Children's Cancer Trials Team

Cancer Research UK Clinical Trials Unit @CRCTU

Ependymoma Programme Synopsis

TITLE	**SIOP Ependymoma program II:** An International Clinical Program for the diagnosis and treatment of children, adolescents and young adults with ependymoma
SPONSOR	Centre Léon Bérard
PROTOCOL NUMBER	ET-13-002
EUDRACT NUMBER	2013-002766-39
NATIONAL INVESTIGATOR-COORDINATOR	**International Chief Investigator General Ependymoma Program**: Dr Didier Frappaz **Stratum 1 (phase III)** International Chief Investigator: Dr Didier Frappaz **Stratum 2 (Phase II)** International Chief Investigator Dr. Maura Massimino - International Chief Investigator Window Study Randomised: Dr Martin English - International Chief Investigator Radiation Boost Study: Dr Lorenza Gandola **Stratum 3 (Phase II)** International Chief Investigator Professor Richard Grundy **National UK Coordinating Investigator**: Professor Richard Grundy
STUDY DESIGN	The ependymoma program is a comprehensive program to improve the accuracy of the primary diagnosis and explore different therapeutic strategies in children, adolescents and young adults accordingly. This program is opened to all patients diagnosed with ependymoma below the age of 22 years. It will include a centralized 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 and to prospectively assess biological markers and molecular subgroups 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 a randomised phase III study for patients who have had a complete resection, with no measurable residual disease (as confirmed by centrally reviewed MRI) 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 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. After completion of the frontline chemotherapy, patients will be assessed for response (MRI) and will receive second look surgery when feasible. For those 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 8Gy that will be administered to the residual tumour immediately after the completion of the conformal radiotherapy. Patients without evidence of residual disease after chemotherapy and/or second look surgery are not eligible for radiotherapy boost. All patients who have not shown progression under chemotherapy will receive as maintenance therapy a 16 week course of VEC –CDDP following completion of radiotherapy. **Stratum 3** is a randomized phase II chemotherapy study in children <12 months or those not eligible to receive radiotherapy (see national criteria). These patients will be randomised to receive a dose dense chemotherapy alternating myelosuppressive and relatively non-myelosuppressive drugs at 2 weekly intervals with or without the addition of the histone deacetylase inhibitor, valproate. **Registry:** Patients that do not fulfil the inclusion criteria of one of the interventional strata will be enrolled and followed up into an observational study which will be analysed descriptively.
PURPOSE	The overall aim of this project is to improve the outcome of patients diagnosed with ependymoma by improving and harmonising the staging and the standard of care of this patient population and to improve our understanding of the underlying biology thereby informing future treatment. 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 different therapeutic strategies. **Stratum 1:** The aim is to evaluate the clinical impact of 16-week chemotherapy regimen with VEC-CDDP following surgical resection and conformal radiotherapy in terms of PFS in patients with completely removed intracranial ependymoma. **Stratum 2:** The aim is to investigate the possible activity of HD-MTX by giving all patients VEC whilst randomising half of patients to receive additional HD-MTX. Safety of boost radiotherapy will also be evaluated. **Stratum 3:** This stratum is designed to evaluate the benefit of postoperative dose intense chemotherapy administered alone or in combination with valproate. The aim is to minimize the risk of drug resistance whilst maximizing the intensity of treatment in very young children. **Linked biological study:** The SIOP Ependymoma II program supports the identification of informative prognostic biomarkers within the collaborative BIOMEC study. This high priority initiative is an essential element of the overall program to improve future treatment of ependymoma.
PRIMARY OBJECTIVE	**Overall program:** **The primary objective:** to determine whether the assessment of residual disease can be improved by a centralized review of post-operative MRI and whether such review increases the rate of complete resection compared to historical controls. Does central neurosurgical and radiological review increase resection rates? **Stratum 1:** **The primary objective** is to test the hypothesis that there will be an improvement in

	progression free survival in patients who receive 16 weeks chemotherapy (VEC-CDDP) following surgical resection and conformal radiotherapy when compared to those that undergo surgical resection and radiotherapy alone. **Stratum 2:** **The primary objective**: To compare the activity of 2 post-operative chemotherapy schedules, VEC or VEC+HD-MTX in patients who have incompletely resected tumour. **Stratum 3:** **Primary objective**: To evaluate the progression free survival in children unable to receive radiation therapy and who receive valproate as a histone deacetylase inhibitor in addition to the primary chemotherapy strategy when compared to those who undergo chemotherapy without valproate.
ENDPOINTS	**Overall program:** **Primary endpoint measure:** Gross Total Resection (GTR)rate **Stratum 1:** **Primary endpoint measure:** • Progression free survival from the date of randomisation to the date of event defined as progression or death due to any cause. **Stratum 2:** **Primary endpoint measure:** • Number of treatment responders. Objective response to chemotherapy is measured based on SIOP-E Neuro Imaging guidelines. **Stratum 3:** **Primary endpoint measure:** • Progression free survival from the date of randomisation to the date of event defined as progression or death due to any cause. *For secondary and exploratory end point measures please refer to the protocol*
SAMPLE SIZE	**A minimum of 480 patients will be enrolled onto the program:** **Stratum 1** - 320 eligible patients will be randomised **Stratum 2** - 60 eligible patients will be randomised **Stratum 3** - A minimum of 100 eligible patients will be randomised -
STUDY TREATMENT	**Stratum 1:** *Conformal Radiotherapy (c RT):* Any patient older than 12 months of age will receive c RT of 59.4 Gy (only 54 Gy if less than 18 months old or with risk factors such as more than two surgeries or poor neurological status) with a 0.5 cm margin in 1.8 Gy daily fractions (under general anaesthesia if required), 5 fractions per week followed by either: *16-weeks of Chemotherapy* VEC-CDDP within 6 weeks after completion of standard 59.4 Gy radiotherapy or *Observation* **Stratum 2:** *Postoperative Induction Chemotherapy:* Patients > 12months with a residual measurable disease after surgery will receive an 8-week course of chemotherapy: VECHD MTX or VEC. Chemotherapy should be started within 3 weeks of surgery (any delay should be discussed with the chief investigator coordinator in the country concerned and the chief investigator coordinator of the program).

	Second look surgery: Patients will be evaluated by MRI for a second look surgery whenever possible. *Conformal Radiotherapy (cRT) :* All patients will receive cRT of 59.4 Gy (only 54 Gy if less than 18 months old or with risk factors such as more than two surgeries or poor neurological status) with a 0.5 cm margin in 1.8 Gy daily fractions (under general anaesthesia if required), 5 fractions per week. *Boost of radiotherapy (if residual tumour):* Patients with tumours that persist despite pre-radiation chemotherapy and cRT will receive a boost of 8Gy of cRT to the residual tumour bed (2 fractions of 4Gy on 2 consecutive treatment days). *16-week maintenance Chemotherapy*: All patients with incompletely resected tumour will receive 16-week maintenance chemotherapy with VEC-CDDP provided they showed no prior progression under first chemotherapy. **Stratum 3:** Patients will be randomized to receive 2 different schedules of chemotherapy. The complete course of chemotherapy comprises 4 administrations of alternating myelosupressive and relatively non-myelosuppressive drugs repeated every 56 days for a total of 7 cycles alone or in association valproate. At the end of the chemotherapy, patients who have received valproate on top of chemotherapy will receive valproate for an additional year. Chemotherapy should be started as soon as recovered from surgery and ideally within 3 weeks of surgery.
Main inclusion criteria	**Inclusion criteria for overall program:** • Main residence in one of the participating countries, • Age below 22 years old at the diagnosis, • Newly diagnosed intracranial or spinal ependymoma (all WHO grades) (including ependymoma variants: cellular, papillary, clear-cell and tanycytic) or anaplastic (malignant) ependymoma • Delivery to national referral pathology centre of FFPE tumour tissue blocks or at least 20 5µm sections on charged slides and 10 10 µm curls in an Eppendorf tube. • Written informed consent 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. **Inclusion criteria for ancillary BIOMECA Studies:** Written informed consent for collection and transfer of BIOMECA biological samples if patients and/or their parents agree to participate in this study. **Inclusion criteria for interventional studies:** **After Initial surgery and staging ,** patients will be enrolled in 1 of 3 different interventional studies **(*)** where they will be offered a set of therapeutic interventions based on the outcome of the intervention (no measurable residue vs residual inoperable disease), their age and/or their eligibility /suitability to receive radiotherapy. Patients with histologically confirmed intracranial ependymoma meeting the following criteria will be enrolled into interventional studies: • Main residence in one of the participating countries, • Age below 22 years old at the diagnosis, • Newly diagnosed with an ependymoma WHO grade II and III (including ependymoma variants: cellular, papillary, clear-cell and tanycytic) or anaplasic (malignant) ependymoma. (Myxopapillary, subependymomas, and patient with spinal cord location of the primary tumour are not eligible), • Post-menarchal female not pregnant or nursing and with a negative beta-HCG pregnancy test prior to commencing the trial and not nursing, • Males and females of reproductive age and childbearing potential with

	effective contraception for the duration of their participation in this study, • Patients and/or their parents or legal guardians willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures. **(*) Inclusion and exclusion criteria have been defined for each stratum of the program – please refer to Section 5 of the protocol.** **Inclusion criteria for observational study:** Patients that do not fulfil the inclusion criteria of one of the interventional studies will be enrolled and followed up into an observational study and descriptive analysis will be performed.
STUDY PERIODS	**Enrolment period:** 5 years **Treatment duration:** - Stratum 1: 7 months; - Stratum 2: 9 months; - Stratum 3: 2 years and 2 months. **Follow up:** Patients of each stratum will be followed 5 years after treatment completion. **Long term evaluation:** PFS and OS evaluation will be performed at a minimum of 5 years after the end of therapy. Beyond the completion of the 5 year follow up all investigations will be performed according to local practice and are not required by protocol. However, the data generated from these additional examinations could be collected. Based on the results observed, an updating of OS and PFS data may be requested by the steering committee beyond study duration. **Long term evaluation of children under the age of 18 at the end of follow up:** • Neuropsychological assessment and QoS evaluation will be performed at 18 years of age for children below 18 at the completion of the 5 year follow up • PFS and OS evaluation will be performed until the 18th year of age
STUDY SITES	This will be a multicentre international program which will involve the following countries: Austria, Belgium, Czech Republic, Denmark, France, Germany, Ireland, Italy, the Netherlands, Norway, Portugal, Slovenia, Spain, Sweden, Switzerland and the United Kingdom.

Flow Diagram of Ependymoma Umbrella