmacogenetics

- Among 25 SNPs tested, the genotype frequency of 2 SNPs (*DNMBP* rs11190303 and *ABCB1* rs1045642 (3435C>T) significantly (unadjusted p-value <.1) differed between the 2 treatment arms of the total PGx population, but the differences were small.
- Most SNPs, except for *ABCB1* rs1045642 and *POR* rs17148944, were not significantly associated with PK parameters (unadjusted p-value >.1). *ABCB1* rs1045642 showed trend associations with AUC and C_{max} and

POR rs17148944 showed a trend association with C_{max}, but neither finding had any significant association with PFS (unadjusted p-values >.1) in either treatment arm.

- With respect to efficacy, 1 SNP in *ABCC2* (rs12762549) showed some evidence of association with better PFS (unadjusted p-value < .05) in the docetaxel alone arm but not in the LY2181308/docetaxel arm.

Safety

- The percentages of patients who had serious adverse events (SAEs) or who discontinued study drugs due to AEs or SAEs were higher in the LY2181308/docetaxel arm than in the docetaxel alone arm.
- Overall, 27 patients (27.6%) in the LY2181308/docetaxel arm had ≥1 SAE assessed as possibly related to study drug and, of these patients, 15 had ≥1 SAE assessed as possibly related to LY2181308 alone. In the docetaxel alone arm, 9.8% (n=5) of patients had ≥1 SAE assessed as possibly related to study drug. Three patients in the LY2181308/docetaxel arm and 1 patient in the docetaxel arm discontinued the study due to possibly study-drug related SAEs.
- Overall, although SAEs were reported more frequently by patients in the LY2181308/docetaxel arm than in the docetaxel alone arm, the observed AE profile was consistent with the known safety profiles of LY2181308 and docetaxel.

Conclusions:

- No statistically significant difference in PFS was observed between the LY2181308/docetaxel and docetaxel alone treatment arms.
- Docetaxel activity as determined by PFS and OS was higher than anticipated in both arms.
- Safety of LY2181308 in combination with docetaxel was acceptable.
- The PD evaluation suggests that docetaxel activity and the combination with LY2181308 was not significantly different between treatment arms.
- The LY2181308 PK profile was consistent with previous studies, and achieved levels at which survivin inhibition was expected to occur.
- Patient-reported outcomes were consistent with known docetaxel activity.