PHASE II FEASIBILITY STUDY USING CH14.18/CHO ANTIBODY AND SUBCUTANEOUS INTERLEUKIN 2 AFTER HAPLOIDENTICAL STEM CELL TRANSPLANTATION IN CHILDREN WITH RELAPSED NEUROBLASTOMA
A joint SIOPEN & EBMT Study

Short title of clinical study	**ch14.18-IL2 1021**
Version:	**1.1**
Date of Protocol	**September, 1 st 2009**
EudraCT-Number	**2009-015936-14**
Sponsor of the Study	**University Hospital Tübingen, Geissweg 3, 72076 Tübingen represented by board of directors (Prof. Dr. med. M. Bamberg, Dipl.-Volksw. Gabriele Sonntag) represented by Prof. Dr. med. R. Handgretinger**
Director of the Study	**Prof. Dr. med. Peter Lang**
Authors	**Peter Lang Rupert Handgretinger Ruth Ladenstein Ulrike Pötschger Holger Lode**
Investigational drug	**ch14.18/CHO antibody Interleukin 2**
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Synopsis

Title	Phase II feasibility study using ch14.18/CHO antibody and subcutaneous interleukin 2 after haploidentical stem cell transplantation in children with relapsed neuroblastoma
Eudra-CT Number **Study Code**	2009-015936-14 ch14.18-IL2
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Sponsor	University Hospital Tübingen, Geissweg 3, 72076 Tübingen represented by board of directors (Prof. Dr. med. M. Bamberg, Dipl.-Volksw. Gabriele Sonntag) represented by Prof. Dr. med. R. Handgretinger University Children's Hospital Hoppe-Seyler-Str. 1 72076 Tuebingen, Germany FAX: 49 7071 2904981 Phone: 49 7071 2980894 Email: Rupert.Handgretinger@med.uni-tuebingen.de
Date of Synopsis	September, 1 st 2009
Study Design	Multicenter Phase II
Number of Patients	35
Patient Population	Pediatric patients with relapsed neuroblastoma who previously received an allogeneic haploidentical stem cell transplantation
Duration of Study	Total study: 3-4 years Individual patient: 1 year
Aim of Study	To determine the safety and feasibility of the humanised chimeric 14.18 anti-GD2 monoclonal antibody produced in Chinese hamster ovary (CHO) cells (ch14.18/CHO) in combination with subcutaneous aldesleukin (IL-2, (Proleukin®)) after haploidentical stem cell transplantation in paediatric patients with relapsed neuroblastoma.
Treatment Protocol	A six courses regimen consisting of a 8 hour infusion (ch14.18/CHOmAb 20 mg/m²) for five consecutive days will be administered every 4 weeks. Interleukin 2 will be added to cycles 4-6 at days 6,8,10 (1 x 10^6 IU/m²/d s.c.) Participants will be premedicated with an intravenous antihistamine and ranitidine within approximately 30 minutes prior and during the infusion of the study agent Pain as an anticipated side effect is managed by a standard pain prophylaxis with Morphium hydrochloride Disease status will be evaluated after 3 and 6 courses and after 1 year.
Primary Objectives	• Evaluation of safety and feasibility of the chimeric 14.18 anti-

	GD2 monoclonal antibody (ch14.18/CHO) in combination with subcutaneous aldesleukin (IL-2, (Proleukin®) Primary endpoint is "success of treatment" defined as a patient receiving the full protocol treatment, still alive 180 days after treatment without progression and without unacceptable toxicity and acute GvHD ≥ Grade III or extensive chronic GvHD. Thus, a composite variable is used as primary endpoint: Treatment success, is defined as a patients who did not experience 1. unacceptable toxicities 2. acute GvHD ≥ Grade III or extensive chronic GvHD 3. other toxicities that did not recover to ≤ Grade 1 within 4 weeks or 4. progressive disease after 6 cycles or 5. deaths within treatment after SCT 6. withdrawal due to other reasons
Secondary Objectives	• To evaluate the anti-tumour responses resulting from this immunotherapy regimen through clinical assessments (radiographic and clinical measurements, including bone marrow immunohistochemistry for those research participants with marrow involvement). • To evaluate pharmacokinetics of the ch14.18/CHO. • To evaluate changes in NK cell activation and proliferation (immunological monitoring).
Inclusion criteria	• Less than or equal to 21 years of age. • Histologically confirmed neuroblastoma. • Refractory to standard treatment (i.e. refractory disease) or relapse after previous autologous or allogenic stem cell transplantation. • Patient has undergone haploidentical stem cell transplantation prior to antibody infusion according to appendix IV at least 60 days prior to starting immunotherapy. • Serum glutamate pyruvate transaminase (SGPT) less than 2.5 times the upper limit of normal for age and total bilirubin less than 2 times the upper limit of normal for age. D-Dimers less than 2 times the upper limit of normal. • Creatinine clearance or radioisotope GFR greater than or equal to 40 ml/min/1.73m^2. • Cardiac shortening fraction greater than or equal to 20% by echocardiogram. • Karnofsky/Lansky performance score (age appropriate) of greater than or equal to 50. • Females of childbearing potential must have a negative pregnancy test. Patients of childbearing potential must agree to use an effective birth control method. Female patients who are lactating must agree to stop breast-feeding. • Written informed consent is obtained, and for minors a written agreement by parents or legal guardian. • All institutional and national requirements for human studies are met.
Exclusion criteria	• Marked baseline prolongation of QT/QTc interval (e.g. demonstration of a QTc interval > 450 milliseconds). • Patients with symptoms of congestive heart failure or uncontrolled cardiac rhythm disturbance.

	• Patients with significant psychiatric disabilities or uncontrolled seizure disorders. • Patients with active infections or active peptic ulcer, unless these conditions are corrected or controlled. • Patients with acute GvHD Grade III or IV or extensive chronic GvHD. • Patients with clinically significant, symptomatic, pleural effusions. • Patients who have had major surgery, (i.e. laparotomy or thoracotomy) within the past two weeks. • Patients who will more than 12 months post haploidentical stem cell transplantation at the time of starting the first cycle of immunotherapy. • Prior administration of ch14.18 antibody. • HIV or Hepatitis B Surface (HBS) Ag positive. As presence of either may influence the ability if the immune system to be stimulated by this treatment.
Safety variables and stopping rules	Unacceptable toxicities are life threatening adverse reactions defined as Grade 3 or 4 toxicity using the NCI Common Toxicity Criteria, version 4.0 (Appendix II) which are in causal relationship with the study protocol. In particular, infusion of the ch14.18/CHO mAb might induce Graft versus host disease by increasing inflammatory cytokines. Occurrence of acute GvHD ≥ grade III or extensive chronic GvHD during antibody infusion will also be defined as unacceptable toxicity. Following exceptions which will not be considered unacceptable toxicity: a) Grade 3 nausea and vomiting; b) Grade 3 fever; c) Grade 3 skin toxicity that improves with treatment within 24 hours. d) Grade 3 electrolytes, especially hyponatraemia ≤124 mEq/L in the absence of CNS symptoms and sequelae which improve with treatment within 24 hours. e) Grade 3 hypotension and hypertension; f) Grade 3 hepatic toxicity which has been present for <3 days or returns to Grade 1 or less prior to the time for next ch14.18/CHO dose; g) Grade 3 neurotoxicity, i.e. interference with function plus objective weakness, will not be DLT if transient and reversing within three days of stopping ch14.18/CHO. Subjective findings, e.g. tingling, hot or cold hands, etc., are expected and will not be unacceptable toxicity. h) Grade 4 haematologic toxicity which improves to at least Grade 2 or baseline pre-therapy values within one week following ch14.18/CHO treatment; i) Grade 3 and 4 allergic reactions, i.e. anaphylaxis, readily controlled with supportive measures; j) Grade 3 performance (Lansky/Karnofsky Score 30 - <50%, see Appendix I); or

	k) Grade 3 capillary leak syndrome that does not persist for more than one week These exceptions are based on the known, transient, reversible, non-dose limiting toxicities as previously published. Any patient demonstrating unacceptable toxicity will have treatment with ch14.18/CHO stopped. If toxicity resolves, treatment may be resumed for that patient at 50% ch14.18/CHO dose. If toxicity does not resolve, the patient has to be taken off study. If GvHD ≥ grade 1 occurs, Interleukin 2 administration will be stopped and ch14.18 will be administered as a single drug. If GvHD ≥ grade 3 occurs, ch14.18 infusion will be also stopped. If all toxicities have recovered to ≤ Grade 1 within 4 weeks (including GvHD), IL2 and ch14.18 can be given in the next course. The study will be stopped, if unexpected, live threatening (grade 4) side effects or severe acute GvHD (Grade III-IV) occurs in ≥ 5 out of 9 patients, despite dose reductions.
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