1. PROTOCOL TITLE

A Randomized, Open-Label Trial Comparing Treatment with Either Pegylated Liposomal Doxorubicin or Capecitabine as First Line Chemotherapy for Metastatic Breast Cancer in Women 60 Years and Older

2. OBJECTIVES

Primary Objective:

- To compare the time to disease progression (TTP) in older women with metastatic breast cancer treated with pegylated liposomal doxorubicin (PLD) or capecitabine.

Secondary Objectives:

- To compare the overall response rates (complete response [CR] + partial response [PR]) between the 2 treatment groups.
- To compare overall survival between the 2 treatment groups.
- To evaluate the effects of PLD and capecitabine on older women's quality of life measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and Subjective Significance Questionnaire (SSQ).
- To compare the safety/tolerability between the 2 treatment groups.

Studies were planned to evaluate the relationship between circulating tumor cells (CTCs) and response to therapy and disease progression. These data were to be analyzed and reported separately from the clinical study report.

3. STUDY DESIGN

This was an open-label, randomized, multi-center study comparing PLD and capecitabine as first line chemotherapy for metastatic breast cancer in women 60 years of age or older. An amendment to the protocol was issued in November 2004 to widen the eligibility criteria by lowering the minimum age from 65 to 60 years of age, among other minor modifications. The study consisted of a screening phase, a treatment phase of up to 1 year, and a post-treatment (follow-up) phase. Regularly scheduled evaluations were performed to assess patient safety and efficacy.

4. DOSAGE AND ADMINISTRATION

Subjects were randomly assigned to one of two treatment groups (PLD or capecitabine) in a 1:1 fashion. PLD 40 mg/m^2 was administered intravenously (IV) over 1 to 2 hours on Day 1 of each 28-day cycle. PLD was diluted in 5% dextrose prior to infusion.

Capecitabine (500-mg tablets) was dosed orally at 1000 mg/m^2 twice a day (b.i.d.) for 14 consecutive days (Days 1 to 14) of each 21-day cycle, followed by a 7-day rest period. Dosing was to occur with meals.

The planned duration of treatment was 1 year in the absence of disease progression or unacceptable toxicity.

5. STUDY POPULATION

Eligible patients were women aged 60 years and older with clinically or pathologically confirmed diagnosis of metastatic breast cancer, no prior chemotherapy for metastatic disease (prior hormonal therapy or chemotherapy in an adjunctive setting and/or trastuzumab [Herceptin] as monotherapy in a metastatic setting was permitted), no history of treatment with PLD or capecitabine in an adjunctive setting, no evidence of anthracycline-resistant disease, and no history of cardiac disease (New York Heart Association ≥ Class II) or clinical evidence of congestive heart failure.

62 of the planned 300 patients were enrolled in the study, including 33 who were assigned to the PLD treatment group and 29 who were assigned to the capecitabine group. The Sponsor terminated the study due to poor accrual after 20 months of enrollment and despite implementing numerous accrual initiatives.

6. EFFICACY/SAFETY RESULTS

As a result of the premature study termination, the protocol-specified efficacy analyses including time to disease progression, overall response rate, and survival between the 2 treatment groups could not be performed. Physician assessments of best response were reported as follows - 16 patients in the PLD group and 13 patients in the capecitabine group had a response of stable disease or better, with 4 patients in the PLD group and 6 patients in the capecitabine group having a complete or partial response.

Approximately 90% of patients in each treatment group reported 1 or more adverse event. The majority of the reported adverse events were either toxicity grade 1 or grade 2 based on NCI-CTC version 2. There was a numerically lower incidence of hand-foot syndrome and diarrhea in patients who received PLD as compared to patients who received capecitabine. Death was reported for 13 patients (7 in the PLD group, 6 in the capecitabine group); 1 patient died after enrollment but prior to receiving the first dose of study medication. Four of the 13 patients had adverse events with an outcome of death. The remaining 8 patients died more than 30 days after the end of study treatment.

7. CONCLUSIONS

21% of the planned enrollment of 300 patients was achieved before the study was terminated after numerous accrual initiatives were implemented. Too few patients were enrolled to allow formal

conclusions. As a result, the primary objective of TTP could not be calculated and evaluation of the secondary objectives could not be performed. With regard to safety, adverse events reported for PLD and capecitabine were consistent with the known profile reported in their respective prescribing information.

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