TITLE: Phase IIB, randomized, multicenter clinical trial, continuation or non-continuation with 6 cycles of temozolomide after the first 6 cycles of standard first-line treatment in patients with glioblastoma.

PROTOCOL NUMBER OF THE sponsor: GEINO 01-14

EUDRACT: 2014-000838-39

VERSION: 1.2 of 8 September 2014

SPONSOR: Spanish Group of Medical Neuro-Oncology - GEINO

RESEARCH COORDINATOR:

[redacted]

The information included in this protocol is confidential. Publication is not permitted without the written consent of the researchers. This material may be used or disclosed by the study investigators and their associates since its use may be necessary for the development of the clinical study, as well as by the patients included in the study, the Public Health authorities and the ethical committees.

PROTOCOL SIGNATURE SHEET

Protocol Code: GEINO 14-01 EudraCT

No .: 2014-000838-39

Version: 1.2 of September 8, 2014

I have read this protocol and I agree to carry it out in accordance with the Good Practice Guidelines Clinic and with the Declaration of Helsinki.

Trial Coordinators	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	
[redacted]	

I have read this protocol and I agree to carry it out in accordance with the Good Clinical Practice Guidelines and the Declaration of Helsinki.

Principal Investigator:

Name:… ....

1. SUMMARY

1.1. Trial

Randomized phase II clinical trial with different types of adjuvant treatment duration after standard first-line treatment.

1.2. Sponsor

SPANISH GROUP FOR RESEARCH IN NEUROONCOLOGY - GEINO

[redacted]

Contact information:
GEINO Technical Secretariat
[redacted]
T[redacted]

1.3. Title

Phase IIB, randomized, multicenter continuation or non-continuation study with 6 cycles of temozolomide after the first 6 cycles of standard first-line treatment of glioblastoma.

1.4 Sponsor code

GEINO Code 14-01

1.5. EudraCT number

2014-000838-39

1.6. Coordinators of the Clinical Trial

[redacted]

1.7. Coordinator of the centralized study

[redacted]

1.8. Participating centers and researchers

[redacted]

The Clinical Trial will be carried out through the participation of members of the Spanish Neuro-Oncology Research Group (GEINO). A complete list of the researchers, centers and Ethics Committees is available as a separate document.

1.9. Name of the Organization in charge of monitoring

PHARMACEUTICAL MARKETING & CLINICAL RESEARCH - MFAR SL
[redacted]
Phone[redacted]

1.10. Study treatment

Patients diagnosed with glioblastoma will be randomized after receiving 6 adjuvant cycles with temozolomide (standard treatment), to continue or not the treatment with temozolomide for 6 more

cycles.

Treatment Groups:

Experimental Arm: Temozolomide 150-200mg / m2 / dx 5 days every 28, for 6

cycles. Control arm: No treatment.

Presentation of the Drug: Temozolomide (Temodal®)

. Pharmaceutical form: Hard capsules. Each capsule contains 5mg, 20mg and 100mg of temozolomide.

The hard capsules have an opaque white body, an opaque green cap, and are imprinted with black ink. The cover is printed with "Temodal".

. Route of administration: oral

. ExcipientsCapsule: content: 132.8 mg anhydrous lactose, colloidal anhydrous silica, sodium starch glycolate, tartaric acid, stearic acid. Capsule bodies contain: gelatin, titanium dioxide (E 171), sodium lauryl sulfate, yellow iron oxide (E 172), red iron oxide (E 172) and are printed with black pharmaceutical ink, containing: rubber lacquer, propylene glycol, purified water , ammonium hydroxide, potassium hydroxide, black iron oxide (E 172).

The medication used in the trial as the experimental arm will be the same as that used in the first 6 adjuvant cycles, according to the usual practice of each center and will not be provided by the trial sponsor, since continuation up to 12 cycles is a standard procedure in most centers participating in the trial.

1.11. Trial phase and design

Phase IIB, multicenter, randomized clinical trial in which patients will be randomized after receiving 6 adjuvant cycles with temozolomide (standard treatment) to continue or not treatment with temozolomide for 6 cycles.

1.12. Study objective

The main objective of the study is to detect differences in the probability of progression-free survival at 6 months between patients with methylated or unmethylated MGMT, when receiving 6 additional cycles of temozolomide and stratifying for residual disease or not.

1.13. Investigational disease

Patients diagnosed with glioblastoma will be included.

1.14. Primary endpoint

The primary endpoint is to determine the differences between the two treatment groups will be progression-free survival at 6 months. This variable will be assessed in patients with glioblastoma who have already received 6 cycles of temozolomide (adjuvant) without progressing and who are randomized to continue with 6 additional cycles of temozolomide or to stop treatment from the date of randomization to the date of progression, defined according to RANO criteria.

1.15. Sample Size

A total of 160 patients with Glioblastoma will be included. Patients will be stratified by MGMT methylation status and presence of residual disease (visible on MRI) at enrollment.

1.16. Duration of treatment

Treatment of randomized patients in the experimental treatment arm will continue until the completion of the 6 additional cycles (12 cycles of adjuvant in total) or until disease progression, development of unacceptable toxicity, non-compliance, withdrawal of consent by part of patient or investigator's decision, whichever occurs first.

1.17. Estimated study period

3 years: 2 years for inclusion and one year for data analysis.

Scheduled dates

Expected start date: third quarter 2014

Expected date of first inclusion: fourth quarter 2014

Recruitment period: 24 months

Expected end date: Second quarter 2017

2. INDEX

3. GENERAL INFORMATION

TITLE: Phase IIB, randomized, multicenter clinical trial of continuation or no continuation with 6 cycles of temozolomide after the first 6 cycles of standard first-line treatment in patients with glioblastoma.

PROTOCOL Number .: GEINO 14-01 EudraCT

EudraCT Number.: 2014-000838-39

3.1. Type of clinical trial

Phase IIB randomized, multicenter, continuation or non-continuation study with 6 cycles of temozolomide after the first 6 cycles of standard first-line treatment of glioblastoma.

3.2. Description of the study drug

Patients diagnosed with glioblastoma will be randomized after having received 6 adjuvant cycles with temozolomide (standard treatment) to continue or not the adjuvant treatment with 6 additional cycles.

Treatment Groups:

Experimental Arm: Temozolomide 150-200mg / m2 / dx 5 days every 28 for 6 cycles.

Control arm: No treatment.

Presentation of the Drug: Temozolomide (Temodal®). Pharmaceutical form: Hard capsules. 5mg, 20mg and 100mg capsules of temozolomide.

The hard capsules have an opaque white body, an opaque green cap, and are imprinted with black ink. The cover is printed with "Temodal".

3.3. Sponsor Data

Spanish Group of Neurooncology Research - GEINO
[redacted]

Contact information:
TechnicalGEINO
[redacted]
Phone
[redacted]

3.4. Name of the Organization in charge of monitoring

PHARMACEUTICAL MARKETING & CLINICAL RESEARCH - MFAR SL

[redacted]

3.5. Investigator General Coordinator of the trial

[redacted] and [redacted] will be the coordinating investigators of the trial, responsible for the preparation of analyyess, findings, conclusions and development of the final report.

3.6. Coordinator of the centralized study

[redacted]

3.7. Participating Centers

A complete list of participating centers available as a separate document.

3.8. Estimated study duration

3 years: 2 years for inclusion and one year for data analysis.

Scheduled dates:

Expected start date: third quarter 2014

Expected date of first inclusion: fourth quarter 2014

Recruitment period: 24 months

Expected end date: first quarter 2017

4. TRIAL OBJECTIVES

4.1. Background

4.1.1 Epidemiology of glioblastoma

Gliomas are the most common tumors of the central nervous system (CNS) with an annual incidence of 5.4 cases per 100,000 inhabitants. Of them, 54% are glioblastomas (GB) according to European statistics and our national registries. It is estimated that in Spain approximately 1,376 patients are diagnosed with this disease each year. The prognosis is inexorably poor with a median survival of 15-18 months and only 10% of patients alive at 5 years. GB (WHO 2007 grade IV astrocytoma) is histologically characterized by presenting in addition to nuclear atypia and mitotic activity (traits that define grade II and III astrocytomas respectively), microvascular proliferation and / or necrosis. It is located preferentially in the cerebral hemispheres. Most arise 'de novo', without there being evidence of a previous precursor lesion, they are the so-called primary GBs. Secondary GBs develop from lower grade (II or III) astrocytomas. Although morphologically similar, these two groups have different clinical characteristics and a different molecular profile. Low-grade tumors that progress to high-grade often have mutations in IDH1 / 2 encoding isocitrate dehydrogenase enzymes. The IDH1 / 2 mutation in glioblastoma diagnosed de novo or primary confers a better prognosis.

In GB, there is a prognostic classification, the Recursive partitioning analysis (RPA) described and validated (based on age, initial Minimental status, previous resection, and Karnofsky Index) that provides the prognosis of patients according to the benefit of treatment cancer and faciltes the comparison of results between studies.

4.2. Treatment of glioblastoma

The initial treatment is surgery that allows obtaining the histological diagnosis and achieves immediate

decompression of the brain. You must achieve maximum resection while maintaining the best neurological function that preserves the patient's quality of life. The age of the patient, and his general condition (KPS) are factors considered in the selection of surgical treatment. Post-operative irradiation has been the traditional treatment as it has been shown to increase survival from 6 to 8 months already in the first trials.

The European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) conducted a randomized phase III trial comparing standard radiotherapy (60Gy focal in 6 weeks) with the same combined treatment with temozolomide (TMZ) concomitant followed by 6 monthly cycles of adjuvant TMZ. 573 patients were included. The median survival was 14.6 months with the combined treatment compared to 12.1 months in the control group. Two-year survival increased from 10.4% to 26.5% for the TMZ-treated group (([HR], 0.63, P <0.001). Toxicity was tolerable with 7% hematologic toxicity degrees III-IV in the concomitance phase and 14% in the adjuvant phase.

In another minor randomized phase II study, the same benefit was repeated. The results after 5 years of follow-up again confirmed the survival benefit for the group of treated patients. with TMZ and the prognostic value of the RPA classification. No other study has improved the results. Concurrent and adjuvant treatment with 6 cycles of TMZ was established as standard after surgery in 2005.

TMZ is a second generation derivative of imidazoltetrazinone, is spontaneously hydrolyzed under physiological conditions to the active metabolite and acts as a DNA methylating agent. It is administered orally and penetrates the blood-brain barrier (BBB).

Due to its mechanism of action, it is known that cells that have the ability to repair methylated DNA to unmethylated DNA by, among other enzymes, 6-methylguanine DNA methyl-transferase (MGMT), they can overcome DNA damage and therefore not enter apoptosis . The enzyme is encoded by the MGMT gene. MGMT can be methylated in the GpG islets and not transcribed correctly, causing enzyme inactivity. MGMT methylation status is a predictive factor of response to TMZ. Methylated patients benefit the most from treatment, but it is not useful for first-line treatment decisions due to marginal benefit in unmethylated patients.

4.3. Rationale

Despite the lack of scientific evidence that prolongation of adjuvant therapy beyond 6 cycles benefits patients, the presence of residual disease before starting adjuvant in all patients, and an excellent tolerability profile of TMZ, it has led to the prolongation of adjuvant treatment beyond 6 cycles, sometimes even until disease progression. Prolongation of treatment beyond 6 cycles occurs basically due to 5 factors.

1- The excellent tolerance profile of TMZ with apparently non-cumulative toxicity.

2- Virtually all GB relapse after first-line treatment. Occasionally they can be re-operated or re-irradiated in very specific cases, but there is no recognized and standardized second-line treatment of effectiveness. Bevacizumab is a promising drug, but it is not approved by the European Medicines Agency (although it is by the FDA) for the treatment of recurrent GB. In Spain, some patients can be treated in selected centers for compassionate use indication. Other drugs such as nitrosoureas may provide some clinical benefit even though they never demonstrated results of undeniable effectiveness before the appearance of TMZ.

3- The concept of adjuvant in GB is not the same as in other diseases since the surgery is never radical and there is always residual disease after the intervention.

4- It is difficult to evaluate the efficacy of the treatment, since magnetic resonance imaging (MRI) is not objective and reproducible to evaluate tumor and residual disease, although it is the recommended imaging technique. Contrast with gadolinium, it can assess tumor size (T1Gd sequences); infiltration and edema can be assessed on sequences (T2 and T2 / FLAIR), along with other imaging methodologies such as perfusion, diffusion, and spectroscopy. However, changes in gadolinium uptake are not pathognomonic for tumor growth but for increases in the permeability of the BBB that may be secondary to necrosis produced by chemoradiotherapy, changes in dexamethasone doses, etc. An event that occurs after treatment with irradiation (with or without TMZ) called pseudo-progression has been described, consisting of a false increase in the lesion in radiology and that can occur in up to 30% of patients who have been treated with TMZ and radiation, especially in the first 3 months after finishing treatment. These false images, sometimes accompanied by reversible neurological deterioration, can last for months and confuse the evaluation of viable disease. Pseudo-progression has been associated with longer survival and has been related to MGMT methylation, but can often lead to a premature and erroneous decision to discontinue TMZ treatment, thus preventing any potential therapeutic benefit. Since it is impossible to differentiate real residual disease from pseudo-progression, it is recommended to continue adjuvant TMZ at least 3 months before changing therapy and if the doubtful image persists,

5- The selection of 6 cycles in the pivotal EORTC / NCIC trial was a random decision not based on previous experience.

The choice of 12 instead of 6 cycles of adjuvant TMZ is based on the opinion that possibly 6 cycles are not sufficient to control a disease in which tumor remains atthe end of the adjuvant. The American first-line clinical studies have been designed with the administration of 12 cycles RTOG 0525, RTOG 0825 and the American and Canadian treatment guidelines recommend continuing treatment with TMZ especially in caseof residual disease. This is not the case in Europe, where 6 cycles are recommended based on the evidence provided in the pivotal EORTC-NCI-C trial. However, treatment is not usually stopped after 6 cycles in most cases, in the absence of effective rescue treatments.

A priori, the prolongation of treatment should benefit patients who present methylation of the MGMT gene, a predictor of benefit from TMZ treatment.

In a study carried out in Spain and recently published in Clin Transl Oncol, it was observed that 80.5% of professionals continue treatment beyond 6 cycles: 44.4% only in case of residual disease, 27.8% always administer 12 cycles and 8.3% continue treatment until progression. The economic and demographic study estimated that this practice leads to spending on the National Health System of 1.5 million euros per year. The majority of the survey participants considered that there was no evidence to continue or stop treatment and that it would be interesting to answer the question about the optimal duration of treatment in a clinical trial. For this reason, a grant was requested from the FIS Fund of the Carlos III Institute, which was granted to carry out the essay presented in this document.

4.4.ORbjectives:

Main Objective

The main objective of the study is to detect differences in the probability of progression-free survival at 6 months between patients with methylated or unmethylated MGMT, when receiving 6 additional cycles of temozolomide and stratifying for residual disease or not.

Secondary Objectives:

Detect differences in:

- Progression-free survival at 6 months for each of the stratification factors after inclusion in the study: Methylation status / residual disease

- Progression-free survival (for all patients and by factors stratification) after inclusion in the study

- Overall survival (for all patients and by stratification factors) after inclusion in the study

- Differences in toxicity between both treatment arms

- Study of markers / enzymes of resistance to temozolomide

5. DESIGN AND TYPE OF CLINICAL TRIAL

5.1. Development phase

Phase IIB study, open, randomized and multicenter

5.2.Control type

lControl without placebo.

5.3. Masking

There will be no masking.

5.4. Study design

5.4.1. Screening of patients

The signature of the informed consent of the patient for the clinical trial will be obtained before starting the selection period.

Pre-screning may be performed in the 6th cycle of adjuvant standard treatment, but the patient will not be randomized until:

the result of the methylation status of the MGMT gene is available.

a baseline MRI has been performed on the patient in which it can be evaluated if there is residual tumor.

The different procedures carried out as part of the usual clinical management of the patient (for example, blood tests, imaging tests, etc.) and carried out before signing the informed consent can be used for selection or as baseline results as long as these tests have been carried out as specified in the protocol.

Once the informed consent has been signed, a selection number will be assigned to each patient. Each center will receive a selection form within the Center's Investigator File in which predetermined selection numbers will be assigned. Said document must always remain in the study center under the custody of the research team. This selection number will identify patients through the necessary procedures to confirm the suitability of the first for the study (laboratory analysis, centralized imaging tests, central pathological review, etc.). An additional document will be added to the Investigator's Manual with detailed information on the identification procedures for the selection of patients.

5.4.2. Centralized pathological review

In the trial, two centralized reviews are carried out at the beginning of the study:

1. To confirm the diagnosis of Glioblastoma: in all cases, a tumor block sample or at least 15 unstained or stained histological slides will be sent with eosin / hematoxylin.

2. For the determination of the methylation status of the MGMT gene: If the center of origin performs the determination of the MGMT methylation status locally, the result of the center will be accepted. If the center of origin does not make the determination of the MGMT, it will be carried out centrally at the Germans Trias i Pujol Hospital. It will therefore be necessary to send a tumor block.

To participate in the study, the patient must sign the informed consent for participation in the clinical trial.

There is associated a subsequent substudy for the determination of resistance proteins (MSH2, MSH6). To participate in this associated substudy (immunohistochemical study of resistance proteins), a tissue microarray (TMA) must be manufactured and for this it is necessary to have the tumor block to manufacture the TMA and subsequent immunohistochemical study. For the participation of the patient in the associated substudy, the patient must sign an informed consent different from that of their participation in the clinical trial.

All samples will be sent by courier to the central laboratory. The response to the result of the review and the MGMT study will be obtained in a maximum of 7 days, at which point the patient can be randomized. All cases must be confirmed by the external reviewing pathologist, and although patients may be registered without waiting for the review report, they could be ineligible a posteriori, if the diagnosis is not confirmed.

All excess slides will be returned to the center of origin together with a report after the central pathological review. The paraffin blocks will be returned after making the MA tissue. Subsequently, all remaining samples will also be returned after the completion of the project.

No tumor sample can be mobilized from the hospital of origin until the patient has signed the informed consent. The centralized review for both pathological confirmation and the determination of MGMT will be carried out at:

[redacted]

To send the sample, please contact:

MFAR, SL - TechnicalGEINO

[redacted]

No inclusion will be possible until:

1- The center has the result of the methylation of the MGMT gene, either the local review or the centralized review of the tumor sample (The centralized review will take place in approximately 7 days).

2- All patients must show before signing the IC (around the 6th adjuvant cycle) of an MRI in which it is demonstrated that there is no radiological progression. The presence of residual tumor or image compatible with residual tumor will be recorded on the patient record sheet for stratification in the assay.

5.4.3. Inclusion of patients

After confirmation that the patient is a candidate to be included in this study (result of MGMT methylation, MRI without progression, and fulfillment of the inclusion / exclusion criteria), patients will be randomized, assigning them centrally a study number to each subject.

The patient enrollment procedure is described below:

1. Complete and sign the patient enrollment form (registration forms must be signed by a clinician (PI or co-PI) identified in the signature list and in the registry delegation of responsibilities).

2. Send the completed and signed form to the CRO:

MARKETING FARMACÉUTICO & INVESTIGACIÓN CLÍNICA, SL

[redacted]

3. The CRO will conduct the patient inclusion process.

4. Respond to the center, sending the confirmation form of the patient's randomization both by fax and by e-mail. Confirmation of patient randomization will contain the patient's study number.

5. Likewise, the treatment arm to which it has been randomized (experimental or control) will be communicated.

6. In no case will treatment be started without knowing the result of the randomization.

The patient's study number will identify subjects throughout their participation in this study.

An additional document will be added to the Center's Investigator File with detailed information on patient inclusion procedures.

5.4.4. Translational substudy

In the event that the patient has given their informed consent to participate in the translational sub-study, the tumor samples sent for the centralized review and determination of the MGMT methylation status will be used to prepare a tissue matrix for subsequent immunohistochemical studies of IDH1 and TMZ resistance or sensitivity protein (MSH6, MSH2), and future studies that may arise as a result of the assay results.

All samples will be coded prior to shipment.

An additional document will be added to the Center's Archive with detailed information on the collection of the samples and the procedure for sending them.

6. SELECTION OF PATIENTS

Glioblastoma patients who meet all eligibility criteria will be included. 6.1. Inclusion

criteria

A subject will be considered eligible for inclusion if they meet each and every one of the following criteria:

1. Ability to understand and sign the informed consent document.
2. Age ≥ 18 years.
3. Patients with glioblastoma according to WHO classification (glioblastoma) who have received chemo-radiotherapy and chemotherapy based on temozolomide (Stupp scheme) and have completed 6 cycles of adjuvant temozolomide (with or without bevacizumab) in the context of standard treatment without having presented disease progression.
4. Availability of tumor tissue from the first surgery to perform the centralized histological review, to determine the methylation of the MGMT gene if it has not been performed in the center of origin (if it had been performed in the center of origin, it will be accepted the result of the center).
5. Stable doses of dexamethasone on inclusion, never higher than the dose of corticosteroids received in cycle 6 of adjuvant.
6. Karnofsky index ≥ 60%
7. All patients must show absence of disease progression on brain MRI as defined in the RANO Criteria prior to randomization.

8. Baseline MRI of the study carried out a maximum of 6 weeks prior to inclusion, in which no progression was observed and allowed the administration of the 6th cycle of care. NMR performed after the 6th cycle of adjuvant is also acceptable as long as no progression is observed.

9. Adequate marrow reserve: hematocrit≥29%, leukocytes> 3,000 / mcl, ANC ≥ 1,500 cells / ul, platelets ≥ 100,000 cells / ul.

10. Creatinine <1.5 times the upper limit of normal for the testing laboratory.

11. Serum bilirubin <1.5 / ULN, SGOT and SGPT <2.5 times the upper limit of normal for the testing laboratory. Serum alkaline phosphatases <3 / ULN.

12. Effective contraceptive method for patients and their partners.

6.2. Exclusion criteria

Subjects who meet any of the following criteria should not be included in the study:

1. Less than 5 years of any previous infiltrating neoplasm. Carcinoma in situ of the cervix or cutaneous basal cell carcinoma are accepted.

2. Concomitant treatment with other investigational agents (except concomitant bevacizumab).

3. Presence of any clinically significant gastrointestinal abnormality that may affect the intake, transit, or absorption of the study drug, such as the inability to take oral tablet medication.

4. Presence of any psychiatric or cognitive disorder that limits the understanding or signing of the informed consent and / or jeopardizes compliance with the requirements of this protocol.

5. Concurrent disease that prevents the continuation of treatment with temozolomide. 6.

Presence of leptomeningeal spread.

7. Pregnant or lactating women.

8. HIV positive patients on combined antiretroviral treatment.

6.3. Diagnostic criteria for the study pathologies

Patients diagnosed with Glioblastoma who have received standard treatment with irradiation, temozolomide and subsequent treatment with 6 adjuvant cycles (with or without bevacizumab) and who have not presented progression will be selected, in whom continued treatment with adjuvant temozolomide is considered until 12 cycles.

Patients will be randomized at that time to continue or stop treatment with temozolomide. For this, they must have an MRI before randomization in which it is demonstrated that there is no disease progression and they have the result of the methylation of the MGMT gene.

6.4. Inclusion

The CRO MFAR SL should be contacted for the inclusion of patients.

Pre-screning can be performed from the beginning of cycle 6, if the patient is clinically stable and by MRI. (An MRI that has been carried out before said cycle will be accepted to sign IC and start the inclusion procedures but it should not exceed 6 weeks).

The patient will not be randomized until:

1. the MGMT methylation result is available

2. Baseline MRI confirms previous disease stability.

3. the patient must remain clinically stable without increasing the dose of dexamethasone. Dexamethasone doses should be equal to or less than the dose received during cycle 6 of the adjuvant.

Once the patient meets the requirements described above, the correctly completed inclusion sheet will be sent by fax and from MFAR SL a fax will be returned to the Center confirming the inclusion and the assigned treatment arm.

Contact information:

6.5. Expected subjects and sample size calculation

A total of 160 patients diagnosed with Glioblastoma will be included. Patients will be stratified by MGMT gene methylation status and presence of residual disease (visible on MRI) at the time of enrollment.

6.6. Patient withdrawal criteria

6.6.1. Permanent interruption of study treatment

Patients will receive the treatment described above until one of the following occurs:

- Completion of treatment according to protocol.
- Termination by decision of the Principal Investigator.
- Unacceptable toxicity or adverse events that could render the administration of treatment an unacceptable risk in the investigator's discretion. In case of unacceptable toxicity, patients will be followed until toxicity is resolved.
- Progression of the disease by RANO criteria.
- Withdrawal of consent by the patient.
- The researcher or the Sponsor considers the patient not complying with the requirements of the study. ● The study ends or is closed early.
- Major protocol deviations:
    - o Non-compliance with the inclusion / exclusion criteria.
    - o Inability to perform the full tumor evaluations required in the protocol.

The reason for discontinuation of treatment should be clearly reflected in the case registration forms (CRD).

6.6.2. Study output

Patients will be encouraged to continue in the study; however, they can voluntarily withdraw their consent at any time. On the other hand, the investigator may withdraw a patient from the study at his discretion. Finally, the Sponsor can suspend the study if necessary.

The reasons for the early withdrawal of a patient from the study should be documented in the CRD as follows:

- The study is closed / finished.
- The patient abandons the follow-up.
- Investigator's decision.
- The patient withdraws consent.
- Major protocol violations.
- Death.

The CRD will detail the date of departure from the study and the cause of it. In the case of death, a death certificate should be obtained (if possible) with the cause of death assessed and documented. Patients who leave the study cannot be included again, whatever the reason for their withdrawal.

6.6.3. Procedures to follow when leaving the study

For all patients who leave the study, the investigator will follow the following procedures:

a) In the event of the end of treatment, the follow-up visits specified in this protocol will be carried out.

b) In case of abandonment of the treatment before its completion, the subsequent treatment and subsequent follow-up will be determined until death, guaranteeing the patient medical assistance according to the usual clinical practice.

6.7. Screening failures (Selection period)

A selection failure is considered to be any patient who has signed the informed consent but withdraws it before inclusion. All potential subjects that are evaluated for inclusion in the study that are screening failures will be registered in the Identification list / Patient Selection Registry but will not be included in the study database. The reasons for exclusion of these patients who do not enter the trial must be recorded in the aforementioned forms. All patients who have been randomized will be registered and documented even if they do not start continuation treatment with temozolomide. These will be analyzed by intention to treat.

7. DESCRIPTION OF THE TREATMENT

7.1. Treatment scheme

Patients will be randomized into the study (depending on the status of MGMT gene methylation and the presence or absence of residual disease on MRI) into one of the following treatment groups:

EXPERIMENTAL GROUP*:* Temozolomide dose 150/200 mg / m2 for 5 days every 28 days for 6 cycles (total 12 cycles of adjuvant temozolomide).

CONTROL GROUP: No treatment (total 6 cycles of adjuvant treatment).

The dose that the patient will receive in the adjuvant cycles before starting the trial will be maintained in such a way that the continuation dose may range between 125mg / m2 / dx 5 days and 200mg / m2 / dx 5 days.

The initiation of treatment should take place a maximum of 2 weeks after the end of cycle 6 of adjuvant, that is, a maximum of 6 weeks is allowed after administration of day 1 of cycle 6 of adjuvant.

6 cycles will be administered, after checking the blood count and other toxicity. The 7th cycle dose level, (1 additional trial cycle) once the patient is randomized to the continuation treatment group will be the same dose that was previously received in the 6th cycle prior to entering the trial. We establish a dose 0 equivalent to the last dose received in cycle 6.

Randomized patients in the control arm will be visited with the same frequency as if they were treated with the 6 additional cycles of temozolomide.

See treatment scheme in Annex VIII.

7.2. Study medication

Temozolomide:

The temozolomide dose is adjusted to the patient's body surface area and the total dose can be rounded to the nearest ten (10 mg).

It is administered in a single oral dose at least 2 hours before or after the intake of any food, the first 5 days of the 28-day cycle. An antiemetic should be prescribed one hour before taking it at least 5 days and exactly follow the pattern that was followed for the first off-trial cycles.

For all phases, lost doses of the drug due to dose adequacy due to toxicity should not be recovered.

7.3. Product accounting and adherence to treatment

In accordance with local legislation, the researcher will state in the clinical history that the patient has taken the medication as prescribed for each new cycle prescribed in the active treatment arm. The dose will be recorded and if there has been a loss of any of them and the reason.

7.4. Concomitant medication

All study subjects will be asked for a complete list of the drugs they have taken during the 4 weeks prior to the screening period, including both prescription and non-prescription drugs. The investigator must be informed of any new drug administered to the patient from the screening visit to the post-treatment follow-up visit. All medications taken by the patient during the study will be recorded in the electronic CRD (eCRD), where the indication, dose and administration data of the new drug will be detailed.

Use with caution

Growth factors can be used, at the discretion of the investigator, to induce neutrophil count elevations when febrile neutropenia is present, but not prophylactically, in order to deliver temozolomide on schedule.

7.5. Criteria for dose modification during the study

7.5.1. General toxicity and dose modifications

Toxicity will be recorded according to the NCIC version 4.0 criteria (Annex VII). Adverse effects will be meticulously recorded and reported according to European and Spanish laws.

7.5.2 Dose adjustment criteria

This phase is considered care management but some recommendations are detailed to homogenize the treatment of patients.

The dose that the patient will receive in the adjuvant cycles before starting the trial will be maintained in such a way that the continuation dose may range between 125mg / m2 / dx 5 days and 200mg / m2 / dx 5 days. 6 cycles will be administered, after checking the blood count and other toxicity. The 7th cycle dose level, once the patient has been randomized to the continuation treatment group, will be the same dose as previously received in the 6th cycle prior to entering the trial. We establish a dose of 0 equivalent to the last dose received in cycle 6.

A dose reduction level will be allowed for subsequent cycles in case of toxicity down to a minimum of 125mg / m2 / dx 5 days.

Dose level cycle 1 (7th)	**Dose mg / m2 / dx 5 days**	**Notes**
0	150-200 mg / m2	Same dose as in cycle 6 before inclusion in the trial.
-1	125 mg / m2	If the patient has to lower the dose due to toxicity according to the monthly hematological controls to a level lower than this, they will exit the study due to toxicity

Table of dose modification for subsequent cycles:

Neutrophils 109 / l	**Platelets 109 / l**	**Tox no hematological**	**Dose**
≥1500	≥100	≤ grade 2 *	Continue treatment at the prescribed doses in cycle and subsequent
≥500 <1500	≥25 <100	Grade 3-4	Any of them: Treatment delay up to a maximum of 2 weeks until normal figures are obtained. Continue treatment with reduction of a dose level in subsequent cycles. If there is no recovery at 2 weeks end of adjuvant treatment.
<500	<25	GRADE 3-4 not recovered in 2 weeks	Any of them: Definitive stop of adjuvant TMZ. Control hemograms every 2-3 days until hematological recovery to Grade 3 (platelets ≥ $25x10^9$/ l, neutrophils≥$0.5x10^9$/ l) and continue evaluation schedule

* except alopecia, nausea and vomiting

8. DETERMINATIONS OF THE STUDY AND PROCEDURES

8.1. Determinations during the study

Screening tests for inclusion of patients in the study should be performed days before the first dose of study drug.

The table summarizes the procedures and determinations to be made throughout the trial and its schedule, in the two trial arms.

All data referring to the patients entering the study will be collected in the specific data collection notebook for this clinical trial.

1- EXPERIMENTAL ARM

DETERMINATION **PATIENTS IN ACTIVE TTO**	**CYCLE 6 ASSISTANCE** **In the previous 28 days**	**During treatment** **ADJUVANCE PHASE cycles / 28 d**					
		CYCLE 1 (7)	**CYCLE 2 (8)**	**CYCLE 3 (9)**	**CYCLE 4 (10)**	**CYCLE 5 (eleven)**	**CYCLE 6 (12)**
Informed consent	X						
AP review	X						
MGMT study	X						
Randomization	X						
NMR (1)	X			X			X
Anamnesis	X						
Physical exploration	X	X	X	X	X	X	X
CORTICOIDS (DOSE / DRUG)	X (2)	X	X	X	X	X	X
ANTICOMICIAL (DOSE / DRUG)	X	X	X	X	X	X	X
KPS	X	X	X	X	X	X	X
TMZ		X	X	X	X	X	X
Toxicity		X	X	X	X	X	X
Clinical Analysis	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X
I. BARTEL	X			X			

MMS	X			X			
RX THORAX (3)	X						
ECG (4)	X						
Patient survival							

(1) MRI: Baseline MRI will be done around cycle 6 (2 weeks before or 3 weeks after) and will be taken as baseline. In case of neurological deterioration, the MRI and response assessment will be advanced.

(2) Corticosteroids: the baseline corticosteroid dose should not be higher than the corticosteroid dose received during cycle 6 of the adjuvant.

(3/4) Chest X-ray and ECG will only be performed if clinically indicated.

2- CONTROL ARM

DETERMINATION PATIENTS WITHOUT TTO	**CYCLE 6TH ASSISTANCE In the previous 28 days**	**Every 28 days for 6 months after randomization**	**Every 12 weeks after 6 months after randomization**
Informed consent	X		
AP review	X		
MGMT study	X		
Randomization	X		

NMR (1)	X	X	X
Anamnesis	X	X	
Physical exploration	X	X	X
CORTICOIDS (dose / drug)	X	X	X
Anticomicials (dose / drug)	X	X	X
KPS	X	X	X
Toxicity		X	X
Clinical Analysis	X	X	X

Concomitant medication	X	X	X
I. BARTEL (1)	X	X	X
MMS (1)	X	X	X
RX THORAX (2)	X		
ECG (2)	X		
Patient survival			

(1) MRI, I. Barthel and MMS will be performed according to the usual clinical practice, every 12 weeks. In case of neurological deterioration, MRI and Barthel response assessment will be carried out

(2) The performance of chest X-rays and ECG will only be performed if clinically indicated

8.2. Description of procedures

1. Informed consent: Each patient must sign written consent prior to undergoing the specific evaluations of the study and prior to the start of treatment. The patient must sign 2 separate informed consents, one for the clinical trial and the other for the biological samples.

2. Tumor analysis: After obtaining the informed consent of the tumor sample, the tumor tissue from the original diagnostic biopsy or a recently obtained biopsy will be sent to the centralized laboratory, for confirmation of the diagnosis. The tumor block should be sent if it is necessary to determine the methylation status of the MGMT gene and to participate in the study of resistance proteins. In general, paraffin blocks are preferred for diagnostic confirmation, but 15 unstained slides are also acceptable. Details of suitable material for molecular analysis and shipping instructions will be provided in the study sample management guide. These determinations will be made in approximately 7 days.

* If the center has the result of the methylation status of the MGMT gene carried out in the center itself, it will not be necessary to perform the centralized review. The methylation result report should be submitted along with the tumor sample for centralized diagnostic review

3. Inclusion / Exclusion Criteria: They must be reviewed in detail for each patient prior to carrying out the specific evaluations of the study and prior to the start of treatment.

4. Anamnesis: it will be carried out in the baseline period (in the 2 weeks prior to inclusion) general anamnesis with evaluation of Minimental Test (MMS), Barthel index and Kasnofsky index (KPS), existence of neurological deficit and severity. Details of coexisting diseases, oncological history (including smoking and history of weight loss in the last 6 months), description of first-line treatment with radiation dose and number of cycles of temozolomide and the concomitance or not with bevacizumab.

5. Complete physical examination:

5.1 Pre-treatment (Screening): Physical examination and vital signs (measurements of resting pulse, blood pressure, respiratory rate, temperature). Functional status will be assessed using the Karnofsky scale, Annex I of this protocol. Neurological and functional deterioration will be assessed using the MMS and IB, annexes II and III of this protocol. Doses of corticosteroids (dose / drug) and anticonvulsants (dose / drug) will be recorded

5.2 During treatment and follow-up visits: Physical examination, functional status, KPS, and neurological deterioration at each treatment visit (on day 1 of each cycle prior to dispensing

treatment), and at all follow-up visits. Control of the drug, dose of corticosteroids and anticonvulsants.

The IB and MMS will be carried out in the visit of cycle 1, in each control visit in which MRI is performed and in the safety visit once the patient has finished the treatment.

6. Concomitant medication: All drugs taken in the last 4 weeks prior to randomization and concomitantly during the study, will be recorded in the clinical history and in the data collection notebook with the indication, information on the dose and the dates of administration. Especially the doses of corticosteroids and anticonvulsants

7. Security Assessment: Safety assessments and adverse events include tumor-related, treatment-related, and unrelated signs and symptoms. Adverse events will be documented and recorded in the CRD upon notification by patients. Specific questions will be asked about adverse events. The reporting period for non-serious AA ends 30 days after the last study treatment dose or subsequent initiation of antineoplastic therapy, whichever is earlier; the reporting period for severe AA ends 30 days after the last study treatment dose regardless of the initiation of any subsequent antineoplastic therapy. Adverse events will be followed up at the post-treatment follow-up visit at least 28 (and no more than 35) days after the end of treatment or until all drug-related toxicities have resolved or are considered. irreversible, whatever happens later. Classification of toxicity will be based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v4.0).

8. Clinical analysis: should be performed on day 1 of each treatment cycle with a window of up to 72 hours prior to the scheduled visit.

8.1 Hemogram: includes complete count of the 3 series: red, white (differential count) and platelet count.

8.2 Biochemistry: includes glucose, sodium, potassium, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, and gamma glutamyltransferase.

8.3 Pregnancy test (for women of childbearing potential): blood or urine pregnancy test (minimum sensitivity of 25 IU / L or equivalent units of beta human chorionic gonadotropin [β-HCG]) during the 7 days prior to inclusion. Subsequently, the blood pregnancy test is only necessary if it is clinically indicated or if it is required by routine clinical practice at the center.

8.4 Coagulation: coagulation studies will be performed if clinically indicated and will include: prothrombin time (PT), partial thromboplastin time TTP, and fibrinogen.

9. Electrocardiogram (ECG): It will be performed on ECG if clinically indicated.

10. Chest X-ray: A chest X-ray will be performed if it is clinically indicated.

11. Radiological images: Baseline and follow-up NMR will consist minimally of T1, T1Gadolinium and FLAIR sequences in the axial planes, to allow the application of the RANO criteria. It is recommended to use the same device for each patient throughout the study.

12. Therapeutic compliance: Any missed or missed dose due to vomiting should be indicated in the patient's medical record and CRDs, in the same way as all administered doses.

13. Dispensing medication: Temozolomide will be dispensed on day 1 to 5 of each 28-day treatment cycle in the active treatment group.

14. Dose of corticosteroids: Record in the patient's clinical history and in the CRD the doses of corticosteroids that the patient has received in cycle 6 of the adjuvant, as well as the basal dose prior to inclusion. At each visit, the dose of corticosteroids that the patient receives at that time should also be recorded in the clinical history and in the CRD.

15. Follow-up: All patients will be followed up to determine subsequent antineoplastic treatments and survival, regardless of the reasons for withdrawal from study treatment. Information regarding post-progression treatments should include the list of subsequent treatments received as well as whether the patient has been re-operated or received re-irradiation. All this will be noted in the clinical history and in the CRD.

8.3. Pre-treatment procedures

Before carrying out any specific study procedure, informed consent of the trial must be obtained, except for MRI, which allows the patient to be offered the study and which is considered healthcare but will be considered baseline.

Procedures that are part of routine treatment are not considered study specific procedures. Procedures that are part of regular attendance can be used as screening procedures to determine eligibility. Before initiating study treatment, all subjects will be evaluated for eligibility. The selection process begins the day the subject signs the informed consent approved by the CEIC and continues until the randomization of the patient in the trial and subsequent start of the study treatment. In this study, only eligible subjects will receive the study treatment.

All subjects must have completed the following procedures in ≤ 28 days (unless otherwise specified) prior to the start of study treatment:

- Review of the inclusion and exclusion criteria.
- Medical and medication history
- The paraffin-embedded tumor block must be identified, prepared, and sent to the central laboratory for molecular analysis at MGMT. The sample can be sent at any time prior to inclusion, even if the patient is still receiving first-line treatment, as long as the specific informed consent for sample submission is signed.
- Physical examination, blood pressure, respiratory rate, temperature, weight and height. ● KPS (Karnofsky performance status) functional status (≤ 14 days before study inclusion).
- Laboratory tests (≤ 14 days before study inclusion) and biochemical tests. ● Serum or urine pregnancy test for women of childbearing age (≤72 hours before the start of study treatment).
- ECG and chest X-ray if clinically indicated.
- IB and MMS.
- Cranial MRI that will be taken as a baseline examination in terms of response evaluation (its performance is admitted in a period ≤ 6 weeks, that is, an MRI prior to the 6th cycle of 15 days, to verify the clinical stability of the disease.) The response it should always be assessed with the same equipment as the initial examination. In the event that the dose of corticosteroids must be increased before the start of treatment, or the patient suffers neurological deterioration during the screening and randomization period (between the 6th cycle and randomization), the patient will not be randomized and will be considered failure screening. For this reason, the dose of corticosteroids on the day of inclusion may never be lower than that on the day of randomization or initiation of treatment.

Treatment should begin as soon as possible to allow a 4-week period between Cycle 6 (care) and Cycle 7 (study), although a 2-week delay will be allowed.

8.4. Tests during treatment

- Experimental arm

Patients will be visited every 4 weeks (28-day cycles) for 6 treatment cycles, and at each visit:

- Physical examination: weight
- KPS
- Analytical and biochemical tests
- Therapeutic compliance
- Dose of corticosteroids and anticonvulsants
- Toxicity registry

If the patient needs to increase the dose of corticosteroids or neurologically worsens, it is advisable to repeat the initial radiology to rule out progression. The dose of corticosteroids on the day of IC inclusion or signature may never be higher than the dose on the day of randomization (to rule out progressions in that period).

Cycle 3 and 6: additionally it will be carried out:

- Response evaluation by RANO criteria on brain lesions visualized in MRI.
- I. Barthel and MMS.

MRI imaging tests, the Barthel Index and MMS will be performed every 12 weeks until disease progression; responses to treatment (PR, CR) must be confirmed at 4 weeks using the same method, if the patient abandons treatment for any reason before progression, MRIs should continue to be performed every 12 weeks as part of the follow-up until progression .

- Control arm

Patients will be visited every 4 weeks for 6 months after enrollment in the trial and at each visit they will:

- Physical examination: weight
- KPS
- Analytical and biochemical tests
- Therapeutic compliance
- Dose of corticosteroids and anticonvulsants

- Toxicity registry

If the patient needs to increase the dose of corticosteroids or neurologically worsens, it is advisable to repeat the initial radiology to rule out progression. The dose of corticosteroids on the day of IC inclusion or signature may never be higher than the dose on the day of randomization (to rule out progressions in that period).

Months 3 and 6: additionally it will be carried out:

- Response evaluation by RANO criteria on brain lesions visualized in MRI.
- I. Barthel and MMS.

MRI imaging tests, Barthel Index and MMS will be performed every 12 weeks until disease progression; responses to treatment (PR, CR) should be confirmed at 4 weeks using the same method.

8.5. Security visit

The safety visit will be carried out in patients treated in the experimental arm 4 weeks after the end of treatment (whatever the cause of termination),

- Physical examination, and vital signs (measurements of resting pulse, blood pressure, respiratory rate, temperature, weight and height).
- Functional status: KPS
- Analytical and biochemistry
- Toxicity registry

MRI imaging tests will be performed every 12 weeks until disease progression. Since progression-free survival is the main objective of the study, it is essential to rule out progression on MRI.

8.6. After end of treatment

- End of treatment without progression:

Once the treatment for any cause other than disease progression has been completed in the experimental arm or after 6 months from inclusion in the control arm, the following procedures will be performed every 12 weeks until disease progression:

- Physical examination, and vital signs (measurements of resting pulse, blood pressure, respiratory rate, temperature).
- KPS
- Barthel index
- Minimental Test
- Analytical tests:
- Analytical and biochemistry
- DXM and anti-seizure doses
- NMR

- After progression of the disease:

Once the patient progresses, follow-up for overall survival until death every 12 weeks, can be both visits to the oncology service and telephone calls. The patient's current status and registration of new cancer treatments will be determined (surgery, radiotherapy, chemotherapy and type, or / and bevacizumab, clinical trial)

The date of death will be verified to determine survival.

8.7. Response evaluation

The RANO criteria will be applied to evaluate the response and define the progression. It will be carried out in each center based on the radiological results, the clinical picture of the patient and the doses of corticosteroids required. It will be based on the RANO response criteria.

The progression is defined as:

1. Radiological worsening (increased contrast uptake area or appearance of new lesions). 2.

significant deterioration in FLAIR together with irreversible neurological deterioration

3. irreversible neurological deterioration even in the absence of radiological deterioration.

4. continuous increase in corticosteroids (> 2 weeks) to prevent neurological deterioration without reducing the dose.

8.7.1. Assessment of Clinical Response by corticosteroids and neurological deterioration

The criteria modified by the RANO Committee are based on radiological response, neurological symptoms, and corticosteroid doses.

Patients should be maintained with the minimum dose of corticosteroids they require throughout the treatment (the dose that keeps them neurologically stable).

If a dose increase is required due to an event (eg fever, seizure with post-critical deficit, etc.), the doses must be returned to the previous dose. If continuous dose increases are required for more than 2 weeks, the patient should be considered as in clinical progression.

In the progression due to sudden neurological deterioration, a radiological examination is recommended. If it cannot be performed, progression of brain disease will be considered.

It is important in patient evaluation visits to report in detail the dose of corticosteroids that the patient receives and the stability or not of the neurological symptoms, in addition to the results of the radiological examination (MRI).

8.7.2 Assessment of Radiological Response

A baseline MRI will be performed, in cycle 3 and every 12 weeks until progression.

The size of the baseline lesion will be evaluated at the beginning of treatment using the product of the 2 largest perpendicular diameters or the sum of the products of the measurable lesions in the axial plane and will be recorded as a baseline measurement. The same measurements will be taken for reference. In case of neurological deterioration or the appearance of new neurological symptoms, the MRI will be carried out to verify the radiological progression

In the assessment of the response, contrast uptake and hyperintensity in FLAIR will be analyzed separately.

Gadolinium T1 Sequence Evaluation

- It will not by itself be the one that will define the criteria for partial response, stability and progression, as it must be accompanied by the absence of deterioration in the Flair sequences.

- Measurement of the component that is enhanced after contrast in axial sections.

- The maximum diameter in axial section and its maximum perpendicular in the same cut will be sought.

- In successive controls the same methodology will be carried out. It will not necessarily correspond to the same cut / diameter made in the previous study, since the lesions often do not expand symmetrically but rather by a margin, which is not always the same.

- If the lesion consists of several separate uptake nodules but within the hyperintense area in FLAIR, it will be measured as if it were a single nodule.

- This value will be noted in the CRD.

- The appearance of new enhancement foci will be noted in continuity or at a distance.

Evaluation in T2 FLAIR sequences

Given the difficulty of quantification, a subjective measurement based on the experience of the radiologist will be made with the following criteria:

+2.	The lesion presents a clearly greater extension (at first glance) than the immediately previous study. From experience in other studies, the clear visual difference represents an increase of more than 20%.
+1.	The lesion has a greater extension than the previous study but must be evaluated in several slices to reach this conclusion.
0.	No changes to the FLAIR extension.
-1.	Extension reduction compared to the previous study
-2.	Obvious reduction.

The appearance of new hyperintense foci in FLAIR other than the initial lesion will be noted. These foci may correspond to new infiltrative areas or changes related to treatment. The opinion of the radiologist

will be indicated in FLAIR NOTES.

8.7.3. RANO response rating

In the present study it is important to determine the date of progression since the response to treatment will not be considered a study objective.

It is recommended to use the following monitoring table to standardize data collection:

		BASAL NMR	CONTROL 1	CONTROL 2
DATE				
T1GD	T target	PRODUCT DIAMETERS INJURY 1,2,3 ...	PRODUCT DIAMETERS INJURY 1,2,	ETC
	New spotlights		IF NOT	IF NOT
Sum products		MM2	MM2	MM2
FLAIR		VISUAL EVALUATION	EQUAL (0) +1, +2	EQUAL (0) +1, +2
	NEW SPOTLIGHTS		IF NOT	IF NOT
DXM DOSE		BASAL DOSE	DOSE	DOSE
CLINIC		BASAL CLINIC	Stable / Better / Worse	Stable / Better / Worse
REPLY			EE / RP / RC / P	EE / RP / RC / P

9. ADVERSE EVENTS

The ICH GCP requires that both Investigators and Promoters follow a specific procedure when reporting adverse effects or reactions within a clinical trial.

Any event related to drug toxicity, illnesses that debut during the study, or exacerbations of pre-existing illnesses must be reported.

Furthermore, clinically relevant changes on physical examination and abnormal parameters found on complementary examinations (eg, radiography, ECG) should also be reported as AE.

The criteria to classify a result found in a complementary examination as abnormal and therefore be classified as AE are:

- that the result of the complementary examination is associated with clinically relevant symptoms, and / or
- that the result of the complementary examination implies a change in the dose of study drug or a study exit, or implies adding another drug for its control or another type of therapy and / or
- that the result of the complementary examination implies an outcome that is included in the definition of AAG, and / or
- that the result of the complementary examination is considered as an AE by the investigator. 9.1.

Definitions

The ICH PCB definitions apply to this protocol.

Adverse event (AA)

Any detrimental health incidence in a patient or clinical trial subject treated with a drug, even if it does not necessarily have a causal relationship with said treatment.

Adverse reaction (AR)

An AR is any unintended and harmful reaction to an investigational drug, regardless of the dose administered.

Serious Adverse Event (AAG) and Serious Adverse Reaction (RAG)

Any adverse event or adverse reaction that, at any dose:

- produces death (be fatal),
- threatens the patient's life,
- make hospitalization necessary or its prolongation,
- produces persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect, or
- is clinically significant

Clinical and scientific judgment should be exercised when deciding whether it is appropriate to make an urgent notification of clinically significant events that may not be life threatening, or that do not require hospitalization, but that could put the patient at risk or require intervention. to prevent one of the outcomes detailed above.

Likewise, all suspicions of transmission of an infectious agent through a drug will be reported as serious.

Suspected Serious and Unexpected Adverse Reaction (RAGI)

It is a serious adverse reaction that is "unexpected" eg. A serious adverse reaction, the nature and severity of which is not consistent with the information on the pharmaceutical product in question, which appears in the summary of product characteristics (or in the investigator's manual).

The reference document to establish the "expectability" of adverse events for Temozolomide will be the latest version of the Product Data Sheet available on the EMEA website.

Life threatening event

Any event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically could have caused death if it had been more severe.

Hospitalization / prolongation of hospitalization

Any event that requires hospitalization (or prolongation of hospitalization) and that occurs or worsens during a patient's participation in a clinical study should be reported as an SAA. Prolongation of hospitalization is defined as any extension of a patient's hospitalization beyond the anticipated / required stay at the initial admission, in the opinion of the investigator or the physician responsible for the patient.

The following cases of hospitalization do not meet the AAG reporting criteria:

a) Reasons described in the protocol (for example, administration of the drug, complementary tests required by the protocol). Hospitalizations or extensions of hospitalization for a complication in the administration of treatment or procedures will be reported as SAG.

b) Hospitalizations or extensions of hospitalization for technical, practical or social reasons, in the absence of an AA.

c) Pre-scheduled hospitalizations (that is, scheduled prior to study entry). Any surgical intervention or procedure scheduled prior to study entry must be documented in the CRD.

Unexpected Adverse Reaction (RAI)

Any adverse reaction whose nature, intensity or consequences does not correspond to the reference information for the medicine (for example, the investigator's manual in the case of an investigational medicine not authorized for marketing, or the technical sheet of the product in the case of an authorized medicine).

The reference document to establish the "expectability" of adverse events for temozolomide will be the latest version of the Product Data Sheet available on the EMEA website.

Associated with the use of the drug

An AA is considered associated with the use of the investigational drug if the causation assessment is related to any of the investigational drugs or is unknown according to the definitions below.

Assessment of causality.

The investigator must provide an assessment of the causality of each investigational drug (including combination products and comparators) according to the following criteria:

AND There is a reasonable possibility that the study drug (s) caused the serious adverse event.

N There is no reasonable possibility that the study drug (s) caused the serious adverse event and other causes are more likely.

UK Unknown. It should only be used in special situations where the investigator has insufficient information (for example, the patient has not been treated at his center), and if none of the above options can be used.

9.2 Notification and Documentation of Adverse Events

The sponsor will collect AA from the signing of the patient's informed consent until 30 days after the administration of the last dose of study treatment.

All AAs must be registered in the source document and in the CRD using medical terminology. Investigators should assess the severity (grade) of the event according to NCI-CTC V 4.0, assign a relationship with each of the trial drugs, and seek and obtain adequate information to determine the outcome and to assess whether it meets the criteria for its classification as AAG requiring immediate communication. The researcher must provide any information requested by the promoter, in addition to that collected in the CRD.

All SAAs (as defined above) that occur during the clinical trial or within 30 days of the last dose of study medication, regardless of the suspected relationship with the study treatment, must be reported by the investigator. In addition, any SAAs that occur as a result of specific diagnostic procedures or interventions in this protocol must also be reported. Beyond this time period, only SAEs suspected of being related to the study drug should be reported.

All AEs that are suspected of being related to study treatment should be followed after the time of treatment suspension until the event or its sequelae have resolved or stabilized at a level acceptable to the Principal Investigator, the Lead Investigator of the Trial. and / or the Promoter.

The research team must notify the sponsor of all pregnancies of patients or patient pairs that occurred during clinical studies within 24 hours. from your knowledge. The outcome of the pregnancy must also be communicated within 24 hours of its knowledge.

The cause of death of a deceased patient in a clinical study, regardless of whether it is an expected event or associated with the investigational agent, is considered an AGA and should therefore be reported using the AGA Document. If the autopsy report is available, it should be sent to the sponsor identified exclusively with the patient's inclusion number.

All serious adverse events must be reported by fax within 24 hours. to MFAR, SL

[redacted]

The AAG report must contain a complete written summary detailing the important aspects of the corresponding adverse events. Where appropriate, information about relevant medical records and autopsy reports should be included. The tracking information must be sent to MFAR, SL within 24 hours.

All AEs that are suspected of being related to study treatment should be followed after the time of treatment suspension until the event or its sequelae have resolved or stabilized at a level acceptable to the Principal Investigator, the Lead Investigator of the Trial. and / or the Promoter.

9.3. Expedited notification of RAGI by the Promoter

The promoter will assume the responsibility of the adequate communication of the RAGI to the regulatory authorities. The procedure indicated in the most up-to-date version of the document "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use", available on the EMEA web portal, will be followed.

All suspected serious and unexpected adverse reactions (RAGI) will be reported in accordance with current regulations on clinical trials in Europe, to the Competent Authorities, to the CEICs, and to researchers, in the terms and in the manner established in the "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use "and following the local regulations that apply.

9.3.1 RAGI expedited notification deadlines to regulatory authorities

The promoter will notify any individual case of suspicion of RAGI within a maximum period of 15 calendar days after having knowledge of the suspected adverse reaction. When the suspicion of RAGI has caused the death of the subject or put his life in danger, the promoter will send the information within a maximum period of 7 calendar days from the moment the promoter becomes aware of the case. Said information must be completed, if possible, within the following eight days. This information should include an assessment of the significance and implication of the findings, including relevant prior experience with the same or similar medications.

9.3.2 Expedited notification of other relevant safety information

The sponsor must notify (as soon as possible and no later than 15 days) all information that could modify the risk / benefit ratio of the investigational drug, or determine changes in its administration schedule or in the conduct of the trial, for example:

- A qualitative change or increase in the percentage of occurrence of the expected SARs, which is considered clinically important.
- RAGIs that occur after the completion of a clinical trial and that are notified by the investigator to the sponsor.

New events related to the conduct of the trial or development of the investigational medicinal product and likely to affect the safety of the subjects, such as:

- Serious adverse events that may be associated with the trial procedures and may modify the conduct of the trial.
- A significant risk to subjects such as the lack of efficacy of an investigational drug used to treat a life-threatening disease.
- Important new safety findings from new animal studies (such as carcinogenicity).
- Any premature termination or temporary stoppage of a clinical trial with the same investigational drug for safety reasons, conducted in another country and by the same promoter.
- RAGs related only to a non-investigational drug that are considered relevant as they are not subject to the general rules for expedited notification of individual RAGI cases.

In addition, if additional relevant information is obtained, it will be notified as soon as possible.

9.3.3 Notification to Investigators

The Sponsor will communicate to the investigators any information that may affect the safety of the trial subjects as soon as possible.

In addition, the sponsor will inform the researchers of the safety aspects that affect the performance of the clinical trial or the development of the product, including the interruption of the development program or modifications to the protocol related to safety.

Notification procedure:

1. The researcher must fill in the AAG form (or the consulting doctor, named in the list of signatures and in the responsibility registration form, which is in charge of the patient), indicating the degree, causality and expectancy of the event according to as stated above. In the absence of the responsible investigator, a member of the center's trial team will fill out the form and sign it. Subsequently, the responsible researcher must check the AAG form, make the appropriate changes, sign it, forward it by fax to MFAR SL (tel: 93 434 44 12 - fax: 93 253 11 68, mail: investigacion@mfar.net) as soon as possible. This initial report will be followed by a detailed, written report if appropriate.

2. Monitoring- Patients should be followed until clinical recovery is complete and laboratory results have returned to normal or baseline, or the event has stabilized. Follow-up should continue until completion of protocol treatment if necessary. Tracking information should be recorded on an additional AAG form, checking the tracking box and faxing to the Secretariat when the information is available. Additional written information and / or copies of test results can be provided separately. The patient should only be identified by the assay number, date of birth and initials. The patient's name should not be used in any communication.

3. MFAR SL will notify to the local ethics committee for clinical research (CEIC) and the Autonomous Community about the event (according to local standard clinical trial procedures) to the AEMPS.

10. STATISTICAL CONSIDERATIONS

10.1. Study variables

10.1.1. Primary efficacy endpoint

The primary study variable to determine the differences between the two treatment groups will be

progression-free survival at 6 months. Said variable will be assessed in patients with glioblastoma who have already received 6 cycles of temozolomide (adjuvant) without progressing and who are randomized to continue with 6 additional cycles of temozolomide or stop treatment, from the date of randomization to the date of defined progression according to RANO criteria. Patients who are alive and without evidence of progression at this time will be considered as successes and those who have progressed or died at this time will be considered as treatment failures. The diagnosis of progression should be based on the RANO criteria.

Disease progression is defined as:

1. Radiological worsening (increased contrast uptake area or appearance of new lesions), that is, RANO criterion for progression.
2. significant worsening in FLAIR together with irreversible neurological deterioration 3. irreversible neurological deterioration even in the absence of radiological deterioration. 4. continuous increase in corticosteroids (> 2 weeks) to prevent neurological deterioration.

10.1.2. Secondary variables

It will be determined and compared in both treatment arms:

Clinical, biological and demographic data: (sex, age, type of surgery, initial MMS, initial IBartel, presence of neurological symptoms (mild, moderate, significant), bevacizumab or not in the first-line treatment, characteristics of the treatment, second-line treatments.

Safety / toxicity profile: Type, incidence, severity, frequency, severity and relationship with the treatment of the adverse events included in the CRD of the participating patients. It will be studied using descriptive statistics techniques, such as frequency tables and contingency tables.

Tumor Activity: Using RANO criteria, Progression Free Survival, progression-free survival rate at 6 months, and response rates in patients with measurable disease.

Overall Survival: Median overall survival. Time from the start of the trial treatment to the date of death from any cause. In those patients who are alive at the last follow-up, the OS will be censored as of the date of the last follow-up in which the patient was alive. The median OS will be estimated using Kaplan Meier curves.

Changes in the use of corticosteroids: Percentage of patients who have increased / decreased the dose of corticosteroids.

Changes in neurological status: Percentage of patients free of neurological deterioration in both arms (MMS / Barthel score).

MGMT gene methylation: Effects of MGMT gene methylation on study results. Correlation of laboratory information with clinical information, response to treatment, toxicity, and overall survival. This correlation will be studied using descriptive statistics techniques, such as frequency tables and contingency tables.

10.2. Efficacy evaluation

All randomized patients will be included in the main response analysis: Progression Free Survival at 6 months, which will be evaluated according to the RANO criteria.

Those patients who discontinue treatment for any reason other than disease progression (toxicity or patient desire) should undergo MRI every 12 weeks until disease progression as a common healthcare practice. Imaging tests should be done using the same method each time (MRI).

Progression Free Survival (PFS): Time from the start of the trial treatment to the date of the first progression according to the RANO criteria (Annex IV of this protocol), or death from any cause. In those patients who are alive and have not progressed in the last follow-up, the date of progression will be censored to the date of the last follow-up.

Disease progression is defined as:

1. Radiological worsening (increased contrast uptake area or appearance of new lesions), that is, RANO criterion of progression.

2. Significant worsening in FLAIR together with irreversible neurological

deterioration 3. Irreversible neurological deterioration even in the absence of

radiological deterioration.

4. Continued increase in dexamethasone (> 2 weeks) to prevent neurological deterioration.

Progression-free survival (PFS) at 6 months as the percentage of patients with / without disease

progression 6 months after starting study treatment

10.3. Safety assessment

Any patient included in the trial and who has been randomized, having ruled out previous progression, or who has received at least a single dose of study medication, will be evaluable for toxicity analysis.

The safety and tolerability of the study medication will be determined by evaluating the type, incidence, severity, frequency, severity, and relationship with the treatment of reported adverse events, physical examinations, and laboratory tests. Toxicity will be classified and tabulated using NCI-CTCAE v 4.0.

Any sign and / or symptom related to the tumor existing at the baseline visit that worsens (in severity or frequency) during the trial should be recorded as an adverse event.

At each visit to this study, all adverse events should be recorded according to NCI-CTCAE version 4.0.

10.4. Study populations

Safety population: All patients who have received at least one dose of the study drug will be included.

Intention-to-treat population (efficacy analysis population): Subject group consisting of all the subjects who have been randomized in the trial.

Population per protocol: All patients who have received 1 dose of study treatment, meet the inclusion / exclusion criteria, have not progressed when randomized and have not incurred major protocol deviations during the study will be included.

10.5. Sample size and statistical analysis

10.5.1. Sample size

The sample size is calculated based on the hypothesis defined in the main objective of non-superiority in progression-free survival at 6 months in the continuation of 6 to 12 months of treatment between methylated and unmethylated patients.

Based on the data from the EORTC-NCIC study (Stupp et al, 2005, 2009 ref 3), a probability of PFS of 0.593 in methylated, of 0.285 in non-methylated is expected. 95% confidence is assumed, 80% statistical power and it is calculated based on a ratio of 1: 1.5 when having more methylated patients, expecting a maximum of 10% losses, the sample must be 32 unmethylated patients and 48 methylated (total n = 80) in the TMZ treatment group. In order to respond to the objective of comparison between values at 6 and 12 months, the same sample is established in a group of patients without additional treatment for 6 cycles with temozolomide. This would lead us to have a sample of 64 unmethylated and 96 methylated patients for a total of 160 included patients. (n = 160).

Taking into account that patients with residual disease can potentially benefit from those who do not, this variable is established as a randomization factor, and taking into account that 60% residual disease is expected in methylated patients and 40% % in non-methylated, 4 randomization groups are established so that of the 32 non-methylated 13 are with residual disease and of the 48 methylated 23 are with residual disease.

10.5.2. Statistic analysis

The main objective is to demonstrate that prolonging treatment to 12 cycles does not improve progression-free survival at 6 months in the patients included in this study, randomized according to MGMT methylation status and whether or not residual disease, to receive 6 additional cycles of temozolomide. Therefore the main date is of the progression that can be presented in the form of a progression.

Progression-free survival, response rate, and overall survival will be evaluated to determine the efficacy of the treatment.

To estimate the total survival (and progression-free survival), the non-parametic Kaplan and Meyer method will be used. For the univariate comparison of the survival curves according to the different variables with potential prognostic effect, the Mantel-Cox test (log rank test) will be used. Finally, in order to perform a multivariate survival analysis and to have estimators of the relative risk adjusted for potential confounding variables, the Cox regression models will be used.

Based on the data from the PIVOTAL study, a 6-month probability of PFS is expected of 0.593 in methylated and 0.285 in unmethylated. We assume 95% confidence, 80% power, and using the comparison formula in the Kaplan-Maier method and log-rank.

First, a descriptive study of the main characteristics of the global series of patients will be carried out. For continuous variables, the mean and standard deviation will be calculated and for qualitative variables the percentages of the corresponding categories will be given without taking into account the missing values. To perform the analysis of survival and progression-free survival, the Kaplan-Meier method was used and, in case of group comparison, the log-rank test with a 95% CI was used. SPSS v15.0 software will be used for this type of analysis.

Progression Free Survival (PFS): Time from the start of the trial treatment to the date of the first progression according to the RANO criteria (Annex IV of this protocol), or death from any cause. For those patients who are alive and have not progressed in the last follow-up, the date of progression will be censored to the date of the last follow-up.

Disease progression is defined as:

1. Radiological worsening (increased contrast uptake area or appearance of new lesions), that is, RANO criterion of progression.
2. Significant worsening in FLAIR together with irreversible neurological deterioration 3. Irreversible neurological deterioration even in the absence of radiological deterioration.
4. Continued increase in dexamethasone (> 2 weeks) to prevent neurological deterioration.

Progression Free Survival will be determined by the non-parametric Kaplan-Meier method. For the univariate comparison of the survival curves according to the different variables with potential prognostic effect, the Mantel-Cox test (log rank test) will be used. Finally, in order to perform a multivariate survival analysis and to have estimators of the relative risk adjusted for potential confounding variables, the Cox regression models will be used.

Overall survival (TS) is defined as the time from randomization to death from any cause. The TS of patients alive at the time of analysis will be censored on the last follow-up date. The median overall survival will be estimated, with their respective 95% confidence intervals. Values of $p < 0.05$ will be considered statistically significant.

Toxicities: The safety and tolerability of the study medication will be determined by evaluating the type, incidence, severity, frequency, severity and relationship with the treatment of the adverse events collected in the CH of the participating patients. It will be studied using descriptive statistics techniques, such as frequency tables and contingency tables.

The variables will be represented by frequency and percentage, the continuous variables will be represented as medians and ranges.

Biomarkers: The frequency of genetic rearrangement will be determined with a 95% confidence interval. The correlation with the survival data will be determined using the Kaplan-Meier method.

11. ETHICAL AND LEGAL CONSIDERATIONS

11.1. Ethics Committee

The study will be carried out in accordance with the ethical principles that have their origin in the Declaration of Helsinki adopted by the 18th General Assembly of the World Medical Association, Helsinki, Finland.

In accordance with directives 95/46 of the European Parliament and 2001/20 / EC which establish the requirements for the development of clinical trials, the information obtained during the clinical trial may only be used by the Promoter of the clinical trial to evaluate the results in accordance with the mentioned directive.

In Spain also applies:

The Oviedo Convention, of April 4, 1997, on human rights and biomedicine, ratified in the BOE in October 1999.

In the rules for the adequate protection of personal data, according to the provisions of Organic Law 15/1999 on the protection of Personal Data.

The rights and obligations regarding information and clinical documentation, according to the provisions of Law 41/2002, of November 14, basic regulating the autonomy of the patient.

The General Assembly Somerset West, South Africa, October 1996 and the General Assembly Edinburgh, Scotland, October 2000.

Law 14/2007, of July 3, on Biomedical Research.

11.2. Authorities

The study protocol and / or documents inherent to it will be sent to you before starting the trial, as established by the national authorities.

11.3. Informed consent

The patient must sign 2 informed consents:

For the clinical trial and for the use of biological samples for centralized pathology review. For patient

participation in the associated translational substudy.

The doctor will have to explain the nature, purposes and possible consequences of the clinical trial, in a way that the patient can understand.

The patient must give their consent before being admitted to the clinical study and biological samples are taken.

The subject of the study will give their consent, signing the corresponding model in duplicate. For this purpose, each model must bear the signature of the investigator and the patient. The investigator will file and keep a copy of the original of each informed consent signed by each patient.

The investigator will not initiate any investigation for the trial until he has obtained the patient's consent.

The informed consent form used in this study, and the changes made during the course of the study, must be prospectively approved by the Ethics Committee.

11.4. Confidentiality

In order to guarantee the confidentiality of the test data according to the provisions of the Directive of the European Parliament 2001/20 / EC, only the Test Promoter or personnel designated by him will have access to them for monitoring / auditing tasks, the researcher and his team of collaborators, the Clinical Research Ethics Committee of the corresponding center or the one supervising the trial and the relevant health authorities.

In the aforementioned case of Monitoring / Audits, the researcher must provide direct access to the source documents and data.

The content of the data collection notebooks (CRD) as well as the documents generated during the study will be protected from unauthorized uses by people outside the research and, therefore, will be considered strictly confidential and will not be disclosed to third parties except to the specified in the previous section.

In Spain, this test will also be carried out in accordance with the provisions of Organic Law 15/1999 on the protection of Personal Data

11.5. insurance

An insurance policy will be contracted according to the regulatory requirements of each country where the trial is carried out.

In Spain, all patients in this clinical study will be insured through the HDI Hannover Internacional Insurance Company (Spain) Seguros y Reaseguros, SA with a policy that will meet the conditions stipulated by RD 223/2004.

11.6. End of trial

The trial will be considered normatively closed after the data on the primary and secondary variables are sufficiently prepared for initial publication.

11.7. Early termination of trial

This study may be interrupted prematurely if in the opinion of the sponsor there is a sufficient reasonable cause. The investigator will receive a written notice that the terminating party documents the reason for suspending the study. Circumstances that justify suspension of the study include, but are not limited to:

- Identification of unforeseen, significant or unacceptable risks for patients ● Impossibility of including an acceptable number of patients
- Insufficient compliance with the protocol requirements
- Plans to modify, suspend or discontinue the development of the study drug.

- In case of premature termination of the study, all material (CRD totally or partially completed and blank, study drug, etc.) must be returned to GEIS.

12. PRACTICAL CONSIDERATIONS

12.1. Diagnostic criteria for the disease under study

Patients included in this trial must have histological confirmation of the diagnosis of glioblastoma as well as the result of the methylation of the MGMT gene.

Paraffin blocks / tumor slides will be collected from all patients for a central pathology review.

12.2. Investigator Responsibilities according to Good Clinical PracticesThe

responsibilities of the principal investigator in each participating Center will be: 1.

Sign the trial project.

2. Know in depth the properties of medicines.

3. Obtain the informed consent of the subjects prior to their inclusion in the trial.

4. Ensure that patients receive appropriate medical care in the event of adverse events, including significant laboratory values, related to the assay.

5. Collect, record and report the data correctly.

6. Report serious or unexpected adverse events immediately to the sponsor.

7. Ensure that all persons involved respect the confidentiality of any information about the trial subjects.

8. Report regularly to the Ethics Committee for Clinical Research on the progress of the trial.

9. Take responsibility for the preparation of the final test report, agreeing to it with your signature.

12.3. Instructions for completing the electronic CRD

Data will be recorded in accordance with GCP through the electronic documentation system at the center.

The application is designed to function entirely over the Internet. All stages of the processing, except for the actual input and display of the data, are carried out centrally on a web / database server. In particular, data storage will be done only centrally.

For data entry and results printing, the system relies entirely on the so-called "network interface", that is, data entry forms and reports are displayed on the client computer as HTML pages (Hyper Text Markup Language, the standard language for describing pages on the Internet) through a web browser. It is not necessary to install any user-specific software to be able to use the system from the investigator's computer. There is the possibility of directly accessing the raw data through an ODBC database for further data processing.

The system checks the correctness of the data by ranges and performs validity and consistency checks. Implausible or missing data can be corrected or completed after discussion with the investigator. Correction documents are stored (audit trail).

The system has a system of keys and passwords that restricts access to different areas of the application depending on the role assigned by the Promoter. Apart from the researcher, only expressly authorized persons who have received specific training for the study may complete the CRD-e.

All the data collected in the e-CRDs must be able to be documented in measurement records or by annotations in the patients' medical records.

12.4. Final Manuscript and Publications

Publication of the clinical trial

The Investigators Responsible for the study and the researchers who contribute at least 3% of the patients will appear as authors.

The order of authors will strictly depend on the number of patients included by the different researchers. The trial coordinators ([redacted], will occupy the first position, last position or 'corresponding author').

Clinical publication will be carried out by those responsible for the clinical study and clinical researchers.

It will be the responsibility of the first author, the Principal Investigators of the study and the study designer to write the final publications.

The anonymity of the source subjects of the study samples will be maintained at all times. The results or conclusions of the study will be communicated as a priority in scientific publications before being disclosed to the non-health public. Procedures of as yet undetermined efficacy will not be released prematurely or sensationally.

Participating investigators should not publish any data, about the patients, that is directly related to the objectives of the study, until the trial report is published.

The trial will be registered in the public access database, www.clinicaltrials.gov
Publication of the Translational Research

The results of the translational research will be published in journals of scientific impact, after the publication of the main results of the clinical study.

The first author will be the Coordinator of the Translational Study. All centers that have contributed at least 5% of the analyzed material will have the right to a co-authorship in the publication; The centers that have contributed a minimum of 15% of the analyzed material will have the right to 2 co-authors. The author or authors will be selected at the discretion of each center (pathologists, molecular biologists, clinicians ...). All centers that have contributed material for the analysis will be considered in the acknowledgments.

The clinical trial will be registered in "clinicaltrials.gov", and in the database of the National Institute of Health of United States of America.

12.5. Monitoring

The study will be monitored through local visits, telephone calls, and periodic inspection of the CRDs frequently enough to verify the following:

- Patient recruitment rate.

- Compliance with the approved protocol and amendments, if applicable.

- That the researcher has received the documents and supplies of the trial necessary to carry out the trial properly and in compliance with current legal regulations.

- That the Investigator and his team are adequately informed about the trial. - Integrity and correctness of the data entered in the CRD (according to the monitoring plan). - Informed consent (version, date and signature).
- Eligibility criteria.

- Selection tests.

- AAG and notifications from AAG.

- Main variable of the trial.

- Collection and storage of biological samples.

- Completion of CRDs and recording of adverse events.

- Communicate deviations from the protocol in accordance with good clinical practices and regulatory requirements, taking necessary actions to prevent the recurrence of detected deviations.

The monitoring visits will be made by the studio monitors. It is understood that these monitors will be able to access the medical records of the patients after the investigator requests it. The researcher will dedicate sufficient time to these visits and will facilitate access to all the documentation to authorized persons.

12.6. Amendments to the Protocol

Supplements or changes to the protocol can be made exclusively by the Promoter, who must send them to the Ethics Committee and the Regulatory Authorities (in Spain AEMPS) as amendments to the protocol.

12.7. Data processing

All data (personal, clinical, economic and from studies of biological material) obtained on patients will be treated in accordance with the Directive of the European Parliament 95/46 / EC of October 24, 1995 on the protection of people with respect to processing of personal data.

In accordance with the provisions of the aforementioned legislation, patients may exercise their rights of access, modification, opposition and cancellation of data, for which they must contact the doctor of the clinical trial.

The content of the CRD as well as the documents generated during the study will be considered strictly confidential and will not be disclosed to third parties.

In Spain, this study will also be carried out in accordance with Organic Law 15/1999, of December 13, on the protection of personal data.

12.8. Documentation

The investigator / institution shall maintain the trial documents in accordance with ICH Topic E6 Section 8, and in accordance with the relevant regulatory requirements.

Essential documents must be archived in accordance with BPC guidelines or for a longer period of time, if required by relevant regulations.

Original study patient data (medical history) should be stored according to the applicable archiving period at the study centers, but not for a period of less than 15 years.

13. TRANSLATIONAL STUDY

See annex V to the protocol

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Annex I. KARNOFSKY INDEX

CLINICAL-FUNCTIONAL SITUATION	PUNCTUATION
Normal	100
Able to perform normal activities	90
Minor signs or symptoms	80
He takes care of himself; incapable of total normal activity or active work	70
Requires occasional assistance but capable of caring for most needs	60
Requires frequent medical care and assistance	fifty
Affected; requires special care and assistance	40
Severely affected; indication for hospitalization; death not imminent	30
Dying	10
Death	0

Annex II. BARTHEL INDEX

THE BARTHEL INDEX

Patient Name: _____
Rater Name: _____
Date: _____

Activity	Score
FEEDING 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	_____
BATHING 0 = dependent 5 = independent (or in shower)	_____
GROOMING 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	_____
DRESSING 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)	_____
BOWELS 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	_____
BLADDER 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent	_____
TOILET USE 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	_____
TRANSFERS (BED TO CHAIR AND BACK) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent	_____
MOBILITY (ON LEVEL SURFACES) 0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards	_____
STAIRS 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	_____
TOTAL (0–100):	_____

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The Barthel ADL Index: Guidelines

1. The index should be used as a record of what a patient does, not as a record of what a patient could do.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. The need for supervision renders the patient not independent.
4. A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives and nurses are the usual sources, but direct observation and common sense are also important. However direct testing is not needed.
5. Usually the patient's performance over the preceding 24-48 hours is important, but occasionally longer periods will be relevant.
6. Middle categories imply that the patient supplies over 50 per cent of the effort.
7. Use of aids to be independent is allowed.

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Annex III. MINIMENTAL TEST. MMS

MINI MENTAL STATE EXAMINATION (MMSE)

Basado en Folstein et al. (1975), Lobo et al. (1979)

Nombre: Varón [ ] Mujer [ ]
Fecha: F. nacimiento: Edad:
Estudios/Profesión: N. Hª:
Observaciones:

¿En qué año estamos? 0-1 ¿En qué estación? 0-1 ¿En qué día (fecha)? 0-1 ¿En qué mes? 0-1 ¿En qué día de la semana? 0-1	**ORIENTACIÓN TEMPORAL** (Máx.5)	
¿En qué hospital (o lugar) estamos? 0-1 ¿En qué piso (o planta, sala, servicio)? 0-1 ¿En qué pueblo (ciudad)? 0-1 ¿En qué provincia estamos? 0-1 ¿En qué país (o nación, autonomía)? 0-1	**ORIENTACIÓN ESPACIAL** (Máx.5)	
Nombre tres palabras Peseta-Caballo-Manzana (o Balón- Bandera-Arbol) a razón de 1 por segundo. Luego se pide al paciente que las repita. Esta primera repetición otorga la puntuación. Otorgue 1 punto por cada palabra correcta, pero continúe diciéndolas hasta que el sujeto repita las 3, hasta un máximo de 6 veces. Peseta 0-1 Caballo 0-1 Manzana 0-1 (Balón 0-1 Bandera 0-1 Árbol 0-1)	**Nº de repeticiones necesarias** **FIJACIÓN-Recuerdo Inmediato** (Máx.3)	
Si tiene 30 pesetas y me va dando de tres en tres, ¿Cuántas le van quedando?. Detenga la prueba tras 5 sustraciones. Si el sujeto no puede realizar esta prueba, pídale que deletree la palabra MUNDO al revés. 30 0-1 27 0-1 24 0-1 21 0-1 18 0-1 (O 0-1 D 0-1 N 0-1 U 0-1 M0-1)	**ATENCIÓN-CÁLCULO** (Máx.5)	
Preguntar por las tres palabras mencionadas anteriormente. Peseta 0-1 Caballo 0-1 Manzana 0-1 (Balón 0-1 Bandera 0-1 Árbol 0-1)	**RECUERDO diferido** (Máx.3)	
DENOMINACIÓN. Mostrarle un lápiz o un bolígrafo y preguntar ¿qué es esto?. Hacer lo mismo con un reloj de pulsera. Lápiz 0-1 Reloj 0-1 *REPETICIÓN*. Pedirle que repita la frase: *"ni sí, ni no, ni pero"* (o *"En un trigal había 5 perros"*) 0-1 *ÓRDENES*. Pedirle que siga la orden: *"coja un papel con la mano derecha, dóblelo por la mitad, y póngalo en el suelo"*. Coje con mano d. 0-1 dobla por mitad 0-1 pone en suelo 0-1 *LECTURA*. Escriba legiblemente en un papel *"Cierre los ojos"*. Pídale que lo lea y haga lo que dice la frase 0-1 *ESCRITURA*. Que escriba una frase (con sujeto y predicado) 0-1 *COPIA*. Dibuje 2 pentágonos intersectados y pida al sujeto que los copie tal cual. Para otorgar un punto deben estar presentes los 10 ángulos y la intersección. 0-1	**LENGUAJE** (Máx.9)	
Puntuaciones de referencia 27 ó más: normal 24 ó menos: sospecha patológica 12-24: deterioro 9-12 : demencia	**Puntuación Total (Máx.: 30 puntos)**	

a.e.g.(1999)

Annex IV. RANO RESPONSE CRITERIA

	RC	RP	EE	PROGRESSION
T1-GD	**0**	**≥50%**	>50% <25% -	³ 25% - *
T2 / FLAIR	**=,**	**=,**	**=,**	**=,** - *
NEW INJURIES	**0**	**0**	**0**	**0. + ***
CORTICOSTERIOIDS	**0**	**=,**	**=,**	**=,** - *
CLINIC	**=,** -	**=,** -	**=,** -	**=,** *
	all	**all**	**all**	**Anyone ***

COMPLETE ANSWER:

- Disappearance of the signal in NMR T1Gd
- Stability or reduction in Flair / T2 images
- No new radiological lesions
- Stability or clinical improvement
- Absence of corticosteroids or stable minimum dose

PARTIAL ANSWER:

- Image reduction in NMR by 50% in T1Gd
- Stability or reduction in Flair / T2 images
- No new radiological lesions
- Stability or clinical improvement
- With reduced or stable steroids

PROGRESSION: Any of the following

- 25% tumor growth on T1Gd MRI
- Significant increase in Flair / T2 images *
- Appearance of new lesions
- Irreversible clinical neurological deterioration, even in the absence of radiological deterioration. ● Need to increase dexamethasone (> 2 weeks) to prevent progressive neurological deterioration.

NOTE: Only progression criteria 1,2 AND 3 are applicable for the purposes of including the patient in the clinical trial.

STABLE DISEASE:

- Image in T1Gd with an increase of less than 25% or a decrease of less than 50%
- Flair / T2 image stability
- No new radiological lesions
- Clinically stable
- Stable cortisone doses (not to be increased to maintain neurological impairment)

* not attributable to radiation therapy, demyelination, ischemia, infection, seizures, postoperative changes or other effects of treatment

Annex V. ASSOCIATED MOLECULAR SUB-STUDY

The drugs most used in neuro-oncology (nitrosoureas, temozolomide, procarbazine) owe their effectiveness to the chloro-ethylating or methylating lesion they produce on DNA. The methylguanine-O6-methyltransferase (MGMT) repair enzyme repairs DNA through the direct removal of an alkyl group from the O6 atom of guanine in the DNA of cells exposed to alkylating agents31-33. In the gene that codes for said enzyme (MGMT) there are CpG dinucleotide islets that act as promoters of the gene coding.34 If these islets present methylation, the gene is silenced and no repair protein is produced, which means that the lesion produced by chemotherapy in the tumor cell it becomes irreversible and the cell enters apoptosis.

TMZ, in a second generation derivative of imidazoltetrazinone, is spontaneously hydrolyzed under physiological conditions in the active metabolite and acts as a DNA methylating agent.

Due to its mechanism of action, it is known that cells that have the ability to repair methylated DNA to unmethylated DNA through, among other enzymes, their richness in the enzyme O-6-methyl-guanine-DNA-methyl-transferase (MGMT), can overcome DNA damage and therefore not enter apoptosis. The enzyme is encoded by the MGMT gene. MGMT may be methylated on GpG islets and not correctly transcribed, causing enzyme inactivity.

The importance of the enzyme and its relationship with the response to alkylating or methylating agents in various tumors was known.31, 32 In the EORTC phase III study that provided the indication for temozolomide in the first line of treatment, it was determined, in the cases in which there was a tumor sample, the MGMT methylation status and it was established that the methylation status was a significant predictive factor of response to TMZ. 35 However, it is not useful yet to discriminate between patients and decide on a different treatment. During the DNA repair process, the enzyme is consumed and has to be synthesized again. Prolonged administration (in continuous regimens or heavy doses) could improve the antitumor activity of the drug. 12

By international consensus, any study performed using temozolomide must be accompanied by a study of the MGMT status in tumor cells.37

Other TMZ resistance enzymes (MSH1 / MSH6) have been described that will be studied a posteriori in the Tissue Microarray.

The histological material in the form of a paraffin block from the material obtained in the initial surgery will be sent to the HUGTIP Anatomy Service, ([redacted]) where the histology was confirmed and a baseline molecular study of MGMT was carried out using the MSP (methylation -specific polymeration chain reaction) technique. ([redacted]). The MGMT result performed at the originating center will be accepted. The results will be reported in the CRO for centralized and stratified randomization and subsequent statistical exploitation and will also be sent to the patient's center of origin. Tissue will be reserved to prepare a tissue matrix for subsequent immunohistochemical study of IDH1 and TMZ

resistance or sensitivity protein (MSH6, MSH2), and future studies that may arise as a result of the test results.

In case of excess material, it will be returned to the center of origin.

Annex VI. HELSINKI DECLARATION

The new update of the Declaration of Helsinki can be found at:

http://www.wma.net/en/30publications/10policies/b3/

Annex VII. NCI COMMON TERMINOLOGY CRITERIA V.4.0 FOR ADVERSE EVENTS

Version 4.0 of the Common Terminology Criteria for Adverse Events (CTCAE) can be found at the following link:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Annex VIII. TEST SCHEME

Esquema del Estudio GEINO 14-01