E.8 : Essai BIOMÈDE-Gliome

Promoteur Gustave ROUSSY	**Pôle : ONU** **Organe et situation :** Gliome, initial	**Identité patient**
Investigateur principal Elodie VAULEON (30.04) **ARCI** Nolwenn GUYOT (29.76)	**BIOMEDE-Gliome**/Phase III Biological Medicine for Diffuse Intrinsic Pontine Glioma (DIPG) Eradication **Critère principal :** Survie sans progression	*Coller ici l'étiquette du patient*

CRITERES D'INCLUSION

- Diagnosis Criteria:
  - **Diagnosis of DIPG (clinical and radiological)**. As biopsy is not standard for these tumors, an informed consent is required for the necessary histological verification. [Biopsy-part of BIOMEDE 2.0 trial]

    or
  - **Histological diagnosis of DIPG** (i.e. H3K28M or EZHIP positive Diffuse Midline Glioma located in the pons) in case the biopsy was performed before study entry. The diagnosis will be defined by 1/ diffuse glioma, 2/ H3K28M mutation or loss of H3K28 trimethylation together with EZHIP overexpression. In this situation, patient will sign the consent after the diagnosis to allow central review and biomarkers assessment thereafter.

    or
  - **Non-DIPG diffuse midline gliomas (ND-DMG), H3K28M mutant or with H3K28 trimethylation loss together with EZHIP overexpression**, will be eligible for the trial after biopsy or surgery. As biopsy and surgery is considered as standard practice for these locations, informed consent for the biopsy will not be necessary. Patient will sign the consent after the diagnosis to allow central review and biomarkers assessment thereafter.

    or
  - **Non-DIPG diffuse midline gliomas (ND-DMG)** will be eligible for the trial before the biopsy in case the diagnosis is clinically or radiologically suspected. Informed consent for the biopsy and molecular analysis will be necessary. *Then, if the central pathology review concludes to a ND-DMG with H3K28M mutant or H3K28 trimethylation loss together with EZHIP overexpression, these patients will be eligible for the treatment part of the trial.*
- Eligible for a biopsy, or biopsy material available for the biomarker assessment.
- Age > 6 months, with no upper age limit. Children between 6 months and 3 years will be discussed on a case by case basis for inclusion in the study for the feasibility of the stereotactic biopsy.
- Eligible for cerebral or craniospinal radiotherapy.
- Tumor at diagnosis: no prior chemotherapy for the present cancer; no prior cerebral radiation therapy even for another neoplasm. Surgery is allowed when performed for diagnostic or therapeutic purpose.
- Metastatic diseases or spinal tumors allowed; in this case, patients would receive craniospinal or spinal radiotherapy and medical treatment (everolimus or ONC201) will be postponed and only started after the end of radiotherapy.
- Patients must be affiliated to a social security system or beneficiary of the same according to local requirements.
- Written informed consent from parents/legal representative, patient, and age-appropriate assent before any study-specific procedures are conducted according to local, regional or national guidelines.

- Patient enrolled in the BIOMEDE 2.0 study
- Life expectancy > 12 weeks after the start of study treatment.
- Histological diagnosis of DIPG (as per the WHO criteria) confirmed by central pathology review,

  or

  Typical radiology of a DIPG (mandatory central radiological review) as well as the short clinical history (less than three months of pre-existing symptoms) in case of suspected DIPG but no histological confirmation (biopsy not informative),

  or

  Histological diagnosis of ND-DMG confirmed by central pathology review, with:
  - mutation in the histone H3.1, H3.2, H3.3 genes

    or
  - loss of H3K28me3 and EZHIP overexpression by immunohistochemistry.
- Karnofsky performance status scale or Lansky Play Scale > 50%. The PS should not take the neurologic deficit per se into account. NB: Children and adults with a worse performance status due to glioma-related motor paresis can be included.
- Effective and appropriate contraception for patients (male and female) of reproductive potential during their entire participation in the study and during 6 months after the end of treatment. Effective contraception is defined in Appendix 5.
- Negative pregnancy test (serum beta-HCG or urinary test) evaluated within one week prior randomization in sexually active females of reproductive potential.
- Absolute neutrophil count > 1.5 x 10^9/l, Platelets > 100 x 10^9/l.
- Total bilirubin < 1.5 x ULN, AST and ALT< 2.5 x ULN.
- Serum creatinine < 1.5 X ULN for age. If serum creatinine > 1.5 x ULN, creatinine clearance must be > 70 ml/min/1.73 m^2 (as per local practice).
- Normal coagulation tests within the local reference ranges.
- Written informed consent from parents/legal representative, patient, and age-appropriate assent before randomization according to local, regional or national guidelines.

CRITÈRES D'EXCLUSION

- Uncontrolled spontaneous massive intratumor bleeding. Patients with post-operative bleeding will be allowed to enter the study provided the hemorrhage is controlled. Same rule applies for the other post-operative complications (infection, CSF leakage, absence of wound closure, subdural collection…).
- Any other concomitant anti-cancer treatment not foreseen by this protocol is not allowed, except corticosteroids and Bevacizumab which are allowed during the protocol. Bevacizumab is not allowed before and until 15 days after the surgery. The use of bevacizumab or corticosteroids will be taken into account when judging the possibility of progression/pseudoprogression.
- Any other cancer diagnosed during the last 5 years.
- Uncontrolled intercurrent illness or active infection.
- Any other co-morbid condition that in the investigator's opinion would impair study participation.
- Unable for medical follow-up (geographic, social or mental reasons).
- Patient previously treated with irradiation on the brainstem for another neoplasm.
- Participation in another clinical study with an investigational product while on study treatment.
- Patient under guardianship or deprived of his/her liberty by a judicial or administrative decision or incapable of giving his/her consent.
- Current organ toxicity > grade 2 according to the NCI-CTCAE version 5.0 (see Appendix 2) especially cardiovascular or renal disease (including but not limited to: congenital long QT syndrome, nephrotic syndrome, glomerulopathy, uncontrolled high blood pressure despite adequate treatment).
- ONC201 administration should be avoided for patients with:
    - Prolongation of QT/QTcF interval (QTc interval > 480 milliseconds) preferably using Frederica's QT correction formula on two ECGs separated by at least 48 hours.
    - A history of Torsades de pointes or heart failure, hypokalemia, or family history of prolonged QT Syndrome.
    - Required concomitant use of medication(s) known to prolong the QT/QTc interval.

  In this case, patients will be treated in the Everolimus arm without randomization (except if contra-indication to Everolimus).
- Pregnant or breastfeeding women.
- Patients with chronic HBV disease compatible with the trial are not excluded from the study. These patients randomized to everolimus treatment will have regular viral load monitoring throughout the study.
- Patients taking strong P450 inhibitors or inducers or PgP inhibitors are not excluded from the study but drug concentration of everolimus should be monitored carefully to avoid toxicity. Preferably alternative medications should be considered. See Appendix 4 for a list of CYP3A4 inducers and inhibitors.
- Patient with known congenital galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption will not be randomized and will be treated in the ONC201 arm (except if contra-indication to ONC201).
- Patients with known hypersensitivity to any component of Everolimus (active substance, other rapamycin derivatives or excipients) will not be randomized and will be treated in the ONC201 arm (except if contra-indication to ONC201).
- Patients with known hypersensitivity to any component of ONC201 (drug product or excipients) will not be randomized and will be treated in the Everolimus arm (except if contra-indication to Everolimus).