# An international clinical program for the diagnosis and treatment of children, adolescents and young adults with ependymoma.

Published: 16-12-2019
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This study has been transitioned to CTIS with ID 2024-512222-28-00 check the CTIS register for the current data. Overall program:The overall aim of this project is to improve the outcome of patients diagnosed with ependymoma by improving the staging…

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Nervous system neoplasms malignant and unspecified NEC |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON54695

**Source**
ToetsingOnline

**Brief title**
SIOP Ependymoma II

### Condition

- Nervous system neoplasms malignant and unspecified NEC

**Synonym**
brain tumor, Ependymoma

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Centre Leon Berard

**Source(s) of monetary or material Support:** Ministerie van OC&W

## Intervention

**Keyword:** Cancer, Children, Ependymoma

## Outcome measures

### Primary outcome

Overall program:

- Gross Total Resection (GTR) rate.

Stratum 1:

-PFS from the date of randomisation to the date of event defined as progression or death due to any cause.

Stratum 2:

- Number of chemotherapy responders. Objective response to chemotherapy is measured based on SIOP-E Neuro Imaging guidelines.

Stratum 3:

-PFS from the date of randomisation to the date of event defined as progression or death due to any cause.

### Secondary outcome

Overall program:

-Second look surgery rate.

Stratum 1:

-The efficacy in each molecular subtype will be described in terms of PFS and OS.

-Overall survival (OS) measured from the date of randomisation to the date of death due to any cause.

-Quality of survival (QoS).

-Neuropsychological outcomes.

-Neuroendocrine outcomes (neuroendocrine late effects).

-Short and long-term safety: Adverse Events

Stratum 2:

-The concordance rate between central and local radiological reviews will be described as the proportion of patients in whom the result of the central radiological review confirms the local review.

-The efficacy in each molecular subtype will be described in terms of PFS and OS.

-Overall survival (OS) measured from the date of randomisation to the date of death due to any cause.

-PFS from the date of randomisation to the date of event defined as progression or death due to any cause.

-Quality of survival (QoS).

-Neuropsychological outcomes.

-Neuroendocrine outcomes (neuroendocrine late effects).

-Short and long-term safety: Adverse Events

Exploratory endpoint measures:

-Event free survival for patients with boost of radiotherapy.

-Toxicity will be monitored in the subgroup receiving radiotherapy boost.

Stratum 3:

-To describe in both study arms, the efficacy in each molecular sub-group.

-Overall survival (OS) measured from the date of randomisation to the date of

death due to any cause.

-Radiotherapy free survival rate.

-Quality of survival (QoS).

-Neuropsychological outcomes.

-Neuroendocrine outcomes (neuroendocrine late effects).

-Short and long-term safety: Adverse Events

Exploratory endpoint measures:

-Pharmacokinetics for valproate.

# Study description

**Background summary**

Ependymomas are one of the most frequent malignant brain tumours in children and adolescents. Their prognosis, especially in young children remains poor and their effective treatment remains one of the most difficult tasks in paediatric oncology, particularly as half of all cases are diagnosed under 5 years of age. The prognosis at relapse is ultimately dismal.

Histological grading of ependymomas is non-consistent. Furthermore, there is controversy about the different variants of epedymoma given within the most

frequently used system, World Health Organization (WHO) 2007.

To date, there are no reliable biological prognostic markers for ependymoma.The role of histologic and molecular subtypes in prognostication remains controversial. Further research into prognostic markers and therapeutic targets in needed.

After 5 years, progression free survival (PFS) rates range from 23 to 74%, while mortality is reported in up to 40% of affected children. This is particularly true for patients with incomplete resection.

A number of prognostic factors have been identified in different studies. The degree of surgical resection is considered as the most consistent prognostic factor for children with ependymoma: residual disease after surgery gives a worse prognosis.
Studies have been performed in which patients were offered re-operations to increase the rate of total resections of the tumor. Such re-operations seem feasible and effective but expert advice should be requested prior to undertaking second look surgery if needed.

It is generally accepted that adjuvant therapy is required even when complete resection is achieved. However, within Europe at present there are marked differences in the post-surgical management of patients. The SIOP Ependymoma II protocol seeks to determine a standardised European approach.

Standard adjuvant therapy for older children is a standard dose of 54 Gy of radiotherapy in 30 fractions to the planning target volume (PTV). Nowadays a dose of 59,4 Gy in 33 fractions is recommended.

Since the early 1990s, chemotherapy has been widely used in the management of brain tumours in young children to defer radiotherapy and thus improve intellectual outcome.

Over the last few years, there has been little improvement, if any, in the outcome of patients with ependymoma. Furthermore, the focus in research into prognostic factors in oncology has shifted from clinical and histological factors towards molecular and cell biology factors.

In light of recent advances in neurosurgical techniques, radiotherapy and molecular diagnostics, there is an urgent need to incorporate and combine current practices to re-evaluate standard of care for children with ependymoma.

In this program we will investigate key molecular events in ependymoma tumorgenesis and test the hypothesis that improvements in risk stratification using a combination of clinical and biological variables will enhance prediction of outcome.
This program will also explore new predictive and prognostic biomarkers

including a new proposal for histological grading.

By installing national committees for review of neurosurgery and imaging and, if needed, giving advice on considerations for second look surgery and referral we aim at improving GTR rate above 50%. Monitoring of patients for increased risk of neurological morbidity will get particular attention.

This protocol is also designed to cover diverse situations according to age, site and post-operative status. It will ask randomised questions in each situation. Patients that do not enter in one of the treatment groups will be included in a registry of European ependymoma.

**Study objective**

This study has been transitioned to CTIS with ID 2024-512222-28-00 check the CTIS register for the current data.

Overall program:
The overall aim of this project is to improve the outcome of patients diagnosed with ependymoma by improving the staging and the standard of care and to improve our understanding of the underlying biology. The program will evaluate new strategies for diagnosis (centralized reviews of pathology and imaging) and new therapeutic strategies in order to develop treatment recommendations. Patients will be stratified into different treatment subgroups according to their age, the tumour location and the outcome of the initial surgery. Each subgroup will be studied in a specific randomised study to evaluate the proposed therapeutic strategies.

Stratum 1, patients with complete resection, older than 12 months and younger than 22 years:
This group of patients that usually gets radiotherapy after surgery has a 5-years progression free survival of only 60%. Survival following relapse after primary treatment is generally very poor and there is thus a need to improve tumour control in order to postpone disease relapse. The aim of stratum 1 is to evaluate the clinical impact of 16-week chemotherapy regimen with VEC-CDDP following surgical resection and conformal radiotherapy.

Stratum 2: patients older than 12 months and younger than 22 years with inoperable measurable residual disease:
The aim of stratum 2 is to investigate the possible efficacy of HD-MTX by giving to all patients the benefit of VEC chemotherapy whilst randomising half of patients to receive additional HD-MTX. This will generate clinical data to decide whether methotrexate should be investigated in future phase III trials or it would support decisions to reduce the use of HD-MTX in the infant population and will support initiatives to try alternative therapies.
Patients with residual inoperable disease after induction chemotherapy and conformal radiotherapy will receive an additional boost of radiotherapy to the

residual tumour. Safety of the boost will also be evaluated.

Stratum 3: patients younger than 12 months or patients not eligible to receive radiotherapy:
The aim of stratum 3 is to evaluate the benefit of intense chemotherapy with or without adjuvant HDAC inhibitor and to minimize the risk of drug resistance whilst maximizing the intensity of treatment in very young children.

## Study design

The overall Ependymoma Program is opened to all patients diagnosed with ependymoma below the age of 22 years. It will include a centralised review of pre and post-operative imaging to assess the completeness of the resection. It will also include a central review of pathology to confirm the histological diagnosis. Several biological markers will be prospectively assessed for prospective evaluation of disease subgroups. Further biological evaluations will be coordinated within the linked BIOMECA study. After surgery and central review of imaging and pathology, patients will be offered the opportunity to undergo second look surgery, if possible. Patients will be enrolled in one of 3 different strata according to the outcome of the initial surgical resection (residual disease vs no residual disease), their age or eligibility / suitability to receive radiotherapy. Stratum 1 is designed as a randomised phase III study for patients who have had a complete resection, with no measurable residual disease and are > 12 months and < 22 years at diagnosis. Those patients will be randomised to receive conformal radiotherapy followed by either 16 weeks of chemotherapy with VEC-CDDP, or observation. Stratum 2 is designed as a randomised phase II study for patients who have inoperable measurable residual disease and who are > 12 months and < 22 years at diagnosis. Those patients will be randomised to two different treatment schedules of chemotherapy either with VEC or VEC+ high dose methotrexate (VEC +HD-MTX). Therapy will be continued with second look surgery, if feasible, radiotherapy and, in case of no progression under frontline chemotherapy, a 16 week course of maintenance chemotherapy (VEC-CCDP). Patients who remain unresectable with residual disease despite frontline chemotherapy and for whom second line surgery is not feasible, there will be a study of the safety of a radiotherapy boost of 8 Gy that will be administered to the residual tumour immediately after the completion of the conformal radiotherapy. Stratum 3 is designed as a randomised phase II chemotherapy study in children <12 months of age or those not eligible to receive radiotherapy. These patients will be randomised to receive a dose dense chemotherapy with or without the addition of the histone deacetylase (HDAC) inhibitor, valproate. Registry: Patients that do not fulfil the inclusion criteria of one of the 3 interventional strata will be enrolled and followed up via an observational study.

## Intervention

Stratum 1: maintenance chemotherapy, 16 weeks VEC-CDDP
Stratum 2: HD-MTX added to standard frontline chemotherapy with VEC
Stratum 3: HDAC-inhibitor (valproate) added to standard chemotherapyschedule

## Study burden and risks

Stratum 1:
Patients randomised to the arm with adjuvant maintenance chemotherapy will receive additional chemotherapy during 16 weeks, on 15 different days. Therefore they will stay in hospital for 1 to 3 days. Usually a Port-a-cath will be placed for administration of medication.

Stratum 2:
Patients randomised to the arm with additional HD-MTX will be administered this medication on 3 different occasions. Therefore they will stay in hospital at least 24 hours each of the 3 occasions. In total treatment with frontline chemotherapy including HD-MTX takes 2 weeks longer than treatment without HD-MTX.

Stratum 3:
Patients randomised to the arm with valproate have to take valproate (oral solution) twice daily during a period of 56 weeks. After those 56 weeks patient receive another year of continuation therapy with valproate.

All patients participating in the protocol will, on various occasions (max. 4), be asked to fill out several questionnaires about quality of life.

# Contacts

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FR
**Scientific**
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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)
Newborns

## Inclusion criteria

OVERALL PROGRAM: • Main residence in one of the participating countries. • Age < 22 years old at diagnosis. • Histological diagnosis of intracranial or spinal, localized or metastatic, ependymoma according to local pathologist (all WHO grades) including: myxopapillary ependymoma, ependymoma (papillary, clear-cell, tanycytic), ependymoma RELA-fusion positive or anaplastic ependymoma. • Delivery to national referral pathology center of FFPE tumour tissue blocks. • Written informed consent (staging) for collection and transfer of biological samples. • All patients and/or their parents or legal guardians willing and able to comply with protocol schedule and agree to sign a written informed consent. • Patients must be affiliated to a Social Security System in countries where this is mandatory.STRATUM I: • Age>12 months and < 22 years at time of study entry. • No residual measurable ependymoma based on the central neuroradiological review This includes: R0: No residual tumour on postoperative MRI in accordance with the neurosurgical report. R1: No residual tumour on MRI but description of a small residual tumour by the neurosurgeon. R2: Small residual tumour on MRI with the maximum diameter below 5mm in any direction. • Newly diagnosed intracranial ependymoma of WHO grade II-III confirmed by central pathological review. • No metastasis on spinal MRI and on CSF cytology assessments. • No previous radiotherapy. • No previous chemotherapy. • No co-existent unrelated disease at the time of study entry that would render the patient unable to receive chemotherapy. • No medical contraindication to radiotherapy, and chemotherapy. • No signs of infection. • Adequate bone marrow, liver and renal function (detailled in protocol). • Post-menarchal female not pregnant or nursing (breast feeding) and with a negative beta-HCG pregnancy test prior to commencing the trial. • Males and females of reproductive age and childbearing potential with effective contraception for the duration of their treatment and 6 months after the completion of their treatment. • Patients and/or their parents or legal guardians must be willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures of the stratum 1. • Written informed consent (stratum 1). • Patients must be affiliated to a Social Security System in countries where this is mandatory.STRATUM 2: • Age > 12 months and < 22 years at time of study entry. • Residual non-reoperable measurable ependymoma based on the central neuroradiological review where: - R3: Residual tumour that can be measured in 3 planes. - R4: Size of the residual tumour not differing from the preoperative status (e.g. after biopsy). • Newly diagnosed intracranial ependymoma of WHO grade II-III confirmed by central pathological review. • No metastasis on spinal MRI and on CSF cytology assessments. • No previous radiotherapy. • No previous chemotherapy. • No co-existent unrelated disease at the time of study entry that would

render the patient unable to receive chemotherapy. • No medical contraindication to radiotherapy, and chemotherapy. • No signs of infection. • Adequate bone marrow, liver and renal functions (detailled in protocol). • Post-menarchal female not pregnant or nursing (breast feeding) and with a negative beta-HCG pregnancy test prior to commencing the trial. • Males and females of reproductive age and childbearing potential with effective contraception for the duration of their treatment and 6 months after the completion of their treatment. • Patients and/or their parents or legal guardians must be willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures of the stratum 2. • Written informed consent (stratum 2). • Patients must be affiliated to a Social Security System in countries where this is mandatory.STRATUM 3 • Children younger than 12 months at time of entry to study or any patient ineligible to receive radiotherapy due to age at diagnosis, tumour location or clinician/parent decision and according to national criteria. • Newly diagnosed intracranial ependymoma of WHO grade II-III confirmed by central pathological review. • Adequate bone marrow, liver and renal functions (detailled in protocol). • No previous chemotherapy. • No previous radiotherapy. • No co-existent unrelated disease at the time of study entry that would render the patient unable to receive chemotherapy. • No medical contraindication to chemotherapy. • No signs of infection. • Patients and/or their parents or legal guardians must be willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures of the stratum 3. • Written informed consent (specific to stratum 3). • Patients must be affiliated to a Social Security System in countries where this is mandatory.OBSERVATIONAL STUDY • Patients who are not eligible to any of the 3 interventional studies proposal or who refuse to comply with protocol specifications of the interventional studies proposed, • Main residence in one of the participating countries, • Age below 22 years old at the diagnosis, • Histological diagnosis of intracranial or spinal, localized or metastatic, ependymoma according to local pathologist (all WHO grades) including : myxopapillary ependymoma, ependymoma (papillary, clear-cell, tanycytic), ependymoma RELA fusion-positive and anaplastic ependymoma, confirmed by central pathological review, • All patients and/or their parents or legal guardians must receive an information sheet. Assent of the child, when appropriate, as well as written consent of parents or legal guardians will be obtained according to institutional / national guidelines. .classa*TU*RE*@

## Exclusion criteria

Exclusion criteria for the overall program
- Patient with subependymomas and ependymoblastomas.
- Primary diagnosis predating the opening of SIOP Ependymoma II (Apr 29th 2015)Exclusion criteria for interventional strata 1,2 and 3:
- Tumour entity other than primary intracranial ependymoma,
- Patients with WHO grade I ependymoma including myxopapillary variant,
- Patients with spinal cord location of the primary tumour,
- Participation within a different trial for treatment of ependymoma,
- Concurrent treatment with any anti-tumour agents,
- Inability to tolerate chemotherapy,
- Unable to tolerate intravenous hydration,

- Other severe acute or chronic medical or psychiatric conditions or laboratory abnormalities that may increase the risk associated with study participation or investigational product administration, or may interfere with the interpretation of study results in the judgment of the investigator,
- Pre-existing mucositis, peptic ulcer, inflammatory bowel disease, ascites, or pleural effusion,
- Contraindication to one of the IMP used in the applicable stratum according to the SmPCs,Additional exlusion criterion for stratum 1 and 2:
- Patient for whom imaging remains RX despite all effort to clarify the MRI conclusion.Additional exclusion criteria for stratum 3:
- Pre-existing severe hepatic and/or renal damage,
- Family history of severe epilepsy in immediate family siblings,
- Presence of previously undiagnosed mitochondrial disorder detected by screening as part of trial,
- Elevated blood ammonium level >= 1.5 x upper limit of the normal
- Elevated blood lactate level >= 1.5 x upper limit of the normal Exclusion criteria observational study:
- Tumour entity other than primary ependymoma
- Patient with subependymomas and ependymoblastomas
- Primary diagnosis predating the activation ofteh SIOP Ependymoma II program (Apr 29th 2015)"Cÿëý**ù*

# Study design

## Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Diagnostic |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 13-07-2020 |
| Enrollment: | 30 |

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|---|---|
| Type: | Actual |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Cytoxan |
| Generic name: | Cyclophosphamid |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | Oncovin, e.a. |
| Generic name: | Vincristinsulphate |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | Paraplatin |
| Generic name: | Carboplatin |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | Platinol |
| Generic name: | Cisplatin |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | Toposar, e.a. |
| Generic name: | Etoposide |
| Registration: | Yes - NL outside intended use |

## Ethics review

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|---|---|
| Approved WMO Date: | 16-12-2019 |
| Application type: | First submission |
| Review commission: | METC NedMec |
| Approved WMO Date: | 05-02-2020 |
| Application type: | First submission |
| Review commission: | METC NedMec |

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|---|---|
| Approved WMO Date: | 01-05-2020 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 19-05-2020 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 10-08-2020 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 13-08-2020 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 01-10-2020 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 06-10-2020 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 12-01-2021 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 14-01-2021 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 21-10-2021 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO | |

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|---|---|
| Date: | 25-07-2023 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 15-09-2023 |
| Application type: | Amendment |
| Review commission: | METC NedMec |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EU-CTR | CTIS2024-512222-28-00 |
| EudraCT | EUCTR2013-002766-39-NL |
| ClinicalTrials.gov | NCT02265770 |
| CCMO | NL46088.041.19 |