SYNOPSIS

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Name of Sponsor/Company	Ortho Biotech Oncology Research & Development Unit of Johnson & Johnson Pharmaceutical Research & Development, L.L.C
Name of Finished Product	R031059, DOXIL®/CAELYX®
Name of Active Ingredient(s)	doxorubicin HCl

Protocol No.: DOXIL-BCA-3001

Title of Study: A Randomized Controlled Study of Docetaxel Monotherapy or DOXIL®/CAELYX® and Docetaxel for the Treatment of Advanced Breast Cancer

Principal Investigator: Joseph Sparano, M.D., Montefiore Medical Center, [redacted]

Publication (Reference): none

Study Period: Study start (first subject randomized): 16 September 2004; Date last subject randomized: 29 November 2006; Date of data cutoff: 15 February 2008.

Phase of Development: 3

Objectives: The primary objective of this study was to evaluate whether the time to progression for the DOXIL/CAELYX and docetaxel combination therapy group was superior to that of the group treated with docetaxel monotherapy.

Secondary objectives were to compare the treatment groups for overall survival, response rate (complete plus partial responses), the effect of treatment on patient-reported outcomes using the Functional Assessment of Cancer Therapy-Breast (FACT-B) instrument, and the safety profile.

Pharmacogenomic studies (e.g., hemochromatosis gene [HFE] genotypes) were planned to evaluate the relationship between genes that might increase the likelihood of anthracyclines-induced cardiotoxicity and clinical events observed during the study treatment. These data are not included in this clinical study report, but will be analyzed and presented separately.

Methods: This was a randomized, active control, parallel-group, open-label, multicenter study designed to determine if women with locally advanced or metastatic breast cancer, who were previously treated with prior anthracycline therapy in the neoadjuvant or adjuvant setting, and who also had a disease-free interval of at least 12 months since the end of their last cytotoxic therapy, would benefit from the addition of DOXIL/CAELYX to docetaxel therapy. Prior to random assignment to treatment, subjects were assigned to strata according to whether they received prior cytotoxic chemotherapy for advanced disease (yes, no) and their Eastern Cooperative Oncology Group (ECOG) Performance Status scores (0, 1, 2) at baseline. Subjects were randomly assigned in a 1:1 allocation within each stratum to receive either docetaxel (75 mg/m^2 on Day 1 of every 21-day cycle) or DOXIL/CAELYX (30 mg/m^2) followed by docetaxel (60 mg/m^2) on Day 1 of every 21-day cycle. Disease assessments were to occur at the end of Cycles 2, 4, 6, and 8, and then every 3 cycles until 52 weeks after the start of the study medication, and then every 4 cycles until disease progression. For subjects who discontinued study medication prior to disease progression, disease assessments were to occur every 6 weeks for the first 24 weeks after the start of study medication, and then every 9 weeks from 25 weeks to 52 weeks after the start of study medication, and then every 12 weeks until disease progression.

Number of Subjects (planned and analyzed): The total number of subjects planned was 720 (n=360 subjects per treatment group) and the total number of subjects randomized was 751 (n=373 in the docetaxel monotherapy group; n=378 in the DOXIL/CAELYX and docetaxel combination therapy group). The total number of subjects analyzed included 751 subjects (n=373 in the docetaxel

monotherapy group; n=378 in the DOXIL/CAELYX and docetaxel combination therapy group) in the intent-to-treat population (ITT), 750 subjects in the safety population (n=373 in the docetaxel monotherapy group; n=377 in DOXIL/CAELYX and docetaxel combination therapy group), and 734 subjects in the evaluable population (n=364 in the docetaxel monotherapy group; n=370 in the DOXIL/CAELYX and docetaxel combination therapy group)

Diagnosis and Main Criteria for Inclusion: Subjects with locally advanced or metastatic breast cancer who received prior anthracycline therapy in the neoadjuvant or adjuvant setting, and had at least a 12-month disease-free interval since the end of their last cytotoxic therapy, were eligible for the study. The study population included subjects who received prior hormonal therapy, or no more than 1 cytotoxic chemotherapy regimen (anthracyclines, taxanes, or antitubulin agents were not permitted), or both for advanced disease. Subjects had normal cardiac function, as evidenced by a normal LVEF.

Test Product, Dose and Mode of Administration, Batch No.: DOXIL/CAELYX 30 mg/m^2 was administered by intravenous infusion to subjects in the DOXIL/CAELYX and docetaxel combination therapy group, followed by docetaxel (60 mg/m^2) on Day 1 of every 21-day cycle. The first infusion of DOXIL/CAELYX was administered over 90 minutes, at a rate specified in the protocol. Subsequent doses of DOXIL/CAELYX were administered over 1 hour, as tolerated. Dose reductions for adverse reactions and delays to allow for recovery from toxic effects were permitted as specified in the protocol.

Bulk lot numbers for DOXIL/CAELYX: 0316184, 0412850, 0523118, 0533090, 0604145, 0616730, 0625059, and 0703386.

Reference Therapy, Dose and Mode of Administration, Batch No: Docetaxel (75 mg/m^2 or 60 mg/m^2) was administered by intravenous infusion (over 1 hour on Day 1 of every 21-day cycle) to subjects in the docetaxel monotherapy group or the DOXIL/CAELYX and docetaxel combination therapy group, respectively.

Bulk lot numbers for docetaxel (20mg): 4B0984A034, D4C154, D4D313, D5G566, D5H085, D6A052, D6A600, D6C600, and D6D333.

Bulk lot numbers for docetaxel (80mg): AQ8213T813, 4D3034D332, D4C155, D4D089, D5G570, D5H004, D6A272, D6C490, D6D367, and D6E607.

Duration of Treatment: Treatment was to continue until disease progression or the occurrence of unacceptable treatment-related toxicity. In the absence of progression and unacceptable treatment-related toxicity, treatment was to continue for at least 2 cycles after a complete response was confirmed. Similarly, for subjects with a partial response or stable disease, treatment could continue after a maximum objective response was obtained, unless the subject experienced unacceptable treatment-related toxicity.

Criteria for Evaluation:

Efficacy: The primary endpoint of this study was time to progression, the interval between the date of randomization and the date of disease progression or death due to progression. The key secondary endpoints were overall survival (the interval between the date of randomization and the subject's death from any cause), and the response rate (the proportion of subjects in the evaluable population who achieved a complete or partial response). Other efficacy endpoints included progression-free survival, and duration of response. Progression-free survival was defined similarly to time to progression; the only difference was that all deaths, regardless of the cause, were considered as events. The duration of response was defined as the time period from the first evaluation at which a subject had a durable response to the first evaluation at which a subject had disease progression, or death due to any cause. For subjects who remained on study without documented disease progression at the time of the data cutoff, the data were censored at the date of the last tumor assessment.

Safety: Safety variables included adverse event reports, changes in clinical laboratory findings, and tests for cardiac function (multiple gated acquisition scan [MUGA]/echocardiogram and electrocardiogram).

SYNOPSIS (CONTINUED)

Patient-reported outcomes: Breast-cancer-related patient-reported outcomes were measured using the Functional Assessment of Cancer Therapy-Breast (FACT-B), a self-administered instrument.

Statistical Methods: The analysis sets included the ITT population (all randomized subjects), the safety population (all subjects who received at least 1 dose of study medication [DOXIL/CAELYX or docetaxel]), and the evaluable population (all randomized subjects who received at least 1 dose of study medication [docetaxel or DOXIL/CAELYX] and who had at least 1 postbaseline tumor assessment).

Sample Size Determination: The sample size for this study was estimated using the assumption that the time to progression for the docetaxel treatment group would be 6 months. Approximately 720 subjects (360 per treatment group) were to be randomized to observe 485 progression events. The study was designed to detect an improvement in median time to progression from 6 months to 7.8 months (corresponding to a hazard ratio of 0.77 for the DOXIL/CAELYX and docetaxel combination therapy group relative to the docetaxel monotherapy group under the proportional hazards assumption) with more than 80% power while maintaining an overall significance level of 5% (2-sided). This study was also powered for overall survival. Subjects will be followed until approximately 485 deaths occur, which will provide greater than 80% power to detect an improvement in overall survival from 15 months to 19.5 months.

Primary Efficacy Analysis: The primary endpoint, time to progression, was based on independent review for the ITT population. The distribution of time to progression was estimated for each treatment group using the Kaplan-Meier method, and was compared between the 2 treatment groups using the stratified log-rank test. The hazard ratio of DOXIL/CAELYX combination therapy over docetaxel monotherapy and corresponding 95% CI was estimated using the stratified Cox regression procedure. Hazard ratios less than 1 indicated a result that favored the DOXIL/CAELYX and docetaxel combination therapy group. The final and only analysis for time to progression, was conducted after 555 events (progression or death due to progression) had occurred. This included 288 events in the docetaxel monotherapy group and 267 events in the DOXIL/CAELYX and docetaxel combination therapy group.

Secondary Efficacy Analyses: The key secondary efficacy analyses included comparisons of the overall survival and the response rates (by independent review) of the 2 treatment groups. Similar analyses were applied to overall survival as those used for the primary efficacy time to progression endpoint. Comparison of the overall response rate (complete response + partial response) between the 2 treatment groups was performed on the evaluable population using the Cochran-Mantel-Haenszel test and controlling for the enrollment strata. Response rate and the associated 95% confidence intervals were provided for each treatment group.

The primary FACT-B analysis used a t-test to compare the change of trial outcome index from baseline (i.e., Day 1 or Cycle1) to the last postbaseline evaluation between treatment groups. Descriptive statistics were presented for baseline trial outcome index, the change of trial outcome index from baseline to the last postbaseline evaluation, and the value and change of trial outcome index by evaluation visit. Similar analyses were reported for secondary FACT-B endpoints including the FACT-B total score and the individual subscales.

Other Efficacy Analyses: The analyses for progression-free survival, as determined by independent review, were similar to those performed for the time to progression endpoint. For subjects who were progression free and alive at the time of data cutoff, the data were censored at the date of the subject's last tumor assessment. The duration of response analysis includes only subjects who had a confirmed response. The median duration of response was estimated for each treatment group using the Kaplan-Meier method.

RESULTS

The demographic and baseline disease characteristics of the ITT analysis set were generally consistent with the inclusion and exclusion criteria and were balanced between the treatment groups. The median prior cumulative dose of anthracyclines (in doxorubicin equivalent) was 245 mg/m^2. Ninety-eight percent of subjects received prior alkylating agents and 75% received prior antimetabolites in the neoadjuvant or adjuvant setting.

SYNOPSIS (CONTINUED)

The mean and median cycle lengths were similar between the 2 treatment groups and were consistent with the protocol planned 21 days. The median of the mean dose of docetaxel administered per dose was 75 mg/m^2 for the docetaxel monotherapy group and 59.89 mg/m^2 for the DOXIL/CAELYX and docetaxel combination therapy group, consistent with the protocol specified initial doses (75 mg/m^2 and 60 mg/m^2 per administration, respectively). Similarly, the median of the mean dose of DOXIL/CAELYX administered per dose was 29.78 mg/m^2, consistent with the protocol-specified initial dose of 30 mg/m^2 per administration.

The median number of cycles of DOXIL/CAELYX treatment was 5 and the median number of cycles of docetaxel treatment (in both treatment groups) was 6. In the DOXIL/CAELYX and docetaxel combination therapy group, 28% of subjects discontinued DOXIL/CAELYX treatment but continued docetaxel only treatment; no subjects discontinued treatment with docetaxel and continued with DOXIL/CAELYX treatment. The median cumulative dose of DOXIL/CAELYX was 143.69 mg/m^2 (range, 28.5 to 925.4 mg/m^2). The median cumulative dose of docetaxel was higher in the docetaxel monotherapy group compared with the DOXIL/CAELYX and docetaxel combination therapy group (451.92 mg/m^2 versus 375.00 mg/m^2) and corresponds to the higher dose of docetaxel administered (75 mg/m^2 versus 60 mg/m^2) in the docetaxel monotherapy group.

The median end-of-treatment cumulative anthracycline dose in the DOXIL/CAELYX and docetaxel combination therapy group was 402.7 mg/m^2 (range: 30 to 1,147 mg/m^2) (in doxorubicin equivalent). Seventy-six subjects in the DOXIL/CAELYX and docetaxel combination therapy group received an end-of-treatment cumulative anthracycline dose of more than 500 mg/m^2.

The most common reason for discontinuation was progressive disease (54%). Discontinuations of all treatment due to an adverse event included 13% of subjects in the DOXIL/CAELYX and docetaxel combination therapy group and 8% of subjects in the docetaxel monotherapy group.

EFFICACY RESULTS: In the protocol-specified primary efficacy analysis, DOXIL/CAELYX and docetaxel combination therapy resulted in a 35% risk reduction for developing disease progression compared with the docetaxel monotherapy group (HR=0.65; 95% CI: 0.55, 0.77; p=0.000001). Median time to progression was 7.0 months for the subjects treated with docetaxel monotherapy and 9.8 months for those treated with DOXIL/CAELYX and docetaxel combination therapy. The primary analysis was robust and internally consistent as shown in multiple prespecified sensitivity analyses and clinically relevant subgroup analyses.

A statistically significant improvement in progression-free survival was also demonstrated in the DOXIL/CAELYX combination therapy group compared with the docetaxel monotherapy group (HR=0.66; 95% CI: 0.56, 0.78; p=0.000001). The median progression-free survival was 6.9 months for the docetaxel monotherapy group compared with 9.5 months for the DOXIL/CAELYX and docetaxel combination therapy group.

The DOXIL/CAELYX and docetaxel combination therapy group had a significantly higher response rate compared with the docetaxel monotherapy group (35% versus 26% respectively, p=0.0085) and the median duration of response was longer in the DOXIL/CAELYX and docetaxel combination therapy group compared with the docetaxel monotherapy group (8.8 months versus 7.4 months, respectively). The best response rate assessed by independent review showed that 15% of subjects in the docetaxel monotherapy group were primarily refractory to treatment (i.e., best response during the study was progressive disease). In contrast, 8% of subjects who received DOXIL/CAELYX and docetaxel combination therapy were primarily refractory to treatment.

Overall survival was similar between the docetaxel monotherapy group and the DOXIL/CAELYX and docetaxel combination therapy group at the time of the interim analysis (HR=1.06; 95% CI: 0.86, 1.30; p=0.5988). The median overall survival was 20.7 months for the docetaxel monotherapy group and 20.4 months for the DOXIL/CAELYX and docetaxel combination therapy group. At the data cutoff, 374 (50%) subjects had died. There was an early trend favoring the DOXIL/CAELYX and docetaxel combination therapy group; the 1-year survival rate was 69% for the docetaxel monotherapy group and 75% for the DOXIL/CAELYX and docetaxel combination therapy group. Of note is that approximately 70% of subjects in both groups had received subsequent anti-cancer therapy. The survival follow-up will continue and the planned final analysis will be performed when approximately 485 deaths have occurred.

SYNOPSIS (CONTINUED)

SAFETY RESULTS: The safety profile of the DOXIL/CAELYX and docetaxel combination was as expected and consistent with the known toxicities of the 2 agents. The incidence of Grade 3 or 4 adverse events and serious adverse was similar for the docetaxel monotherapy group (72% and 16%, respectively) and the DOXIL/CAELYX and docetaxel combination therapy group (78% and 18%, respectively).

The incidence of cardiac events was similar in the docetaxel monotherapy group and DOXIL/CAELYX and docetaxel combination therapy group (8% and 12%, respectively). Symptomatic cardiac events (severity of Grade 2 or higher) were reported in 4% of subjects in the docetaxel monotherapy group and 5% of subjects in the DOXIL/CAELYX and docetaxel combination therapy group. Of the reported symptomatic cardiac events, congestive heart failure was reported in 4 (1%) subjects in the docetaxel monotherapy group and 3 (1%) subjects in the DOXIL/CAELYX and docetaxel combination therapy group. Protocol-defined LVEF decreases from baseline were reported in 5% of the subjects in both treatment groups. The median decrease of LVEF from baseline to last evaluation was the same (1%) for both treatment groups. Of the 77 subjects in the DOXIL/CAELYX and docetaxel combination therapy group who received an end-of-treatment cumulative dose of anthracycline of 500 mg/m^2 or higher, 1 subject had a protocol-defined LVEF decrease (baseline LVEF was 59% and worst LVEF on treatment was 53%) and no subjects had congestive heart failure.

The incidence of myelosuppression was also similar between the 2 treatment groups. Grade 3 or 4 neutropenia was reported in 59% of subjects in the docetaxel monotherapy group and 57% of subjects in the DOXIL/CAELYX and docetaxel combination therapy group. The incidence of febrile neutropenia was low in both the docetaxel monotherapy and DOXIL/CAELYX and docetaxel combination therapy groups (6% and 7% of subjects, respectively). Less than 1% of subjects in both groups experienced Grade 3 thrombocytopenia. No Grade 4 thrombocytopenia was reported. Grade 3 anemia was reported in 2% or less of subjects in both groups. No Grade 4 anemia was reported.

There was an increased incidence of hand-foot syndrome and stomatitis in the DOXIL/CAELYX and docetaxel combination therapy group compared with the docetaxel monotherapy group. Hand-foot syndrome was reported 1% of subjects in the docetaxel monotherapy group and in 61% of the subjects in the DOXIL/CAELYX combination therapy group (24% of subjects with Grade 3 and 1% of subjects with Grade 4). Stomatitis was reported in 14% of subjects in the docetaxel monotherapy group (1% of subjects with Grade 3) and in 52% of subjects in the DOXIL/CAELYX combination therapy group (11% of subjects with Grade 3 and less than 1% of subjects with Grade 4). Hand-foot syndrome and stomatitis led to discontinuation of DOXIL/CAELYX treatment in 77 (20%) subjects and 22 (6%) ubjects, respectively.

Infusion reactions were reported in 1% of subjects in the docetaxel monotherapy group and 7% of subjects in the DOXIL/CAELYX and docetaxel combination therapy group. Grade 3 infusion reactions were reported in 2 (1)% subjects in the DOXIL/CAELYX and docetaxel combination therapy group. No Grade 4 infusion reactions were reported. A Grade 3 hypersensitivity reaction led to discontinuation of docetaxel treatment in 1 subject in the docetaxel monotherapy group and to discontinuation of DOXIL/CAELYX treatment in 1 subject in the DOXIL/CAELYX and docetaxel combination therapy group.

The incidence of peripheral neuropathy was similar in the docetaxel monotherapy group (19%) and the DOXIL/CAELYX and docetaxel combination therapy group (21%). The incidence of Grade 3 or worse peripheral neuropathy was low in both treatment groups (1% or less).

The number of deaths occurring within 30 days of the last dose of study medication was similar with 13 (3%) deaths in the docetaxel monotherapy group and 10 (3%) deaths in the DOXIL/CAELYX and docetaxel combination therapy group. No primary causes of deaths in the DOXIL/CAELYX and docetaxel combination therapy group that occurred during the conduct of the study were judged by the investigator to be related to study medication.

CONCLUSION: DOXIL/CAELYX and docetaxel combination therapy provides clinically meaningful benefit for patients with locally advanced or metastatic breast cancer who received prior anthracycline therapy. Treatment with DOXIL/CAELYX and docetaxel combination therapy resulted in a 35% risk reduction in developing progressive disease ($p=0.000001$) and a significant improvement in overall response rate (35% versus 26%; $p=0.0085$) when compared with docetaxel monotherapy. The safety

SYNOPSIS (CONTINUED)

profile of the DOXIL/CAELYX and docetaxel combination was as expected and consistent with the known toxicities of the 2 agents. Consistent with the results of a previous randomized controlled study of DOXIL/CAELYX, the results of this study confirm the cardiac safety of DOXIL/CAELYX in a patient population with substantial prior exposure to conventional anthracyclines. DOXIL/CAELYX in combination with docetaxel is safe and effective in women with locally advanced or metastatic breast cancer following prior anthracycline therapy in the neoadjuvant or adjuvant setting.

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