EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

Avenue E. Mounier 83/11
1200 Brussels
Belgium
Tel: +32 2 774 1611
Email: eortc@eortc.org
www.eortc.org

Short Study Report for Regulatory Bodies

Name of Sponsor/Company: EORTC	Individual study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of the finished product:Temodal	Volume:	
Name of Active Ingredient: Temozolomide	Page	
Title of the Study	IDH mutated 1p/19q intact lower grade glioma following resection: Wait Or Treat? IWOT - A phase III study	
Investigators & Study Centres	Here is the list of sites which enrolled patients: Dr.Meijnders Paul,GasthuisZusters Antwerpen - Sint-Augustinus,Oosterveldlaan 24,2610,Wilrijk,Belgium Dr.Ducray Francois,CHU Lyon - Hopital neurologique Pierre Wertheimer,59 Boulevard Pinel,69677,BRON CEDEX,France Dr.Touat Medhi,Assistance Publique - Hopitaux de Paris - La Pitie Salpetriere,47-83, boulevard de l'Hopital,75651,PARIS CEDEX 13,France Dr.Livi Lorenzo,Azienda Ospedaliero-Universitaria Careggi,Largo Brambilla, 3 ,50134,Firenze,Italy Dr.Lombardi Giuseppe,IRCCS - Istituto Oncologico Veneto,Via Gattamelata, 64,35128,Padova,Italy Dr.Silvani Antonio,IRCCS - Istituto Neurologico Carlo Besta,Via Celoria 11,20133,Milano,Italy Dr.Simonelli Matteo,Istituto Clinico Humanitas,Via Manzoni 56,20089,Rozzano, Milano,Italy Dr.Koekkoek Johan,Leiden University Medical Centre,Albinusdreef 2 - Postbus 9600,2300 RC,Leiden,Netherlands Dr.Sepulveda Juan Manuel,Hospital Universitario 12 De Octubre,Avda.de Cordoba, s/n,28041,Madrid,Spain Dr.Bruna Jordi,ICO L'Hospitalet - Hospital Duran i Reynals (Institut Catala D'Oncologia),Avda. Gran Via de L'Hospitalet,08908,L' Hospitalet De Llobregat,Spain	

Dr.Comas Anton Silvia,ICO Badalona - Hospital Germans Trias i Pujol (Institut Catala D'Oncologia),Carretera Del Canyet, s/n (Can Ruti),08916,Badalona - (Barcelona),Spain
Dr.Erridge Sara C.,NHS Lothian - Western General Hospital,Crewe Road South,EH4 2XU,Edinburgh,United Kingdom

Site Name	Total enrolled subjects	Active surveillance arm	Early treatment arm
Assistance Publique - Hopitaux de Paris - La Pitie Salpetriere	2	0	2
Azienda Ospedaliero-Universitaria Careggi	2	1	1
CHU Lyon - Hopital neurologique Pierre Wertheimer	1	1	0
Fondazione IRCCS Istituto Neurologico Carlo Besta	1	1	0
GasthuisZusters Antwerpen - Sint-Augustinus	1	0	1
Hospital Universitario 12 De Octubre	1	1	0
ICO Badalona - Hospital Germans Trias i Pujol (Institut Catala D'Oncologia)	2	0	2
ICO L'Hospitalet - Hospital Duran i Reynals (Institut Catala D'Oncologia)	1	1	0
Istituto Clinico Humanitas	1	1	0
Istituto Oncologico Veneto IRCCS	4	1	3
Leiden University Medical Centre	1	1	0
Western General Hospital	1	1	0
Total	18	9	9

Publication (reference)	There was no publication for this study which was closed for poor accrual with small number of patients registered.
Phase of development	Phase 3
Studied period	Date of first enrolment: 02/07/2021 Date of last enrolment: 14/10/2021 Clinical cut-off and database lock date: 25/01/2022 Date of early termination: 29/12/2021
Substantial changes to the protocol	**Protocol v1.0 to v2.0:** • Clarification on frequency of follow up as well as tests and procedures during temozolomide administration • Criteria for early study termination

	• Primary endpoint was updated to include surgery as possible treatment • Clarifications on usage of growth factors were added • Section on safety reporting was updated **Protocol v2.0 to v3.0:** • Exclusion criteria were updated (hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucosegalactose malabsorption). • Background rationale for 12 cycles TMZ post RT was added. • The acceptable birth control methods were clarified. • Pregnancy was added as withdrawal criterion. **Protocol v3.0 to v4.0:** • Exclusion criteria were updated (MRI contraindications). • Several items regarding radiotherapy were clarified. • Two appendices were added: Appendix H with specific guidelines for sites during the COVID-19 pandemic and Appendix I on Mini Mental State Examination (MMSE).
Objective(s)	Main objective: To determine whether in patients with oligosymptomatic isocitrate dehydrogenase mutated (IDHmt) diffuse and anaplastic astrocytoma immediate post-surgery radiotherapy (RT) followed by 12 cycles temozolomide (TMZ) improves the next intervention free survival (NIFS) compared to a postoperative active surveillance period followed by a first treatment, (preferably radio and/or chemotherapy). Secondary objectives: • To assess progression free survival in each arm separately (no comparison between arms) • To assess if RT followed by 12 cycles TMZ improves overall survival, neurological deterioration free survival, time to deterioration of QOL or cognition function, seizure activity, Patient Reported Outcome compared to active surveillance • To assess the occurrence of adverse events in both arms • To collect tumor samples obtained at first surgery for identification of molecular profiles including methylation profiles associated with outcome • To collect magnetic resonance (MR) images for analysis of radiological patterns associated with early progression, both at baseline and at follow-up In the active surveillance arm only: • To assess first intervention free survival (FIFS)
Methodology	This is a phase III study that will include a clinically favorable group of patients with IDHmt astrocytoma (oligo-symptomatic), without a need for immediate post-operative treatment. Patients will be centrally randomized. A minimization technique will be used for random treatment allocation stratifying by: • Institution • Residual disease (< 2 vs ≥ 2cm) • Age (≤ 40 vs > 40y) • Tumor grade (II vs III)

Number of patients Number planed (Statistical design)	From EORTC trial 22845 data and more recent data from study coordinator's institution the median time to first intervention after active surveillance was estimated to be about 3 years. In the 22033 trial, median PFS after RT or TMZ was 48 months in the study cohort (IDHmt and 1p/19q intact). In 22033 trial, times to first and second intervention were not correlated. Based on these assumptions, simulations were performed to assess the time to second intervention or death. The median next intervention free survival (NIFS) was estimated to about 7.5 years. Active surveillance is a well-accepted approach in Europe and is considered the standard arm here. A superior NIFS in the early treatment arm is required to have this treatment accepted by the clinical community despite potential side-effects. This study will be powered to demonstrate a reduction in the hazard of next intervention of 30% (HR=0.70) after randomization. Assuming piecewise hazards rates obtained by simulation in the active surveillance arm, alpha 2.5% one sided, 80% power and median time to second intervention or death of 8 years in the active surveillance arm vs 10 years in the RT/TMZ arm and one efficacy interim analysis, 252 NIFS events are needed to show the target treatment effect. As a result, a sample size of about 624 patients is needed which with 96 patients per year taking a 1year activation period would require about 7 years to be recruited. All events would be observed within 4.5 years after end of accrual (total duration 11.5 years). It is assumed that all patients will be followed up till second intervention i.e., dropout is 0% or negligible in both arms.
Number analysed	Eighteen patients out of 624 planned were enrolled in this study and results available are presented in this short report.
Diagnosis and main criteria for inclusion	Inclusion criteria: • Histologically WHO grade II (diffuse) or III (anaplastic) astrocytoma, IDHmt without 1p/19q co-deletion (local diagnosis) • Time since diagnostic surgery or first resection ≤ 6 months • No need for immediate radiotherapy followed by chemotherapy • Having seizures only, without functional deficits due to the tumor (but the presence of functional deficits due to the resection is allowed) • Patients for whom by local judgment an active surveillance policy is a realistic management alternative • Adults ≥ 18 years of age • WHO PS 0-2 • Adequate hematological, renal, and hepatic function, as follows: o Absolute neutrophil count ≥ 1.5 x 109/L o Platelets ≥ 100 × 109/L o Serum creatinine ≤ 1.5 times upper limit of laboratory normal (ULN) o Total serum bilirubin ≤ 1.5 × ULN o AST and ALT ≤ 2.5 × ULN o Alkaline phosphatase of ≤ 2.5 × ULN • Presence of at least one paraffin block from the initial diagnosis for pathology review and translational research. If a representative formalin-

EORTC-1635-BTG IWOT Version 4.0 13 / 88 January 21, 2021 fixed, paraffin-embedded (FFPE) block is not available, the collection of optimally 36, minimally 24 x 5 µm, unstained slides is required.

- At the time of randomization presence only of a non-enhancing tumor on T1 weighted contrast enhanced MR images; some faint non-nodular enhancement or enhancement that can be ascribed to the surgical resection or peri-operative ischemia is allowed. Preoperative enhancement is allowed provided this area is resected as shown on postoperative imaging
- Ability to take oral medication
- Women of child bearing potential (WOCBP) must have a negative serum or urine pregnancy test done within 72 hours prior to randomization
- Patients of childbearing / reproductive potential must agree to use adequate birth control measures, as defined by the investigator, during RT and TMZ treatment and for at least 6 months after the last TMZ cycle. A highly effective method of birth control is defined as those which result in low failure rate (i.e., less than 1% per year) when used consistently and correctly
- Women who are breast feeding must agree to discontinue nursing prior to the first dose of study treatment and until 6 months after the last study treatment
- Male patients should be advised not to father a child and not to donate sperm up to 6 months after receiving the last dose of TMZ, and to seek advice on cryoconservation of sperm prior to treatment start
- Ability to understand the requirements of the study, provide written informed consent and authorization of use and disclosure of protected health information, and agree to abide by the study restrictions and return for the required assessments
- Before patient registration/randomization, written informed consent must be given according to ICH/GCP, and national/local regulations.

Exclusion criteria:

- Presence of signs of increased intracranial pressure after surgery
- Requirement of steroids for control of tumor symptoms
- Presence of uncontrolled seizures after surgery, defined as having both:
    - persistent seizures interfering with everyday life activities AND
    - failed three lines of anti-epileptic drug regimen, including at least one combination regimen
- Presence of contra-indications for radiotherapy
- Presence of MRI contraindications such as aneurism clips, IOFB, other ferrous/metalic bodies in the participant
- Hypersensitivity to dacarbazine (DTIC), to the active substance or to any of the excipients used for TMZ capsules, including hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucosegalactose malabsorption.
- Prior chemotherapy, or prior radiotherapy to the brain
- Pregnancy or breastfeeding
- Known HIV, chronic hepatitis B, or hepatitis C infection
- Inability to take oral medication (e.g., frequent vomiting, partial bowel obstruction)

	• Concurrent severe or uncontrolled medical disease (e.g., active systemic infection, diabetes, hypertension, coronary artery disease, psychiatric disorder) that, in the opinion of the investigator, would compromise the safety of the patient or compromise the ability of the patient to complete the study • Prior or second invasive malignancy, except non-melanoma skin cancer, completely resected cervical or prostate cancer (with PSA of less than or equal to 0.1 ng/mL). Other cancers for which the subject has completed potentially curative treatment more than 3 years prior to study entry are allowed • Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
Treatment Test product, dose and mode of administration Duration of treatment	The early treatment arm is considered as the investigational arm: • Radiation therapy – total dose of 50.4 Gy in 28 fractions 5 days/week for diffuse astrocytoma and 59.4 Gy in 33 fractions for anaplastic astrocytoma; to be started within 6 weeks of randomization • Followed after a 4-week break with 12 cycles of temozolomide 200 mg/m2 the first 5 days of a 28-day cycle
Reference therapy, dose and mode of administration	Standard arm or active surveillance, with first treatment once, according to the treating physician, the patient has any one of the following: • Clinically significant radiological progression, defined as 25% increase in tumor area (2D RANO) or a 15% increase in Mean Tumor Diameter (and at least a 2-cm diameter increase of the longest diameter, or the development of enhancement not due to surgery) • New interictal clinical symptoms and signs related to tumor progression • The development of uncontrollable seizures that cannot be adequately controlled by anti-epileptic drugs • Any other reason for first treatment (which includes more limited radiological or clinical progression) and to be documented by the treating physician Patients will then be treated at the discretion of the treating physician. This will preferably consist of: • Radiation therapy – total dose of 50.4 Gy in 28 fractions 5 days/week unless the lesion shows evidence of malignant progression and in which case a total dose of 59.4 Gy or 60 Gy in 33 fractions can be considered • Followed after a 4-week break with 12 cycles of temozolomide 200 mg/m2 the first 5 days of a 28-day cycle. • Surgery alone without subsequent radio- and or chemotherapy will not be considered the 'first treatment' for the primary endpoint of this study.
Criteria for evaluation	Primary endpoint Next intervention free survival (NIFS) is defined as the number of days measured from date of randomization until initiation of further treatment after radio- and/or chemotherapy with or without surgery (i.e., second treatment after early treatment

	or second treatment after active surveillance) or death (any cause) whichever occurs first. Secondary endpoints In the active surveillance arm only, first intervention free survival (FIFS) is defined as the number of days measured from the date of randomization until initiation of preferably RT/TMZ or any other first therapeutic intervention (second surgery, RT, chemotherapy) or death (any cause) whichever occurs first. In both arms, the following will be analyzed: • Progression free survival • Overall survival • Neurological deterioration free survival • Time to deterioration of QOL • Time to deterioration of cognition • Seizure activity • Patient reported outcome • Safety profile (adverse events) • Correlation between molecular markers and outcome
Statistical methods	Per protocol, all primary efficacy analyses had to be performed in the Intent-To-Treat population when the targeted number of NIFS is observed (252). The following analyses had to be included in the final analysis report. Primary NIFS analysis In the primary analyses, difference in NIFS between the treatment groups had to be assessed by a LogRank test stratified by the stratification factors assessed at randomization (except institution), testing the null hypothesis (H0): • H0: HR early arm/active surveillance = 1 Versus the alternative hypothesis (H1) • H1: HR early arm/active surveillance < 1 We considered this test as confirmatory and would perform it at a 1-sided significance level α=0.025. Kaplan-Meier survival curves (product-limit estimates) hat to be presented by treatment group together with a summary of associated statistics (median NIFS time, 6-, 12-, 18-, 24-month NIFS rate estimates and estimates for every 6 months thereafter as applicable) including the corresponding two-sided 95% confidence intervals (calculated by Greenwood formula's estimation of the standard deviation for rates and by Brookmeyer and Crowley technique for the median). The hazard ratio (including two-sided 95% confidence interval) of the early treatment arm over the active surveillance (control) group had to calculated by Cox's proportional hazards model stratified by the stratification factors assessed at randomization (except institution).

	Secondary endpoints analyses had to be performed at the same time as the primary analyses but are not detailed in this short report and could not be performed for the same reasons. The study was closed for poor accrual and therefore analyses described above could not be performed. Instead in this short report, a descriptive overview of randomized patients, response, efficacy, and AEs numbers available is presented.
Summary of Results Efficacy Results	At the database lock date 25/01/2022, 18 patients out of the planned 624 were randomized, 9 to standard arm (active surveillance arm) and 9 to investigational arm (early treatment arm). Overall response: 1 partial response was observed in early treatment arm. No progressions or death were reported. However, follow-up for the patients in this study was very limited due to closure for poor accrual.
Safety Results	Reported grade 4 AEs: Neutropenia (1 AE , 1 patient in early treatment arm) Reported grade 3 AEs: Seizure (2 AEs , 1 patient in early treatment arm)
Conclusions	At time of study closure, efficacy and safety data reported in EORTC database were very limited.
Date of Report	No final analysis report was generated for this study which was stopped for poor accrual. Date of short report: 18/02/2022