Randomized Phase 2 trial comparing experimental immunotherapy(anti-gd2 antibody,il-2 s.c.,GM-CSF) in recurrent high risk neuroblastoma patients with standard immunotherapy (antI-gd2 antibody, il-2 i.v., GM-CSF) in patients with recurrent and newly diagnosed High risk neuroblastoma

Prüfpräparate: anti-GD2 antibody ch14.18, sargramostin (GM-CSF), aldesleukin

Eudra-CT Nummer: 2013-004481-34

Sponsor-ID: Uni-Köln-1694

Kurzbezeichnung: NB2013-HR PILOT GPOH/DCOG) ...

Final Report

27.07.2017

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Trial start: 22.10.2015
Premature trial stop: 23.12.2016

Authorized signatures

The authors declare their agreement with the content of the final report. The clinical trial has been conducted according the actual version of the Declaration of Helsinki, the recommendations of the Good Clinical Practice and the German and Dutch law.

Representative of the sponsor / principal investigator	F. Berthold	2017-07-28
	Prof. Dr. Frank Berthold	Cologne, date
Biometrician	M. Hellmich	2017-07-28
	Prof. Dr. Martin Hellmich	Cologne, date

Title of the trial	*NB2013-HR PILOT GPOH/DCOG* *Version 1.3 dated 09.09.2016*
Final Amendment	*Version 1.3 dated 09.09.2016*
Type of trial	Randomized phase 2 clinical trial
Sponsor	University of Cologne Dept. of Pediatric Oncology and Hematology Kerpener Straße 62 50931 Köln
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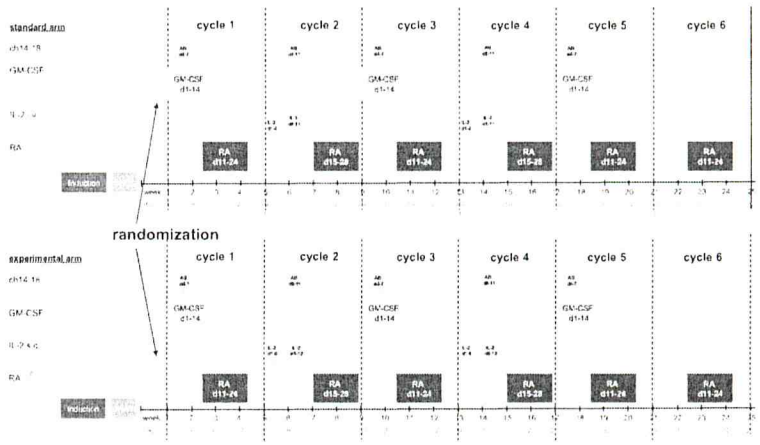
Sub-investigators	None The trial was prematurely terminated before green light of planned participating institutions
Participating centers	None
Publication (Reference)	None because of insufficient amount of data
Trial period **Reason for premature termination of the trial**	Date of first patient first visit: 23.10.2015 Date of last patient last visit: 15.09.2016 The trial was halted dated 10.11.2016 and terminated 23.12.2016 The reason for the premature termination was the information of the pharmaceutical sponsor United Therapeutics Corporation (UT) that UT is unable to further provide the monoclonal antibody Unituxin after February 2017 (see document attached).
Primary trial objective	The primary trial objective is the safety and tolerability of the two immunotherapy regimens for patients with recurrent high risk neuroblastoma (randomized) and of the

	standard immunotherapy regimen for newly diagnosed high risk neuroblastoma (three arm trial)
Primary endpoint	Safety (toxic deaths) and tolerability (relevant grade 4 toxicities) for the three treatment arms.
Secundary endpoints	• Reduction of grade 2-4 key side effects in the experimental arm by 30 % compared to the standard arm. Key side effects are presence of capillary leak and cytokine release syndromes. They will be assessed collectively. • Neuralgia (with assessment of pain duration (days requiring morphin) and maximum grade of pain scores during first 2 antibody cycles) will be evaluated descriptive in both arms. No difference between the arms is expected. • Comparison of pharmacokinetics of antibody ch14.18 (levels of antibody and presence of antiidiotype antibodies) in both arms (descriptive). • Comparison of immune response (antiidiotype antibodies, immune cell phenotypes, immune mediators, functional assays as ADCC and CDC) between treatment cycles, treatment arms and between recurrent and newly diagnosed patients (descriptive). • Comparison of grade 2-4 toxicities (ascites, ARDS, dyspnea, hypotension in addition to capillary leak and cytokine release syndromes) between intravenously and subcutaneously administered IL-2 (standard vs. experimental arm and recurrent vs. newly diagnosed patients) (descriptive). • 2 year event free (EFS), progression free (PFS) and overall survival rates (OS) from time of randomization. 2 year minimum follow-up for at least 24 enrolled patients (descriptive). • Tumor response at the end of treatment and time to progression (TTP) • Quality of Life (QoL) evaluated using PedsQL questionnaires with scale rating (descriptive comparison between the standard and the experimental arm).
Type of trial **Trial design** **methodology**	Prospective, multicenter, comparative, open label clinical trial with 2 cohorts of recurrent neuroblastoma patients (randomized) and 1 cohort in newly diagnosed HR neuroblastoma patients. Recurrent neuroblastoma patients: Randomization between an experimental antibody-based immunotherapy regimen using subcutaneous IL-2 and the standard triple antibody-

	based immunotherapy regimen using intravenous IL-2 in recurrent HR neuroblastoma patients after achievement of response (CR,VGPR,PR,SD) to second-line chemotherapy. Randomization is stratified by MYCN amplification and remission status at trial entry (CR/VGPR vs. PR/SD). Newly diagnosed patients: Treatment with standard triple immunotherapy (i.v. IL-2). NB2013-HR pilot GPOH/DCOG trial 
Investigational products	Investigational Products: Unituxin®, Leukine®, Proleukin® S • anti GD2 monoclonal antibody (Unituxin®) chimeric antibody exploiting ADCC and CDC Daily dose: 17.5 mg/m²xd intravenous (i.v.) infusion over 10 (-20) hours over five monthly cycles at a dosage of 17.5 mg/m2xd for 4 consecutive days (= 70 mg/m² x cycle). d 4-7 cycles 1, 3, 5 standard arm and experimental arm d 8-11 cycles 2, 4 standard arm and experimental arm Formulation: Provided as a sterile solution in single-dose vials containing 17.5 mg/5 mL (3.5 mg/mL) in 20 mM Histidine, 150 mM NaCl, 0.05% Tween 20 at pH 6.8. • GM-CSF (Leukine®) Granulocyte and macrophage colony stimulation factor Daily Dose: 250 µg/m²d d1-14, s.c. cycles 1, 3, 5 Subcutaneous injection is strongly recommended, prior to the antibody and ideally between 8-9h. Alternatively a 2h intravenous infusion is allowed if the children do not tolerate subcutaneous Leukine® injection. Leukine® is provided as "Lyophilized Leukine". Formulation: Lyophilized LEUKINE is a sterile, white, preservative-free powder (250 µg) that requires reconstitution with 1 mL sterile water for injection, USP or 1 mL bacteriostatic water for injection, USP. For more information see

	http://products.sanofi.us/Leukine/Leukine.html. • Interleukin 2 (aldesleukin, Proleukin® S) Interleukin 2 propagates natural killer (NK) cells, generates lymphokine activated killer cells and augments ADCC in patients with melanoma and neuroblastoma Doses: Standard arm 3.0 mioIU/m²xd d1-4 continuous infusion cycles 2, 4, then 4.5 mioIU/m²xd d8-11 continuous infusion cycles 2, 4 Experimental arm test dosis: 0.06 mio IU/m² i.v. in 30 min. at least 2h before first s.c. application, then 6.0 mio/m²xd d1-5 and d 8-12 s.c. cycles 2, 4 Formulation: Powder for reconstitution with 1.2 ml Aqua ad injectionem
Intervention	The intervention is scheduled • in patients with recurrent or progressive neuroblastoma after re-induction chemotherapy and at least disease stabilisation. • in patients with de novo neuroblastoma after myeloablative treatment with autologous stem cell reinfusion and at least disease stabilisation
Number of subjects	The planned number: 36 (3 cohorts of 12 patients). Screened patients: 3 Patients included in the trial: 3 (experimental arm: 1, standard arm: 2) Patients randomized: 3 Drop-outs: 0
Trial population	3 patients Included patients with deviation from study protocol: Type of deviation: platelet transfusion dependency according to Dutch interpretation (1 patient) Reason for inclusion: Platelet transfusion dependency was differently estimated in the Dutch and the German site. The exclusion criterium 'platelet transfusion dependency' in the protocol was adopted to prevent serious bleeding. The clinical condition of the patient was always good and no bleeding at all was observed during the study time. Other deviations from protocol recommendations (inclusion criteria, exclusion criteria, trial conduct, management of patients, diagnostic procedures, not allowed concomitant medication): none
Inclusion criteria	Recurrent or newly diagnosed high risk neuroblastoma Key inclusion criteria:

	• Established diagnosis of neuroblastoma according to the international INSS criteria • High risk (HR): stage 4 over 18 months of age and MYCN amplified neuroblastoma of any stage and any age until 25 years • Recurrent disease (Germany and The Netherlands): after re-induction chemotherapy (+/- other modalities) Newly diagnosed disease (The Netherlands): Complete front-line treatment including induction chemotherapy, mIBG treatment, appropriate local therapy such as surgical removal and/ or local irradiation of the primary tumor and myeloablative chemotherapy with autologous stem cell reinfusion according to the actual guidelines of the GPOH/DCOG • Achieved response status: stable disease or better (CR, VGPR, PR, SD). • Written informed consent of parents or guardian and – if appropriate – of the patient. • For at least two weeks prior to start of trial medication off any standard or experimental treatment and fully recovered from short-term major toxic effects and no tumour surgerand fully recovered from any post-surgical complications • no immediate requirements for palliative chemotherapy, radiotherapy or surgery • The patient may have had prior CNS metastases provided the following criteria are all met: The patient's CNS disease has been previously treated and the patient's CNS disease has been clinically stable for four weeks prior to starting this study (assessed clinically and by MRI or CT) and the patient is off steroids for four weeks prior to starting the study and will not require them during the course of the study • A patient with seizure disorders may be enrolled if well controlled on anticonvulsants and if no seizures have occurred within a 6 week period prior to starting trial treatment • HIV sero-negative and neither active nor chronic-replicative hepatitis B infection • Laboratory testing: The patients should have adequate functions of the • Cor: defined by a shortening fraction >30% by echocardiography • Lung: defined by FEV1 and FVC >60%. Children unable to do the tests should have no dyspnoea at rest and a SaO2 of >94% with room air • Bone marrow: defined by ANC >0.5/nl, platelets >20/nl and no transfusion dependency, haemoglobin >8.0g/dl

	• Liver: defined by ALT or AST <5x normal and a total bilirubin <1.0mg/dl • Kidney: defined by serum creatinine <1.5mg/dl or a creatinine clearance or radioisotope GFR > 60ml/minx1.73m²
Exclusion criteria	Key exclusion criteria: ▪ Significant intercurrent illnesses and/or any of the following: - Symptoms of congestive heart failure or of uncontrolled cardiac arrhythmia - Significant psychiatric disabilities or psychological conditions preventing treatment realization - Uncontrolled seizure disorders - Active infections - Clinically significant neurologic deficit or objective peripheral neuropathy (> grade 2) - Significant, symptomatic pleural effusions ▪ Requirement or likely requirement for corticosteroids or other immunosuppressive drugs (except the medications recommended for conditions mentioned in the protocol) ▪ Platelet transfusion dependency ▪ Concurrent treatment with any non-trial anticancer therapy or interventional study ▪ Positive pregnancy test, lactation ▪ Sexually active patients (male and female) at reproductive age not willing to use highly effective contraceptive methods according to the guidelines ICH M3 ▪ Neuroblastoma patients with actively progressing disease ▪ Patients with HACA detected after previous antiGD2 immunotherapy ▪ Known allergy or contraindications against one of the study drugs (IMP)
Demographic and baseline data	• Demographic and baseline data all subjects with data: 3 (9 year male, 9 year female, 9year male) subjects per protocol:3 randomized to experimental arm: 1 randomized to control arm: 2 ▪ Comparison of trial sites: only one trial site open for recruitment during the trial period.
Efficacy	• Compliance: Antibody pharmacokinetic studies, CDC, ADCC and genetic analyses were performed by the lab

	of Prof. Lode (Greifswald). Entended immune cell phenotyping, cytokines and chemokines were determinated by the laboratory of Dr. Nierkens (Utrecht). Shipping was announced and successfully completed for all three patients during the trial period. Results are not available and would be not meaningful. Two patients (9 year male, 9 year male at trial start) are still in complete remission at the date of this report, one patient (9 year female at trial start) had an early tumor progression during the trial (15.09.16) and died of tumor progression (16.02.17).
Adverse Events **Relevant toxicities**	Severe adverse events (SAE): none Adverse events (AE)/relevant toxicities (definition see protocol): *standard arm* (patient 1) symptom / grade / cycle / week capillary leak syndrome / 2 / 2 / 1+2 . / / 5 / 1* hypotension / 2-3 / 4 / 1* peripheral motor neuropathy / 3 / 4 / 4 *stop interleukin-2 infusion Other adverse events (AE) *standard arm* (patient 1) symptom / grade / cycle / week neutropenia / 3 / 1 / 4 . / / 2 / 1+2+3+4 . / / 4 / 2+3+4 . / / 5 / 1+4 thrombocytopenia / 3 / 2 / 1+2 liver enzyme elevation (γGT) / 3 / 1+3+4** / 2 lipase elevation / 3 / 4** / 2 hypophosphatemia / 3 / 2 / 2 ** stop antibody and interleukin-2 infusion Adverse events (AE)/relevant toxicities (definition see protocol): *experimental arm* (patient 2) symptom / grade / cycle / week capillary leak syndrome / 3 / 2 / 1+2 . / / 4 / 2 hypotension / 2 / 2 / 1 . / / 4 / 2* peripheral motor neuropathy / 2 / 3 / 2 *stop antibody infusion Other adverse events (AE) *experimental arm* (patient 2)

symptom	grade	cycle	week
neutropenia	3	2	3+4
.		4	4
thrombocytopenia	3	2	2
liver enzyme elevation (γGT)	3	1	2
.		2	3+4
.		3	1+2+3 .
.		4	2
hypomagnesemia	3	2	2
fever	3	1	2

Adverse events (AE)/relevant toxicities (definition see protocol): *experimental arm* (patient 3)

symptom	grade	cycle	week
capillary leak syndrome	2	2	2
dyspnoe	2	2	2

Other adverse events (AE) *experimental arm* (patient 3)

symptom	grade	cycle	week
neutropenia	3	1	2+3
.		2	2+4+5
thrombocytopenia	3	1	5
.		2	2+3+5
.	4	1	1+2+3
.		2	1+2+4
anemia	3	1	1+4
.		2	1+2
liver enzyme elevation (γGT)	3	2	3+4
hypokalemia	3	2	2
hypophosphatemia	3	2	2
fever	3	1	1

No patient experienced further expected relevant toxicities:

- Ascites
- Adult respiratory distress syndrome
- Cytokine release syndrome
- Peripheral sensory neuropathy.

In summary, the observed side effects were mild and could be managed by standard clinical interventions including stop of antibody and interleukin-2 infusion. Comparison between the arms is not meaningful with 1 vs. 2 patients per arm.

The only death (patient 3) was caused by tumor progression. The treatment was stopped as soon as tumor progression

	was diagnosed (>4 months before death).
Statistical methods	Not applicable due to premature closure and recruitment of three patients treated in one center.

SUMMARY:

The trial was prematurely stopped because of the unexpected information of United Therapeutics Corporation (Europe) that the antibody supply was permanently interrupted and the trial must be finished. The drug Unituxin was withdrawn from the European market.

Estimated efficacy:

Of three patients, one died of tumor progression and two are still in complete remission 14+ and 13+ months after end of the individual treatment.

Estimated toxicity:

The observed toxicities were manageable by standard clinical interventions and were in general relatively mild. Some of the expected side effects were not at all observed. Comparative estimations between the arms are not meaningful.

Safety:

The therapy was safe in the 3 treated patients. No severe adverse events (SAE), no unexpected adverse drug reactions, and no suspected unexpected serious adverse reactions occured.

Conclusions:

The investigators regret to be unable to complete the study.