Synopsis (C1034T02)

Name of Sponsor/Company: Ortho Biotech Oncology Research & Development, Unit of Centocor Research & Development, Inc.	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 95		
Name of Active Ingredient: CNTO 95		

Protocol: C1034T02	**EudraCT No.:** 2004-002130-18

Title of the study: A Phase 1/2, Multi-Center, Blinded, Randomized, Controlled Study of the Safety and Efficacy of the Human Monoclonal Antibody to Human α_v Integrins (CNTO 95), Alone and in Combination with Dacarbazine, in Subjects with Stage IV Melanoma

Principal and Coordinating Investigators:
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Study Centers: Four study centers were initiated in Phase 1, and 3 enrolled subjects. In Phase 2, 37 study centers were initiated; 16 in the US, 7 in the UK, and 14 in Germany. Of those 37 study centers, 30 enrolled subjects; 13 in the US, 7 in the UK, and 10 in Germany.

Publication (reference): None.

Studied Period: 26 May 2005/23 Jun 2008	**Phase of Development:** 1/2

Objectives:
Primary Objective
The primary objectives of Phase 1, Part 1 of this study were to evaluate the safety and single-dose pharmacokinetics of CNTO 95 when administered alone. The primary objectives of Phase 1, Part 2 and Phase 2 of this study were to evaluate the safety and efficacy of CNTO 95, alone and in combination with DTIC, as compared to DTIC alone.
Secondary Objectives
The secondary objectives in all phases of the study were to assess the pharmacokinetics and pharmacodynamics of CNTO 95 when used alone or in combination with DTIC. In addition, in Phase 2 only, exploratory pharmacogenomics were evaluated in consenting subjects.

Methodology:
Phase 1
Phase 1 was nonrandomized, open-label, and conducted in 2 parts. In Part 1, subjects were administered 1 of 3 dose levels of single-agent CNTO 95 (3 mg/kg, 5 mg/kg, or 10 mg/kg). The Safety Data Monitoring Committee (SDMC) reviewed 21-day safety data from all subjects in a dose level prior to dose escalation. It was originally planned that if, after an evaluation of the preliminary single-dose pharmacokinetics, receptor saturation was not observed at the 3 mg/kg or 5 mg/kg dose level, that dose of CNTO 95 was to be discontinued in Part 1 and subjects were to be treated at the highest, documented safe dose level at which receptor saturation was observed. At the end of Part 1, the SDMC reviewed all available safety and preliminary single-dose pharmacokinetic data up to 21 days post first infusion from the last treated subject. In Part 2, up to 2 dose cohorts of the combination of DTIC and CNTO 95 were to be studied. DTIC 1000 mg/m2 was administered in combination with 5 mg/kg or 10 mg/kg of CNTO 95. The SDMC reviewed 21-day safety data from each dose cohort.

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When the maximum tolerated dose (MTD) was reached, or when the final dose cohort had been enrolled, the SDMC was to review all available safety and preliminary pharmacokinetic data up to 21 days post first infusion from the last treated subject to recommend a dose to be used in Phase 2.

Phase 2

Phase 2 was randomized, blinded, and controlled. Subjects were randomized to 1 of 4 treatment groups. Treatment groups with DTIC in combination with placebo or CNTO 95 were blinded, and single-agent CNTO 95 treatment groups were open-label. Subjects were stratified by site of metastases and by ECOG performance status at baseline. An independent Data Monitoring Committee (DMC) monitored unblinded safety data during the study. In addition, in Phase 2, subjects who experienced disease progression in the DTIC plus placebo treatment group could cross over to open-label DTIC plus 10 mg/kg CNTO 95 or 10 mg/kg CNTO 95 alone. Response to treatment, in all groups (Phase 1 and 2), was to be evaluated by a site radiologist blinded to treatment assignments.

In either phase of the study, subjects unable to tolerate DTIC after 2 dose reductions had the option to receive CNTO 95 alone. For the determination of serum CNTO 95 concentrations, intensive and sparse serum samples were collected from all Phase 1 and Phase 2 subjects, respectively. The incidence of antibodies to CNTO 95 was determined for all subjects at baseline, the final visit, and during the follow-up period.

Number of Subjects (Planned and Analyzed): In Phase 1, up to 30 subjects were planned to be enrolled: 9 to 18 subjects in Part 1 and 6 to 12 subjects in Part 2; 15 subjects were treated. In Phase 2, a total of 120 subjects were planned to be enrolled; 129 were randomized, and 127 were treated.

Diagnosis and Main Criteria for Inclusion: Subjects with metastatic melanoma and measurable disease with an ECOG performance status of ≤ 2 and no clinical or radiological evidence of brain metastases who were ≥ 18 years. In Phase 1, the study population was to include subjects with American Joint Committee on Cancer (AJCC) Stage III unresectable or Stage IV melanoma; prior chemotherapy for metastatic melanoma was allowed. In Phase 2, subjects were to have AJCC Stage IV melanoma and no prior chemotherapy.

Test Product, Dose and Mode of Administration, Batch Number: CNTO 95 was supplied at a concentration of 20 mg/mL (a total of 106 mg/vial). The study agent was administered intravenously at the specified doses and dosing schedule. All subjects received study agent from cell line C1034I. The CNTO 95 production lot numbers were D04PF7371, D04PM7406, D05PJ7462, D06PK7529, and D07PE7584.

Duration of Treatment: Up to 52 weeks (including screening, 8 cycles of treatment, and 24 weeks follow-up). Extended dosing (including screening, 16 cycles of treatment, and 24 weeks follow-up): up to 76 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number:
Commercially available normal saline solution (250 mL of 0.9% NaCl solution) was used as placebo for CNTO 95. The sites used commercially available DTIC for administration in this study.

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Criteria for Evaluation: All randomized subjects were included in the primary efficacy and selected secondary analyses. Response-evaluable population was used for the efficacy analyses of tumor responses. Safety evaluations were based on subjects who received at least 1 dose of study medication (CNTO 95, DTIC, or placebo); subjects were analyzed according to the actual treatment received. The evaluable pharmacokinetic population included subjects who had at least 1 pharmacokinetic sample, received at least 1 dose of CNTO 95, and completed at least 1 full cycle (dosing and 21 days of observation).

Primary Endpoint:

Phase 1 Part 1

- Incidence of DLTs
- Single-dose pharmacokinetics

Phase 1 Part 2

- Incidence of DLTs

Phase 2

Progression-free survival (PFS): PFS was defined as the time from the date of randomization to the date of initial documented progressive disease (PD), or the date of initial documented symptomatic deterioration, or the date of death, whichever occurred first. The date of initial documented PD was the earliest date among the date of initial documented PD in target lesions, the date of initial documented PD in non-target lesions, and the date of first documented new lesion. At the time of data cutoff for analysis, if neither PD nor symptomatic deterioration nor death occurred, PFS was to be censored at the date of last visit with adequate assessment for PD.

Other Efficacy (Phase 2):

- Proportion of subjects who achieve tumor response (complete response [CR] and partial response [PR])
- Proportion of subjects who achieve CR
- Proportion of subjects who achieve stable disease
- Survival
- Duration of response
- Change in ECOG performance status

Health Related Quality of Life (HRQoL)

- Change in HRQoL

Pharmacokinetics/Pharmacodynamics/Pharmacogenomic:

- Pharmacokinetics of CNTO 95: The evaluable pharmacokinetic population included subjects who had at least 1 pharmacokinetic sample, received at least 1 administration of CNTO 95, and completed at least 1 full cycle (dosing and 21 days of observation). Serum CNTO 95 concentrations, pharmacokinetic parameter estimates in Phase 1 subjects (estimated by non-compartmental analysis ([NCA]), and antibody status to CNTO 95 are presented. In addition, the relationship between serum concentrations and antibody to CNTO 95 status and the relationship between pharmacokinetic parameters and efficacy measures were also assessed.
- Exploratory pharmacodynamic endpoints
- Exploratory pharmacogenomic endpoints (Phase 2 only)

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Immune Response Analysis

- Incidence of antibodies to CNTO 95

Safety:

- Incidence of all adverse events (AEs)
- Incidence of Grade 3 or higher AEs
- Incidence of serious adverse events (SAEs)
- Incidence of CNTO 95-related AEs and SAEs
- Incidence of infusion reactions
- Incidence of markedly abnormal safety-related laboratory parameters
- Incidence of markedly abnormal vital signs
- Deaths

Statistical Methods:

Phase 1

Descriptive statistics were used to summarize safety and pharmacokinetic data.

Phase 2

All analysis specified in the Statistical Analysis Plan, and additional exploratory analyses, were performed. Details of the methods can be found in the Statistical Analysis Plan.

Descriptive statistics were used to summarize the secondary endpoints and other exploratory analyses. In general, the treatment group comparison was made using the parameter estimate and its 95% confidence interval. Though no hypothesis testing was carried out for the comparison, nominal p-values were presented as a measure of strength of associations.

1. Continuous variables: summary statistics included mean, median, standard deviation, and range. The group comparison was presented by the difference in mean and its 95% confidence interval. In situations where the normality assumption did not hold, proper transformation, determined by exploratory analysis, was used.
2. Categorical variables: the data were summarized by frequency and percentage. The group comparison was presented by the difference in the percentage and its 95% confidence interval using normal approximation. In case of rare events, the exact method was used to compute the confidence intervals.
3. Time to event variables: the data were summarized by the Kaplan-Meier estimates and event-free rates at specific time points. The group comparison was presented by the hazard ratio and its 95% confidence interval using Cox proportional hazards model.

The primary endpoint (PFS) was analyzed primarily based on the ITT population. The distribution of PFS along with its 25, 50, and 75 percentiles and the survival (event-free) probabilities at specific time points was estimated using the Kaplan-Meier method for each treatment arm. The 95% confidence intervals around the Kaplan-Meier estimates at specified time points was constructed via the Greenwood's formula (Collett, 1994). Treatment comparison (to DTIC plus placebo arm) was performed using hazard ratios (95% CI) estimated from the stratified Cox's regression (Cox, 1972), with site of metastases (M1a and M1b versus M1c) at baseline and baseline ECOG performance status (0 and 1 versus 2) as the stratification factors. In addition, Cox's regression with treatment as the only explanatory factor were also performed as part of the sensitivity

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analysis. Treatment differences were also presented by p-values from the stratified Log-Rank test as well as unstratified log-rank test.

SUMMARY – CONCLUSIONS

Study Population Results:

Phase 1

- A total of 18 subjects were enrolled and 15 subjects were treated in Phase 1. Three subjects were treated in each of the following treatment groups: 3, 5, 10 mg/kg CNTO 95, DTIC + 5 mg/kg CNTO 95, and DTIC + 10 mg/kg CNTO 95.

Phase 2

- Baseline characteristics were balanced across all Phase 2 subjects.
- A total of 129 subjects were randomized, and 127 subjects were treated in Phase 2. Subjects were treated as follows: DTIC + placebo (31 subjects), 5 mg/kg CNTO 95 (31 subjects), 10 mg/kg CNTO 95 (33 subjects), DTIC + 10 mg/kg CNTO 95 (32 subjects). Three subjects in the DTIC + placebo treatment group crossed over to treatment with 10 mg/kg CNTO 95, and 17 subjects in the DTIC + placebo treatment group crossed over to treatment with DTIC + 10 mg/kg CNTO 95.
- In Phase 2, 113 randomized subjects discontinued study agent. Of those who discontinued study agent, the majority (108 subjects) discontinued due to disease progression and/or symptomatic deterioration.
- A total of 52 Phase 2 subjects had their treatment unblinded. As per the protocol, subjects were to be unblinded for PD or DTIC intolerance in the DTIC + placebo or DTIC + 10 mg/kg CNTO 95 treatment group. DTIC treatment was open label.
- Twenty (15.5%) Phase 2 subjects did not meet the protocol defined study selection criteria. Nearly all subjects who had protocol deviations in study agent administration had an administration outside the protocol-specified window.
- In Phase 2, nearly all subjects (117; 95.9%) had prior cancer-related surgery, 57 (46.7%) subjects had prior systemic therapy, and 38 (31.1%) subjects had prior radiotherapy.

Pharmacokinetic/Pharmacodynamic Results:

- Regardless of DTIC administration, median serum CNTO 95 concentrations increased as the dose increased from 3 to 10 mg/kg CNTO 95.
- The pharmacokinetic behavior of CNTO 95 appeared to be nonlinear. A greater than dose-proportional increase in AUC was observed along with a dose dependent decrease in clearance. Consistently, half-life ranged from 2.03 days at 3 mg/kg CNTO 95 to 5.16 days at 10 mg/kg CNTO 95.
- No apparent accumulation was observed with dosing every 3 weeks.
- When CNTO 95 was co-administered with DTIC, the median values of Cmax and AUCinf for CNTO 95 decreased by 26.7% to 39.0% with a corresponding increase in clearance following a 5 and 10 mg/kg CNTO 95 dose, respectively. Due to the small number of subjects (n = 1 to 3) and observed inter-subject variability, no meaningful conclusions can be drawn about the clinical relevance of this finding.
- The incidence and titer of antibodies to CNTO 95 were low (3 of 11 subjects in Phase 1 and 1 of 73 subjects in Phase 2).

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- (Pretreatment Cycle 3 only) CTx levels and VEGF decreased from baseline in Phase 2 subjects, who received CNTO 95 either alone or in combination with DTIC, however the changes were not sustained.
- The median values for the pharmacodynamic markers (NTx, CTx, BSAP, VEGF, and bFGF) showed considerable variability and did not display any specific and sustained change from baseline. The number of subjects treated with CNTO 95 alone or in combination with DTIC with an objective response was rather small and makes the statistical interpretation of a possible correlation difficult.
- Two responders who received CNTO 95 showed at least 1 of the favorable genotypes (FCGR2A) homozygous for the histidine allele and/or FCGR3A homozygous for the phenylalanine allele.

Efficacy Results:

- In Phase 2, there was a trend toward prolongation of PFS among subjects in the DTIC + 10 mg/kg CNTO 95 treatment group compared with subjects in the DTIC + placebo treatment group (median PFS: 75.0 days [2.5 months] versus 54.0 days [1.8 months], respectively; hazard ratio = 0.79 [0.457, 1.365]). There was a trend against prolongation of PFS in subjects in the 5 and 10 mg/kg CNTO 95 treatment groups (median: 42.0 days [1.4 months] versus 54.0 days [1.8 months], respectively; hazard ratio = 1.70 [0.989, 2.928] and 1.25 [0.727, 2.140]).
- Overall Response
  - Six Phase 2 subjects had a PR: 3 (9.7%) subjects in DTIC + placebo; 2 (6.1%) subjects in 10 mg/kg CNTO 95; and 1 (3.3%) subject in DTIC + 10 mg/kg CNTO 95 treatment group. The duration of these responses ranged from 117 days to 308 days.
  - A total of 42 Phase 2 subjects had SD. Treatment with DTIC + 10 mg/kg CNTO 95 resulted in a higher SD rate in comparison with DTIC + placebo; 16 (53.3%) versus 10 (32.3%) subjects.
  - Treatment with DTIC + 10 mg/kg CNTO 95 resulted in improved disease control in comparison with treatment with DTIC + placebo; 17 (56.7%) versus 13 (41.9%) Phase 2 subjects.
  - One Phase 1 subject (5 mg/kg CNTO 95 dose cohort) achieved a CR. The duration of this response was 462 days. Three of 15 Phase 1 subjects achieved SD (1 each in the 5 mg/kg CNTO 95, 10 mg/kg CNTO 95, and 10 mg/kg CNTO 95 + DTIC dose cohorts).
- In Phase 2, there was a trend toward prolongation of OS among subjects in the CNTO 95-containing treatment groups compared with subjects in the DTIC + placebo treatment group (median 233.0 days or 7.6 months) as follows: 5 mg/kg (298.0 days or 9.8 months; hazard ratio = 0.997 [0.557, 1.785]); 10 mg/kg (426.0 days or 14.0 months; hazard ratio = 0.62 [0.339, 1.147]); and DTIC + 10 mg/kg (333.5 days or 10.9 months; hazard ratio = 0.76 [0.414, 1.393]).
- All groups appeared to have a comparable hazard rate in ECOG worsening.
- Health-related quality of life data in Phase 2 suggested a positive impact on pain and disease-related health issues when CNTO 95 was administered at the 10 mg/kg dose either alone or in combination with DTIC.

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Safety Results:

- There were no DLTs among Phase 1 subjects.
- All but 1 of the 15 Phase 1 subjects experienced 1 or more AEs. The AE profile was relatively similar across all dose cohorts. The most frequently reported AEs were headache (80.0%), fatigue (53.3%), chills and pyrexia (40%) and nausea (33.3%). Five (33.3%) subjects had 1 or more AEs with a toxicity Grade 3 or higher, 12 (80%) subjects experienced 1 or more AEs considered by the investigator to be reasonably related to CNTO 95, and 6 (40%) subjects experienced 1 or more SAE.
- All but 1 of the 127 treated Phase 2 subjects experienced 1 or more AEs. The most frequently reported AEs were headache, nausea, fatigue, pyrexia, vomiting, and uveitis. Subjects treated in the DTIC alone and DTIC + CNTO 95 treatment groups experienced more Grade 3 and higher AEs and more SAEs compared with subjects treated in the single-agent CNTO 95 treatment groups (5 and 10 mg/kg).
- No Phase 1 subjects discontinued CNTO 95 due to an AE. Three Phase 2 subjects (2 in the DTIC + 10 mg/kg CNTO 95 treatment group and 1 who crossed over from DTIC + placebo to the DTIC + 10 mg/kg CNTO 95 treatment group) discontinued CNTO 95 treatment due to an AE (Grade 4 hypersensitivity reaction, Grade 2 uveitis and Grade 2 confusional state, respectively).
- For Phase 1 and Phase 2, there were no treatment-related deaths reported by the investigator.
- Six subjects in Phase 1, and 45 subjects in Phase 2 experienced 1 or more infusion reactions. The majority of the infusion reactions were considered by the investigator to be related to CNTO 95. With the exception of 2 Grade 3 headaches (in Phase 2), all infusion reactions were toxicity Grade 1 or 2.
- One subject in Phase 1, and 11 subjects in Phase 2 experienced an allergic/hypersensitivity reaction. The majority of allergic/hypersensitivity reactions were considered by the investigator to be related to CNTO 95. With the exception of 3 events (in Phase 2) all allergic/ hypersensitivity reactions were toxicity Grade 1 or 2.
- One subject in Phase 1, and 26 subjects in Phase 2 experienced uveitis. For Phase 2 subjects, all but 2 occurrences were considered by the investigator to be reasonably related to CNTO 95.
- No remarkable laboratory test results were observed among Phase 1 and Phase 2 subjects.
- No remarkable ECG findings were observed among Phase 1 and Phase 2 subjects.

Conclusions:

The objectives of this Phase 1/2 study were to investigate the safety and efficacy of CNTO 95 alone and in combination with DTIC in subjects with metastatic melanoma. In addition, the pharmacokinetics and pharmacodynamics of CNTO 95 alone and in combination with DTIC were evaluated. Preliminary pharmacogenomics for consenting Phase 2 subjects were also evaluated. The objectives of the study were achieved as follows:

- CNTO 95 alone or in combination with DTIC was well tolerated.
- There was a trend toward prolongation in favor of DTIC + 10 mg/kg CNTO 95 in terms of:
  - Progression-free survival
  - Overall survival
  - Disease control
- Subjects treated with 10 mg/kg CNTO 95 had comparable tumor responses compared with subjects treated with DTIC alone.

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- Subjects treated with 5 mg/kg CNTO 95 did not demonstrate better outcomes compared with subjects treated with DTIC alone in terms of PFS and disease control.
- There appeared to be a dose response between 2 the single-agent CNTO 95 treatment groups in terms of:
  - Progression-free survival
  - Overall survival
  - Disease control
- CNTO 95 appeared to present nonlinear kinetics from 3 to 10 mg/kg with greater than dose-proportional increase in exposure. Median terminal half-lives were 5.16 days following a dose of 10 mg/kg of CNTO 95. No apparent accumulation was observed with dosing every 3 weeks.
- Few subjects developed an immune response to CNTO 95.
- Due to inherent variability in the biomarkers tested and the limited number of responders, no specific conclusions can be drawn from the biomarker data at this time.

Date of Report: 12 May 2009

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