Synopsis (C0328T07)

Name of Sponsor/Company: Centocor, Inc	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 328		
Name of Active Ingredient: CNTO 328		

Protocol: C0328T07	**EudraCT No.:** 2006-001671-38

Title of the study: A Phase 2 Multicenter, Open-label Study of CNTO 328 (Anti-IL-6 Monoclonal Antibody) in Combination with Mitoxantrone versus Mitoxantrone in Subjects with Metastatic Hormone-Refractory Prostate Cancer (HRPC)

Principal/Coordinating Investigator(s): Gary Hudes, MD- Fox Chase Cancer Center, 333 Cottmann Avenue, Philadelphia, PA 19111, USA and Karim Fizazi, MD, PhD. – Institut Gustave Roussy, 39 Camille Desmoulins 94800, Villejuif, France

Study Center(s): The study was conducted in 31 investigational sites 21 sites in Europe and 10 in the US.

Publication (reference): None

Studied Period: 06 Nov 2006/03 Nov 2008	**Phase of Development:** 2

Objectives: The primary objective of Part 1 of this study was to assess the safety of CNTO 328 administered as an IV infusion in combination with mitoxantrone in subjects with metastatic hormone refractory prostate cancer (HRPC) (also known as, castration-resistant prostate cancer [CRPC]) who had received only one prior docetaxel-based chemotherapy regimen.
The primary objective of Part 2 was to compare CNTO 328 in combination with mitoxantrone versus mitoxantrone with respect to the progression free survival (PFS).
The secondary objectives of Part 2 were to evaluate and compare safety and other efficacy endpoints of CNTO 328 in combination with mitoxantrone versus mitoxantrone. In addition, pharmacodynamic biomarker and health outcomes responses were to be evaluated.

Methodology: This was a 2-part, open-label, multicenter, Phase 2 study of the safety and efficacy of the combination of CNTO 328 plus mitoxantrone versus mitoxantrone alone. The safety profile of the combination of CNTO 328 and mitoxantrone in Part 1 of the study (9 subjects) was evaluated by the Data Monitoring Committee before proceeding to Part 2. Part 2 was designed to test the hypothesis that treatment with the combination of CNTO 328 plus mitoxantrone is superior to treatment with mitoxantrone in prolongation of the PFS of subjects with CRPC. PFS for the 2 treatment arms was compared using log rank test at 2-sided level of significance of 0.05.
CNTO 328 dosing and enrollment were suspended by the internal Centocor Safety Board after an unplanned interim analysis showed numerically more deaths in the combination arm of the study (6 versus 1). The subsequent Independent Data Monitoring Committee (IDMC) review did not disclose any safety concerns; however, enrollment was prematurely stopped by the IDMC since an apparent imbalance in subject characteristics (favoring the mitoxantrone arm) made it very unlikely, in their view, that the study could achieve its primary efficacy endpoint.

Number of Subjects (Planned and Analyzed): 143 subjects were planned for this study. Nine subjects in Part 1 were treated. In Part 2, 97 subjects were randomized and analyzed for efficacy and 93 were treated and analyzed for safety. Total of 106 subjects were randomized and 102 subjects were treated.

Diagnosis and Main Criteria for Inclusion: To be eligible for the study, subjects were to have confirmed adenocarcinoma of the prostate and have disease progression within 6 months of cessation of prior docetaxel based therapy confirmed by serum prostate-specific antigen (PSA) or radiologic disease progression. Subjects should not have had prostate cancer that did not express PSA or PSA level is < 5.0 ng/mL at screening or received prior mitoxantrone treatment for CRPC.

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Test Product, Dose and Mode of Administration, Batch Number: In Part 1, subjects received mitoxantrone, prednisone, and CNTO 328 in combination. Mitoxantrone was administered at a dose of 12 mg/m^2 IV as a 30 minute infusion on Day 1 of each 3-week cycle, oral prednisone at a dose of 5 mg twice daily starting with the first administration of mitoxantrone, plus CNTO 328 at a dose of 6 mg/kg IV as a 2-hour infusion, starting Day 1 of Cycle 1 and continued every 2 weeks.
Part 2, mitoxantrone arm: Mitoxantrone was administered at a dose of 12 mg/m^2 IV as a 30 minute infusion on Day 1 of each 3-week cycle, oral prednisone at a dose of 5 mg twice daily starting with the first administration of mitoxantrone. CNTO 328 + mitoxantrone arm: Treatment with mitoxantrone (12 mg/m^2 IV as a 30 minute infusion on Day 1 of each 3-week cycle), oral prednisone (5 mg twice daily starting with the first administration of mitoxantrone) plus CNTO 328 (6 mg/kg IV as a 2 hour infusion, starting Day 1 of Cycle 1 to continue every 2 weeks).
Lot numbers used (CNTO 328): D05PA7410, D05PM7467, P06PJ7520

Reference Therapy, Dose and Mode of Administration: Part 2 mitoxantrone arm: treatment with mitoxantrone (12 mg/m^2 IV as a 30 minute infusion on Day 1 of each 3-week cycle) plus oral prednisone (5 mg twice daily starting with the first administration of mitoxantrone).

Duration of Treatment:
Screening: Up to 4 weeks
Treatment Phase: Up to approximately 7 months (10 cycles) for mitoxantrone treatment or up to 12 months for CNTO 328 treatment
Short-term Follow-up: Monthly for 2 months
Long-term Follow-up: Every 3 months to death or end of study

Criteria for Evaluation: All subjects who received at least 1 administration of study agent were considered evaluable for safety. Only subjects who have measurable disease at baseline were considered evaluable for tumor response.

Pharmacology/Pharmacodynamics:
Serum concentration of CNTO 328 were determined from serum samples prepared from blood drawn solely to interpret the assay data for determination of antibodies to CNTO 328.
Immunogenicity was to be evaluated by detecting antibodies to CNTO 328 in serum samples prepared from blood drawn. Detection of antibodies to CNTO 328 was to be performed using a bridging immunoassay in which CNTO 328-derived reagents were used to capture and also detect antibodies.
The major exploratory pharmacodynamic endpoints included: Percent change from baseline in C-reactive proten (CRP) and percent change from baseline in IL-6 levels (total and bioactive, if available).
Note: Samples for pharmacodynamic assessments were to be collected in Part 2 of the study. All pharmacodynamic results will be available in a separate technical report.

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Efficacy: Part 2, the randomized portion of this study was designed to test the hypothesis that treatment with the combination of CNTO 328 plus mitoxantrone is superior to treatment with mitoxantrone in prolongation of the PFS of subjects with CRPC. The primary analysis included all randomized subjects.
Two ad hoc analyses were performed to fully explore the primary endpoint of PFS.

Safety: The safety endpoints include the incidence of the each of the following: all AEs, Grade 3 or higher adverse events (AEs), serious adverse events (SAEs), Grade 2 allergic reactions/hypersensitivity (including drug fever), Grade 3 cytokine release syndrome/acute infusion reaction, incidence of clinically significant changes in safety-related laboratory parameters, incidence of new, clinically important electrocardiograms (ECGs), left ventricular ejection fraction (LVEF) and deaths.

Statistical Methods: For continuous parameters, number of observations, means, standard deviations, medians, and ranges were used. For discrete parameters, frequency was summarized. For time-to-event parameters, Kaplan-Meier estimates, hazard ratio and its 95% confidence interval were provided. PFS for the 2 treatment arms in Part 2 was compared using log rank test at 2–sided α level of 0.05.

SUMMARY – CONCLUSIONS

Study Population Results: The subjects were mostly Caucasians (93.4%), the overall median age was 67.5 years, and the overall median weight was 83.0 kg. The treatment groups were balanced across the demographic characteristics.
Nine subjects were treated in Part 1 of the study. In the randomized portion of the study, 49 and 48 subjects were randomized to receive mitoxantrone and the combination of mitoxantrone and CNTO 328 respectively. Of these, two subjects in each arm were randomized but not treated. Of the 4 randomized but not treated subjects, one subject withdrew consent due to randomization to mitoxantrone arm. The other three subjects all discontinued due to an AE.
In Part 2, 21 subjects (45.7%) discontinued CNTO 328 due to "other" reasons, 18 due to suspension of CNTO 328 by the Sponsor. The proportion of subjects who discontinued mitoxantrone prior to completion of the maximum 10 cycles was 8 (88.9%) in Part 1, 31 (66.0%) in the mitoxantrone arm of Part 2 and 38 (82.6%) in the CNTO 328 + mitoxantrone arm in Part 2. The most common reason for discontinuation of mitoxantrone was disease progression (30% and 35% in the mitoxantrone and the CNTO 328 + mitoxantrone arm respectively). Twelve subjects discontinued mitoxantrone due to AEs in the CNTO 328 + mitoxantrone arm as compared with 6 in the mitoxantrone arm. These were mostly hematologic in nature and not associated with clinical relevant outcomes like infection or febrile neutropenia.

Pharmacology/Pharmacodynamic Results:
Other pharmacodynamic results for biomarkers, CRP, IL-6, bone-specific alkaline phosphatase (BSAP), IL-10, CTx, and NTx including circulating tumor cells (CTuCs) will be discussed in a separate technical report.
No antibodies to CNTO 328 were detected in treated subjects with appropriate samples for immunogenicity assessment (2 subjects with appropriate samples in Part 1, 7 subjects with appropriate samples in the CNTO 328 + mitoxantrone arm of Part 2).

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Efficacy Results: The PFS in the mitoxantrone arm (228 days) was significantly higher than that in the CNTO 328 + mitoxantrone arm (97 days). The hazard ratio was 1.72 (p-value = 0.043, 95% CI = [1.01, 2.93]).
Two additional ad hoc analyses were performed:

- The exploratory by-quartile analysis suggested that apparent superiority of the mitoxantrone arm was driven by the particularly favorable PFS seen in subjects with the lowest exposure to mitoxantrone (Table 12). PFS in the mitoxantrone arm with the lowest dose intensity was considerably longer than that in the next highest quartiles, and was comparable to that experienced by subjects receiving the highest dose intensity of mitoxantrone. This is in contrast to the CNTO 328 + mitoxantrone arm where the predicted dose-response relationship for the cytotoxic was evident. Because this result is paradoxical, addition exploratory analyses were done.
- Censoring was considerably reduced when new PFS definitions were employed, and the PFS for the mitoxantrone arm was also shorter (Table 13). PFS for the CNTO 328 + mitoxantrone arm remained the same, consistent with the minor reduction in censoring seen for this arm. With the revised definition, the median PFS in the mitoxantrone arm (128 days) was not significantly different than the median PFS in the CNTO 328 + mitoxantrone arm (87 days, p value = 0.215). The hazard ratio (HR) was 1.33 (p-value = 0.215, 95% CI = [0.845, 2.103]).

Safety Results:

- Part 1 of the study demonstrated acceptable safety of the CNTO 328 + mitoxantrone combination.
- In Part 2, AEs and AEs of Grade 3 or higher occurred more frequently with the CNTO 328 + mitoxantrone combination than with mitoxantrone alone. This difference was most apparent for hematologic AEs (eg, neutropenia). However most of these were not associated with clinically relevant outcomes like infection or febrile neutropenia.
- SAEs occurred with equal frequency in both arms.
- Although dose delays and dose reductions of mitoxantrone occurred with equal frequency in both arms, treatment discontinuations due to AEs occurred more frequently in the CNTO 328 + mitoxantrone arm. Most of these discontinuations occurred during the first cycle of treatment.
- Major deviations from protocol defined study agent administrations were common in the CNTO 328 + mitoxantrone arm. Some of which were associated with serious consequences.
- More deaths occurred during the study in the CNTO 328 + mitoxantrone arm. Most of these deaths were due to disease progression.
- No important nonhematological laboratory differences were seen; in particular no clinically significant differences in lipid profiles, liver function tests, or cardiac effects were evident.
- No serious CNTO 328-related infusion reactions were reported.

Conclusions: Although a higher frequency of AEs (including Grade 3 or 4 AEs), SAEs, and treatment discontinuations were seen, the combination of CNTO 328 plus standard dose mitoxantrone and prednisone is a tolerable regimen. This study is best viewed as inconclusive due to the multiple biases in the study design and execution. However, in the absence of any demonstration of improved efficacy over standard mitoxantrone plus prednisone dosing, no further exploration of the combination is currently planned.

Date of Report: 24 Aug 2009

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