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International Society of Paediatric Oncology (SIOP) PNET 5 Medulloblastoma

This study is currently recruiting participants. (see Contacts and Locations)

Verified September 2016 by Universitätsklinikum Hamburg-Eppendorf

Sponsor:
Universitätsklinikum Hamburg-Eppendorf

Collaborator:
Deutsche Kinderkrebsstiftung

Information provided by (Responsible Party):
Universitätsklinikum Hamburg-Eppendorf

ClinicalTrials.gov Identifier:
NCT02066220

First received: February 7, 2014
Last updated: September 8, 2016
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History of Changes

Purpose

The study **PNET 5 MB** has been designed for children with medulloblastoma of standard risk (according to the risk-group definitions which have been used so far; e.g. in **PNET** 4). With the advent of biological parameters for stratification into clinical medulloblastoma trials, the ß-catenin status will be the only criterion according to which study patients will be assigned to either treatment arm **PNET 5 MB** - LR or to **PNET 5 MB** - SR, respectively. The initial diagnostic assessments (imaging, staging, histology, and tumor biology) required for study entry are the same for both treatment arms.

Condition	Intervention	Phase
Brain Tumors	Radiation: Radiotherapy without Carboplatin Drug: Reduced-intensity maintenance chemotherapy Radiation: Radiotherapy with Carboplatin Drug: Maintenance chemotherapy	Phase 2 Phase 3

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: An International Prospective Study on Clinically Standard-risk Medulloblastoma in Children Older Than 3 to **5** Years With Low-risk Biological Profile (**PNET 5 MB**-LR) or Average-risk Biological Profile (**PNET 5 MB**-SR)

Resource links provided by NLM:

Drug Information available for: Carboplatin

Genetic and Rare Diseases Information Center resources: Medulloblastoma Brain Tumor, Childhood Glioma Neuroepithelioma

U.S. FDA Resources

Further study details as provided by Universitätsklinikum Hamburg-Eppendorf:

Primary Outcome Measures:

- 3-year Event-Free Survival (EFS) [Time Frame: LR-arm after 9 years, SR-arm after 105 events (approx. 10 years)]
  [Designated as safety issue: No]

Secondary Outcome Measures:

- Overall survival [Time Frame: 10 years] [Designated as safety issue: No]

- Pattern of relapse [Time Frame: 10 years] [Designated as safety issue: No]

  Defined in 5 categorical variables: no relapse, local relapse, distant relapse, local and distant relapse, death

- Late effects of therapy on endocrine function [Time Frame: 10 years] [Designated as safety issue: No]

  measured as

  a. subfertility (FSH > 15 IU/L)
  b. endocrine deficits (hormone supplementation necessary)
  c. growth retardation (calculated as the difference in height standard deviation score from diagnose) 2 and 5 years after diagnosis and age of 18 years

- Late effects of therapy on audiology [Time Frame: 8 years] [Designated as safety issue: No]

  measured on audiogram performed 2 years after diagnosis, grading according to Chang ototoxicity grading (Chang and Chinosornvatana 2010)

- Late effects of therapy on neurology [Time Frame: 10 years] [Designated as safety issue: No]

  Measured as

  a. presence, duration, and therapy of hydrocephalus symptoms (pre- and post-operatively)
  b. presence of posterior fossa syndrome (cerebellar mutism survey after surgery, before radiotherapy)
  c. cerebellar symptoms (brief ataxia rating scales 2 and 5 years after diagnosis and age of 18 years)
  d. presence of symptoms for brain nerve dysfunction (2 and 5 years after diagnosis and age of 18 years)

- Late effects of therapy on quality of survival [Time Frame: 10 years] [Designated as safety issue: No]

  measured with standardized questionnaires/ scores:

  a. HUI3 (health status)
  b. BRIEF (executive functions)
  c. SDQ (behavioural outcome)
  d. PedsQL (quality of life)
  e. QLQ-C30 (quality of life)
  f. MEES (neurological function, educational provision)
  g. MFI (fatigue) 2 and 5 years after diagnosis and age of 18 years

- Progression-free survival [Time Frame: 10 years] [Designated as safety issue: No]
- Feasibility of carboplatin treatment [Time Frame: approx. 7 years] [Designated as safety issue: No]

  measured as timely delivery of chemotherapy number of interruptions days during radiotherapy toxicities within 8 weeks after end of radiotherapy

- Residual tumor [Time Frame: 6 years] [Designated as safety issue: No]

  measured by central MRI review postoperatively

- Leukoencephalopathy grading [Time Frame: 8 years] [Designated as safety issue: No]

  measured 2 years after diagnosis grades 0, 1, 2, 3, 4

Estimated Enrollment:	360
Study Start Date:	June 2014
Estimated Study Completion Date:	April 2024
Estimated Primary Completion Date:	April 2024 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: **PNET 5 MB-**LR (low-risk) Radiotherapy and reduced-intensity maintenance chemotherapy. Total treatment duration is 39 weeks.	Radiation: Radiotherapy without Carboplatin Brain - 23.40 Gy in 13 daily fractions of 1.80 Gy Spine - 23.40 Gy in 13 daily fractions of 1.80 Gy Primary tumour boost - 30.60 Gy in 17 daily fractions of 1.80 Gy Total dose - 54 Gy Duration of radiotherapy 6 weeks LR Arm after Amendment (Protocol version 11- 17 Nov 2014): Brain - 18.0 Gy in 10 daily fractions of 1.80 Gy Spine - 18.0 Gy in 10 daily fractions of 1.80 Gy Primary tumour boost - 36.0 Gy in 20 daily fractions of 1.80 Gy Total dose - 54 Gy Duration of radiotherapy 6 weeks Drug: Reduced-intensity maintenance chemotherapy

	Starts 6 weeks after radiotherapy. 6 cycles alternating Regimen A and Regimen B. Regimen A (cycles 1, 3, **5**): cisplatin 70 mg/m2 day 1, CCNU 75 mg/m2 day 1, vincristine 1.5 mg/m2 days 1, 8 and 15, Regimen B: (cycles 2, 4, 6): cyclophosphamide 1 x 1000 mg/m2 days 1-2, vincristine 1.5 mg/m2 day 1. Interval after cycle A: 6 weeks, after cycle B: 3 weeks, for a total duration of 27 weeks. Cumulative doses of chemotherapy drugs: cisplatin 210 mg/m2, lomustine (CCNU) 225 mg/m2, vincristine 18 mg/m2, cyclophosphamide 6 g/m2. Other Names: • Cisplatin • Lomustin (CCNU) • Vincristine • Cyclophosphamide
Experimental: **PNET 5 MB-**SR (standard-risk) Radiotherapy with carboplatin or radiotherapy without carboplatin and maintenance chemotherapy. Total treatment duration is 48 weeks.	Radiation: Radiotherapy without Carboplatin Brain - 23.40 Gy in 13 daily fractions of 1.80 Gy Spine - 23.40 Gy in 13 daily fractions of 1.80 Gy Primary tumour boost - 30.60 Gy in 17 daily fractions of 1.80 Gy Total dose - 54 Gy Duration of radiotherapy 6 weeks LR Arm after Amendment (Protocol version 11- 17 Nov 2014): Brain - 18.0 Gy in 10 daily fractions of 1.80 Gy Spine - 18.0 Gy in 10 daily fractions of 1.80 Gy Primary tumour boost - 36.0 Gy in 20 daily fractions of 1.80 Gy Total dose - 54 Gy Duration of radiotherapy 6 weeks Radiation: Radiotherapy with Carboplatin Brain - 23.40 Gy in 13 daily fractions of 1.80 Gy Spine - 23.40 Gy in 13 daily fractions of 1.80 Gy Primary tumour boost - 30.60 Gy in 17 daily fractions of 1.80 Gy Total dose - 54 G Carboplatin 35 mg/m2 **5** times/week. Other Name: Carboplatin Drug: Maintenance chemotherapy Starts 6 weeks after radiotherapy. 8 cycles alternating Regimen A and Regimen B. Regimen A (cycles 1, 3, **5**, 7): cisplatin 70 mg/m2 day 1, CCNU 75 mg/m2 day 1, vincristine 1.5 mg/m2 days 1, 8 and 15 Regimen B: (cycles 2, 4, 6, 8): cyclophosphamide 1 x 1000 mg/m2 days 1-2, vincristine 1.5 mg/m2 day 1. Interval after cycle A: 6 weeks, after cycle B: 3 weeks. Duration 36 weeks. Cumulative doses of chemotherapy drugs: cisplatin 280 mg/m2, lomustine (CCNU) 300 mg/m2, vincristine 24 mg/m2, cyclophosphamide 8 g/m2, carboplatin 1050 mg/m2 (in randomized patients). Other Names: • Cisplatin • Lomustine (CCNU) • Vincristine • Cyclophosphamide

Detailed Description:

The aim of the LR-treatment arm is to confirm the high rate of event-free survival in patients between the ages of 3 to 5 years and less than 22, with 'standard risk' medulloblastoma with a low-risk biological profile. Patients eligible for the study will be those with non-metastatic medulloblastoma (by CSF cytology and centrally reviewed MRI imaging) at diagnosis and low-risk biological profile, defined as ß-catenin nuclear immuno-positivity by immuno-histochemistry (IHC). Patients will have undergone total or near-total tumour resection and will receive conventionally fractionated (once a day) radiotherapy with a dose of 54 Gy to the primary tumor and 18.0 Gy to the craniospinal axis. Following radiotherapy, patients will receive a reduced-intensity chemotherapy with a total of 6 cycles of chemotherapy consisting of 3 courses of cisplatin, CCNU and vincristine alternating with 3 courses of cyclophosphamide and vincristine.

The aim of the SR-arm is to test whether concurrent carboplatin during radiotherapy followed by 8 cycles of maintenance chemotherapy in patients with 'standard risk' medulloblastoma with an average-risk biological profile may improve outcome. Patients eligible for the study will be those with non-metastatic medulloblastoma (by CSF cytology and centrally reviewed MRI imaging) at diagnosis and average-risk biological profile, defined as ß-catenin nuclear immuno-negativity by IHC. Patients will have undergone total or near-total tumour resection and will receive conventionally fractionated (once a day) radiotherapy with a dose of 54 Gy to the primary tumor and 23.4 Gy to the craniospinal axis. Following radiotherapy, patients will receive a modified-intensity chemotherapy with a total of 8 cycles of chemotherapy consisting of 4 courses of cisplatin, CCNU and vincristine alternating with 4 courses of cyclophosphamide and vincristine.

Eligibility

Ages Eligible for Study:	3 Years to 21 Years (Child, Adult)
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

1. Age at diagnosis, at least 3 - 5 years (depending on the country) and less than 22 years (LR-arm: less than 16 years). The date of diagnosis is the date on which surgery is undertaken.
2. Histologically proven medulloblastoma, including the following subtypes, as defined in the WHO classification (2007): classic medulloblastoma, desmoplastic/nodular medulloblastoma. Pre-treatment central pathology review is considered mandatory.
3. Standard-risk medulloblastoma, defined as;
    - total or near total surgical resection with less than or equal to 1.5 cm2 (measured on axial plane) of residual tumour on early post-operative MRI, without and with contrast, on central review;
    - no central nervous system (CNS) metastasis on MRI (cranial and spinal) on central review;
    - no tumour cells on the cytospin of lumbar CSF
    - no clinical evidence of extra-CNS metastasis; Patients with a reduction of postoperative residual tumor through second surgery to less than or equal to 1.5 cm2 are eligible, if if timeline for start of radiotherapy can be kept.
4. Submission of high quality biological material including fresh frozen tumor samples for the molecular assessment of biological markers (such as the assessment of myelocytomatosis oncogene (MYC) copy number status) in national biological reference centers. Submission of blood is mandatory for all patients, who agree on germline DNA studies. Submission of CSF is recommended.
5. No amplification of MYC or MYCN (determined by FISH).
6. For LR-arm: Low-risk biological profile, defined as WNT subgroup positivity. The WNT subgroup is defined by the presence of (i) ß-catenin mutation (mandatory testing), or (ii) ß-catenin nuclear immuno-positivity by IHC (mandatory testing) and ß-catenin mutation, or (iii) ß-catenin nuclear immuno-positivity by IHC and monosomy 6 (optional testing). For SR-arm: average-risk biological profile, defined as ß-catenin nuclear immuno-negativity by IHC (mandatory) and mutation analysis (optional).
7. No prior therapy for medulloblastoma other than surgery.
8. Radiotherapy aiming to start no more than 28 days after surgery. Foreseeable inability to start radiotherapy within 40 days after surgery renders patients ineligible for the study.
9. Screening for the compliance with eligibility criteria should be completed, and patient should be included into the study within 28 days after first surgery (in case of second surgery within 35 days after first surgery). Inclusion of patients is not possible later than 40 days after first tumour surgery, or after start of radiotherapy.
10. Common toxicity criteria (CTC) grades < 2 for liver, renal, haematological function
11. no significant sensorineural hearing deficit as defined by pure tone audiometry with bone conduction or air conduction and normal tympanogram showing no impairment ≥ 20 decibel (dB) at 1-3 kilohertz (kHz). If performance of pure tone audiometry is not possible postoperatively, normal otoacoustic emissions are acceptable, if there is no history for hearing deficit.
12. No medical contraindication to radiotherapy or chemotherapy, such as preexisting DNA breakage syndromes (e.g. Fanconi Anemia, Nijmegen breakage syndrome), Gorlin Syndrome or other reasons as defined by patient's clinician.
13. No identified Turcot and Li Fraumeni syndrome.
14. Written informed consent (and patient assent where appropriate) for therapy according to the laws of each participating country. Information must be provided to the patient on biological studies (tumour and germline), and written informed consent obtained of agreement for participation.
15. National and local ethical committee approval according to the laws of each participating country (to include approval for biological studies).

Exclusion Criteria:

1. One of the inclusion criteria is lacking.
2. Brainstem or supratentorial primitive neuro-ectodermal tumour.
3. Atypical teratoid rhabdoid tumour.
4. Medulloepithelioma; Ependymoblastoma
5. Large-cell medulloblastoma, anaplastic medulloblastoma, or medulloblastoma with extensive nodularity (MBEN), centrally confirmed.
6. Unfavourable or undeterminable biological profile, defined as amplification of MYC or MYCN, or MYC or MYCN or WNT subgroup status not determinable.
7. Metastatic medulloblastoma (on CNS MRI and/or positive cytospin of postoperative lumbar CSF).
8. Patient previously treated for a brain tumour or any type of malignant disease.
9. DNA breakage syndromes (e.g. Fanconi anemia, Nijmegen breakage syndrome) or other, or identified Gorlin,Turcot, or Li Fraumeni syndrome.
10. Patients who are pregnant.
11. Female patients who are sexually active and not taking reliable contraception.
12. Patients who cannot be regularly followed up due to psychological, social, familial or geographic reasons.
13. Patients in whom non-compliance with toxicity management guidelines can be expected.

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: NCT02066220

Contacts

Contact: Stefan Rutkowski, Prof. Dr. med. +49-40-7410 ext 58200 r.rutkowski@uke.de

Contact: Katja von Hoff, Dr. med. +49-40-7410 ext 53394 k.von-hoff@uke.uni-hamburg.de

Show 77 Study Locations

Sponsors and Collaborators

Universitätsklinikum Hamburg-Eppendorf

Deutsche Kinderkrebsstiftung

Investigators

Principal Investigator: Francois Doz, Prof. Dr. Institut Curie Paris, France

More Information

Responsible Party:	Universitätsklinikum Hamburg-Eppendorf
ClinicalTrials.gov Identifier:	NCT02066220 History of Changes
Other Study ID Numbers:	SIOP **PNET 5 MB** 2011-004868-30
Study First Received:	February 7, 2014
Last Updated:	September 8, 2016
Health Authority:	Germany: Federal Institute for Drugs and Medical Devices

Keywords provided by Universitätsklinikum Hamburg-Eppendorf:

PNET	posterior fossa
pediatric brain tumor	chemotherapy
medulloblastoma	radiotherapy
event-free survival (EFS)	biological profile
progression-free survival (PFS)	ß-catenin
overall survival (OS)	

Additional relevant MeSH terms:

Neuroectodermal Tumors	Neoplasms, Glandular and Epithelial
Neuroectodermal Tumors, Primitive	Neoplasms, Nerve Tissue
Brain Neoplasms	Cisplatin
Medulloblastoma	Cyclophosphamide
Central Nervous System Neoplasms	Carboplatin
Nervous System Neoplasms	Vincristine
Neoplasms by Site	Lomustine
Neoplasms	Antineoplastic Agents
Brain Diseases	Immunosuppressive Agents
Central Nervous System Diseases	Immunologic Factors
Nervous System Diseases	Physiological Effects of Drugs
Glioma	Antirheumatic Agents
Neoplasms, Neuroepithelial	Antineoplastic Agents, Alkylating
Neoplasms, Germ Cell and Embryonal	Alkylating Agents
Neoplasms by Histologic Type	Molecular Mechanisms of Pharmacological Action

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