SYNOPSIS

Issue Date: 17 Jan 2011

Name of Sponsor/Company	Ortho Biotech Oncology Research & Development, Unit of Centocor Research & Development, Inc
Name of Finished Product	Siltuximab
Name of Active Ingredient(s)	CNTO 328

Protocol No.: C0328T04

Title of Study: A Phase 1 Study of a Chimeric Antibody Against Interleukin-6 (CNTO 328) Combined with Docetaxel in Subjects with Metastatic Hormone-Refractory Prostate Cancer.

Coordinating/Principal Investigator: Gary Hudes, MD- Fox Chase Cancer Center, Philadelphia, PA USA

Publication (Reference): None

Study Period: 11 Oct 2005 to 19 Jan 2010

Phase of Development: 1

Objectives: The primary objective was to assess the safety and tolerability of multiple dosing regimens of CNTO 328 when administered in combination with docetaxel in subjects with metastatic hormone-refractory prostate cancer (HRPC). In addition, the pharmacokinetics of docetaxel when administered alone and in combination with CNTO 328 were assessed.

The secondary objectives were to evaluate the efficacy and pharmacodynamics of CNTO 328 administered in combination with docetaxel in the treatment of subjects with metastatic HRPC. In a limited number of subjects, the pharmacokinetics of CNTO 328 alone and in combination with docetaxel were also evaluated.

Methods: This was an open-label, multicenter, Phase 1 nonrandomized study to assess the safety and pharmacokinetics of the combination of CNTO 328 and docetaxel in subjects with metastatic HRPC. The study was conducted in 4 phases: Screening, Run-in Phase, Cycles 1 through 17, and the Follow-up Period. After all screening procedures, eligible subjects entered a 2- or 3-week Run-in Phase, and received intravenous (IV) docetaxel 75 mg/m^2 or CNTO 328 at the assigned dosage regimen. The subjects who were able to tolerate single-agent docetaxel or CNTO 328 during the Run-in Phase were assigned combination treatment beginning with Cycle 1, and received treatment up to 14 cycles provided there was no evidence of disease progression or unacceptable toxicity. However, subjects responding to treatment with at least stable disease (SD) after 14 cycles were permitted to receive 3 additional cycles of treatment. A dose delay of $\leq$ 2 weeks was permitted with either CNTO 328 or docetaxel, and no more than 2 dose delays for each subject was allowed during the study for either study treatment. Dose reductions for docetaxel toxicity were permitted once during the entire course of treatment. If a dose reduction was required, docetaxel 75 mg/m^2 was reduced to 60 mg/m^2 for all subsequent cycles. Dose reductions for CNTO 328 were not permitted. Safety and pharmacokinetics of multiple regimens of CNTO 328 administered in combination with docetaxel were evaluated starting with Cycle 1. Safety, pharmacokinetics, pharmacodynamics, and immunogenicity were also evaluated during the Follow-up Period. Subjects were followed every 3 months for approximately 1 year after the last study agent administration to assess disease status and survival. Tumor response to treatment was evaluated by the

radiologist at the site and was assessed using the modified World Health Organization (WHO) criteria. Radiologic assessments were performed at screening, within 7 days prior to Cycle 3, then every 3 cycles (up to 7 days prior) throughout the study, and at the End of Treatment Visit. Serum prostate specific antigen (PSA) was evaluated every 3 weeks until progressive disease.

Number of Subjects (planned and analyzed): A total of 40 subjects consented in the study, which was 7 subjects more than planned for the study. Of the 40 subjects, 39 subjects received treatment and were analyzed, 1 subject was never treated due to an adverse event (AE) during screening.

Diagnosis and Main Criteria for Inclusion: Male subjects of ≥ 18 years of age, histologically or cytologically confirmed adenocarcinoma of the prostate and radiologically documented metastatic disease were included in the study. Prior systemic chemotherapy for metastatic HRPC was not allowed. Subjects who had prostate cancer that did not express serum PSA or had PSA values of < 5.0 ng/mL at screening were excluded from the study. Also subjects who received any investigational drug/agent within 30 days or 5 half-lives (whichever is longer) or had prior use of radionucleotide therapy were not included in the study.

Test Product, Dose and Mode of Administration, Batch No.: CNTO 328 was supplied as 100 mg vials containing 5 mL liquid at a concentration of 20 mg/mL. The sites used commercially available docetaxel for administration in this study.

CNTO 328 and docetaxel were administered IV in the three dose regimens as follows:

Dose Cohort 1A (6 subjects)

Run-in Phase: Docetaxel 75 mg/m^2

Treatment Phase: Docetaxel 75 mg/m^2 every 3 weeks plus 6 mg/kg CNTO 328 every 2 weeks

Dose Cohort 1B (3 subjects)

Run-in Phase: 6 mg/kg CNTO 328

Treatment Phase: Docetaxel 75 mg/m^2 every 3 weeks plus 6 mg/kg CNTO 328 every 2 weeks

Dose Cohort 2 (6 subjects in Dose Escalation Phase) + (6 subjects in Dose Expansion Phase)

Run-in Phase: Docetaxel 75 mg/m^2

Treatment Phase: Docetaxel 75 mg/m^2 every 3 weeks plus 9 mg/kg CNTO 328 every 3 weeks

Dose Cohort 3 (6 subjects in Dose Escalation Phase) + (6 subjects in Dose Expansion Phase)

Run-in Phase: Docetaxel 75 mg/m^2

Treatment Phase: Docetaxel 75 mg/m^2 every 3 weeks plus 12 mg/kg CNTO 328 every 3 weeks

Lot numbers used (CNTO 328): D04PJ7380, D04PL7405, D06PJ7520, D06PM7543, D07PK7615, and DO4P27405.

Duration of Treatment:

Screening: Up to 4 weeks

Run-in Phase: Up to 3 weeks

Treatment Phase: 14 cycles (up to 46 weeks), and additional 3 cycles (up to 55 weeks)

Follow-up: 24 weeks

Post Treatment Follow-up: Every 3 Months for up to 1 year after the last study agent administration.

Criteria for Evaluation: All subjects who received at least 1 administration of either CNTO 328 or docetaxel, whether alone or in combination were evaluable for safety. Only subjects who had measurable disease at baseline according to modified WHO criteria were considered evaluable for tumor response.

Pharmacokinetic Evaluations: CNTO 328 concentration was determined from serum samples and docetaxel concentration was determined from plasma samples. Serum concentrations were also used to interpret the assay data for determination of antibodies to CNTO 328. The major pharmacokinetic parameters evaluated for docetaxel when administered alone and in combination with CNTO 328 included AUCinf, Cmax, t1/2, CL, and Vz. The pharmacokinetic parameters evaluated for CNTO 328 when administered alone and in combination with docetaxel included AUC(0-t), AUC(t1-t2), and Cmax.

Immunogenicity Evaluations: Immunogenicity was evaluated by detecting antibodies to CNTO 328 in serum samples prepared from blood drawn. Detection of antibodies to CNTO 328 was performed using a bridging immunoassay in which CNTO 328-derived reagents were used to capture and detect antibodies.

Pharmacodynamic Evaluations: Serum pharmacodynamic markers included C-reactive protein (CRP) and exploratory biomarkers related to angiogenesis included vascular endothelial growth factor (VEGF), fibroblastic growth factor (bFGF), and soluble fms-like tyrosine kinase 1 (sFlt-1). Circulating tumor cells (CTCs) were analyzed from whole blood.

Efficacy Evaluations: The efficacy assessments included radiologic responses to treatment (objective tumor response and duration of response) and serum PSA response (duration of PSA response, PSA reduction within 3 months and PSA progression).

Safety Evaluations: The safety evaluations included an assessment of all reported AEs, incidence of dose-limiting toxicity, Grade 3 or higher AEs, serious adverse events (SAEs), allergic reactions/hypersensitivity and cytokine release syndrome/acute infusion reactions, incidence of clinically important changes from baseline vital signs, neurologic exams, and laboratory parameters, incidence of new, clinically important electrocardiograms (ECGs), and deaths.

Statistical Methods: Descriptive statistics (eg, number of observations, means, standard deviations, medians, and ranges) were used to summarize data. No formal hypothesis testing was performed. No formal interim analysis was planned.

RESULTS:

STUDY POPULATION:

- The subjects were mostly Caucasian (87.2%), the overall median age was 66 years, and the overall median weight was 91.2 kg.
- Forty subjects were consented in this study. Of these, 39 subjects (12 each in Cohorts 1 and 2, and 15 in Cohort 3) received at least 1 dose of docetaxel administration either alone or in combination with CNTO 328, 37 subjects received combination treatment (CNTO 328 + docetaxel), and 1 subject was consented but never treated due to an AE.
- Median duration of exposure to CNTO 328 was 148.0 days and ranged from 1 to 912 days and median number of CNTO 328 administration was 8 (range 1 to 62). Median number of docetaxel treatment cycles was 8 (range 1 to 42), and 4 (10.3%) subjects received more than 14 cycles of docetaxel treatment.

EFFICACY RESULTS:

- Of 37 subjects receiving combination treatment, 23 (62.2%) subjects achieved a confirmed PSA response.
- PSA response rates in all three cohorts were similar (7 subjects in Cohort 1, 6 in Cohort 2, and 10 in Cohort 3).
- The median duration of PSA response was 184 days (range 30 to 463).
- Two confirmed and 2 unconfirmed radiologic PRs (as assessed by the investigator) were observed in the higher dose cohorts (9 mg/kg and 12 mg/kg CNTO 328).

PHARMACOKINETIC RESULTS:

- CNTO 328 serum concentration increased in a dose-proportional manner.
- Moderate accumulation occurred after repeated administrations of 9 mg/kg and 12 mg/kg of CNTO 328 once every 3 weeks and the accumulation was consistent with the previously reported 14-18 days half-life of CNTO 328.
- In the 14 evaluable subjects, the geometric mean for docetaxel Cmax for all cohorts in Cycle 2 of 1703.60 ng/mL was similar to the Run-in Phase geometric mean Cmax of 1795.60 ng/mL. In the 12 evaluable subjects, the geometric mean for docetaxel AUCinf for all cohorts in Cycle 2 of 74.35 ng.day/mL was similar to the Run-in Phase geometric mean AUCinf of 87.85 ng.day/mL.
- The pharmacokinetic profile of CNTO 328 in subjects with prostate cancer appears to be similar to previously reported single-agent pharmacokinetic data in renal cell carcinoma patients.

PHARMACODYNAMIC RESULTS:

- Strong CRP suppression was observed with CNTO 328 treatment in combination with docetaxel which was sustained throughout the treatment period.
- Treatment with CNTO 328 in combination with docetaxel did not show apparent effects on angiogenesis markers (VEGF, sFlt-1, and bFGF).

IMMUNOGENICITY RESULTS:

- None of the 26 evaluable subjects with appropriate samples were positive for antibodies to CNTO 328 at any timepoint tested.

SAFETY RESULTS:

- Dose escalation from 6 mg/kg once every 2 weeks to 9 mg/kg once every 3 weeks and 12 mg/kg once every 3 weeks was completed successfully.
- One DLT was observed at each dose level of CNTO 328, (Grade 3 dehydration in Cohort 1B, Grade 2 urticaria in Cohort 2, and Grade 3 GI bleeding due to duodenal ulcer in Cohort 3).
- The safety profile for all cohorts was similar. All subjects in the study had 1 or more AE; and 11 (100%), 10 (83.3%), and 12 (85.7%) subjects had 1 or more Grade 3 or higher AE in Cohorts 1, 2 and 3 respectively.
- Grade 3 or higher AEs were seen in most subjects regardless of CNTO 328 dose level. The most common (≥ 15%) Grade 3 or higher treatment-emergent AEs by preferred term were neutropenia (71.8%) which was reversible, leukopenia (61.5%), lymphopenia (28.2%), and fatigue and dyspnea (17.9% each).
- The most common SAEs reported to occur at a frequency of ≥ 5% were dyspnea, dehydration, pleural effusion (3 subjects each, 7.7%), and neutropenic infection, hypotension, syncope, pneumonitis, pneumonia (2 subjects each, 5.1%).

- Of 39 treated subjects, 35 (89.7%) subjects permanently discontinued study treatment prior to completion of Cycle 14. Twenty (51.3%) subjects discontinued combination treatment permanently due to AEs, 12 (30.8%) subjects discontinued treatment due to disease progression, 2 (5.1%) subjects discontinued treatment due to other reasons. and 1 (2.6%) subject died.
- One subject developed infusion related reaction, Grade 2 urticaria during first CNTO 328 infusion.
- Hematologic toxicities were seen as expected. However, these toxicities were reversible and did not appear to be cumulative.
- Two deaths were reported during study, 1 (Subject 0104-00002) due to sepsis during treatment and 1 (Subject 0101-00020) due to late complications of pneumonitis and pulmonary fibrosis.

STUDY LIMITATIONS: No notable study limitations were identified by the sponsor.

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