E.6 : Essai CINGLIO

Promoteur Labcorp Drug Development	RCP : Neuro-Oncologie Organe et situation : Glioblastome/Adjuvant	Identité patient
	CLINGLIO/Phase II	
Investigateur principal Elodie VAULEON (30.04) ARCI Ina DEMBELE (44.11)	A randomized, double-blind, placebo-controlled adjuvant trial in newly diagnosed primary glioblastoma subjects to assess the efficacy and safety of 2-hydroxyoleic acid (2-OHOA) in combination with radiotherapy and temozolomide standard of care treatment	*Coller ici l'étiquette du patient*
	Co-critères principaux : Survie sans progression Survie globale	

CRITÈRES D'INCLUSION

1. Written informed consent, signed and dated
2. Subjects who are able to understand and follow instructions during the trial
3. Age ≥18 and ≤75
4. Subjects with newly histologically confirmed intracranial malignant glioma (glioblastoma WHO Grade IV) that is IDH1 wild type (local assessment) and who are scheduled to receive chemo-radiotherapy with temozolomide
5. Ability to swallow and retain oral medication
6. Centrally obtained MGMT promoter methylation status
7. Subjects who underwent total or partial / incomplete resection, and with the appropriate quantity of tumour tissue releasable for eligibility and signature assessments
8. Karnofsky Performance Score (KPS) > 50 %
9. Female subjects with a childbearing potential must have a negative pregnancy test within one week before inclusion in the trial. Those female and male subjects admitted in the study must use a reliable method of contraception, for female subjects during the study period up until 32 days after last study treatment and for male subjects up until 92 days after last study administration.

   Women must be:

   a. Either of NOT childbearing potential: postmenopausal (≥ 60 years of age, or < 60 years of age and amenorrhoea for 12 months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression with follicle-stimulating hormone (FSH) above 40 U/L and oestradiol below 30 ng/L, or if taking tamoxifen or toremifene, and age < 60 years, then FSH and oestradiol in the postmenopausal range), permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy), or otherwise incapable of pregnancy
   b. Or of childbearing potential and practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: e.g., established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device or intrauterine system; male partner sterilization (the vasectomized partner should be the sole partner for that subject).
10. A man who is sexually active and has not had a vasectomy must agree to use a barrier method of birth control e.g., either condom or partner with occlusive cap (diaphragm or cervical/vault caps).

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11. Adequate bone marrow function including: Absolute neutrophil count (ANC) ≥1,500/mm3 or ≥1.5 x 109/L; Platelets ≥ 100,000/mm3 or ≥100 x 109/L; Haemoglobin ≥ 9 g/dL (may have been transfused).
12. Adequate hepatic function defined by a total bilirubin level ≤ 1.5 × the upper limit of normal range (ULN), an aspartate aminotransferase (AST), level ≤ 2.5 × ULN, and an alanine aminotransferase (ALT) level ≤ 2.5 × ULN or, for subjects with documented metastatic disease to the liver, AST and ALT levels ≤ 5 × ULN. Subjects with documented Gilbert disease are allowed if total bilirubin ≤ 3 x ULN
13. Adequate renal function defined by an estimated creatinine clearance ≥ 30 mL/min according to the Cockcroft-Gault formula

CRITÈRES D'EXCLUSION

1. Known hypersensitivity to any component of the investigational product
2. Any other investigational drug within the preceding 30 days. Prior, concomitant, or planned concomitant treatment with anti-neoplastic aim including (but not limited) to NovoTumor Treatment Fields (Novo TTF), bevacizumab, intratumoural or intracavitary anti-neoplastic therapy (e.g Gliadel wafers), or other experimental therapeutics intended to treat the tumour.
3. Subjects who underwent "only biopsy" resection
4. Anticancer therapy within 4 weeks of study entry (6 weeks for mitomycin and nitrosoureas)
5. Other major surgery within the preceding 30 days
6. Allergy, hypersensitivity or other intolerability to temozolomide and its excipients, patients with hypersensitivity to dacarbazine and patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
7. Unable to undergo MRI
8. Presenting with diffuse midline gliomas or multifocal GBM (distant from the flare or contralateral) or rapid progression between early post-surgery MRI and pre-radiotherapy MRI
9. Uncontrolled or significant cardiovascular disease
10. A history of uncontrolled hyperlipidaemia and/or the need for concurrent lipid lowering therapy
11. Need for warfarin, phenytoin or sulphonylureas (glibenclamide, glimepiride, glipizide, glyburide or nateglanide)
12. Past medical history of uncontrolled clinically significant active or chronic gastrointestinal disorders (for example, crohn's disease, celiac disease, untreated stomach ulcers, etc) and gastro-inflammatory pathologies
13. Uncontrolled diabetes mellitus, with glycated haemoglobin (HbA1c) levels at the screening visit of ≥7.5%
14. Cardiac disease, defined specifically as either
    a. Mean resting corrected QT interval (QTc) > 470 msec (for women) and > 450 ms (for men) obtained from 3 consecutive ECGs
    b. Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (example, complete left bundle branch block, third degree heart block)
    c. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, potential for Torsades de Pointes, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age
15. Previous malignancies within the last three years other than ndGBM, except successfully treated squamous cell carcinoma of the skin, superficial bladder cancer, and in situ carcinoma of the cervix

BILAN D'INCLUSION

Dans les 49 jours avant le début de traitement
1. Chirurgie (biopsie seule non acceptée).

Avant le screening :
1. Consentement.
2. Envoi d'un échantillon tumoral en centralisé pour détermination du statut MGMT.

Dans les 21 jours avant le début de traitement :
1. Index de Karnofsky.
2. IRM cérébrale (avec et sans contraste).
3. Biologie : NFS-Plaquettes, ionogramme sanguin, bilan hépatique, bilan de coagulation (INR, PTT, APTT), magnésium, acide urique, CK, cholestérol, triglycérides, amylase, lipase.
4. Test sérique de grossesse (si applicable).
5. Bandelette urinaire.
6. ECG.
7. Questionnaires : QLQ-C30, BN-20.
8. Score NANO.

Prescription médicale à fournir

☐ IRM cérébrale

TRAITEMENT

Randomisation ratio 1 :1, à faire au C1J1
Bras A : Radiochimiothérapie + 2-OHOA placebo
Bras B : Radiochimiothérapie + 2-OHOA 12g/j

Les 2 bras de traitement suivent le même design :

1. Radiochimiothérapie :
- RT 60 Gy + TMZ 75 mg/m²/j PO pendant 7 semaines au maximum
- 2-OHOA/placebo 3x/j PO à partir du J1 de la semaine 3 et jusqu'à la fin de la radiochimiothérapie.

2. Maintenance :
- 6 cycles de 28 jours de TMZ 150 puis 200 mg/m²/j PO de J1 à J5
- 2-OHOA/placebo 3x/j PO les 3 premières semaines de chaque cycle.

3. Monothérapie : 2-OHOA/placebo 3x/j PO jusqu'à progression.

Traitement à débuter :
- Radiochimiothérapie à débuter dans les 49 jours post-chirurgie.
- Phase de maintenance à débuter dans les 28 jours après le dernier jour de radiochimiothérapie (en cas de délai de plus de 42 jours, demander l'accord du médical monitor).

Critères de stratification

Statut MGMT : ☐ méthylé ☐ non méthylé
RTOG-RPA : ☐ 3 ☐ 4 ☐ 5

Traçabilité du recueil du consentement

A renseigner dans l'onglet « Information complémentaire » du formulaire de Recherche Clinique sur HM

Validation des critères d'éligibilité par l'investigateur

A renseigner dans la partie « Inclusion du patient » du formulaire de Recherche Clinique sur HM

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