PLEASE NOTE: *This study has been imported from ClinicalTrials.gov without additional data checks.*

Trial Description

Title

Prospective, Open Label, Randomized Phase II Trial to Assess a Multimodal Molecular Targeted Therapy in Children, Adolescent and Young Adults With Relapsed or Refractory High-risk Neuroblastoma

Trial Acronym

RIST-rNB-2011

URL of the trial

[---]*

Brief Summary in Lay Language

Children, adolescents and young adults with high risk relapsed or treatment refractory neuroblastoma (rNB) represent a group of patients with dismal prognosis for whom a recommended standard salvage therapy is currently not available.

The multimodal metronomic approach combining molecular targeted drugs (rapamycin and dasatinib) with conventional chemotherapy (irinotecan and temozolomide) will be investigated in a randomized fashion as new treatment strategy for patients with rNB. The intention is to assess the therapeutic benefit of molecular targeted drugs for the treatment of rNB.

The combination of irinotecan and temozolomide showed activity in the treatment of several solid organ tumors, brain tumors and neuroblastoma. In one study rNB patients received a median of 5 courses of 5 days irinotecan and temozolomide every 3 to 4 weeks with a cumulative dose of 35% lower than in the RIST design. 33% had disease regression with 8% CR or PR. A phase II study in rNB also using irinotecan and temozolomide with a substantially lower intensity showed a response rate of 15%.

The combination of a mTOR inhibitor with a multi-kinase inhibitor demonstrated in preclinical studies a synergistic effect on cell cycle arrest, apoptosis and sensitization

for radio- and chemotherapy. It is assumed that this combination of molecular targeted drugs with a tolerable conventional chemotherapy consisting of irinotecan and temozolomide can substantially improve the outcome of this patient population. A group of 20 rNB patients treated with the RIST therapy approach in a compassionate use setting showed an overall survival of 55% at a median of 80 weeks with a tolerable adverse event profile.

Brief Summary in Scientific Language

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Organizational Data

- DRKS-ID: **DRKS00007540**
- Date of Registration in DRKS: **2014/12/22**
- Date of Registration in Partner Registry or other Primary Registry: **2011/10/27**
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **[---]***
- (leading) Ethics Committee Nr.: **[---]***

Secondary IDs

- EudraCT-No. (for studies acc. to Drug Law): **2011-004062-15**
- Primary Registry-ID: **NCT01467986 (ClinicalTrials.gov)**
- Sponsor-ID: **RIST-rNB-2011 (University of Regensburg)**

Health condition or Problem studied

- Free text: **Neuroblastoma Recurrent**
- ICD10: **C74 - Malignant neoplasm of adrenal gland**

Interventions/Observational Groups

- Arm 1: **Drug: Dasatinib**
- Arm 2: **Drug: Rapamycin**
- Arm 3: **Drug: Irinotecan**
- Arm 4: **Drug: Temozolomide**

- Arm 5: **Drug: Irinotecan**
- Arm 6: **Drug: Temozolomide**

Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: **[---]***
- Allocation: **Randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **[---]***
- Control: **Active control (effective treament of control group)**
- Purpose: **Treatment**
- Assignment: **Factorial**
- Phase: **II**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **[---]***

Primary Outcome

- The primary endpoint is progression-free survival (PFS); time frame: Time interval from date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 52 weeks; The primary objective of this trial is the evaluation of progression-free survival of rNB in children, adolescents and young adults, comparing a multimodal treatment regimen consisting of temozolomide (T), irinotecan (I), rapamycin (R) and dasatinib (S) against irinotecan (I) and temozolomide (T) (I/T) alone

Secondary Outcome

- Overall survival (OS); time frame: Response to the investigational treatment after 4 courses and 8 courses of I/T and 1-year-follow-up
- Response to the investigational treatment after 4 and 8 courses of I/T and 1-year-follow-up in the RIST treatment arm; time frame: Response to the investigational treatment after 4 courses and 8 courses of I/T and 1-year-follow-up
- Duration until adequate response to this treatment regimen; time frame: Response to the investigational treatment after 4 courses and 8 courses of I/T and 1-year-follow-up
- Assessment of quality of life (Lansky and Karnofsky Scores); time frame: • Response to the investigational treatment after 4 courses and 8 courses of I/T and 1-year-follow-up
- Toxicity of this combination of drugs in children, adolescents and young adults with rNB; time frame: From the first course of the investigational treatment up to the end of the trial assessed to 52 weeks.; Assessment according to the latest version of the CTC criteria. In particular due to the expected AE Profile: Myelosuppressive measures (RBC, PLT units)
Infectious complications
Gastrointestinal problems
- Safety and tolerability of the investigational treatment; time frame: Response to

the investigational treatment after 4 courses and 8 courses of I/T and 1-year-follow-up; Assessment according to the latest version of the CTC criteria. In particular due to the expected AE Profile:
Myelosuppressive measures (RBC, PLT units)
Infectious complications
Gastrointestinal problems
- Assessment of the prognostic relevance of International Neuroblastoma Risk Group (INRG) classification system on the event free survival; time frame: Response to the investigational treatment after 4 courses and 8 courses of I/T and 1-year-follow-up
- Prognostic relevance of defined factors on the event free survival in this patient population (i.e. response assessment of HVA, VMA, NSE); time frame: Response to the investigational treatment after 4 courses and 8 courses of I/T and 1-year-follow-up

Countries of recruitment

- DE **Germany**

Locations of Recruitment

- **University Hospital Regensburg, Department of Pediatric Hematology and Oncology, Regensburg**

Recruitment

- Planned/Actual: **[---]***
- (Anticipated or Actual) Date of First Enrollment: **2013/08/31**
- Target Sample Size: **114**
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **no minimum age**
- Maximum Age: **25 Years**

Additional Inclusion Criteria

Patients with relapsed high-risk neuroblastoma (stage IV and all MYCN pos. stages) or progressive disease during primary treatment (=rNB) and all of the following criteria will be considered for admission to the clinical trial:

- Children, adolescents and young adults less than 25 years

- Signed written informed consent

- Females of childbearing age must have a negative urine pregnancy test prior to starting the study drug. The first pregnancy test must be performed within 10-14 days prior to the start of the study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The subject may not receive the study drug until the investigator has verified that the results of these pregnancy tests are negative.

- Females of childbearing age must comply with the institutional standards of birth control with a pearl index <1%. Contraception must be started at least four weeks before the start of the investigational therapy.

- Females of childbearing age must be willing to abstain from breastfeeding for the duration of the clinical trial and for at least 30 days after discontinuation of the clinical trial.

- Males must agree not to father a child and must use latex condom during any sexual contact with women of childbearing age during and for 6 months after therapy ends or is stopped, even if they have undergone successful vasectomy.

- Willing and able to complete the clinical trial procedures, as described in the protocol

- Non-smoker for at least the previous 3 months. Smoking is not allowed during the entire study period

- Abstain from alcohol within the last 24 hours before screening and before admission to the clinical trial center as well as during the entire clinical trial. The regular daily ethanol intake has to be less than 20g/day for at least the previous three month.

- Patients are required to have an absolute neutrophil count (ANC) ≥ 500/µL, hemoglobin ≥8g/dL (transfusion permitted), and an unsupported platelet count ≥30,000/µL unless:

1. extensive bone marrow involvement was documented

2. patient is refractory or relapsed early after primary therapy

Exclusion criteria

- Pregnancy, nursing

- Patients who suffered from a thrombotic event and need anticoagulation (i.e. coumadin derivatives or low molecular weight heparin derivatives, LMWH)

- Patients with cardiac arrhythmias especially prolonged QT

- Patients with chronic inflammatory bowel diseases and/or bowel obstruction

- Patients with bilirubin serum levels 1,5 fold above the upper normal limit

- Vaccination with a live virus vaccine during the clinical trial

- Impaired liver function and/or impaired renal function (hepatic and renal index parameter two times above normal range; see below)

- Potentially unreliable subjects, probably non compliant subjects and those judged by the investigator to be unsuitable for the study

- Doubts about the patient's cooperation

- Any contraindications or known hypersensitivity to the IMPs or to any of the other components: (see SPC ("Fachinformation", appendix)

- Known allergic reactions to the treatment medication

- Patients who were treated with radiation and/or chemotherapy for any other oncological condition

- Participation in any other phase I to III trial

- Sexually active patients who refuse to use contraception according to the institutional requirements

- Patients with extremely poor general condition (Karnofsky or Lansky score <50%)

- Neutrophil count (ANC) <500/µL, hemoglobin <8g/dL (transfusion permitted), and an unsupported platelet count <30 000/µL

- 12-lead ECG with QTc>500 msec / QTc>60 msec baseline

Addresses

- **Primary Sponsor**

  University of Regensburg

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Sources of Monetary or Material Support

- **[---]***

  Bitte wenden Sie sich an den Sponsor / Please refer to primary sponsor

  Telephone: **[---]***
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  URL: **[---]***

Status

- Recruitment Status: **Recruiting ongoing**
- Study Closing (LPLV): **[---]***

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Trial Publications, Results and other documents

The parameters in ClinicalTrials.gov and DRKS are not identical. Therefore the data import from ClinicalTrials.gov required adjustments. For full details please see the DRKS FAQs.

- Translation on version: 3
- Last processed date by ClinicalTrials.gov: 2014/12/17

** This entry means the parameter is not applicable or has not been set.*

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