Title: Pilot, open-label, multicenter and prospective Phase II Clinical Trial to evaluate the safety and efficacy of Palbociclib (PD0332991), an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), in patients with recurrent Oligodendroglioma with preservation of activity of the RB protein.

Protocol Code:GEINO-13

Nº EudraCT: 2015-001722-42

Version:4.0 (July 1, 2019)

District Att[redacted]

Coordinator:J[redacted]

PROTOCOL SIGNATURE PAGE

Protocol Code: GEINO-13
Version: 4.0 (July 1, 2019)

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and the Declaration of Helsinki.

Signature of the Coordinating Investigator and representative of the promoter

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and the Declaration of Helsinki.

Signature of Principal Investigator: _____

Name: _____

Center: _____

1. SUMMARY

1.1. Type of request
Clinical Trial of a Medicine Not Authorized by the EMA.

1.2. Promoter Data
[redacted]

1.3. Essay Title
Pilot, open-label, multicenter and prospective Phase II Clinical Trial to evaluate the safety and efficacy of Palbociclib (PD0332991), an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), in patients with recurrent Oligodendroglioma with preservation of activity of the RB protein.

1.4. Protocol Code
GEINO-13

1.5. Nº EudraCT
2015-001722-42

1.6. Coordinating researcher
[redacted]

1.7. Principal researchers
See appendix

1.8. Participating Centers
See appendix

1.9. Name of the Organization in charge of Monitoring
[redacted]

1.10. Treatment description
All patients included in the study will be treated with the experimental drug, Palbociclib, at a dose of 125 mg/day on days 1-21 in 28-day cycles. That is, administered 21 days followed by 7 days of rest. The treatment cycles will continue until there is unacceptable toxicity, tumor progression, withdrawal of consent or death of the patient.

1.11. Clinical trial phase
Phase II pilot clinical trial.

1.12. Main goal
To evaluate six-month progression-free survival (PFS) (6mPFS) in patients with recurrent anaplastic oligodendroglial tumors.

1.13. Disease under study
Recurrent oligodendroglioma with preservation of RB protein activity.

1.14. Variable Principal
Percentage of patients who have relapsed/not relapsed to the study treatment 6 months after starting it.

1.15. Study population
Patients with anaplastic Oligodendroglioma, defined according to the 2016 Edition of the WHO, histologically confirmed and with preservation of RB protein activity, may be included in this study.

1.16. Sample size
40 patients will be included in the study.

1.17. Treatment duration
Treatment will continue until disease progression, unacceptable toxicity, non-compliance or revocation of consent by the patient.

1.18. Planned schedule
Start Closing: 2nd quarter of 2015
Inclusion of the 1st patient: 4th quarter of 2015
Estimated recruitment period: 28 months
Follow-up period: 6 months
End of study: 4th quarter 2019

Table of Contents

2. LIST OF ABBREVIATIONS

AA	Adverse event
AAG	Serious adverse event
EVERYTHING	Alanine transaminase
AST	Aspartate transaminase
BPC	Good Clinical Practice
CRD	Data collection notebook
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group Performance Status Eastern Cooperative)
MOTHER	European Medicines Agency
EP	Progressive disease
FDA	Food and Drug Administration (Departamento Salud U.S.)
INR	International normalized index
HERE	intention to treat
LDH	Lactate dehydrogenase
LIN	Lower limit of normal
LSN	Upper limit of normal
MUI	Millions of international units
NCI-CTCAE v4.0	Common toxicity criteria for adverse events according to the Institute Cancer National, version 4.0
OH	Oligodendroglioma Anaplastic
FROM	Oligodendroglioma
RC	Complete answer
RM	Magnetic resonance
SG	Global Survival
SLP	Progression Free Survival
TAC	Axial computed tomography
TLD	Dose Limiting Toxicity
City	Prothrombin Time
TTP	Activated partial thromboplastin time

3. GENERAL INFORMATION

3.1. Type of Clinical Trial

Clinical Trial of a Medicine Not Authorized by the EMA.

3.2. Description of the Study Treatment Scheme

Palbociclib (PD0332991) is a selective inhibitor of Cyclin-dependent Kinases 4 and 6 (CDK4 and CDK6).

*Pharmacotherapeutic group:*Antineoplastic agents

Presentation: hard capsules containing 125, 100 and 75 mg of Palbociclib

*Pharmaceutical form:*hard capsules

*Route of administration:*oral

Supplied by the Promoter through an agreement signed with the laboratory producing the molecule.

3.3. District Attorney

[redacted]

3.4. Name of the Organization responsible for Monitoring

[redacted]

3.5. Researcher Coordinator

[redacted]

3.6. Participating centers

See attached document

3.7. Planned schedule

Start Closing: 2nd quarter of 2015

Inclusion of the 1st patient: 4th quarter of 2015

Estimated recruitment period: 28 months

Follow-up period: 6 months

End of study: 4th quarter 2019

4. JUSTIFICATION AND OBJECTIVES

4.1. Introduction

Palbociclib (PD0332991) is a selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6) whose function is to facilitate the transition from the G1 phase to the S phase of the cell cycle through the phosphorylation of the retinoblastoma protein (RB). Palbociclib is being evaluated in different tumors such as breast cancer or glioblastoma. In metastatic breast cancer RH +/Her2 - has shown an important and significant increase in Progression Free Survival (PFS) when associated with letrozole compared to treatment with letrozole monotherapy (20.2 months of the combination versus 10.2 months)[1], which has led to its approval by the FDA in February 2015 as a first-line hormonal treatment associated with letrozole in this patient population

Anaplastic oligodendroglioma (AO) responds to alkylating chemotherapy agents such as temozolomide or the PCV regimen and also to focal radiotherapy. However, when it has progressed to these treatments, the prognosis is very poor, with survival of a few months and no treatment. This neoplasm is a type of glioma that frequently presents alterations in the BR pathway, so blocking CDK4 and CDK6 with palbociclib may be a therapeutic approach of greatest interest when conventional treatment with chemotherapy and radiotherapy has failed.

4.2. Background

4.2.1. Histology of oligodendroglial tumors

The classic image of oligodendroglioma (OD) is cells with a round central nucleus and clear cytoplasm around them. They have a characteristic growth pattern, with cells very close to each other. There are no immunohistochemical markers that allow specific recognition of oligodendroglioma. When astrocytes also appear in the sample, they are considered, according to the 2007 WHO classification[2] Oligoastrocytomas (OA), which can be low or high grade. However, in the new WHO classification that will be published in 2016 (although the changes that concern oligodendroglial tumors have already been presented)[23,24,25]. In this new classification, molecular alterations determine whether cases are classified as astrocytomas or oligodendrogliomas when patients have mixed morphological characteristics.

Anaplastic oligodendroglioma (OA) presents features of focal or diffuse malignancy, usually marked atypia and elevated mitotic activity. The presence of microvascular proliferation or necrosis are signs of grade III (anaplastic). There is no such thing as grade IV oligodendroglioma. Anaplastic oligoastrocytomas (AOA) with areas of necrosis or vascular proliferation are classified as Glioblastomas with oligodendroglial differentiation (Grade IV)[2].

The finding of allelic losses on chromosomes 1p and 19q favors the diagnosis of OD, given the frequency of said losses in these tumors (above 50% and up to 80% in low-grade cases) and in the last classification it passes to be a mandatory condition to have this molecular alteration.

4.2.2. Epidemiology of oligodendroglial tumors

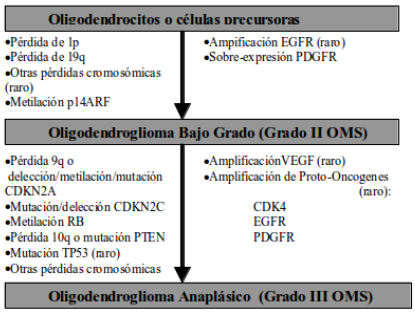
Oligodendroglial tumors are rare neoplasms. The Central Tumor Registry of the United States reported in 1995 an annual incidence for all oligodendroglial tumors of 9.3 cases per 100,000 inhabitants/year.[3]. The Norwegian Tumor Registry, which analyzed data from the previous 25 years in 1985, determined that

oligodendroglial tumors accounted for 4.2% of all brain neoplasms.[4]. In other studies, these tumors represent between 5% and 18% of intracranial neoplasias[5].
Within oligodendrogliomas, the proportion of the two WHO grades differs in different studies. Celli et al.[6] y Nijjar et al.[7] They found 20% of anaplastic oligodendrogliomas. In the Mayo Clinic series, the group of anaplastic tumors represented 54% of oligodendrogliomas[8].

4.2.3. Molecular biology of oligodendroglial tumors

Table 1 summarizes the current knowledge on the molecular and genetic alterations that are present in the development and progression of oligodendrogliomas. Deletions in chromosomes 1p and 19q (loss of heterozygosity, PH) are the most frequent and earliest alterations in the tumor progression of oligodendrogliomas. In fact, the frequency of PH 1p and 19q in WHO grade II oligodendrogliomas is 80-90%, while in anaplastic oligodendrogliomas it is 31-70%.[5]. In most cases, the losses of 1p and 19q are combined, and the mechanism of the associated loss of these two chromosomal portions is currently not known. In recent years, it has been determined that the loss of 1p/19q is closely associated with mutations in IDH1/2 and also with the existence of a methylator phenotype.
The transformation of a low-grade tumor into anaplastic oligodendroglioma occurs due to the accumulation of genetic alterations (Table 1). The most important are the deletions of 9p and 10q. These alterations were found in a small number of WHO grade II oligodendrogliomas, being much more common in grade III. The CDKN2A gene, which is located at 9p21, presents homozygous deletions in more than 1/3 of anaplastic oligodendrogliomas[9-11]. It is also interesting that homozygous deletions of CDKN2A are particularly common in oligodendrogliomas that do not have loss of 1p and 19q. The suppressor genes CDKN2A and CDKN2B encode the proteins p16 (INK4a) and p15 (INK4b), respectively, whose function is to inhibit CDK4 and CDK6. Similar to what happens in astrocytomas, the pRb pathway is altered in a significant percentage of anaplastic oligodendrogliomas, either through homozygous deletion or hypermethylation of CDKN2A; the amplification and elevated expression of CDK4A; or hypermethylation and loss of pRb expression.

Figure 1. Most important genetic alterations in oligodendrogliomas[5]



4.2.4. Treatment of Anaplastic Oligodendroglioma

Regarding treatment, the first approach is surgical intervention. In this sense, retrospective studies as well as subgroup analyzes reach the same conclusion: a wide resection improves the patient's prognosis. Given the high possibility of tumor progression, in the 1980s radiotherapy was established as the standard of post-surgical treatment in high-grade gliomas.

In the 90s, studies were published that showed that they are chemosensitive tumors (PCV), unlike other brain tumors.[12]. With these data, two studies were then designed, from which we have just obtained

results.[13,14]: the RTOG 9402 study and the EORTC study 26951. In both cases, after an initial surgical approach, the question of whether chemotherapy (PCV: Procarbazine, CCNU and Vincristine) provided benefit to the radiotherapy treatment was attempted. , so the 2 randomized phase III studies were designed.

The primary endpoint in the EORTC study was PFS and OS. A total of 368 patients with oligodendroglial tumor were included between 1995 and 2002, aged between 16 and 70 years. The branches were well balanced for known prognostic factors. Adding PCV to radiotherapy increases median PFS from 13 to 24 months and OS from 31 to 42 months, statistically significantly. These results were further maintained when performing an analysis that included risk stratification by age, type of surgery, PS, and prior surgery for low-grade glioma.[15]. The next question he tried to answer is whether there is any way to identify those patients who will benefit the most. The results analyzed prospectively for 1p/19q, and retrospectively for MGMT and IDH, can help with this. 1p/19 was analyzed in 316 patients and 25% were co-deleted. MGMT was analyzed in 183 patients and 75% were methylated and IDH was analyzed in 176 patients and was mutated in 46%. For 1p/19 there is a benefit in PFS from 50 to 157 months and in OS from 9 years to a median not yet reached (>12 years) (p=0.059). However, in non-co-deleted patients, the differences do not reach statistical significance.

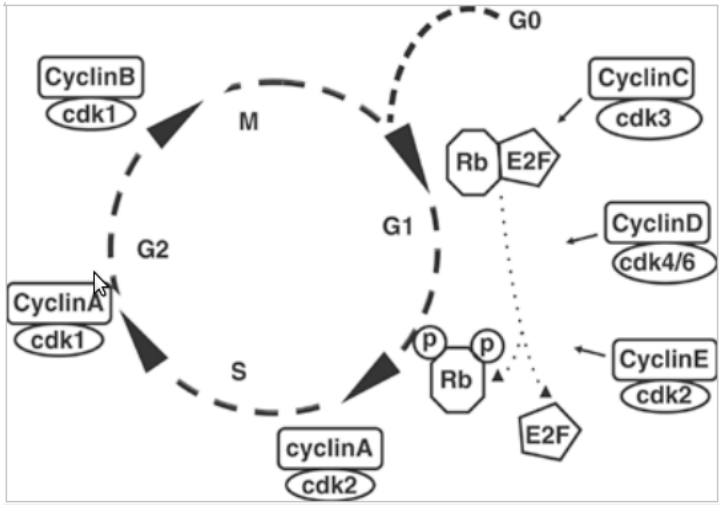
In 2012 we also learned the final results of the RTOG 9462 study, which were very similar to those of the EORTC study.[16]. Based on these data, post-surgical radiotherapy treatment will be complemented with chemotherapy in the event that there is loss of 1p/19q. In cases without chromosome loss, it is usual to use radiotherapy exclusively.
In both the RTOG9462 and EORTC 26951 studies, patients were treated with chemotherapy at relapse, still achieving responses in some cases. Temozolomide was the most used alkylating agent in cases of recurrence. However, there is currently no standard treatment for OA recurrence.

4.3. Implications of CDK4 and CDK6 in Oligodendroglial Tumors

4.3.1.CDK4/6 in Cancer

The proliferation of eukaryotic cells depends on an orderly progression through the different phases of the cell cycle: G1, S, G2 and M (mitosis). Cyclin-dependent kinases (CDKs) play an important role in regulating these steps throughout the cell cycle and, especially in the step from G1 to DNA replication (S) and in the step between G2 and mitosis (M). The regulation of the catalytic activity of CDKs occurs at multiple levels such as their own phosphorylation/dephosphorylation; its synthesis and degradation rate; and the expression or degradation of selective inhibitory proteins.
The transition from the G1 phase to the S phase requires the phosphorylation of the retinoblastoma protein (Rb) by CDK4 and its analogous protein CDK6, forming a complex with their activating subunits, the D-type cyclins, D1, D2 and D3. Hyperphosphorylation of RB decreases its ability to repress E2F family transcription factors and, consequently, the activation of multiple genes whose products are essential for DNA replication. The p16 and p18 proteins, encoded by the CDKN2A/B gene, are responsible for inhibiting the CDK4/6-Cyclin D complexes, preventing overactivity of the pathway. The loss of p16 and p18 are, therefore, alterations frequently involved in neoplastic transformation.

Graph 1. Control of the cell cycle by the different Cyclin-CDK complexes.



4.3.2. CDK4/6 in High Grade Gliomas

Genetic alterations affecting the CDK4/6-CyclinD-INK4-RB regulatory axis in gliomas are well documented.[17] and have been corroborated in large-scale genetic analyzes[18,19]. The most frequent alteration of this molecular pathway in glioblastomas is the homozygous deletion of the CDKN2A/B gene that encodes the p16 proteins.^{INK4a} the p15^{INK4B}, which affect more than 50% of this tumor line. Other alterations are amplification of CDK4 (15-20%) and homozygous deletion of RB1 (10%). Amplification of CDK6 and cyclins D as well as homozygous deletion of p18^{INK4c} They are less frequent.

Of all these alterations, only genetic inactivation of RB leads the tumor to be resistant to CDK4/6 inhibition. In fact, “in vitro” studies with PD0332991 against a panel of glioblastoma showed that all those with conservation of the RB protein were sensitive to the drug while the 5 cell lines with homozygous inactivation of RB were resistant to PD0332991.

4.3.3. CDK4/6 in Oligodendrogliomas

As mentioned above, the most important genetic alteration in the transformation towards the grade of anaplasia is the loss of the suppressor gene CDKN2A, which is located on chromosome 9p21 and its alteration is very rare in low-grade gliomas. In most cases, there is loss of both copies of suppressor genes adjacent to CDKN2A such as p14ARF and CDKN2B. CDKN2A and CDKN2B encode p16^{INK4a} the p15^{INK4b} respectively whose function is to regulate the G1-S transition of the cell cycle through the inhibition of CDK4 and CDK6. As also previously reviewed, CDK4 and CDK6 cause phosphorylation of RB. In addition to the loss of CDKN2A, OAs present other alterations in the RB pathway, so that practically all cases ultimately present a severe dysfunction of this tumor suppressor pathway. Other alterations of this molecular pathway are: hypermethylation of CDKN2A and CDKN2B, amplification and overexpression of CDK4.

4.4. Palbociclib (PD0332991)

Palbociclib is an oral CDK4 and CDK6 inhibitor that has been evaluated in various phase 1 and phase 2 clinical trials in various indications. Palbociclib prevents the normal development of the cell cycle from the

G1 phase to the S phase and has demonstrated important antitumor activity in preclinical models such as glioblastoma and also in human tumors such as metastatic breast cancer luminal phenotype[1].

Treatment of cultured tumor cells with PD 0332991 causes growth arrest that is accompanied by inhibition of specific phosphorylation of Rb by CDK4 or CDK6 at serine residues 780 and 795 of Rb. Consequently, the phosphorylation status of these sites makes them specific biomarkers of CDK4/6 inhibition by PD 0332991. IC50 values of reduced Rb phosphorylation at serine residues 780 and 795 in MDA mammary carcinoma cells -MB-435 were 0.066 and 0.063 µM, respectively. The IC50 values of the reduction of Rb phosphorylation are similar to those of the inhibition of thymidine incorporation in various cultured normal and tumor cells.

In a group of 16 RB+ glioblastoma cell lines Palbociclib caused a potent cell cycle arrest effect in the G1 phase followed by senescence. However, 5 RB- Glioblastoma cell lines were resistant to treatment.[20]. The selectivity of its mechanism of action is also proven by the fact that reducing the expression of RB RNA in glioblastoma cell lines results in the cell lines becoming resistant to treatment. Also in intracerebral glioblastoma xenografts it has been seen that Palbociclib can cross the blood-brain barrier by producing a reduction in the implanted tumors. Also in glioblastoma xenografts it has been found that there may be an enhancing action between Palbociclib and radiotherapy in this disease. Given these findings, a clinical trial with Palbociclib in recurrent glioblastoma has been initiated (NCT01227434).

4.4.1. Background on preclinical pharmacokinetics and drug metabolism

Palbociclib inhibits RB phosphorylation by CDK4 with an IC_{50} of less than 20nM and is capable of reducing tumor growth of multiple tumor xenografts in immunodeficient mice. A stable plasma drug concentration of 1000 mg/mL caused an 80-90% inhibition in RB phosphorylation in addition to a 50% reduction in tumor growth.

In non-human species (dog, monkey and mouse), Palbociclib shows low to moderate plasma clearance, a large volume of distribution and an oral bioavailability around 23%-56%. Plasma protein binding is moderate in mice, dogs and human plasma. In humans, Palbociclib is distributed more in erythrocytes than in plasma. Radioequivalents of Palbociclib were widely distributed in most rat tissues after oral intake of the drug. Palbociclib generates multiple metabolites detected in concentrations in all species studied, including humans. It is metabolized by CYP3A enzymes, undergoing several steps including oxidation, glucuronidation, sulfation and the combination of several of these processes. After administration of radioisotope-labeled Palbociclib in rats, it was observed that the majority of the radiopharmaceutical was eliminated via the fecal route. Neither Palbociclib nor its primary metabolism PF-05089326 showed significant inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. It was found that Palbociclib and PF-05089326 produced an inhibition of CYP3A, so this drug potentially presents pharmacokinetic interactions with other drugs metabolized by CYP3A. It has also been found in preclinical studies that Palbociclib can inhibit the absorption and pharmacodynamics of drugs that are substrates of P-glycoprotein and Breast Cancer Resistance Protein (BCRP).

4.4.2. Background on the preclinical toxicology of the drug

Palbociclib had no effects on heart rate, heart rate, or blood pressure in dogs. However, an increase in the QT interval was detected.
At the lung level, transient toxicity was found in dogs anesthetized with a dose of 100 mg/m2 with a peak concentration of 2040 ng/mL. With lower doses (20 mg/m2, peak of 414 ng/mL) this type of toxicity was not detected.

In animal studies, Palbociclib was lethal in rats when AUC values were reached.$_{(0\text{-}24)}$ of 46600 and 11100 ng/h/mL in males and females respectively. The cause of the greater susceptibility on the part of females is not known.
Reversible pancytopenia occurred in both male and female rats at doses of 300 mg/m2 and 600 mg/m2, respectively. Testicular degeneration in rats occurred at doses of 300 mg/m2. The dose that produced the decrease in hematological markers was 12 mg/m2 in dogs, associating an AUC$_{(0\text{-}24)}$ at steady state of 548 ng/h/mL. Monocytes and neutrophils were the most affected. The nadir was reached at the end of dosing and all variations in these parameters were reversible.

In preclinical studies conducted in rats and dogs that took Palbociclib for a minimum of 3 weeks, effects on the male reproductive organs were observed, such as disintegration of the structure of the seminiferous tubules (tubes in the testicles where sperm are produced) as a decrease in semen secretion. Dose-dependent effects, even in the 4 weeks after the last intake of palbociclib. None of these effects have been observed at human dosages or in any clinical study.

4.4.3. Pharmacokinetics, Toxicity and Metabolism of the product in humans

PD 0332991 has been tested in a phase 1 dose-escalating study (A5481001) in 74 patients with advanced cancer. Two dosing regimens were evaluated: regimen 3/1 (3 weeks of treatment/1 week off treatment) and regimen 2/1 (2 weeks of treatment/1 week off treatment).
All DLTs observed in this study were related to myelosuppression, and were mainly grade 3 neutropenia lasting more than 7 days after the end of the treatment cycle. However, the neutropenia was reversible and not cumulative. The most frequent non-hematological adverse events were fatigue, anemia, diarrhea, constipation, vomiting and dyspnea, all of which were mild or moderate in severity. A partial response was reported in a patient with testicular cancer. Stable disease (SE) was seen in a total of 13/37 patients treated with the 3/1 regimen evaluable for efficacy, including 6 patients with SE for 40 or more weeks. One of these patients was a woman with ER+ breast cancer who had previously received 7 lines of treatment for the disease. This patient remained on treatment for 80 weeks (7 cycles with 50 mg/day and 13 cycles with 75 mg/day) and ended up abandoning it due to disease progression. Based on the efficacy results of this study, the 3/1 regimen has been chosen for further clinical development. The DF2R for the 3/2 schedule is 125 mg/day.

In the Phase 1 dose escalation study (A5481001), PD 0332991 was slowly absorbed. The median maximum concentration appeared ~4 hours post-dose on day 1, and exposure generally increased in proportion to dose. The mean volume of distribution of PD 0332991 was 3103 L, significantly higher than total body water (42 L), indicating that PD 0332991 penetrates widely into peripheral tissues. PD 0332991 was slowly removed; the mean terminal half-life was 26.5 hours, and the mean apparent oral clearance was

86.1 L/hour. Renal excretion is a minor route of elimination of PD 0332991. The pilot evaluation of the effect of food in this study observed higher exposures in fed than fasted subjects. Based on these data, and because administration of PD 0332991 with a high-fat meal may increase exposure, patients should fast from 1 hour before to 2 hours after administration. The effects of a non-fat meal on the pharmacokinetics of PD 0332991 have not been evaluated. In clinical trials with palbociclib until December 10, 2014, two different formulations of palbociclib have been provided: as isotethionate salt (PD-0332991) or as free base (PD-0332991). Due to the inherent differences between the two in their solubility as a function of pH, the administration recommendations in relation to meals and the potential effect of antacids on their absorption differ between both formulations.

Patients receiving palbociclib isethionate capsules should take the drug on an empty stomach, while palbociclib freebase capsules should be administered with food. Results from study A5481036 demonstrated that palbociclib freebase capsules administered with food were bioequivalent to isethionate capsules administered under fasted conditions. In an interaction trial in healthy subjects, coadministration of a single dose of 125 mg of palbociclib free base with food and multiple doses of the proton pump inhibitor (PPI) rabeprazole reduced the Cmax of palbociclib by 41%, but with limited impact on AUCinf (13% decrease) when compared to a single dose of palbociclib free base. Given the small effect on gastric pH of H2 antagonists and locally acting antacids compared to PPIs, it is expected that the effect that these drugs could have on the exposure to palbociclib when administered with food is expected to be minimal.

4.4.4. Clinical experience with Palbociclib in humans

In addition to the phase 1 study with increasing doses (A5481001), there are others evaluating tolerance and activity of the compound in different tumors. The second study launched with Palbociclib (A5481002) is evaluating the pharmacodynamics, clinical activity and safety of PD 0332991 in patients with previously treated mantle cell lymphoma. PD 0332991 is being administered according to the 3/1 schedule at a dose of 125 mg once daily. 17 patients have been included in the study. One complete response and two partial responses were observed. The safety profile has been similar to that observed in the study with increasing doses.

Another study (A5481004) is aimed at evaluating the safety and clinical activity of PD 0332991 in combination with bortezomib and dexamethasone in patients with refractory multiple myeloma.

The A5481003 clinical trial is the first phase 2 study in which we have information on the activity of the drug in a specific tumor, in this case metastatic Her2-negative, hormone receptor-positive breast cancer. In these patients, Palbociclib has shown an important and significant increase in Progression-Free Survival (PFS) when associated with letrozole compared to treatment with letrozole as monotherapy (20.2 months for the combination versus 10.2 months).[1]. The combination was well tolerated when compared to treatment with letrozole monotherapy. The most common side effects of the combination were uncomplicated neutropenia, leukopenia and asthenia and the most common Grade 3 side effect was neutropenia (54%) and leukopenia (21%). The most common Grade 4 side effect was neutropenia and asthenia, 6% each. Only 9% of patients in this trial who received Palbocilclib had to stop treatment. Given the promising data from this phase II clinical trial, study A5481008 has recently been launched to compare the efficacy of letrozole + Palbociclib versus letrozole in patients with ER+HER2- metastatic breast cancer in an extensive randomized phase III.

In brain tumors, a study has already been launched (NCT01227434) that evaluates the activity and safety of the drug in recurrent glioblastoma and also associates a pharmacokinetic and pharmacodynamic study in samples of glioblastoma operated on days after the start of treatment with the drug.

After reviewing data accumulated from cases described in In clinical trials, interstitial lung disease (ILD)/pneumonitis has been reported as a possible adverse reaction to palbociclib (IBRANCE®), with this information reported in reference safety documents, the safety database, and in the literature. published.
Complete information on this compound can be obtained from the single safety reference document, which in this study is the investigator's manual.

4.5. Justification

OA are rare tumors characterized by being chemosensitive and radiosensitive. In fact, although most patients respond to a first line (temozolomide or PCV), the majority of patients suffer a relapse in less than 2 years after treatment. Other cytotoxic agents such as irinotecan, paclitaxel, carboplatin and etoposic have been evaluated in the second line but with very low response rates in this context. There is, therefore, a need to find new drugs useful in these patients. In this sense, palbociclib has an interesting and solid rationale for conducting an exploratory clinical trial in patients with OA.
Palbociclib could be especially active in patients with OA because these tumors frequently present alterations in the RB pathway that could be reversible by blocking CDK4 and CDK6. Furthermore, alterations in this pathway, such as the loss of CDKN2A, seem to be fundamental in the transformation from low to high grade since they are very rare in grade 2 oligodendrogliomas. Knowing that glioblastoma cell lines with loss of the RB protein are resistant to treatment with Palbociclib, only patients who maintain RB expression would be included in the present clinical trial.

Given the preclinical data in glioblastoma cell lines and xenografts, a clinical trial has been initiated with Palbociclib in recurrent glioblastoma. However, we think that the RB pathway may be more decisive in the oncogenesis of anaplastic oligodendrogliomas than in Glioblastomas where a very significant number of cases have mutations in p53, EGFR and PDGFR, even coinciding with those that may exist in CDKN2A.
Data from phase 1 and 2 clinical trials with palbociclib indicate that it is an active drug in various types of cancer and that it has a tolerable, known and controllable toxicity profile. The Palbociclib dose of 125 mg/day on days 1-21 in 28-day cycles has been chosen as it is the dose established as safe and effective in the various phase 1 and 2 clinical trials already published.[21] and which is being used in phase 3 clinical trials in patients with metastatic breast cancer.

In the previous classification of brain tumors, from 2007, oligodendroglioma was defined based on its morphological characteristics and cases in which there were cells resembling astrocytes were diagnosed as Oligoastrocytomas or mixed gliomas. This led to significant interobserver variability when making the diagnosis, which undermined the conclusions of any study or clinical trial carried out on oligodendroglial tumors. The new 2016 WHO classification represents a significant advance as it requires that, to be diagnosed as such, oligodendrogliomas must present mutations in the IDH1 or IDH2 genes and also present codeletion of 1p/19q. On the other hand, the new classification eliminates the diagnosis of oligoastrocytoma and cases that have astrocyte populations mixed with oligodendrocytes will have to

undergo a molecular study to classify them either as oligodendrogliomas (with loss of 1p/19q) or as astrocytomas (without loss of 1p/19q).[23, 24,25]

4.6. Goals

4.6.1. Main goal

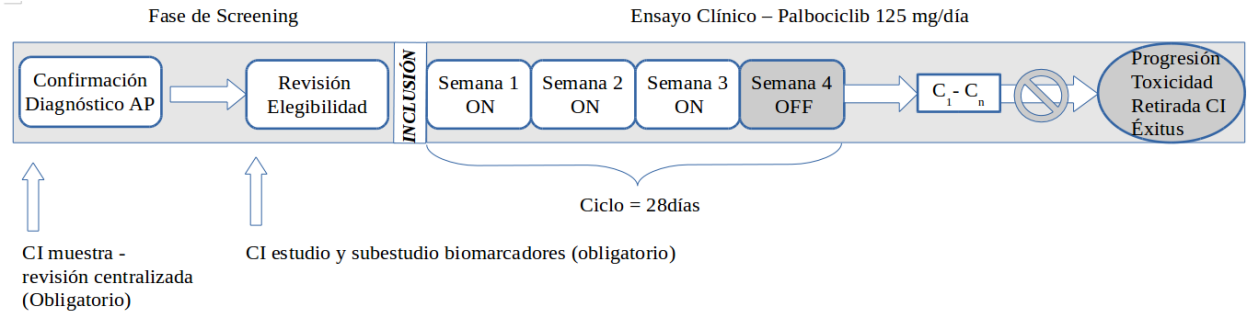
To evaluate six-month progression-free survival (PFS) (6mPFS) in patients with recurrent anaplastic oligodendrogliomas (Grade III).

4.6.2. Secondary objectives

- To evaluate the safety and tolerability of oral administration of Palbociclib in patients with recurrent anaplastic oligodendrogliomas.
- Evaluate the antitumor response according to the RANO criteria
- Assess Global Survival (GS)
- To evaluate the duration of response in patients with an objective response.
- Assess changes in glucocorticoid use.
- Assess changes in neurological status
- To evaluate whether the following biomarkers are related to PFS and OS: deletions in CDKN2A, deletions in CDKN2B, CDK4 amplification, CDK6 amplification, cyclin D amplification.
- To evaluate whether the following biomarkers are related to the response rate: deletions in CDKN2A, CDKN2B deletions, CDK4 amplification, CDK6 amplification, Cyclin D amplification.

5. DESIGN AND TYPE OF CLINICAL TRIALS

The GEINO-13 study has been designed as a pilot, open-label, multicenter and prospective Phase II clinical trial with a single treatment arm. The primary objective of the study is to evaluate six-month progression-free survival (PFS) (6mPFS) in patients with recurrent anaplastic oligodendroglial tumors.



5.1. Tumor Screening Period

Informed consent will be obtained for the use of biological samples from the patient before starting the selection period.

5.2. Centralized block review

A centralized pathological review will be carried out to confirm the anatomopathological and molecular diagnosis of Anaplastic Oligodendroglioma (OA) in the Pathological Anatomy Service of [redacted], a central neuropathology laboratory that will also determine if there is nuclear expression of the RB protein through immunohistochemistry. .

As part of screening, all patients must have a paraffin-embedded tissue block available from a previous biopsy or surgery (previously archived tumor samples). If there are several surgeries, samples from the last intervention with areas of tumor must be sent.
In addition to determining the expression of the RB protein, the central laboratory will also carry out the study of biomarkers in which fluorescent in situ hybridization (FISH) techniques and also sequencing techniques will be required to determine the following genetic alterations: mutations in IDH1/2, 1p/19q losses, CDKN2A deletions, CDKN2B deletions, CDK4 amplification, CDK6 amplification, cyclin amplificationD.

For this trial, 2 informed consents have been prepared. In the first, authorization is obtained from the patient to send the tumor sample and perform the centralized histological review. The second corresponds to the clinical part of the trial and the molecular study. The informed consent for sample shipment can be signed by the patient once the researcher identifies them as a potential patient for the trial, even if they have not yet progressed to standard treatment.
No tumor sample can be mobilized from the hospital of origin until the patient has signed the first informed consent.
The approximate response time to confirm if the patient is eligible will be 10 calendar days.

To send the tumor sample:

The center must contact MFA[redacted]sending the centralized review form and sample collection form to FAX 93 253 11 68 and she wi[redacted] collect the samples. A copy of the centralized review form must be submitted with the sample.

[redacted]

Tumor samples will be prepared according to the instructions detailed by the sponsor in the specific guide and will be coded to preserve patient confidentiality. The central laboratory will send a report to each of the principal investigators to inform them of the result of the histological review and immunohistochemical analysis of RB. If there is leftover material once the initial determinations and the biomarker study have been carried out, it will be returned to the hospital of origin at the end of the trial.

5.3. Patient Screening Period

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

5.4. Screening Failures

A patient will be considered a screening failure when they sign the informed consent but abandon the trial for any reason before inclusion. All patients who are screening failures will be registered in the list of patients undergoing screening 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 on the aforementioned forms.
An additional document will be added to the Center's Researcher File with detailed information on the identification procedures for patient selection.

5.5. Patient inclusion procedure

Inclusion will be done online through the electronic CRD. The inclusion form must be completed in the CRD and, once the center confirms that the patient meets all the inclusion criteria and none of the exclusion criteria described in the protocol, the system will centrally assign a number to each patient. .
The system will send to the center, to the email registered in the eCRD, confirmation of the patient's inclusion. Treatment will only begin if the center has received the email confirming the inclusion.
The patient's study number will identify subjects throughout participation in this study.

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

5.6. Start of treatment

Treatment will only begin if the center has received confirmation of inclusion as detailed in section 5.4 of this protocol.
All patients included in the study will be treated with the experimental drug, Palbociclib, at a dose of 125 mg/day on days 1-21 in 28-day cycles. That is, administered 21 days followed by 7 days of rest. The treatment cycles will continue until there is unacceptable toxicity, tumor progression, withdrawal of consent or death of the patient. The visits and evaluations are detailed in section 8.1 of this protocol.

5.7. Associated Molecular Substudy

- The molecular studies will be carried out at the Hospital 12 de Octubre, in the Section of Neuropathology.
- Translational assessment will be carried out to evaluate the association between drug activity and different biomarkers such as p16 or CDK4/6 expression.
- Additional tissue will be obtained from previous surgeries to study the presence of alterations molecular in the tumor:
- p16 expression will be evaluated retrospectively
- The predictive role of potential biomarkers in basal samples will be explored retrospectively: for example, among others, RNA pol II levels (effector of the CDK4/cyclin complex).

6. PATIENT SELECTION CRITERIA

6.1. Inclusion criteria

1. Ability to understand and sign the informed consent document approved by the CEIC
2. Men or women aged ≥ 18 years.
3. Patients with anaplastic oligodendroglioma according to the new WHO (WHO) classification of 2016 (In Press)[23,24,25] and confirmed histologically and molecularly at a central level. According to this classification, oligodendrogliomas must present mutations in IDH1/2 as well as a co-deletion of chromosomes 1p/19q.

USE: Patients with the initial diagnosis of grade 2 oligodendroglioma may be included as long as they have suffered a recurrence in which a new resection was performed whose diagnosis was grade 3.

USE 2: Patients previously diagnosed with Oligoastrocytoma grade 3 according to the WHO 2007 classification could be included if, in the centralized review, the criteria for Anaplastic Oligodendroglioma according to the new classification are met.

4. Patients in a relapse situation after having received radiotherapy and one or two lines of chemotherapy.

USE: Both previous radiotherapy and previous chemotherapy may have been received in an adjuvant situation or in previous recurrences. It is also admitted to have received concurrent chemoradiotherapy. In anaplastic oligodendrogliomas, patients have been able to receive chemotherapy or radiotherapy when they were still grade 2 tumors.

5. All patients must present positivity in the immunohistochemical study for the Rb protein in the tumor material analyzed by the central laboratory (Neuropathology Laboratory. Hospital Universitario 12 de Octubre).
6. Cases must have a paraffin-embedded tissue block available from a previous biopsy or surgery (previously archived tumor samples) for central histological and molecular determinations.
7. All patients must show disease progression on brain MRI as defined in the RANO Criteria.
8. Interval of at least one week between previous intracranial biopsy, adequately healed, and inclusion.
9. Interval of at least 12 weeks between previous radiotherapy and inclusion, unless:

a. Histopathological confirmation of recurrent tumor, the
b. Recurrence on MRI outside the radiotherapy field.

10. Patients must have recovered from prior therapies: 28 days from completion of any investigational compound and/or from completion of any cytotoxic treatment.
11. ECOG functional status ≤ 2.
12. Stable or decreasing dose of corticosteroids during the five days prior to inclusion in the study.
13. Patients who had tumor resection performed at the last recurrence are eligible if the following are true:

a. There is adequate recovery from surgery.
b. There must be measurable or evaluable disease after surgery. For adequate radiological evaluation of residual disease, MRI must have been performed within 72 hours after surgery or 4 weeks after surgery.

14. Adequate spinal and organic function:

a. Neutrophils ≥ 1500/mm^3 (1.5 X 10^9/L)
b. Platelets ≥ 100,000/mm^3 (100 X 10^9)
c. Hemoglobin ≥ 9 g/dL

d. Serum creatinine ≤ 1.5 X center ULN or estimated clearance ≥ 60 mL/min calculated.
e. Bilirubin ≤ 1.5 times the ULN (in the case of Gilbert's Disease ≤ 3 times the ULN. AST (SGOT) and/or ALT ≤ 3 x ULN;
f. Alkaline phosphatase ≤ 2.5 X ULN.
15. Women who are not pregnant or breastfeeding. Women of childbearing age, that is, of reproductive age, between puberty and menopause, must have a negative pregnancy test (in blood or urine) before inclusion in the study, both women of childbearing age and men. They must use a medically accepted method of contraception while taking study medication and for 1 month after completion of treatment. Appropriate methods (when used continuously and according to doctor and product instructions) are as follows:
a. Complete sexual abstinence that will begin during the 14 days prior to the first exposure to the study drug, will continue throughout the treatment within the clinical trial and will be maintained until at least 21 days after the last dose of the drug.
b. Oral contraceptives, both progestins in monotherapy and in combination with other agents.
c. Injectable progesterone. Levonorgestrel implants.
d. Vaginal ring with estrogen. Percutaneous contraceptive patches. Intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year.
e. Male partner sterilized (vasectomy with documented azoospermia) prior to his partner's entry into the study (provided it is a monogamous couple).
f. Double barrier method: Male condom and diaphragm/cervical cap with vaginal spermicidal agent (foam/gel/film/cream/suppository).
g. Breastfeeding women should discontinue natural feeding of the baby from before receiving the first dose of the study drug until 14 days after the last dose of treatment.

6.2. Exclusion criteria

1. Presence of disseminated meningeal carcinomatosis.
2. Concomitant treatment with other investigational agents.
3. Prior treatment with an investigational agent known or assumed to be active by the action of any of the components against CDK4/6.
4. Surgery of any type (does not include minor diagnostic procedures such as lymph node biopsy) within 2 weeks prior to baseline disease assessments, or presence of side effects from previous procedures.
5. 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.
6. Presence of any psychiatric or cognitive disorder that limits understanding or signing of the informed consent and/or jeopardizes compliance with the requirements of this protocol.
7. Having received any of the following pharmacological treatments in the 7 days prior to the start of treatment: Strong CYP3A4 inhibitor drugs (e.g., amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole and grapefruit or grapefruit juice). CYP3A4-inducing drugs (e.g., carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, pidone, rifabutin, rifampicin, rifapentin). Drugs that increase the QT interval.

8. QTc interval >480 msec (based on the average of the value taken in three ECG recordings), family or personal history of long QT syndrome, short QT syndrome, Brugada syndrome, QTc prolongation or history of Torsade de Pointes.
9. Electrolyte disorder that may affect the QTc interval (e.g. hypocalcemia, hypokalemia and hypomagnesemia).
10. Significant or uncontrolled cardiovascular disease, including:
- Myocardial infarction in the previous 12 months
- Uncontrolled angina in the previous 6 months Congestive heart failure in the previous 6 months
- History of clinically significant ventricular arrhythmias of any type (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes)
- History of second or third degree heart block (these patients may be eligible if they currently have a pacemaker)
- Stroke in the previous 3 months
- Pulmonary thromboembolism in the previous 3 months

11. History of any cancer except for the following circumstances: Patients with a history of other malignancies are eligible if they have been disease-free for at least the last 3 years and in the investigator's opinion there is a low risk of disease recurrence. People with the following cancers are eligible even if they were diagnosed and treated within the last 3 years: cervical carcinoma in situ, cutaneous squamous cell carcinoma and basal cell or basal cell cutaneous carcinoma.
12. Human immunodeficiency virus infection.
13. Inflammatory bowel disease, chronic diarrhea, short bowel syndrome or any upper gastrointestinal surgery including gastric resection.
14. Known sensitivity to Palbociclib.
15. Other serious acute or chronic medical condition, uncontrolled intercurrent illness, or laboratory abnormality that may increase the risk associated with participation in the trial or administration of the investigational product or may interfere with the interpretation of trial results and that, Investigator's discretion, make the patient unsuitable for entry into this trial. Uncontrolled intercurrent illness includes, but is not limited to, ongoing or active infection or psychiatric illness/social situations that limit compliance with study requirements.

6.3. Criteria provided for the permanent interruption of the IMP

Patients will receive the investigational product until one of the following occurs:
- Progression according to RANO criteria.
- Unacceptable toxicity or adverse events that could make the administration of the treatment an unacceptable risk, in the opinion of the investigator.
- Non-compliance by the patient, at the discretion of the researcher or the Sponsor, with the requirements of the protocol.
- Delay in administration of treatment of more than 4 weeks.
- Premature termination of the trial.
- Investigator's Decision.
- That the patient withdraws his consent to participate in the trial.

The reason why the investigational product has been discontinued must be clearly recorded in the data collection notebook (CRD).

Note: Temporary discontinuation of study medication due to an adverse event will not be considered permanent discontinuation of the investigational product.

6.4. Criteria for withdrawal from the study

Patients will be encouraged to complete the trial, however, patients may voluntarily withdraw from the trial at any time. The investigator may also, at his or her discretion, withdraw patients from this trial, or the Sponsor may discontinue the trial.
The causes of premature abandonment of the trial must be documented in the data collection notebook (CRD) as:

- Closed/finished trial
- Adverse event
- Patient loss to follow-up
- Investigator's Decision
- Withdrawal of consent by the patient
- Major protocol violation
- Death

Both the date of withdrawal from the study and the reason for withdrawal will be recorded in the CRD. Subsequent treatment and follow-up until death will be determined, guaranteeing the patient medical assistance according to usual clinical practice. In the event of death, the autopsy certificate with the documented cause of death should be obtained, if possible.
Note: Patients who abandon the trial for any reason will not be able to be included again.

7. DESCRIPTION OF THE TREATMENT

All patients included in the study will be treated with the experimental drug, Palbociclib, at a dose of 125 mg once daily continuously for three weeks followed by 1 week of rest. The 100 mg and 75 mg presentations are planned in case of dose reductions. For the scheduling of visits and evaluations, 28-day cycles will be considered.

7.1. Preparation and dispensing

Palbociclib capsules will be dispensed for 21-day treatment periods. The formulation of palbociclib that will be administered to study patients is the free base. Palbociclib comes as yellow/caramel-colored capsules containing 75, 100, or 125 mg of study medication. The capsules can be distinguished by size and color.

The patient and protocol numbers will be noted in the spaces reserved for this purpose on the bottle label. Facility staff should ensure that patients clearly understand the instructions for self-medication, especially

the need to take the drug with food. Unused drug or empty vials must be returned to the facility at the next study visit.
Palbociclib is an agent that has to be handled and administered with care. The patient should be instructed to store the study drug out of the reach of children, at a temperature of between 15-30ºC in case the investigational product delivered to the patient corresponds to the 'investigational presentation' in the bottle/canister, while that if the re-labeled commercial presentation for testing (box of 3 blister packs) has been dispensed to the patient, no special measures will be required for its conservation. Patients should be instructed to keep the medication in the bottles provided and not transfer them to any other container. Due to potential unknown risks associated with topical and environmental exposure to experimental compounds, capsules should not be opened or emptied into any vehicle for oral intake; They should be swallowed intact.

7.2. Administration

Patients should be instructed to swallow Palbociclib capsules whole, without chewing, before swallowing. A capsule should not be swallowed if it is broken, cracked, or not intact for any other reason. Patients must take the drug**with food** and they should be encouraged to take each dose at approximately the same time each day. The treatment will be administered for 21 days followed by 7 days of rest.

7.3. Therapeutic compliance

Patients will keep diaries noting doses administered, missed, or modified, as well as significant delays in administration (i.e., > 6 hours from the planned administration time). There are no predetermined compliance criteria to be included in the study endpoint analyses.
Patients will bring unused study medication and empty containers to all study visits. Treatment compliance will be evaluated by counting the number of tablets and reflecting in the clinical history any possible discrepancies between the theoretical number of tablets left and the actual one. Study site staff will monitor potential reasons for noncompliance (e.g., adverse event, loss of medication), and take measures to improve this.

General rules:

- Patients who miss a full dose on one day should NOT “make up” on the next day.
- Patients who vomit at any time after taking the dose should NOT “make up” for it and will continue treatment the next day as prescribed.
- Patients who inadvertently take an extra dose on the same day should skip the next day's dose.

7.4. Dose modifications

Every effort should be made to administer the study treatment at the dose and schedule established in the protocol. However, in the event of significant treatment-related toxicity, an adjustment in the administration of the study medication (palbociclib) may be necessary as described in the following sections.

Depending on the nature of the toxicity observed, it may be necessary to adjust the dose of study drugs or discontinue treatment.

In the event of significant treatment-related toxicity, administration of PD-0332991 (palbociclib) may be interrupted or postponed and/or the dose may be decreased as explained below. If multiple types of toxicity occur, dose modification should be based on the worst toxicity observed. Patients will be instructed to notify

the investigator of any adverse signs or symptoms.

Dose modifications can be made in three ways:

- Within a cycle: Administration will be stopped until adequate recovery occurs and the dose will be reduced (if necessary) during a given treatment cycle.
- Between one cycle and the next: the next cycle can be postponed when persistent toxicity is observed at the time when a new cycle should be started.
- In the next cycle: it may be necessary to decrease the dose in the next cycle due to toxicity observed during the previous cycle.

7.4.1. Treatment interruptions

Treatment should be postponed/interrupted in patients who experience the following events:
- Grade 3 uncomplicated neutropenia (ANC<1,000/mm^3).
- Grade 3 Neutropenia (ANC<1,000/mm^3) associated with documented infection or fever ≥ 38.5ºC.
- Grade 4 Neutropenia (ANC<500/mm^3).
- Grade 4 thrombopenia (platelet count <25,000/mm^3).
- Non-hematological toxicity of Grade ≥3 (including nausea, vomiting, diarrhea and high blood pressure, only if they persist despite optimal medical treatment).
- Grade 3 QTc prolongation (QTc ≥501 msec) on at least two different ECGs.

Follow-up evaluations should be performed until recovery occurs according to the investigator's criteria. The requirements that must be met to restart treatment are listed in Section 7.4.2 (“Delays in administration”)

Administration may be postponed as necessary until toxicity resolves. Depending on when the adverse event resolves, discontinuation of treatment may result in the patient having to skip all subsequent planned doses within that same cycle or even having to postpone the start of the next cycle.
If recovery from the adverse event that led to discontinuation of treatment occurs within the same cycle, restarting administration of the medication is permitted in that cycle. Doses missed due to toxicity will not be replaced within the same cycle. The need to reduce the dose at the time of restarting treatment should be based on the criteria in Section 7.4.3 (Dose reductions) unless otherwise agreed after the case is discussed between the investigator and the promoter of the clinical trial. If a dose reduction is finally applied in the same cycle, the patient will have to go to the center again for a new dispensation of the medication.
In the event that the interruption of treatment is duefor reasons other than toxicity related to treatment(e.g., non-cancer surgical intervention) and the interruption lasts >2 weeks, the sponsor will be consulted before restarting treatment after interruption.

7.4.2. Administration delays

Restart of treatment after discontinuation due to the development of treatment-related toxicity or the start of a new cycle cannot be carried out until all of the following criteria are met:

- Platelet count ≥50,000/mm^3
- RAN ≥1.000/mm^3 and absence of fever.
- Recovery to Grade ≤ 1 or baseline (or, at the discretion of the investigator, to Grade ≤2 if not considered a risk to patient safety) of Grade 3 or higher non-hematologic AEs related to the treatment (including nausea, nausea, vomiting, diarrhea and high blood pressure only if they persist despite optimal

medical treatment having been instituted), with the exception of alopecia. QTc <501 msec and potentially reversible causes (eg, electrolyte imbalance, concomitant medications known to prolong QTc) have been corrected. If QTc remains above 480 msec, the ECG should be monitored more frequently, at the investigator's discretion, until QTc ≤480 msec.

If treatment is postponed due to a decrease in hematologic parameters, the frequency with which blood cell count determination is performed should be increased as clinically indicated.
If these parameters reach normal within 2 weeks of stopping treatment or delaying the start of the cycle, treatment with PD-0332991/palbociclib can be restarted. For adverse events requiring a dose reduction at the time of restarting treatment, see Section 7.4.3 Dose reductions.
If the above parameters have not returned to normal within the first 2 weeks after stopping treatment administration (including the planned 1-week treatment-free period) or within 2 weeks after delaying the start of the cycle, you should Consider the possibility of permanently discontinuing treatment with PD-0332991/palbociclib. Restarting treatment for patients who recover from treatment-related toxicity after > 2 weeks of treatment interruption or delay in cycle initiation, but for whom the investigator believes that benefit is occurring clinically obvious, it is left to the discretion of the investigator.
A new cycle will only be started when the previously indicated criteria are met and the treatment can be administered; Otherwise, the beginning of the new cycle will be postponed until said criteria are met.
In the event that the start of a new cycle is delayed due to treatment-related toxicity, the procedures required on Day 1 of that cycle will be performed when PD-0332991/palbociclib therapy is reinstated. It will not be necessary to repeat the procedures on Day 1 of the new cycle (physical examination, ECOG functional status, ECG, blood biochemistry, blood count) that had been performed before knowing the need to delay the start of the cycle (1) if they are not required. to determine if the study drug can be reintroduced and (2) whether they have been carried out within 7 days prior to the reintroduction of the study drug.

7.4.3. Dose reductions

After discontinuation of PD-0332991/palbociclib or delay in starting a new cycle, a dose reduction may be necessary when restarting treatment.
No specific dose adjustment is recommended when discontinuation of treatment or delay in starting a new cycle is due to the occurrence of treatment-related Grade 1/2 toxicity. However, the researcher must always treat patients according to his or her discretion and in accordance with the specific clinical circumstances of each case.
PD0332991/ palbociclib dose reduction is allowed by 1 and, if necessary, 2 dose levels (**Table 1**), depending on the type and intensity of the toxicity observed. Patients requiring more than 2 dose reductions will be removed from study treatment and enter the follow-up phase. All dose modifications/adjustments must be clearly documented in the patient's source documents and in the investigational product administration section of the CRD.

Once the dose has been reduced in a given patient, the new dose will be used in all subsequent cycles, unless it is necessary to reduce it again. Re-escalation of doses is not allowed.

Table 1. Available dose levels

Dose level	PD-0332991/palbociclib for 3 out of every 4 weeks (3/1 treatment regimen)

Starting dose	125 mg/day
-1	100 mg/day
-2	75 mg/day*
	Discontinue study treatment

***Dose reduction of PD-0332991/palbociclib below 75 mg/day is not permitted.**

Recommended PD-0332991/palbociclib dose modifications for treatment-related toxicity that requires treatment interruption or delay or that persists despite initiation of optimal medical therapy are described in theTable 2.

Table 2. PD-0332991/palbociclib dose modifications for treatment-related toxicity that requires treatment interruption or delay or that persists despite optimal medical treatment.

Toxicity	Restart treatment with PD-0332991/ palbociclib con:
Grade 3 uncomplicated neutropenia*(RAN<1.000/mm3)*	The same dose level
Grade 3 Neutropenia*(RAN<1.000/mm3)***associated with a documented infection or fever ≥38.5°C**	↓ 1 Dose level
Grade 4 Neutropenia*(RAN<500/mm3)*	↓ 1 Dose level
Grade 4 thrombopenia*(Platelet count <25,000/mm3)*	↓ 1 Dose level
Grade ≥3 non-hematological toxicity*(includes nausea, vomiting, diarrhea and high blood pressure, only if they persist despite optimal medical treatment)*	↓ 1 Dose level

Management of QTc prolongation

In case of QTc prolongation, possible alternative potentially reversible causes should be investigated, such as alterations in serum electrolytes or use of concomitant medication that may cause QTc prolongation.

If any reversible cause is identified, it should be corrected in a medically appropriate manner (i.e., correction of electrolyte disturbances with nutritional supplements until values are within normal limits and/or discontinuation, if possible, of concomitant medication. which is known to cause QT prolongation).

Recommendations on dose modification in case of QTc prolongation are presented in Table 3:

	Toxicity (NCI CTC Grade, Version 4.0)		
	Grade 2 QTc prolongation	**Grade 3 QTc prolongation**	**Grade 4 QTc prolongation**
Reversible cause identified	Treat the reversible cause. Initiate more frequent ECG monitoring according to investigator's clinical judgment until QTc ≤480 msec. Continue with the<u>same dose level</u>(1)	Treat the reversible cause. Discontinue study treatment until QTc < 501 msec. Restart study treatment with<u>same dose level.</u> Initiate more frequent ECG monitoring according to investigator's clinical judgment until QTc ≤ 480 msec	Permanently discontinue study treatment
Unidentified reversible cause	Initiate more frequent ECG monitoring according to investigator's clinical judgment until QTc ≤480 msec. Continue with the<u>same dose level</u>(1)	Interrupt study treatment until QTc < 501 msec. Restart treatment at the next lower dose level.(2) Initiate more frequent ECG monitoring according to investigator's clinical judgment until QTc ≤ 480 msec	Permanently discontinue study treatment

1. If the QTc interval persists above 480 msec for more than 2 cycles, or if Grade 2 QTc prolongation recurs in the absence of other alternative causes or despite correction of the alternative causes, treatment should be considered. possibility of adjusting the dose and/or definitively discontinuing study treatment after consulting with a cardiologist and the clinical trial medical monitor, taking into account the safety data that have been obtained up to that point in the clinical development program of PD-0332991 and based on the investigator's clinical judgment.
2. If Grade 3 QTc prolongation occurs again after a dose reduction, consideration should be given to further dose adjustment and/or definitive discontinuation of study treatment after consultation with a physician. cardiologist and with the medical monitor of the clinical trial, taking into account the safety data that have been obtained to that point in the clinical development program of PD-0332991 and based on the clinical judgment of the investigator.

7.5. Medication errors and overdoses

In this clinical trial, medication errors may consist of administering or taking the wrong drug, by the wrong patient, at the wrong time, or with the wrong drug dose. Any medication error must be recorded in the data collection notebook (CRD), and, when applicable, in the serious adverse events form (SAE). If an error occurs in the medication dosage, the clinical trial sponsor must be notified immediately.

Medication errors should be reported regardless of the presence or absence of an associated AE/SAE, including:

- Medication errors that affect the patient's exposure to the investigational product;
- Possible errors with medication or its use outside of what is foreseen in the protocol, regardless of whether or not they affect the patients participating in the clinical trial.

Regardless of whether the medication error is accompanied by an AE, as determined by the investigator, the error should be recorded on the adverse event (AE) page and, if applicable, the associated AE(s) will be recorded on the adverse events (AEs) section of the CRD.

7.6. Conservation and accounting of medication

The Promoter will supply the study treatment (Palbociclib). Special storage conditions (15-30ºC) are required for “presentation as an investigational drug” (cans/flasks) within its original container. For the re-labeled commercial presentation (box of 3 blister packs), no special conservation measures are required as long as it is kept in its original packaging. The pharmacy service must keep a detailed inventory of this drug in the center. Medication must be kept in a secure closed area of the study center in accordance with applicable legal requirements. Returned medication must be kept separate from medication to be dispensed. Subjects included in the trial will be provided with instructions for self-administration and a sufficient amount of drug for their treatment until the next scheduled visit.
In addition, a patient diary will also be provided to each of the study participants to record the taking of the scheduled doses. Compliance with study treatment regimens by subjects will be documented using the patient diary, dispensing log, and pharmacy service returns log. Any study treatment not used by the patient must be returned to the pharmacy service for inventory and subsequent disposal. The pharmacy service will keep the registration of the investigational product updated.

7.7. Concomitant medication

All medication, including herbal supplements and vitamins, or treatment received by the patient during the trial and the reason for its administration must be recorded in the CRD.
Because inhibition of CYP3A isoenzymes may increase exposure to PD 0332991, potentially increasing toxicity, the use of known strong CYP3A inhibitors (such as ketoconazole, miconazole, itraconazole, posaconazole, clarithromycin, erythromycin) is not permitted. , tilithromycin, nefazodone, diltiazem, verapamil, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir, delavirdine and grapefruit juice).
Additionally, drugs that are known strong CYP3A inducers (such as carbamazepine, dexamethasone, felbamate, omeprazole, Primodone, phenobarbital, rifampicin, phenytoin, rifabutin, rifapentine, and St. John's wort) are not recommended for use. While receiving study treatment, patients will not be allowed to receive other antitumor treatment. Medications intended exclusively for supportive care (e.g., corticosteroids, anticonvulsants, analgesics, antidiarrheals, antidepressants) may be used at the investigator's discretion.
Primary prophylactic use of granulocyte colony-stimulating factors is not permitted, but may be used to treat treatment-onset neutropenia in accordance with current WHO guidelines.*American Society of Clinical*

Oncology (ASCO)[22]. Colony-stimulating factors (CSFs) should not be used for prophylactic purposes in cycle 1. If neutropenic complications are observed in a cycle in which primary CSF prophylaxis has not been received, secondary prophylaxis may be administered at the discretion of the investigator, but only if dose reduction or deferral is not considered a reasonable alternative.
Erythropoietin may be used for supportive treatment of anemia at the investigator's discretion.

8. DEVELOPMENT OF THE TEST AND EVALUATION OF THE RESPONSE

8.1. Study procedures

	Selection (within 14 days prior to inclusion)	C1 D1	C1 D15	C2 D1	C2 D15	Each 4 weeks	Each 8 weeks	Each 12 weeks	End of treatment (after 4 weeks)	Follow-up if treatment ends without progression (every 6 weeks)	Follow-up after progression (every 4 weeks until death)
Informed consent	X										
Eligibility	X										
Anamnesis	X										
Demographics	X										
Physical exam[4]	X	X	X	X	X	X			X	X	
ECOG	X	X		X		X			X	X	
Barthel index		X		X		X			X	X	
Test minimental		X		X			X[5]		X	X	
Concomitant medication	X	X	X	X	X	X					
Complete hematology	X	X	X	X	X	X			X	X	
Complete biochemistry	X	X	X	X	X	X			X	X	
Urine analysis	X	X		X		X			X	X	
Coagulation tests	X			X		X					
ECG	X						X				
pregnancy test	X[1]								X		
Magnetic resonance	X[2]							X[6]		X[6]	
Sending tumor sample	X[7]										
Palbociclib Dispensing		X		X		X					
Therapeutic compliance				X		X					
Corticosteroid dosage	X[3]	X	X	X	X	X					
Toxicities registry		X	X	X	X	X			X		
Survival											X

1- The serum or urine pregnancy test for women of childbearing age must be performed ≤ 72 hours before the start of the study treatment and at the end of treatment visit.
2- Cranial Magnetic Resonance is admitted in a period of ≤ 28 days
3- Dose of corticosteroids in the 5 days prior to inclusion
4- Physical examination, measurements of pulse at rest, blood pressure, respiratory rate, temperature, weight, height and ophthalmic examination Those patients undergoing treatment who report new symptoms or worsening of visual symptoms should be immediately referred to an ophthalmology specialist for examination. complementary.
5- The Mini Mental test will be carried out on C1D1 and also on day 1 of each even cycle, that is, every 8 weeks from C2D1
6- MRI imaging tests 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.
7- The sending of the tumor sample may be carried out after obtaining the informed consent of the tumor sample from the candidate patient. The tumor tissue from the original diagnostic biopsy or a recently obtained biopsy will be sent to the Neuropathology laboratory of the 12 de Octubre [redacted]

Description of procedures:

Informed consent: For this trial, two informed consents have been prepared, one for sending the tumor sample for centralized review and confirming the diagnosis and another informed consent for the clinical part of the trial

and carrying out the molecular analysis. No sample can be mobilized from the hospital of origin until the patient has signed the informed consent for the tumor sample.

Eligibility: Verification that the patient meets all the inclusion criteria and none of the exclusion criteria.

History: During the baseline period in the 2 weeks prior to inclusion, a general anamnesis with details of coexisting diseases, oncological history (specific history of cancer, date of diagnosis, type of primary tumor with histological diagnosis, previous surgical processes with dates, and any other relevant medical history in the previous 6 months), smoking habit and history of weight loss in the last 6 months, previous systemic treatments (in the previous 4 weeks), dates of administration, as well as reason for discontinuation.

Demographics: Date of birth, race and sex.

Physical exam: Physical examination, measurements of resting pulse, blood pressure, respiratory rate, temperature, weight, height, and an ophthalmic examination**.** Those patients undergoing treatment who report new symptoms or worsening of visual symptoms should be immediately referred to an ophthalmology specialist for complementary examination.

ECOG: Functional status will be assessed using the ECOG (Eastern Cooperative Oncology Group) scale.

Barthel Index and Minimental Test: The neurological and functional examination will be assessed using the Barthel index and the Minimental Test.

Concomitant medication: All drugs taken in the last 4 weeks prior to inclusion and concomitantly during the study will be recorded in the medical record and in the data collection notebook with the indication, information on the dose and dates of administration.

Complete hematology: Complete blood count including a total white blood cell count with differential, hemoglobin, and platelet count.

Complete biochemistry: Serum chemistry including glucose, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST) or SGOT, alanine aminotransferase (ALT) or SGPT.

Urine analysis: In the baseline period, every 4 weeks during treatment, at the end of treatment visit and in follow-ups if treatment ends without progression.

Coagulation tests: Coagulation studies will include prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen.

ECG: An electrocardiogram (ECG) value must be obtained at baseline, within 28 days before inclusion, and every 8 weeks thereafter.

Pregnancy test: Serum or urine pregnancy test for women of childbearing age.

Cranial Magnetic Resonance: Cranial MRI that will be taken as a base examination in terms of response evaluation (it is allowed to be performed in a period ≤ 28 days). The response should always be assessed with the same equipment as the initial examination. If the corticosteroid dose increases after the cranial MRI and the start of treatment, a new baseline MRI should be performed. That is, at the time of starting treatment, the dose of corticosteroids must be equal to or less than the dose that the patient was taking at the time of the MRI used as baseline.

Response evaluation will follow the RANO and McDonald criteria for brain lesions visualized on MRI.

Send tumor sample: Submission of tumor for centralized review to confirm the diagnosis of Anaplastic Oligodendroglioma (OA) in a central neuropathology laboratory. It will also be determined if there is nuclear expression of the RB protein by Immunohistochemistry.

Palbociclib Dispensing: Palbociclib capsules will be dispensed for 21-day treatment periods.

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

Corticosteroid dosage: Record in the patient's medical history and in the CRD the doses of corticosteroids for the 5 days prior to inclusion. At each visit, the dose of corticosteroid received by the patient must be recorded in the clinical history and in the CRD.
Toxicities record: 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. Adverse events will be monitored at the post-treatment follow-up visit 30+/-3 days after the end of treatment or until all drug-related toxicities have resolved or are considered irreversible, whichever occurs. later. Toxicity grading will be based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v4.0).
Survival: All patients will be followed for subsequent antineoplastic treatments and survival, regardless of the reasons for withdrawal of study treatment. It is recommended to maintain telephone/face-to-face contacts every 4 weeks in order to carry out timely periodic follow-up. Information regarding subsequent treatments should include the list of post-study treatments, drugs administered, and the start and stop date of administration of each drug; All of this will be noted in the medical history and in the CRD.
Follow-up for overall survival will be carried out until death. The date of death will be verified to determine survival.

8.2. Determinations in the selection phase (baseline determinations)

Before carrying out any study-specific procedure, dated and signed CEIC-approved informed consent must be obtained. All urine, hematological and biochemical tests, pregnancy tests will be analyzed at a local laboratory. Procedures that are part of usual treatment are not considered study-specific procedures. Procedures that are part of regular care may be used as screening procedures to determine eligibility. Before starting study treatment, all subjects will be assessed for eligibility. The selection process begins on the day the subject signs the informed consent approved by the CEIC and continues until the patient's inclusion in the trial and subsequent initiation of the study treatment. In this study, only eligible subjects will receive the study treatment.

All subjects must have completed the following procedures ≤ 14 days (unless otherwise specified) prior to the start of study treatment:

- Review of the inclusion and exclusion criteria.
- Clinical and medication history.
- Physical examination, measurements of resting pulse, blood pressure, respiratory rate, temperature, weight and height.
- ECOG (Eastern Cooperative Oncology Group) performance status (≤ 14 days before study inclusion).
- Analytical tests (≤ 14 days before inclusion in the study):

- Complete blood count including a total white blood cell count with differential, hemoglobin, and platelet count.
- Serum biochemistry including creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST) or SGOT, alanine aminotransferase (ALT) or SGPT.

- Coagulation studies will include prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen.
- Systematic urine analysis.
- Serum or urine pregnancy test for women of childbearing potential (≤72 hours before onset of the treatment under study).
- ECG (investigator will clinically evaluate all reports)
- Cranial MRI that will be taken as a base examination in terms of response evaluation (it is allowed to be performed in a period ≤ 28 days). The response should always be assessed with the same equipment as the

initial examination. If the corticosteroid dose increases after the cranial MRI and the start of treatment, a new baseline MRI should be performed. That is, at the time of starting treatment, the dose of corticosteroids must be equal to or less than the dose that the patient was taking at the time of the MRI used as baseline.

- Dose of corticosteroids in the 5 days prior to inclusion.
- The paraffin-embedded tumor block must be identified, prepared and sent to the central laboratory [redacted] and have received confirmation of diagnosis and molecular analysis. FISH will be performed to study the deletions in chromosomes 1p and 19q in addition to DNA extraction and High Resolution Melting (HRM) to determine mutations in the IDH1 and IDH2 genes. The sample may be submitted at any time prior to inclusion, even if the patient is still receiving active treatment for the oligodendroglial tumor.

Treatment should begin as soon as possible and no later than 4 weeks after the baseline radiological examination.

8.3. Tests during treatment

Patients will be visited on days 1 and 14 of the first 2 cycles and on days 1 of the subsequent cycles, during which time the following will be performed:

- Physical examination, resting pulse measurements, blood pressure, respiratory rate, temperature, weight
- Concomitant medication
- Analytical tests:

- Complete blood count including a total white blood cell count with differential, hemoglobin, and platelet count.

- Serum chemistry including creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST) or SGOT, alanine aminotransferase (ALT) or SGPT.

- Therapeutic compliance.
- Coagulation tests (only in C2D1 and every 4 weeks thereafter).
- Corticosteroid dosage.
- Registry of adverse events.

If the patient needs to increase the doses of dexamethasone or worsens neurologically, it is advisable to repeat the initial radiology to rule out progression.
Response evaluation will follow the RANO and McDonald criteria for brain lesions visualized on MRI.
On day 1 of each cycle, the patient will be given the trial medication, in addition, systematic urine analysis, Barthel Index and ECOG performance status will be performed. The Minimental Test will be carried out on C1D1 and also on day 1 of each even cycle, that is, every 8 weeks from C2D1.
MRI imaging tests 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.
Heart function will be monitored with an ECG every 8 weeks.

8.4. Security Visit

4 weeks after the end of treatment for any reason, the safety visit will be carried out, during which the following will be carried out:

- Physical examination, and vital signs (resting pulse measurements, blood pressure, respiratory rate, temperature, weight, and height).
- ECOG (Eastern Cooperative Oncology Group) functional status
- Barthel index
- Minimental Test
- Analytical tests:

- Complete blood count including a total white blood cell count with differential, hemoglobin, and platelet count.
- Serum biochemistry including creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST) or SGOT, alanine aminotransferase (ALT) or SGPT.

- Systematic urine analysis
- Registry of adverse events

MRI imaging tests 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.

8.5. Follow-up visits from the end of treatment without progression to PE

Once treatment is completed for any cause other than disease progression, the following procedures will be performed every 6 weeks until disease progression:

- Physical examination, and vital signs (resting pulse measurements, blood pressure, respiratory rate, temperature).
- ECOG (Eastern Cooperative Oncology Group) functional status
- Barthel index
- Minimental Test
- Analytical tests:

- Complete blood count including a total white blood cell count with differential, hemoglobin, and platelet count.
- Serum biochemistry including creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST) or SGOT, alanine aminotransferase (ALT) or SGPT

- Systematic urine analysis
- Radiological images in localization of the disease using MRI. Cranial MRI that will be taken as a base scan in terms of response scan. The response should always be assessed with the same equipment as the baseline MRI.

8.6. Post-progression follow-up

Once the patient progresses, follow-up for overall survival until death every 4 weeks, which can be either visits to the oncology service or telephone calls. The patient's current status and registration of new cancer treatments will be determined.
The date of death will be verified to determine survival.

8.7. Response evaluation

The evaluation of the response will be carried out in each center using the radiological results, the patient's symptoms and the doses of dexamethasone required. It will be based on the recently modified RANO response criteria. The RANO criteria will be followed for the global assessment of response. In the progression due to sudden neurological deterioration, it is advisable to perform a radiological examination. If the radiological examination cannot be performed, progression of brain disease will be considered.
Imaging tests (MRIs) will be performed every 12 weeks until disease progression. Responses to treatment (PR, CR) must be confirmed at 4 weeks using the same method, as required by the RANO criteria. If the patient discontinues treatment for any reason before progression, MRIs should continue to be performed every 12 weeks as part of the follow-up until progression.
Once the patient progresses, follow-up for overall survival will be done until death, every 4 weeks. It 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.

8.8. Centralized image review

A centralized review of the MRIs performed on all patients will be carried out on Octobe[redacted]ble radiologist will be Dr. Ana Ran[redacted]

[redacted]

The MRIs will be sent to the external reviewer in electronic format, conveniently anonymized, indicating the inclusion number assigned to the patient and the date of the determination.
An additional document will be added to the Center's Investigator File with detailed information on the centralized image review procedures.

9. ADVERSE EVENTS

Timely, accurate and complete communication and analysis of safety information from clinical studies is crucial for the protection of patients, investigators and the sponsor, and is a requirement enforced by regulatory agencies around the world. The sponsor has established standard operating procedures (SOPs) in accordance with international regulatory provisions to ensure proper communication of safety information; All clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with these procedures.

9.1. Definition

Adverse event (AA):
An AE is any unfavorable medical incident in a patient or subject of a clinical investigation, even if it does not necessarily have a causal relationship with the study treatment. Any event involving adverse reactions to the drug, illnesses that begin during the study, or exacerbations of preexisting illnesses should be recorded.

In addition, clinically important abnormalities found on physical examination and abnormal findings on objective tests (e.g., x-rays or ECG) should also be recorded as AEs. The
Criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:
• the test result is associated with clinically important symptoms, and/or
• the test result leads to a change in study treatment or withdrawal of the patient from the study, significant additional concomitant drug or other treatment, and/or
• the test result leads to one of the outcomes indicated in the definition of AAG, and/or
• the investigator considers the test result to be an AA.

Serious adverse event (SAE):
An SAE is any adverse event occurring with any dose that:

• produces death (is fatal),
• threatens the patient's life,
• makes hospitalization or prolonged hospitalization necessary,
• produces persistent or significant disability or disability,
• is a congenital anomaly or birth defect, or
• is medically important.

Medical and scientific judgment should be exercised to decide whether urgent communication is appropriate in other situations, such as important medical events that do not immediately threaten the patient's life or lead to hospitalization but may endanger the patient or may require intervention to prevent one of the outcomes listed in the definition above.

Any suspected transmission of an infectious agent through a medication is also considered a serious adverse reaction.

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 requiring hospitalization (or prolonged hospitalization) that occurs or worsens during a patient's participation in a clinical study should be reported as an SAE. Prolongation of hospitalization is defined as any extension of a patient's hospitalization beyond the planned/required stay at initial admission, in the judgment of the investigator or the doctor responsible for the patient.

The following hospitalization cases do not meet the SAE reporting criteria:

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

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

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

Unexpected adverse event (not listed):
An unexpected AE, the nature or severity of which does not correspond to the information regarding the product.

The reference document to establish expectability will be the current version of the palbociclib investigator's manual.

Associated with drug use
An AE is considered associated with the use of the investigational medicinal product if the causality assessment is related to one of the investigational medicinal products or is unknown according to the definitions below.

Causality assessment
The investigator must provide a causality assessment for each investigational medicinal product (including combination products and comparators) according to the following criteria:

AND There is a reasonable possibility that the study medication(s) will cause the serious adverse event.
N There is no reasonable possibility that the study medication(s) will cause the serious adverse event and other causes are more likely.
UK Unknown. It should only be used in special situations where the researcher has insufficient information (for example, the patient has not been treated at your center), and if none of the previous options can be used.

Urgent communication
The promoter will assume responsibility for the proper communication of AAs to the regulatory authorities. The sponsor will also report all unexpected SAEs associated with the use of the study treatment to the investigators

and clinical research ethics committees (CEIC) in accordance with current regulations, unless other measures are required and documented by the CEIC. .

9.2. Notification and Documentation of Adverse Events

AEs will be collected by the sponsor up to 30 days after administration of the last dose of study treatment.

All AEs must be recorded in the source document and in the CRD using medical terminology. Investigators should assess the severity (grade) of the event according to NCI-CTC AE V 4.0, assign a relationship to the trial drug, and seek and obtain appropriate information to determine the outcome and to evaluate whether it meets the criteria for classification as AAG that requires immediate communication. The researcher must provide any information requested by the promoter, in addition to that collected in the CRD.

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

Todos los Acontecimientos adversos graves deben ser reportados por FAX en las 24 h. posteriores de haber sido detectados a [redacted]

The AAG report must contain a complete written summary detailing the important aspects of the applicable adverse events. Where applicable, information about relevant medical records and autopsy reports should be included. Tracking information must be sent to MFAR, S.L. in the next 24 hours.

All SAEs suspected to be related to study treatment should be followed after withdrawal until the event or its sequelae have resolved or stabilized at a level acceptable to the investigator or designee.

9.3. Pregnancy notification

The pregnancy of a female patient or the partner of a male patient, not being a serious adverse event in itself, should also be managed expeditiously just like an SAE.

It must be registered on a specific pregnancy notification form, notified expeditiously (within 24 hours) from when it is known and followed until the end, even if a voluntary or spontaneous interruption occurs, describing the details of the birth and the presence or absence of any defect in the fetus or any congenital anomaly.

Potential effects of spermatogenesis: pregnancies that occur in the partner of a male patient must also be notified within 24 hours using the specific pregnancy form and followed until the end, even if a voluntary or spontaneous interruption occurs, describing the details of the pregnancy. birth and the presence or absence of any defect in the fetus or any congenital anomaly. Likewise, your pregnant partner would be instructed to contact his or her doctor immediately.

10. STATISTICAL CONSIDERATIONS

10.1. Study variables

Percentage of patients who have relapsed/not relapsed to the study treatment 6 months after starting it.

10.2. Primary objective

To determine whether palbociclib could delay disease progression in patients with anaplastic oligodendroglioma.

10.3. Hypothesis

Clinical basis: historical data for the elaboration of the study hypothesis have been obtained from the analysis of a database containing 350 patients with recurrent high-grade gliomas (125 anaplastic gliomas) who were prospectively treated in phase II studies. The 6-month progression-free survival (PFS-6m) was 31% for anaplastic gliomas (Wong et al. J Clin Oncol 17:2572-2578). The authors acknowledge the limitation because in this study the results were analyzed for all anaplastic gliomas and not only anaplastic oligodendrogliomas. However, no further published data are available regarding the results in recurrent anaplastic oligodendrogliomas.
Null hypothesis (H0): $P \leq P0$
Alternative hypothesis to test (H1): $P \geq P1$
Assumptions:
P: probability of remaining alive and progression-free at 6 months

- P0: 25%
- P1: 45%
- Expected profit: 20% (25% vs. 45%)
- Type I error, $\alpha \leq 0.05$
- Type II error, $\beta \geq 0.20$

Sample size: 40 patients
A benefit will be considered if 18/40 patients are alive and progression-free at 6 months.

10.4. Statistic analysis

Associations between overall survival and progression-free survival with patients' baseline characteristics will be evaluated using the log-rank test.
The maximum relative risk value based on the log-rank test will be used to provide a quantitative summary of the data, with 95% confidence intervals. Median survival, time to progression, and associated 95% confidence intervals will be calculated. Kaplan-Meier curves will be constructed to show the estimated probabilities of overall survival and time to progression.

11. ETHICAL AND LEGAL CONSIDERATIONS

11.1. Ethics Committee

The study will be carried out in accordance with the principles of the Declaration of Helsinki Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964 updated to its latest version Fortaleza, Brazil, October 2013.

With the standards of Good Clinical Practice (GCP) issued by the working group on the Efficacy of Medicinal Substances of the European Economic Community (1990) (CPMP/ICH/135/95).

And the Laws and Regulations in force in Spain:

- Royal Decree 1090/2015, of December 4, which regulates clinical trials with medicines, the Ethics Committees for Research with medicines and the Spanish Registry of Clinical Studies.
- 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, as provided in Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016 regarding the protection of natural persons with regard to processing of personal data and the free circulation of these data and repealing the European Parliament Directive 95/46/EC of October 24, 1995 on the protection of individuals with respect to the processing of personal data and Organic Law 3 /2018 on Protection of Personal Data and guarantee of digital rights. The rights and obligations regarding clinical information and documentation, as provided in Law 41/2002, of November 14, the basic regulator of patient autonomy.
- 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 them before starting the trial, as established by national authorities.

11.3. Informed consent

The patient must sign two separate informed consents: one for the clinical trial, another for biological samples.
The doctor will have to explain the nature, purposes and possible consequences of the clinical trial, in a way that is understandable to the patient.
The subject of the study will give his or her consent by signing the corresponding model in duplicate. For this purpose, each model must bear the signature of the researcher and the patient.
The investigator will not initiate any determination corresponding to the trial until the patient's consent has been obtained.
The informed consent used in the trial and any changes made during the study must be approved by the Ethics Committee.

11.4. Confidentiality

In order to guarantee the confidentiality of the trial data in accordance with the provisions of Organic Law 3/2018 on the Protection of Personal Data and guarantee of digital rights and Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 of April 2016 relating to the protection of natural persons with

regard to the processing of personal data and the free circulation of these data and repealing the European Parliament Directive 95/46/EC of October 24, 1995 on the protection of people with respect to the processing of personal data, only the personnel designated by the Promoter, for monitoring/auditing tasks, the researcher and his team of collaborators, the Clinical Research Ethics Committee of the corresponding center will have access to them. or the one who oversees 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 revealed to third parties except those specified in the previous section.

11.5. Safe

All patients in this clinical study will be insured through an insurance policy, in compliance with the conditions stipulated by the R.D. 1090/2015 of December 4 and European Regulation 536/2014 of April 16, which regulate clinical trials with medicines.

11.6. End of study

The trial will be considered regulatory closed after the primary and secondary endpoints are sufficiently prepared for initial publication. Follow-up observations of patients included in the trial can be maintained indefinitely.

11.7. Premature end of study

This study may be stopped prematurely if, in the opinion of the sponsor, there is sufficient reasonable cause. The investigator will receive written notification in which the terminated party documents the reason for discontinuing the study.
Circumstances justifying study discontinuation include, but are not limited to:
• Determination of unforeseen, considerable or unacceptable risks to patients
• Impossibility of including an acceptable number of patients
• Insufficient compliance with protocol requirements
• Plans to modify, suspend or discontinue the development of the study drug.

In the event of premature termination of the study, all materials (fully or partially completed and blank CRDs, study drug, etc.) must be returned to the Sponsor.

12. PRACTICAL CONSIDERATIONS

12.1. Diagnostic Criteria for the Pathology Under Study

Patients with confirmation of the diagnosis of Anaplastic Oligodendroglioma (OA) in the Pathological Anatomy Service of the 12 de Octubre University Hospita[redacted] that will also determine if there is nuclear expression of the RB protein through immunohistochemistry, and who comply with the criteria, may be included in this study. the eligibility criteria detailed in point 6 of this protocol.

12.2. Researcher Responsibilities According to Good Clinical Practices

The responsibilities of the principal investigator in each participating Center will be:
1. Sign the essay project.
2. Know in depth the properties of medications.
3. Obtain informed consent from subjects prior to inclusion in the trial.
4. Ensure that patients will receive appropriate medical care in case of adverse events, including significant laboratory values related to the assay.
5. Collect, record and report data correctly.
6. Immediately report serious or unexpected adverse events to the sponsor.
7. Guarantee that all people involved will respect the confidentiality of any information about the test subjects.
8. Regularly inform the Clinical Research Ethics Committee of the progress of the trial.
9. Be responsible for preparing the final report of the test, giving your agreement to it with your signature.

12.3. Instructions for completing the CRD

The CRD completion guide is located in the center's researcher file.

12.4. Supply of study medication

Palbociclib will be supplied by the Promoter through the Pfizer SLU laboratory.

12.5. Conditioning and Labeling

Labels of study drugs will contain information that complies with applicable regulatory requirements.

12.6. Articles and Publications

As indicated in Royal Decree 1090/2015 of December 4 and European Regulation 536/2014 of April 16, which regulate clinical trials with medicines, the promoter is obliged to publish both positive and negative results. negative results, from clinical trials authorized in scientific journals and with mention of the Clinical Research Ethics Committee that approved the study.
The Responsible Investigators of the study and the researchers who contribute at least 3% of the patients will appear as authors.
The order of authors will be strictly based on the number of patients included by the different researchers.
The clinical publication will be carried out by those responsible for the clinical study and the 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 subjects who are the source of the study samples will be maintained at all times. The results or conclusions of the study will be communicated primarily in scientific publications before being disclosed to the non-health public. Procedures of as yet undetermined effectiveness will not be made known in a premature or sensational manner.
Participating investigators should not publish any data about patients that are 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 and, according to the provisions of Royal Decree 1090/2015 of December 4 and European Regulation 536/2014 of April 16, which regulate clinical trials with medicines, in the Spanish Registry of Clinical Studies (REec).

12.7. Monitoring

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

- Study Medication: storage conditions, that supplies are adequate throughout the clinical trial, that the Principal Investigators only administer the trial medication to patients included in the clinical trial, that the receipt, use and return of the study medication trial is adequately controlled and documented and that the disposal of unused medication complies with applicable regulatory requirements.
- Patient recruitment rate
- That written informed consent has been obtained prior to inclusion in the trial
- Compliance with approved protocol and amendments, if applicable
- That the researcher has the latest version of the Investigator's manual or the summary of product characteristics, all the supplies necessary for the correct development of the trial to comply with the applicable regulatory requirements.
- That the Investigator and his team are adequately informed about the trial
- Integrity and correctness of the data entered in the CRD, 100% SDV of the monitored patients
- CI/HIP: Signature/date and name of patient/investigator
- Eligibility criteria and selection tests
- Recording of adverse events, SAEs and SAE reports
- Main variable of the trial
- Dispensing/stock of IMP in the pharmacy service, traceability (brand, units, lot, etc.)
- Protocol deviations
- Collection, storage and shipping of biological samples/images
- Communicate deviations from the protocol, standard work procedures, good clinical practices and regulatory requirements applicable to the researcher and taking necessary actions to prevent the recurrence of detected deviations.

Monitoring visits will be carried out by the study monitors. It is understood that these monitors will be able to access the patients' medical records after requesting it from the researcher. The researcher will dedicate sufficient time to these visits and will facilitate access to all documentation to authorized persons.
The study may be audited by an independent body. Likewise, members of the CEIC of the Hospital where the trial is being carried out may make “follow-up visits” to it.

12.8. 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.

12.9. Data processing

All data (personal, clinical, economic and from studies of biological material) obtained about patients will be processed in accordance with Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016 regarding the protection of natural persons with regard to the processing of personal data and the free circulation of these data and repealing the European Parliament Directive 95/46/EC of October 24, 1995 on the protection of individuals with respect to processing of personal data.

This study will also be carried out in accordance with Organic Law 15/1999, of December 13, on the protection of personal data.
In accordance with the provisions of the aforementioned legislation, patients may exercise the rights of access, modification, opposition and cancellation of data, for which they must contact the clinical trial doctor.
The content of the CRD as well as the documents generated during the study will be considered strictly confidential and will not be revealed to third parties.

12.10. Documentation

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

Essential documents should be archived in accordance with BPC guidelines or for a longer period of time, if required by relevant regulations.
The original data of study patients (medical records) should be stored according to the archival period applicable at the study centers, but not for a period shorter than 25 years.

13. BIBLIOGRAPHY

1. Finn R. Results of a randomized phase 2 study of PD 0332991, a cyclin-dependent kinase (CDK) 4/6 inhibitor, in combination with letrozole vs letrozole alone for first-line treatment of ER+/HER2- advanced breast cancer (BC). Abstract. Publication Number CT-101. Presented at AACR 2014; April 6, 2014; San Diego, CA USA.
2. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (eds) (2007). *World Health Organization Classification of Tumours of the Central Nervous System*. IARC, *Lyon ISBN 92-832-2430-2*.
3. Central Brain Tumor Registry of the United States. First Annual Report (1995).
4. Mork SJ, Lindegaard KF, Halvorsen TB, Lehmann EH, Solgaard T, Hatlevoll R, et al. Oligodendroglioma: incidence and biological behavior in a defined population. J Neurosurg 1985;63:881-9.
5. Reifenberger G. Kros JM, Burger PC, Louis DN, Collins VP. Chapter 2: Oligodendroglial tumours and mixed gliomas. En Kleihues P, Cavenne WK eds. Pathology and genetics of tumours of the nervous system. WHO Classification of tumours. Lyon: IARC Press, 2000:55-70.
6. Celli P, Nofrone I, Palma L, Cantore G, Fortuna A. Cerebral oligodendroglioma: prognostic factors and life history. Neurosurgery 1994;35:1018-34.
7. Nijjar TS, Simpson WJ, Gadalla T, McCartney M. Oligodendroglioma. The princess Margaret Hospital experience (1958-1984). Cancer 1993;71:4002-6.
8. Shaw EG, Scheithauer BW, O'Fallon JR, Tazelaar HD, Davis DH. Oligodendrogliomas: The Mayo Clinic experience. J Neurosurg 1992;76:428–34.
9. Bigner SH, Matthews MR, Rasheed BK, et al. Molecular genetic aspects of oligodendrogliomas including analysis by comparative genomic hybridization. Am J Pathol 1999;155:375-86.
10. Bortolotto S, Chiado-Piat L, Cavalla P, Bosone I,Chio A, Mauro A, et al. CDKN2A/p16 inactivation in the prognosis of oligodendrogliomas. Int J Cancer 2000;88:554–88.
11. Watanabe T, Yokoo LL, Yokoo M, Yonekawa Y, Kleihues P, Ogaki H.Concurrent inactivation of RB1 and TP53 pathways in anaplastic oligodendrogliomas. J Neuropathol Exp Neurol 2001;60:1181-9.
12. Cairncross JG, Ueki K, Zlatescu MC et al. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. J Natl Cancer Inst 1998; 90:1473-1479.
13. Cairncross G, Berckey B, shaw E et al. Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. JCO 2006; 24:2707.
14. Van den Bent , Carpentier A, Brandes A et al. Adjuvant procarbazine, Lomustine and Vincristine improves progresión-free survival but nor overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: A randomized European Organisation for Research and Treatment of cancer phase II trial. JCO 2006; 24:2715.
15. Van den Bent M, Brandes A, Taphroorn M, et al. Adjuvant procarbazine, lomustine and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-wp of EORTC Brain Tumor Study 26951. J Clin Oncol. 2013: 344-350.
16. Cairncross G, wang M, shaw E et al. Phase III of chemoradiotherapy for anaplastic oligodendroglioma: long term results of RTOG 9402. J Clin Oncol. 2013 Jan 20;31(3):337-43.
17. Wiedemeyer R, Brennan C, Heffernan TP, et al. Feedback circuit among INK4 tumor suppressors constrains human glioblastoma development. *Cancer Cell 2008;13:355–64*.
18. The Cancer Genome Atlas (TCGA) Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature 2008;455:1061–8.

19. Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. Science 2008;321:1807–12.
20. Michaud K, Solomon DA, Oermann E, et al. Pharmacologic inhibition of cyclin-dependent kinases 4 and 6 arrests the growth of glioblastoma multiforme intracranial xenografts. Cancer Res. 2010; 70: 3228-38.
21. Keith T. Flaherty, Patricia M. LoRusso, Angela DeMichele, et al. Phase I, Dose-Escalation Trial of the Oral Cyclin-Dependent Kinase 4/6 Inhibitor PD 0332991, Administered Using a 21-Day Schedule in Patients with Advanced Cancer. Clin Cancer Res 2012;18:568-576.
22. Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, Benner CL, Cantor SB, Crawford J, Cross SJ, Demetri G, Desch CE, Pizzo PA, Schiffer CA, Schwartzberg L, Somerfield MR, Somlo G, Wade JC, Wade JL, Winn RJ, Wozniak AJ, Wolff AC. 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. Journal of Clinical Oncology 2006; 24, 19: 3187-3205.
23. Rushing Elisabeth J. and Wesseling Pieter. Towards an integrated morphological and molecular WHO diagnosis of central nervous system tumors: a paradigm shift. Current opinion in neurology. 2015 Sep 19; 28:000–000.
24. Louis David N., von Deimling Andreas, Aldape Kenneth, Figarella-Branger Dominique, et al. International Society of Neuropathology-Haarlem Consensus Guidelines for Nervous System Tumor Classification and Grading. Brain Pathology 24 (2014) 429–435.
25. D. Capper, G. Reifenberger. Classification of gliomas. Neurologist. 2015; 86:672–683

ANNEX I - PATIENT INFORMATION SHEET AND INFORMED CONSENT

Separate document

ANNEX II - BARTHEL INDEX

Item	Patient Situation	Points
Eat	Totally independent	10
	Need help cutting meat, bread, etc.	5
	Dependent	0
wash up	Independent: enters and leaves the bathroom alone	5
	Dependent	0
Get dressed	Independent: Able to put on and take off clothes, button, tie shoes	10
	Need help	5
	Dependent	0
To get ready	Independent for washing your face, hands, combing your hair, shaving, putting on makeup, etc.	5
	Dependent	0
Depositions (assess the previous week)	Normal continence	10
	Occasionally an episode of incontinence, or need help administering suppositories or lavatinas	5
	Incontinence	0
Urination (assess the previous week)	Normal continence, or able to care for the catheter if it is inserted	10
	At most one episode of incontinence per day, or needs help caring for the catheter	5
	Incontinence	0
Use the toilet	Independent to go to the toilet room, take off and put on clothes	10
	He needs help to go to the toilet but he cleans himself	5
	Dependent	0
Move	Independent to go from the chair to the bed	15
	Minimal physical help or supervision to do it	10
	Needs a lot of help, but is able to sit alone	5
	Dependent	0
Wander	Independent, walks only a distance of 50 meters	15
	Needs physical assistance or supervision to walk a distance of 50 meters	10
	Independent in a wheelchair without assistance	5
	Dependent	0
Steps	Independent for going down and up stairs	10
	Need physical help or supervision to do it	5
	Dependent	0

Total:

Maximum score: 100 points (90 if you are in a wheelchair)

Result and degree of dependency

<20	Total
20-35	Grave
40-55	Moderate
>= 60	Light
100	Independent

ANNEX III - MINI MENTAL STATE EXAMINATION (MMSE) - Adapted ESPAÑA

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	PROGRESIÓN
T1-GD	0	≥50% ↓	>50% ↓ <25 %↑	≥ 25 % ↑*
T2/FLAIR	=, ↓	=, ↓	=, ↓	=, ↑*
NUEVAS LESIONES	0	0	0	0. +*
CORTICOESTERIOIDES	0	=, ↓	=, ↓	=, ↑*
CLÍNICA	=, ↑	=, ↑	=, ↑	=, ↓*
	todas	todas	todas	Cualquiera *

COMPLETE ANSWER:
Disappearance of signal in T1Gd MRI
Stability or reduction in Flair/T2 images
No new radiological lesions
Stability or clinical improvement
Absence of corticosteroids or minimum stable dose

PARTIAL ANSWER:
MRI image reduction 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% growth of the tumor in T1Gd MRI
Significant increase in Flair/T2 images*
Appearance of new lesions
Irreversible clinical neurological worsening, even in the absence of radiological worsening.
Need to increase dexamethasone (>2 weeks) to prevent progressive neurological deterioration.
USE: Only progression criteria 1,2 and 3 are applicable for the purposes of patient inclusion in the clinical trial.

STABLE DISEASE:
T1Gd image 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 (which should not be increased to maintain neurological deterioration)

*not attributable to radiotherapy, demyelination, ischemia, infection, seizures, postoperative changes or other treatment effects.