

## Multimodal Molecular Targeted Therapy to Treat Relapsed or Refractory High-risk Neuroblastoma (RIST-rNB-2011)

**This study is currently recruiting participants.** (see [Contacts and Locations](#))

*Verified October 2016* by University of Regensburg

**Sponsor:**

University of Regensburg

**Information provided by (Responsible Party):**

Prof. Dr. med. Selim Corbacioglu, University of Regensburg

**ClinicalTrials.gov Identifier:**

NCT01467986

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[History of Changes](#)

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[No Study Results Posted](#)

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### Purpose

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.

Condition	Intervention	Phase
Neuroblastoma Recurrent	Drug: Dasatinib Drug: Rapamycin Drug: Irinotecan Drug: Temozolomide	Phase 2

Study Type: **Interventional**

Study Design: Allocation: **Randomized**

Endpoint Classification: **Safety/Efficacy Study**

Intervention Model: **Factorial Assignment**

Masking: **Open Label**

Primary Purpose: **Treatment**

Official 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**

**Resource links provided by NLM:**

[Genetics Home Reference](#) related topics: [neuroblastoma](#)

[MedlinePlus](#) related topics: [Neuroblastoma](#)

[Genetic and Rare Diseases Information Center](#) resources: [Neuroblastoma](#) [Neuroepithelioma](#)

[U.S. FDA Resources](#)

**Further study details as provided by University of Regensburg:**

Primary Outcome Measures:

- 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 ] [ Designated as safety issue: No ]

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 Measures:

- Overall survival (OS) [ Time Frame: Response to the investigational treatment after 4 courses and 8 courses of I/T and 1-year-follow-up ] [ Designated as safety issue: No ]
- 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 ] [ Designated as safety issue: No ]
- 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 ] [ Designated as safety issue: No ]
- 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 ] [ Designated as safety issue: No ]
- 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. ] [ Designated as safety issue: Yes ]

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 ] [ Designated as safety issue: Yes ]

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 ] [ Designated as safety issue: No ]
- 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 ] [ Designated as safety issue: No ]

Estimated Enrollment: 114  
Study Start Date: August 2013  
Estimated Study Completion Date: December 2018  
Estimated Primary Completion Date: September 2018 (Final data collection date for primary outcome measure)

<u>Arms</u>	<u>Assigned Interventions</u>
Active Comparator: Irinotecan, Temozolomide Patients randomized to the control arm receive irinotecan (I) and temozolomide (T) alone.	Drug: Temozolomide Pharmacotheapeutic Group: Antineoplastic agents - Other alkylating agents, ATC-Code: L01A X03 Excipients: Capsule content: Anhydrous lactose, Sodium starch glycolate Type A, Colloida anhydrous silica, Tartaric acid, Stearic acid. Capsule shell: Gelatine, Titanium dioxide (E171). Printing ink: Shellac Propylene glycol, Titanium dioxide (E171), Sunset yellow FCF Aluminium Lake (E110) Formulation: capsule, hard Route of Administration: orally; Temomedac hard capsules should be administered in the fasting state. The capsules must be swallowed whole with a glass of water and must not be opened or chewed Other Name: Temomedac® Drug: Irinotecan Pharmacotheapeutic Group: cytostatic topoisomerase-I-inhibitor ATC-Code: L01XX19 Excipients: Sorbitol (E420), lactic acid, sodium hydroxid (to adjust the pH to 3.5), water for injection Formulation: concentrate for solution for infusion Route of Administration: intravenously

	Other Name: Irinomedac®
<p>Experimental: Rapamycin, Dasatinib, Temozolomide, Irinotecan</p> <p>Patients with rNB receive on the study arm the experimental combination of rapamycin (R)- mTOR Inhibitor, dasatinib (D)- protein kinase inhibitor irinotecan (I)- cytostatic topoisomerase-I-inhibitor and temozolomide (T)- Antineoplastic agent</p>	<p>Drug: Dasatinib</p> <p>Pharmacotherapeutic Group: protein kinase inhibitor ATC-Code: L01XE06 Excipients: Tablet core: Lactose monohydrate, Cellulose, microcrystalline, Croscarmellose sodium, Hydroxypropyl cellulose, Magnesium stearate. Film-coating: Hypromellose, Titanium dioxide, Macrogol 400 Formulation: film coated tablet Route of Administration: orally. Patients should be instructed to swallow the tablets as a whole and not to split, chew, or crush them.</p> <p>Other Name: Sprycel®</p> <p>Drug: Rapamycin</p> <p>Pharmacotherapeutic Group: Immunosuppressive agents - mTOR Inhibitors ATC-Code: L04A A10 Excipients: Polysorbat 80, Phosal 50 PG ((3-sn-Phosphatidyl)cholin from Soy beans, Propylenglycol, lipid acid mono- and -diglyzeride from Soy oil, Ethanol (1,5% bis 2,5%), Soy liid acid and Palmitoyl ascorbic acid) Formulation: Oral solution Route of Administration:orally</p> <p>Other Name: Rapamune®</p> <p>Drug: Irinotecan</p> <p>Pharmacotherapeutic Group: cytostatic topoisomerase-I-inhibitor ATC-Code: L01XX19 Excipients: Sorbitol (E420), lactic acid, sodium hydroxid (to adjust the pH to 3.5), water for injection Formulation: concentrate for solution for infusion Route of Administration: intravenously</p> <p>Other Name: Irinomedac®</p> <p>Drug: Temozolomide</p> <p>Pharmacotherapeutic Group: Antineoplastic agents - Other alkylating agents, ATC-Code: L01A X03 Excipients: Capsule content: Anhydrous lactose, Sodium starch glycolate Type A, Colloida anhydrous silica, Tartaric acid, Stearic acid. Capsule shell: Gelatine, Titanium dioxide (E171).</p> <p>Printing ink: Shellac Propylene glycol, Titanium dioxide (E171), Sunset yellow FCF Aluminium Lake (E110) Formulation: capsule, hard Route of Administration: orally; Temomedac hard capsules should be administered in the fasting state. The capsules must be swallowed whole with a glass of water and must not be opened or chewed</p> <p>Other Name: Temomedac®</p>

## ► Eligibility

Ages Eligible for Study: up to 25 Years (Child, Adult)  
 Genders Eligible for Study: Both  
 Accepts Healthy Volunteers: No

### Criteria

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)  $\geq 500/\mu\text{L}$ , hemoglobin  $\geq 8\text{g/dL}$  (transfusion permitted), and an unsupported platelet count  $\geq 30,000/\mu\text{L}$  unless:
  - a. extensive bone marrow involvement was documented
  - b. 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

## ▶ **Contacts and Locations**

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see [Learn About Clinical Studies](#).

Please refer to this study by its ClinicalTrials.gov identifier: NCT01467986

### **Contacts**

Contact: Selim Corbacioglu, MD +49(0)941 944-2101 [selim.corbacioglu@ukr.de](mailto:selim.corbacioglu@ukr.de)

Contact: Susanne Ellinger +49(0)941 944-2063 [susanne.ellinger@ukr.de](mailto:susanne.ellinger@ukr.de)

### **Locations**

#### **Germany**

University Hospital Regensburg, Department of Pediatric Hematology and Oncology **Recruiting**  
 Regensburg, Germany, 93053  
 Contact: Selim Corbacioglu, MD +49(0)941 944-2101 [selim.corbacioglu@ukr.de](mailto:selim.corbacioglu@ukr.de)  
 Principal Investigator: Selim Corbacioglu, MD

### **Sponsors and Collaborators**

University of Regensburg

### **Investigators**

Principal Investigator: Selim Corbacioglu, MD University of Regensburg, Department of Pediatric Hematology and Oncology

## ▶ **More Information**

Responsible Party: Prof. Dr. med. Selim Corbacioglu, Prof. Dr. med., University of Regensburg  
 ClinicalTrials.gov Identifier: [NCT01467986](#) [History of Changes](#)  
 Other Study ID Numbers: RIST-rNB-2011  
 Study First Received: October 27, 2011  
 Last Updated: October 26, 2016  
 Health Authority: Germany: Federal Institute for Drugs and Medical Devices

Keywords provided by University of Regensburg:

neuroblastoma	temozolomide
molecular targeted therapy	irinotecan
protein kinase inhibitor	dasatinib
mTOR Inhibitor	rapamycin
cytostatic topoisomerase-I-inhibitor	

Additional relevant MeSH terms:

Neuroblastoma	Dasatinib
Neuroectodermal Tumors, Primitive, Peripheral	Antineoplastic Agents

Neuroectodermal Tumors, Primitive  
Neoplasms, Neuroepithelial  
Neuroectodermal Tumors  
Neoplasms, Germ Cell and Embryonal  
Neoplasms by Histologic Type  
Neoplasms  
Neoplasms, Glandular and Epithelial  
Neoplasms, Nerve Tissue  
Irinotecan  
Camptothecin  
Topoisomerase I Inhibitors  
Temozolomide  
Dacarbazine

Everolimus  
Sunitinib  
Alkylating Agents  
Protein Kinase Inhibitors  
Titanium dioxide  
Antineoplastic Agents, Phytochemical  
Topoisomerase Inhibitors  
Enzyme Inhibitors  
Molecular Mechanisms of Pharmacological Action  
Antineoplastic Agents, Alkylating  
Immunosuppressive Agents  
Immunologic Factors  
Physiological Effects of Drugs

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