

Intergroup Trial



EORTC Brain Tumor Group
EORTC Radiation Oncology Group
EORTC protocol 26052_22053

EORTC Group Specific Appendix to RTOG protocol

(EudraCT number 2005-005177-29)

Phase III trial comparing conventional adjuvant temozolomide with dose-intensive temozolomide in patients with newly diagnosed Glioblastoma

**EORTC Study
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Warning:

The enclosed protocol has not be initiated and written by the EORTC and it does not follow the usual sequence of chapters of EORTC protocols.

All practical and administrative aspects of the protocol specific to the EORTC (Randomization, data flow, responsibilities, insurance, safety reporting, informed consent....) are included under this EORTC Group Specific Appendix of the protocol.

Date of PRC approval/notification	Subject	Group Specific Appendix	Coordinating Full Protocol
September 05, 2005	Intergroup protocol outline		RTOG Protocol - Activation version January 17, 2006
February 10, 2006	EORTC Group Specific Appendix	Version 1.0	RTOG Protocol - Activation version January 17, 2006
October 03, 2006	First amendment (<i>substantial</i>)	Version 2.0	RTOG Protocol – version September 21, 2006
22 January, 2007	Second amendment (<i>substantial</i>)	Version 3.0	RTOG Protocol – version September 21, 2006
July 19, 2007	Third amendment (<i>non-substantial</i>)	Version 3.1	RTOG Protocol – version July 12, 2007
February 22, 2008	Fourth amendment (<i>substantial</i>)	Version 4.0	RTOG Protocol – version January 15, 2008

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1 Trial organization

This trial is an Intergroup Trial, jointly conducted by Radiation Therapy Oncology Group (RTOG), and the EORTC Brain and Radiotherapy groups and.

The RTOG is the coordinating group in this Intergroup trial and therefore is responsible for the trial design and activation, data management (including the quality control of data), statistical analysis and publication.

The protocol developed by the Coordinating Group is compliant with specific EORTC guidelines for Intergroup trials and will be used by EORTC. The present EORTC specific Appendix details the participation of the EORTC institutions in the trial. The content of this appendix is therefore applicable only to the EORTC investigators, for whom they supercede entirely or partially the corresponding chapters in the protocol.

The EORTC is collaborating group in this trial.

EORTC is the legal sponsor for all EORTC patients. Only the EORTC can authorize the EORTC investigators to register/randomize patients.

All EORTC investigators will call the EORTC Headquarters to register / randomize patients. EORTC will subsequently register / randomize patients in to the RTOG.

The EORTC Headquarters will follow a “standard mail-box” procedure for this trial:

Only the Coordinating Data Center will code the data, perform consistency checks on data and modify them. Only the Coordinating Data Center will do the analysis.

There will be no direct communication between EORTC investigators and the Coordinating Data Center.

This trial is an academic trial with an educational grant from Schering Plough.

In addition, Schering Plough will provide Temozolomide for the study.

2 Investigator authorization procedure

Investigators will be authorized to register or randomize patients in this trial only when they have returned to the EORTC Headquarters:

- ◆ The updated signed and dated Curriculum Vitae of the Principle Investigator
- ◆ The (updated) list of the normal ranges, in their own institution, of all laboratory data required by the protocol, preferably signed and dated by the head of the laboratory.
- ◆ A commitment statement / study acknowledgment form, indicating that they will fully comply with the protocol, to include an estimate of their yearly accrual and if any conflict of interest may arise due to their participation in the trial,
 - ◆ A signed conflict of interest disclosure form: this document will be required only if a possible conflict is declared on the commitment form.
- ◆ A copy of the favorable opinion of their local or national (whichever is applicable) ethics committee mentioning the documents that have been reviewed (incl. version number and date of documents) and indicating the list of the ethics committee members.

- ◆ A copy of the translated and adapted (according to all national requirements), Patient Information / Informed Consent sheet, clearly mentioning the version number and the date.
- ◆ The signature log-list of the staff members with a sample of each authorized signature and the indication of the level or delegations. In case patients receive treatment at a satellite institution, i.e. outside the authorized institution, details on the satellite institution, including the CV of the local investigator, normal lab ranges and the approval of an ethics committee will have to be transmitted to the EORTC Headquarters. **Please keep in mind that all communication is done ONLY between the primary institution and the EORTC Headquarters.**
- ◆ The coordinates of the pharmacist who will be responsible for the trial medication (for any trial where the drug will be provided).
- ◆ The accreditation letter for the laboratory. (if available for your center and/or applicable by your national law)

The center specific applicable list of required documents will be included in the protocol activation package, with proper instructions as required by this protocol and / or the applicable national law

The new investigator will be added to the “authorization list”, and will be allowed to register/randomize patients in the trial as soon as

- ◆ All the above mentioned documents are available at the EORTC Headquarters
- ◆ All applicable national legal and regulatory requirements are being fulfilled

Patient registration/randomization from centers not (yet) included on the authorization list will not be accepted.

The Coordinating Data Center will be immediately informed about each investigator included on the authorization list using the standard form clearly indicating the name of principle investigator, the name of the institution and the EORTC institution number

3 Patient registration & randomization procedure

3.1 General procedure

The EORTC investigators will register and/or randomize patients through the EORTC, following the standard EORTC procedure. Patient registration and/or randomization will only be accepted from investigators authorized by the EORTC (see "Authorization procedure").

A patient **should** be registered or randomized only after verification of eligibility directly **on the EORTC online randomization system (ORTA = online randomized trials access)**.

To access the interactive randomization program, the investigator needs a username and a password (that can be interactively requested: <http://www.eortc.be/random>).

In case of problems, investigators can **call** the EORTC Headquarters from 9.00 am to 5.00 pm (Brussels local time) from Monday through Friday. **Randomization via the call center is not available on Belgian bank holidays. A list of these holidays is available on the EORTC web site (www.eortc.be/random) and it is updated annually.**

This must be done before the start of the protocol treatment.

Call center (in case of problems): +32 2 774 16 00

3.2 Registration

This EORTC registration check-list should be completed by the responsible investigator before contacting the EORTC registration program.

An exhaustive list of questions to be answered during the registration procedure is included in the EORTC registration check-list.

Standard questions:

- ◆ EORTC institution number?
- ◆ protocol number ?
- ◆ step number: 1
- ◆ name of the responsible investigator ?
- ◆ patient's code (maximum 4 letters) ?
- ◆ patient's birth date (day/month/year) ?

Group affiliation:

- ◆ primary group affiliation ? Your primary group affiliation
- ◆ secondary group affiliation ? Your double affiliation e.g. EORTC group

Protocol specific questions:

- ◆ eligibility criteria ?
all eligibility criteria will be checked;
actual values of the eligibility parameters will be requested when applicable
- ◆ date of written informed consent

At the end of this procedure, the EORTC sequential identification number will be allocated to the patient.

This EORTC number will only be used during the randomization procedure and on EORTC forms.

Once the registration at the EORTC has been completed, the EORTC Headquarters will contact the Coordinating Data Center and the central registration will be performed. During this procedure RTOG will allocate an RTOG patient ID and confirm RTOG number to be used for you institution. The registration will be confirmed (fax/e-mail) to the EORTC investigator within 24 hours (working days).

The RTOG patient ID and RTOG institution number must be reported on all case report forms (EORTC and RTOG).

After the registration, the originals of EORTC Registration Checklist together with the initial data of the patient should be sent to the EORTC Headquarters by regular mail and the copies kept on-site.

The treatment can start only after the confirmation of registration at RTOG has been provided to the responsible investigator by the EORTC Headquarters.

A patient who has not been registered at the RTOG (through the EORTC Headquarters) before the first treatment administration will not be accepted for the study at a later date.

3.3 Randomization

This EORTC randomization check-list should be completed by the responsible investigator before contacting the EORTC randomization program.

An exhaustive list of questions to be answered during the registration procedure is included in the EORTC Randomization checklist that is part of the case report forms.

Standard questions:

- ◆ EORTC institution number?
- ◆ protocol number ?
- ◆ step number: 2
- ◆ name of the responsible investigator ?
- ◆ patient's code (maximum 4 letters) ?
- ◆ patient's birth date (day/month/year) ?

Protocol specific questions

- ◆ eligibility criteria ?
 - all eligibility criteria will be checked;
 - actual values of the eligibility parameters will be requested when applicable
- ◆ stratification factors ?

At the end of this procedure, the investigators will receive the confirmation mail, but not the treatment arm allocated to the patient.

As soon as the ORTA confirmation mail is available for the responsible data manager (working days), he/she will contact the Coordinating Data Center where the central randomization will take place and only then the treatment will be allocated to the patient. The result of the central randomization will be immediately communicated (fax/e-mail) to the EORTC Headquarters. The EORTC Headquarters will immediately forward this information to the EORTC investigator.

However, investigators should consider that due to this procedure they would receive the treatment within 24 hours at the maximum (working days).

The treatment allocated should be completed on the EORTC Randomization Checklist that should be sent to the EORTC Headquarters by regular mail together with the all initial data.

4 Forms and procedures for collecting data

4.1 Case report forms and schedule for completion

Data will be reported on the **EORTC forms** and sent to:

Steve Douterlungne
EORTC Headquarters
Avenue Emmanuel Mounier, 83, bte 11
B-1200 Brussels, Belgium

A. Before the treatment starts:

- ◆ the patient must be registered & randomized at the EORTC Headquarters by INTERNET or by phone

The optimal way to work is to complete the EORTC registration or randomization check-list first and to register/randomize the patient as soon as it is completed. The date of registration and patient sequential identification number are then completed on the check-list, and this form can be sent to the EORTC Headquarters.

B. The list of forms to be completed for this study and their submission schedule is appended to the set of case report forms

C. Upon occurrence of a Pregnancy

- ◆ Any pregnancy in a female subject or in a female partner of a male subject diagnosed during the treatment period or within 30 days after last study treatment administration must be reported to the EORTC Pharmacovigilance Unit.
- ◆ This must be reported **within 24 hours** of first becoming aware of the event **by fax** to the **EORTC Pharmacovigilance Unit** on a **Pregnancy Notification Form/Fax**.
- ◆ If a Serious Adverse Event (SAE) occurs in conjunction with the pregnancy, please also complete an SAE form as explained in the SAE chapter
- ◆ Upon notification of a pregnancy, it will be the responsibility of the pharmaceutical company to follow up the development and outcome of the pregnancy.

D. Upon occurrence of a Serious Adverse Event (SAE)

- ◆ SAEs occurring from the time a subject is registered until 30 days after last protocol treatment must be promptly reported.
- ◆ Any SAE occurring after the 30-days period and considered to be reasonably related to the investigational product or study participation, also have to be promptly notified
- ◆ All these events must be reported **by fax** to the **EORTC Pharmacovigilance Unit** on a Serious Adverse Event Form **within 24 hours** of the initial observation.
- ◆ A completed SAE-form must be returned to the EORTC Headquarters within 10 calendar days of the initial observation of the Serious Adverse Event.

**ALL Forms must be dated and signed by the responsible investigator
or one of his/her authorized staff members**

4.2 Data flow

EORTC Headquarters will follow the "standard mail-box" system in this trial.

- ◆ **There will be no direct communication between EORTC investigators and the Coordinating Data Center:**

EORTC investigators will not be allowed to send CRFs, Query or any correspondence directly to the Coordinating DC

The Coordinating DC will not be allowed to send Query Forms or any correspondence directly to the EORTC investigators

- ◆ **Only the Coordinating DC will enter the data in the computer, perform the quality control of data and modify them. Only the Coordinating DC will do the analysis**

The case report forms must be completed, dated and signed by the investigator or one of his/her authorized staff members as soon as the requested information is available.

The list of staff members authorized to sign case report forms (with a sample of their signature) must be sent to the EORTC Headquarters by the responsible investigators before the start of the study.

In all cases, it remains the responsibility of the investigator to check that original case report forms are sent to the EORTC Headquarters and that they are completely and correctly filled out.

The original copy must be immediately returned to the EORTC Headquarters and the investigator must keep a copy.

EORTC Headquarters will send regularly all CRFs to the Coordinating DC according to the form flow schedule (sorted by trial, institution and patient with a short notice summarizing the content of the package)

When necessary, the Coordinating DC will issue Query Forms and transmit them to the EORTC Headquarters, which will send them to the EORTC investigators.

Those Query Forms must be immediately answered and signed by the investigator (or an authorized staff member). The original must be returned to the EORTC Headquarters and a copy must be appended to the investigator's copy of the CRFs. The EORTC Headquarters will then send the reply of the investigators back to the Coordinating DC.

If an EORTC investigator (or an authorized staff member) needs to modify a CRF after the original copy has been returned to the EORTC Headquarters, he/she should notify the EORTC Headquarters in writing (and sign the notification). A copy of this notification has to be appended to his own copy of the CRFs. The EORTC Headquarters will forward this notification to the Coordinating DC.

The investigator's copy of the CRFs may not be modified unless modifications are reported on a Query Form (or a written and signed notification) and the Query Form (or notification) reference is attached to the CRF.

5 Reporting of Serious Adverse Events

5.1 Definitions

AE: An **Adverse Event** is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended signs (such as rash or enlarged liver), symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment, whether or not considered related to the investigational medicinal product.

AR: An **Adverse reaction of an investigational medicinal product** is any untoward and unintended responses to an investigational medicinal product related to any dose administered.

All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

UAR: An **Unexpected Adverse Reaction** is any adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Severity: The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious,” which is based on patient/event outcome or action criteria.

SAE: A **Serious Adverse Event** is defined as any undesirable experience occurring to a patient, whether or not considered related to the protocol treatment.

SAR: A Serious Adverse Event (SAE) which is considered related to the protocol treatment is defined as a **Serious Adverse Reaction**

An **Adverse Event** or **Adverse Reaction** which is considered as **serious**:

- ◆ results in death,
- ◆ is life-threatening (i.e. an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- ◆ requires hospitalisation or prolongation of existing inpatients' hospitalisation,
- ◆ results in persistent or significant disability or incapacity,
- ◆ is a congenital anomaly or birth defect.
- ◆ results in any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above).

SUSAR: Suspected Unexpected Serious Adverse Reactions

5.2 Reporting procedure

5.2.1 Non- serious adverse events and/or non-serious adverse drug reactions

Adverse Events (AE) and /or Adverse Reactions (AR) must be recorded as indicated in the protocol.

5.2.2 Serious adverse events or serious adverse drug reactions

All Serious Adverse Events (SAE) occurring from the time a subject is registered until 30 days after last protocol treatment, must be reported to the EORTC Pharmacovigilance Unit within 24 hours. (Ref: <http://ctep.info.nih.gov/reporting/ctc.html>).

All SAEs that are simply signs and symptoms of the disease being studied do NOT need to be collected!

Examples of SAEs that do not need to be reported:

- ◆ Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- ◆ Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- ◆ Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- ◆ The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
- ◆ A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated.

Any SAE that occurs outside of the SAE detection period (after the 30-days period), considered to be reasonably related to the investigational product or study participation, have to be promptly notified to the EORTC Pharmacovigilance Unit.

This must be done by fax within 24 hours of the initial observation of the event. The principal investigator will decide if these events are related to the protocol treatment and the decision will be recorded on the Serious Adverse Event form, if necessary with the reasoning of the principal investigator.

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated.

The product reference documents are

For marketed products: Summary Of Product Characteristics which can be found on <http://www.emea.eu.int/htms/human/epar/epar.htm#>

Details should be documented on the specified Serious Adverse Event Form.

PLEASE FAX THE REPORT TO:

EORTC Pharmacovigilance Unit:
Fax No. +32 2 772 8027

The EORTC Pharmacovigilance Unit will forward all Serious Adverse Event reports within 24 hours of receipt to all appropriate persons (**See Administrative chapter**).

To enable the sponsor to comply with regulatory reporting requirements, completed documentation of any reported serious adverse events or serious adverse reactions must be returned within 10 calendar days of the initial report. If the completed form is not received within this deadline, the Pharmacovigilance Unit will make a written request to the investigator.

It should be recognized that Serious Adverse Reactions (SAR) which have not been previously documented in the Investigators' Brochure, or which occur in a more severe form than anticipated (i.e. they are 'unexpected' by nature or severity), are subject to rapid reporting to the Regulatory Authorities.

ANY QUESTION CONCERNING SAE OR SAR REPORTING CAN BE DIRECTED TO:

EORTC Pharmacovigilance Unit
Phone: +32 2 774 1676
Fax: +32 2 772 8027
e-mail: pharmacovigilance@eortc.be

ALL FORMS MUST BE DATED AND SIGNED BY THE RESPONSIBLE INVESTIGATOR OR ONE OF HIS/HER AUTHORIZED STAFF MEMBERS.

6 Quality assurance

6.1 Control of data consistency

The EORTC follows the "standard mailbox" system (see forms and procedures for collecting data).

Therefore, data forms will not be entered in the database of the EORTC Headquarters (with the exception of the registration & randomization check-lists for regulatory and QA purposes only) and the EORTC Headquarters will not perform any consistency checks on the CRFs. However, EORTC will track which forms have been received in order to perform the data timeliness procedure every 3 month (according to standard EORTC QA policy).

The EORTC Headquarters will keep copies of all forms and queries for QA purposes.

6.2 Quality assurance

All participating institutions will be part of the EORTC quality assurance audit program to verify local facilities, organisation of clinical research on-site, quality of data reported, ethics and informed consent processes, study integrity and compliance with Good Clinical Practice (GCP) and applicable regulations.

A site visit will be organised in each recruiting institution within 18 months after the first patient has been entered, and once every 3 years thereafter.

6.3 Pathology review, MGMT methylation status & research on biological material

Pathology review is required for all patients participating in this study.

Analysis of the MGMT methylation status and consent for future research on biological material is also mandatory for all patients participating in this study.

6.3.1 Material Routing

All materials should be sent to the central reference laboratory for further processing.

A standard procedure for the shipment of the histological material will be established at the EORTC and adequate instructions will be given to the centers at the time of the activation of the trial.

Material to be collected and sent to the central reference laboratory (Monika Hegi, Lausanne, Switzerland):

- ◆ Paraffin blocks of embedded tumor material
- ◆ Unstained/stained histological slides is strongly encouraged
- ◆ Fresh-frozen tissue and serum will be needed for the research on biological material (this material can be kept at the center and will be collected at a later stage).

Central reference laboratory:

Monika HEGI
Dep.: Dept of Neurosurgery
CENTRE HOSPITALIER UNIVERSITAIRE VAUDOIS
rue du Bugnon 46
CH 1011 LAUSANNE
Switzerland
Phone: +41 21 3142582 (2580 labs)
Fax: +41 21 3142587

Monika.Hegi@chuv.ch

Material to be accompanied by the following information

- ◆ Patient character code
- ◆ Trial and RTOG patient ID number
- ◆ Date of birth
- ◆ Copy of the original local histopathological report (anonymized)

6.4 Quality Assurance for Radiotherapy

The objectives will be to check compliance to the protocol guidelines regarding PTV definition, planning technique and documentation.

The center specific applicable list of required documents will be included in the protocol activation package, with adequate instructions.

7 Ethical considerations

7.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at <http://www.emea.eu.int/pdfs/human/ich/013595en.pdf>).

The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

7.2 Subject identification

The name of the patient will neither be asked for nor recorded at the EORTC Headquarters. A sequential identification number will be automatically allocated to each patient registered in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, the patient's code (maximum of 4 letters) and date of birth will also be reported on the case report forms.

7.3 Informed consent

All patients will be informed about

- ◆ the aims of the study
- ◆ the possible adverse events
- ◆ the procedures and possible hazards to which the patient will be exposed
- ◆ the mechanism of treatment allocation
- ◆ strict confidentiality of any patient data
- ◆ medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician.

The template of the patient's informed consent statement is given as an appendix to this protocol.

It is the responsibility of the Coordinating Investigators for this trial (sometimes called National Coordinators) to translate the enclosed informed consent document. The translated version should be dated and version controlled.

The bold sections of the informed consent document must be reflected in any translation. The content of these bold sections can either be translated literally or translated in any way that best captures the information given.

The translated informed consent documents are to be submitted to ethics committees for approval. The competent ethics committee for each institution must approve the informed consent documents before the center can join the study. It is the responsibility of the competent ethics committee to ensure that the translated informed documents comply with ICH-GCP guidelines and all applicable national legislation.

It is emphasized in the patient information sheet that participation is voluntary and that the patient is free to refuse further participation in the protocol whenever he/she wants to. This will not have any impact on the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered and/or randomized at the EORTC Headquarters. The written informed consent form must be signed and personally dated by the patient or by the patient's legally acceptable representative".

All of the above must be done in accordance with the applicable national legislation and local regulatory requirements.

8 Administrative responsibilities

8.1 The study coordinator

The EORTC Study Coordinator (in cooperation with the EORTC Headquarters) will be responsible for reviewing and discussing all the amendments to the protocol with the coordinating group.

At the time of publication, the EORTC study coordinator's responsibility is to assure, along with the EORTC Headquarters Team, that the results are used and analyzed following the EORTC policy and quality.

Study coordinator:

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Fax: +44 131 5372240
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8.2 The EORTC Headquarters

The EORTC Headquarters is responsible for handling investigator authorization procedure, for registration and randomization of patients and will act as a "mail box" in this trial (see forms and procedures for collecting data). All methodological questions should be addressed to the EORTC Headquarters that will address them to the person competent for this trial.

EORTC HEADQUARTERS

83, avenue Emmanuel Mounier, Bte 11
B-1200 Brussels, Belgium
Fax: +32 2 7723545

Registration of patients:

Phone: +32 2 7741600
or
<http://www.eortc.be/random>

Statistician:

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Project Manager

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The EORTC Pharmacovigilance Unit will forward all SAEs from EORTC centers, within one business day of receipt to the Coordinating data center, the EORTC Study Coordinator, the EORTC Data Manager and the SPRI Drug Safety Surveillance Department.

All SUSARs will additionally be notified to all EORTC participating investigators and EC's.

The EORTC Pharmacovigilance Unit will take in charge the expedited reporting to the EU Competent Authorities and Eudravigilance, whenever applicable.

The EORTC Pharmacovigilance Unit will ensure that EORTC SAEs are encoded in the AdEERs system.

SPRI Drug Safety Surveillance Department

Fax: +1 973 921 7422 or +1 973 921 7423

8.3 The EORTC groups

All questions concerning ongoing membership in the group should be addressed to the chairman and/or secretary of the group.

For new membership contact Membership Committee at membership@eortc.be

Brain EORTC group

Chairman:

Martin J. VAN DEN BENT
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Secretary:

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Radiotherapy EORTC group

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9 Trial sponsorship and financing

EORTC is the legal Sponsor for all EORTC participants.

The contact details of the EORTC are:

EORTC Headquarters
Avenue Mounier 83/11
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10 Trial insurance

A clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

Clinical trial insurance is only valid in centers authorized by the EORTC Headquarters. For details please refer to the chapter on investigator authorization.

Patients treated at **satellite institutions** are only covered by clinical trial insurance, if these satellite institutions are properly reported to the EORTC Headquarters. For details please refer to the chapter on investigator authorization.

11 Radiotherapy Volumes and Treatment definitions for glioblastoma (for European centers; elective)

11.1 Introduction

In some European centers, clinical practice regarding radiotherapy target volumes and imaging in planning of radiotherapy for high-grade glioma is a little different from that practiced in North America. Though a two-phase planning target volume was used in past, with increased experience of 3D conformal radiotherapy and data demonstrating that toxicity is related to radiotherapy volumes (Ref. 1) and that the majority of recurrences occur with 3 cm of the enhancing lesion (Ref. 2, Ref. 3, Ref. 4), a single-phase PTV is now accepted practice in many European centers (Ref. 5). With the variations in access to MRI in Europe a more flexible to approach is required. Postoperative MRI is best done within 48 hours in order to distinguish between post-op changes and residual tumour. This is not standard in all European centres partly due to differing MRI availabilities. Based on the protocol guidelines there will be at least one MRI scan: either pre-operative, or if not done, post-operatively which shall be used for planning purposes also. However European sites may use either the US radiotherapy specifications as defined in the protocol or the European specifications as described here in.

11.2 Dose

The regime consists of a total dose of 60 Gy in 30 daily fractions delivered over six to seven weeks.

11.3 Planning volumes

- ◆ A single phase treatment volume will be used throughout treatment – a cone-down volume or boost volume is not foreseen.
- ◆ The Gross Tumour Volume (GTV) is defined by the region of enhancement (without oedema) on pre-operative Computer Tomography (CT)/Magnet Resonance Imaging (MRI) or postoperative CT/MRI - whichever is larger.
- ◆ Postoperative imaging is not mandatory, and it is acceptable to define GTV on pre-operative scans.
- ◆ For non-enhancing tumours on CT/MRI, the GTV shall be defined as the visible region on T2 weighted MRI images.
- ◆ The Clinical Target Volume (CTV) is defined as the GTV plus a margin to account for microscopic spread. This will usually be in the order of 2 to 3 cm, but should include all areas of persisting oedema (T2 weighted area on MRI/hypo dense area on CT), but can be reduced in anatomical regions where spread is unlikely (e.g. bony structures).
- ◆ In case of complete or subtotal removal, the position of the tumour bed can have shifted, and the CTV should take into account the new position of the abnormality on the planning CT scan and any post-operative imaging.
- ◆ The Planning Target Volume (PTV) will take into account uncertainties of planning and setup. This margin should be based upon known departmental values, but will usually be of the order of 0.5-0.7 cm.
- ◆ All margins should be added using a three-dimensional (3-D) growth algorithm where possible.
- ◆ Organs-at-risk (OAR): the eyes, optic nerves, chiasm, lacrimal glands and brain stem (from superior limit of posterior clinoids to foramen magnum) should be outlined and dose-volume histograms (DVH) calculated. A whole brain DVH, excluding the PTV, should also be calculated.

11.4 Planning procedure

- ◆ Patients are treated either supine or prone depending on site of lesion, in an immobilization device (any mask or frame system with relocation accuracy ≤ 5 mm)
- ◆ Planning CT scan is mandatory.
- ◆ Pre-operative imaging, and if available post-operative CT scan and/or MRI with contrast, is required for simulation and planning.
- ◆ Three-dimensional (3-D) treatment planning computers and beams' eye-view (BEV) planning are mandatory. A dose calculation grid of 2 mm or less should be used.
- ◆ The use of DVH for planning is mandatory.
- ◆ Use of a classical simulator or virtual simulation is mandatory.
- ◆ Use of shielding blocks/multi-leaf collimator (MLC) is mandatory. The position of shielding blocks/MLC should be indicated on the simulation films, printed BEV, or DRR.

- ◆ Planning should conform to ICRU 50/62 criteria for coverage and homogeneity. Any field arrangement is possible providing the dose homogeneity within the volume is kept within -5% and +7% of the prescribed dose.

11.5 Treatment technique

- ◆ A linear accelerator with energy of 4 to 18 MV should be used.
- ◆ The volume should be treated by a multiple field technique, with all fields treated at each fraction.
- ◆ The use of vertex fields requires either a diagram or photograph of treatment position or another control procedure.
- ◆ Treatment verification with a minimum of weekly portal imaging or portal films is recommended if no local verification protocol is in use.
- ◆ Treatment with a single beam is not acceptable and parallel pair alone is discouraged.

11.6 Dose prescription, fractionation and intervals

- ◆ Dose prescription and recording should be according to ICRU 50/62 criteria. Dose homogeneity requirements in the PTV shall be within -5% and +7% of the prescribed dose.
- ◆ The PTV should be encompassed by the 95% isodose. However, if the PTV is in close proximity to an organ at risk the 90% isodose is acceptable. The 80% isodose is acceptable if this is on a single transverse CT slice, in which the PTV is delineated.
- ◆ A maximum overall treatment time (OTT) should be 44 days or less.

11.7 Dose limitation to critical structures

- ◆ Whenever possible, without compromising the CTV, attempts should be made to limit the dose to the optic chiasm and brainstem to less than 55Gy and to the retina less than 50Gy. The lens dose should be minimized by avoiding direct fields.
- ◆ Due to the small size of some of the OAR e.g. optic chiasm, the DVH of OAR should be calculated using a calculation grid of 2 mm maximum on an appropriate calculation mode using a high point density.

- Ref. 1 Gregor A, Cull A, Traynor E, Stewart M, Lander F, Love S. Neuropsychometric evaluation of long-term survivors of adult brain tumours: relationship with tumour and treatment parameters. *Radiother Oncol.* 1996 Oct;41(1):55-9.
- Ref. 2 Chan JL, Lee SW, Fraass BA et al. Survival and failure patterns of high-grade gliomas after three-dimensional conformal radiotherapy. *J Clin Oncol* 2002 Mar 15;20(6):1635-42.
- Ref. 3 Aydin H, Sillen I and von Lieven H. Patterns of failure following CT-based 3-D irradiation for malignant glioma. *Strahlenther Onkol* 2001 Aug;177(8):424-31.
- Ref. 4 Oppitz U, Maessen D, Zunterer H, Richter S, Flentje M. 3D-recurrence-patterns of glioblastomas after CT-planned postoperative irradiation. *Radiother Oncol.* 1999 Oct;53(1):53-7.
- Ref. 5 Laperriere N, Zuraw L, Cairncross G; Cancer Care Ontario Practice Guidelines Initiative Neuro-Oncology Disease Site Group. Radiotherapy for newly diagnosed malignant glioma in adults: a systematic review. *Radiother Oncol.* 2002 Sep;64(3):259-73.

12 Quality of life assessment

Quality of life assessment will not be performed by the EORTC sites.

Appendix A: Patient Information Sheet and Informed consent document for clinical trials

INFORMATION FOR INVESTIGATORS:

This document is an English version of the Patient information sheet & informed consent for clinical trials (PIS & IC). The translation and national regulatory submission process of this document is the responsibility of the National Coordinator for this trial. He/she will keep you aware and informed and will send the translated and approved document as soon as available.

INFORMATION FOR THE NATIONAL COORDINATORS:

- this document represents an English version of PIS & IC to be used in the present study

 - it is the responsibility of the national coordinator to:
 - translate the patient information sheet and informed consent in preparation for the submission of the dossier to the ethics committee (the submission may be the responsibility of EORTC or the investigator depending on the local regulations)

 - send a copy of the approved translated document to EORTC Headquarters who will then distribute the document to other national participating investigators

 - bold parts, appearing in the English template, **must** appear also in the translated version of the PIS & IC

 - final translated and approved PIS & IC must have version number and date
-

RTOG 0525/EORTC 26052-22053**PHASE III TRIAL COMPARING CONVENTIONAL ADJUVANT TEMOZOLOMIDE WITH DOSE-INTENSIVE TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA**

The European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumor and Radiotherapy Groups in collaboration with the US Radiotherapy Oncology Group (RTOG) is conducting an international clinical trial. This research study has been designed by a panel of physicians and recognized experts in this field. This document and your physician will explain the reasons and details to you. Clinical trials include only people who choose to take part. Please study this document carefully and take your time to make your decision. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study, also called protocol, because you have a brain tumor called glioblastoma. This information letter has the purpose to inform you in detail on the proposed research protocol, which has already been explained to you by your physician. This information is composed of two parts, part 1 will explain the treatment, the procedures and potential inconveniences and risks. Part 2 will explain why additional research on the tumor tissue needs to be conducted, without directly affecting your care.

Why is this study being done?

You have been recently diagnosed with a malignant brain tumor called glioblastoma, for which you have undergone surgery or a biopsy and additional treatment is required. Until recently this condition was treated with radiotherapy alone. A previous international study by the EORTC showed an improved outcome has by adding temozolomide (Temodal[®]) chemotherapy during and after radiation.

The purpose of this study is to determine whether increasing the intensity of the temozolomide treatment after completion of radiotherapy from 5 days out of 28 days (standard-dose schedule) to 21 days out of 28 days (dose-dense schedule) will further improve the outcome. This study will find out what effects, good and/or bad, this change in drug schedule has on you and on your tumor compared with the standard treatment.

Based on the previous trial we have evidence suggesting that a particular gene is responsible for resistance of the tumor against the temozolomide chemotherapy. We will thus determine the status of the MGMT gene on the previously resected tumor material. We hope that the more intensive temozolomide treatment schedule will be able to overcome this resistance. After you register for the study, a sample of your tumor tissue will be submitted to a central laboratory in order to confirm the diagnosis and to determine the MGMT gene activation status in the tumor.

It is planned that a total of 1153 patients participate in this study.

What will happen if I take part in this research study?

Before you begin the study...

You will need to have the following exams, tests, and procedures to find out if this treatment can be safely administered to you and to confirm that you are eligible. These exams, tests, and procedures are part of regular cancer care and are usually done even if you do not join the study.

- ◆ Blood exams for blood counts and biochemistry
- ◆ MRI scan of your brain (an image of your brain produced by magnetic rays) [NOTE: If unavailable, a CT scan, which takes computerized images of your brain, may be done instead]
- ◆ Pregnancy test if indicated

When you enter the study, your study physician will organize that a block of tumor tissue, which has been obtained at the time of your brain tumor surgery, is being sent to a central pathology laboratory for review. **To verify the initial diagnosis (done by the pathologist in your hospital), the block of tumor tissue (taken at the time of establishing the diagnosis or during surgical procedure you undergo) will be reviewed by pathologists experts in this field (generally using the microscope). The expert(s) will not necessarily be working in the hospital where you receive(d) protocol treatment, nor even the same country. In some cases, a sample of your tumor biopsy, removed at the time of establishing the diagnosis or during a surgical procedure that you may undergo, might be used to perform additional examinations necessary to assure the correct diagnosis.** If the diagnosis is not confirmed or the tissue is not adequate, you will not be able to continue on the study.

During Radiotherapy

Standard radiotherapy will be delivered for 30 treatments (Monday to Friday) over 6-7 weeks. From the first day of radiotherapy until the last day of radiation you will take the temozolomide orally once daily (7 days a week) for a maximum of 49 days (7 weeks). This part of the treatment will be performed at the medical center of your choice, is considered standard of care and not part of the proposed study.

During the study...

If you choose to take part in the study and if the previous exams and procedures confirm that you are eligible to participate, you will be allocated (randomized) to one of the following treatment groups. This happens only after completion of the radiotherapy. Randomization means that you are put into a group by chance with the help of a computer program. Neither you nor your physicians have any influence on which treatment group you are assigned to, you will have an equal chance of being in either group. Treatment according to the assigned regimen will begin in the 4th week after the end of radiotherapy.

If you are in group 1 (often called “Arm A”).... You will receive temozolomide at the standard-dose schedule. You will take temozolomide once daily for 5 days, every 28 days for up to 6 cycles (6 months; 1 cycle = 1 month (28 days)).

If you are in group 2 (often called “Arm B”).... You will receive temozolomide at the dose-dense schedule. You will take temozolomide once daily (at a smaller daily dose) for 3 weeks (21 days) out of every 28 days, for up to 6 cycles (6 months; 1 cycle = 1 month (28 days)).

Before starting and during the treatment the following tests and exams will be performed in order to monitor your state of health carefully. If the exams, tests, and procedures show that you can be in the study, and you choose to take part, then you will need the following tests.

- ◆ Physical exam (once per month)
- ◆ MRI (or CT) scan of your brain (every 3 months)
- ◆ Blood work for blood counts, kidney and liver function tests (2-3 times per month)
- ◆ A questionnaire about side effects of treatment (once per month)

Although all these tests are part of regular medical practice, it is possible that these tests are performed more frequently in patients who take part in this study. Especially blood counts are usually performed only twice per month, patients receiving the intensified treatment will have their blood counts checked three times per month.

MRI/CT scans, blood work, and side effect questionnaires will be repeated throughout the study so that the study doctor can monitor you. You will also be asked to complete a medication diary while you are receiving treatment; this will help document when you take your medication and any side effects you experience.

Can I stop being in the study?

Yes. You can decide to stop treatment at any time. Please inform your physician (study doctor) if you are thinking about stopping or decide to stop. He or she will assist you to discontinue treatment safely and arrange for an end of study visit.

You do not need to justify your decision to discontinue treatment, and it will have no influence on the care and attention you receive from your health care team. Your physician will then advise you about the best options of care available outside the study protocol.

Your study physician or the physicians and team overseeing the trial for the EORTC and RTOG may decide to discontinue your treatment or the study at any time, if it is believed to be in your best interest or if you are unable to follow the study rules.

What side effects or risks can I expect from being in the study?

You may have side effects while receiving temozolomide chemotherapy. Everyone taking part in the study will be watched carefully for any side effects. Although thousands of patients have been treated with temozolomide and the drug has been approved, there may be yet unknown side effects observed. Side effects may be mild or very serious. Your health care team will give you medicines to help lessen side effects, if necessary. Many side effects go away soon after you stop taking the drugs but in some cases, side effects can be serious, long lasting, or may even cause death.

You should talk to your study doctor about any side effects that you have while taking part in the study. There may be unexpected or previously unknown side effects with this treatment. Everything foreseeable has been done and will be done to prevent health problems occurring as a result of taking part in this trial.

If you need to undergo another medical treatment while receiving therapy on this protocol, we advise you to inform your study doctor and treating physician to ensure that this will not have any negative effect nor affect your participation in this trial. Everything has been done and will continue to be done to prevent health problems occurring as a result of your taking part in this trial.

During Radiotherapy...:

During radiotherapy you may experience the following side effects: Scalp redness or soreness; hair loss, which may be temporary or permanent ; ear/ear canal reactions, possibly resulting in short-term hearing impairment; fatigue; lethargy; temporary aggravation of brain tumor symptoms such as headaches, seizures, or weakness . Occasionally patients may develop also mental slowing; permanent hearing impairment; cataracts; behavioral changes, nausea or vomiting; dry mouth or altered taste; or hormonal deficiency.

Very rarely radiation may induce severe local damage to normal brain tissue, a condition called necrosis (tissue deterioration). Radiation necrosis can mimic recurrent brain tumor and may require surgery for diagnosis and treatment. Depending on the tumor location may also lead to blindness or other functional deficits. Radiation may induce other tumors (either benign or malignant) years after the treatment.

Risks and side effects related of temozolomide chemotherapy:

Nausea and/or vomiting, usually well controlled with standard anti-nausea medicine, decreased appetite and fatigue. Temozolomide may induce low blood counts, which may require a blood transfusion. It has been found that women have a higher incidence than men, of severe decrease in the neutrophils (white blood cells) and in the platelet count. Temozolomide's effect on the blood counts is usually temporary and the blood counts usually return to normal on their own. However, there is a risk that these blood counts will not return to normal and that might make you even more likely to get a severe infection or bleed. This is a condition called aplasia. This condition may be prolonged and result in as a disease called aplastic anaemia. This is rare but occurs more often when temozolomide is given for a longer period of time. Occasionally a skin rash is observed. Other side effects of temozolomide may include constipation, headache, loss of weight, diarrhea, mouth sores, hair loss, weakness, allergic reactions (including anaphylaxis which is a sudden and severe allergic reaction and may include breathing difficulty and drop of blood pressure, leading to loss of consciousness or death), fever, chills, pruritus (itching), dyspepsia (upset stomach) , erythema (redness) and edema (swelling), elevation of liver enzymes (elevation of the amount of enzymes liver secretes in the blood as a sign of irritation or damage it has encountered), deep vein thrombosis (blood clots in large venous blood vessels usually in legs) and pulmonary embolism (blood clots in large blood vessels in the lung).

Temozolomide has been reported to possibly contribute in very rare and isolated cases to the occurrence of severe mucosal and cutaneous toxicity (severe damage to skin and linings of body cavities) (as Stevens Johnson Syndrome). Secondary cancers (cancers possibly caused by the treatment of a previous cancer) such as myeloid leukemia (cancer of the blood and bone marrow), and myelodysplastic syndrome (caused by the bone marrow producing faulty blood cells) have been reported very rarely.

Leiomyosarcoma (a rare cancer of the smooth muscle cells), development of another type of cancer, pneumonia and multi-organ failure have also been reported in rare cases. Due to the dose-dense schedule of temozolomide, the risks listed could be more likely to occur or worse if the event does occur.

All side effects will be treated in the best way possible and this may involve anti-nausea medications, hospitalization for antibiotics, platelet transfusions, stool softeners or laxatives, and steroids or antihistamines for allergic reactions. Prolonged antibiotic prophylaxis may be recommended in cases where the lymphocyte count is low. There are guidelines for reducing the doses of chemotherapy drugs or eliminating them altogether should you experience serious or intolerable side effects. To avoid potential drug interactions, you should consult your physician or pharmacist before taking any new medications, including over the counter (non-prescription) medications.

Reproductive risks/Pregnancy:

You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breast feed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. If you are a woman of childbearing age, and have not been surgically sterilized (tubal ligation or hysterectomy), you must have a pregnancy test before enrolling in this study.

Temozolomide may make it harder for a woman to become pregnant or for a man to cause a woman to become pregnant even after the chemotherapy has been completed. There is currently not enough information available about temozolomide in men and women of childbearing age who subsequently tried to have children to know how likely problems will be.

What are the goals of the research?

The goal of the study is to take care of your condition with the best available treatments. The study will compare the overall survival and the time until tumor progression of patients treated in arm A (standard dose temozolomide) with the outcome of patients treated in the experimental arm B (dose-intensive temozolomide).

Further, we will compare side effects and tolerance to the treatment between the two administration schedules.

As second major objective is to try to identify who are the patients most likely to benefit from this specific treatment based on molecular markers analyzed on the tumor specimen previously resected. This will ultimately allow to developing new treatments more specific for each patients tumor characteristics.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope the dose-dense schedule of temozolomide will be more useful against your brain tumor compared to the usual treatment, there is no proof of this yet.

The information learned from this study will help improve treatments for brain tumors. **This research will teach us more about cancer and might enable us to improve treatments. This information will help future cancer patients. Nobody can predict whether you will directly benefit from participating in the clinical trial.**

What other choices do I have if I do not take part in this study?

Your participation in this clinical trial is entirely voluntary and you will be given sufficient time to decide whether or not you wish to participate. You are free to decide at any time without giving any reason that you no longer wish to participate in the trial. Such decision will not affect your subsequent treatment or relationship with your treating doctor or the hospital staff in any way. Medical data collected during your participation to the clinical trial as well as follow up data which will still be prospectively collected will be kept for research and analysis unless you specify otherwise.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

If you decide not to participate in this trial, your physician will discuss with you alternative non-investigational treatment options. This is likely going to be the same treatment according to the standard arm A of this trial.

Will my medical information be kept private?

Data are housed at RTOG Headquarters in a password-protected database. Your data will also be kept in a confidential file at EORTC.

We will do our best to make sure that the personal information in your medical record will be kept private. All persons having access to your medical records are strictly held to keep the medical secret. Data will be coded and recorded in a computerized format, here only date of birth and a personal code number will appear, which does not allow to identify you outside the treating medical center.

Your consent for participation in this Protocol includes your consent to allow the use of the data in your medical/clinical record to be used for research purposes. Your consent also includes allowing this data to be linked to data coming from other sources (such as cancer registries, medical/clinical records, ...). All data (personal, clinical, economic and data coming from research on biological material) collected on your behalf will be treated in compliance with the European and national applicable laws.

Data will exclusively be used for approved research projects aiming at improving understanding and treatments of brain tumors.

In order to assure the accuracy of the computerized information, the recorded medical information may be checked by authorized persons under strict confidentiality by health authorities, representatives of the sponsoring cooperative groups (EORTC / RTOG) or other duly authorized persons, including potentially representatives from the company supporting this trial and supplying the trial medication. With the exception of access by duly authorized persons, your personal data on your medical record and all information therein will be kept strictly confidential.”

What are the costs of taking part in this study?

The medical care like most clinical visits, radiological and blood exams are part of the routine medical practice and will be charged to your health insurance. However, the chemotherapy drugs (temozolomide) given after the end of radiotherapy will be provided for free for all patients by the manufacturer Schering-Plough Pharmaceuticals, Kenilworth, NJ/USA, irrespective whether you are treated in the standard arm or in the experimental treatment arm. Taking part in this study will not cost your insurance company more than the cost of getting regular cancer treatment.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor if you feel that you have been injured because of taking part in this study. The sponsor of the Study is the European Organisation for Research and Treatment of Cancer (EORTC). This clinical trial is conducted under the legal framework of the EORTC with partial financial contribution of the pharmaceutical company Schering-Plough. EORTC as sponsor of the study has concluded a clinical trial insurance according to the applicable law of your country. This insurance covers the risks related to your participation in this study.

Ethical approval

This research protocol has been submitted and approved to the ethics committee responsible for the hospital or country where you receive your care. The mission of the Ethics committee is to verify that all conditions with respect to your safety and rights are respected. The protocol has also been approved by the Health Regulatory Authorities in your country.

Approval to this research has been given by the Ethics Committee of..... on

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

In case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

Please take your time to consider this information and do not hesitate to ask further questions to your doctor if anything is unclear. For any further question you may have, do not hesitate to ask your physician or you may contact the local study coordinator, Dr., address.....phone no.

If you consent to join this trial, you will be given a telephone number of the hospital that you can contact at any time if you feel unwell or have further questions. With your agreement, your family doctor will also be informed about your taking part in this trial and what is involved.

You will receive a copy of this document. You will also receive a copy of the informed consent form to be signed by you and your physician.

About Using Tissue for Research

As explained above, one goal of this research is to identify specific molecular markers in the tumor in order to develop more specific and personalized treatment in the future. The tumor tissue removed by the neurosurgeon has allowed to establishing the precise cancer diagnosis and tumor type. For this not all tissue needed to be analyzed, the remaining tissue is necessary to determine the MGMT gene status (described previously). Further, we intent to test the tumor tissue in a anonymous way for many other markers or genes in order to have a better understanding why these tumors develop, and to develop new and more specific, more effective and also less toxic treatments. These studies are essential components of the clinical trial and therefore permission to use the tissue block or frozen tumor tissue is mandatory. Further, it may be necessary to have a small blood sample and/or urinary sample available for comparison and other analyses. This may also allow to developing novel tests for easy monitoring or early diagnosis in the future.

Why do I need to give my consent now?

Some of this research will only be conducted after the clinical trial has been completed, and we do not know today what will be the best methods or markers to study in three to five years time. In order to have the tissue available in the future we need to receive your permission already today in order to keep this tumor tissue stored and perform the appropriate research at a later stage. All this will be done in an anonymous way and it will impossible to identify you personally. No individual information will become available to your you or your family, nor to any insurance company.

The biological material (tumor tissue, blood or urine) will not be used to investigate any genetic or hereditary disturbances. In the future, people who do research may need to know more about your health. However, as all records are kept in an anonymous and coded way, your identity will never be revealed.

Your consent for participation in this trial implies also consenting to the ancillary research on biological material. You agree that this material is stored for several years in an anonymized form. The biological material will be handled and stored at the institution where you are/were treated, or sometimes at the institution where the tests are/were being performed or a central laboratory mandated by the EORTC, in accordance with all existing applicable laws.

Benefits

The research that may be done with your tissue is not designed specifically to help you personally. It might help people who have brain tumors and other diseases in the future. This research will not have an effect on your care.

The aim is to learn more about causes for brain tumors, and derive potential strategies to prevent tumor development or for specific treatments.

Your tissue will be used only for the purpose of cancer research and will not be sold. The research done with your tissue may help to develop new products in the future.

It cannot be excluded that results from use of biological material could lead to acquisition of exclusive rights, which are based on research discoveries. You will not receive any financial return. Should there be any financial return for the EORTC, it will exclusively be reinvested in cancer research to improve cancer care and outcome.”

Data protection

Any research project conducted with this biological material will begin only if it has been previously reviewed and approved by the scientific committees of the EORTC and RTOG and by an Ethics/Scientific Committee according to all applicable laws.

Your consent allows the use of the data in your medical/clinical record or data resulting from research on tissue to be used for research purposes. It includes allowing this data to be linked to data coming from other sources (such as cancer registries, medical/clinical records,...).

Handling of biological material will be done in such a way, that scientists, analyzing it for research purposes, will not be able to find out your identity. All data (personal, clinical, economic and data coming from research on biological material) collected on your behalf will be treated in compliance with the European and national applicable laws.

About the EORTC

The EORTC (European Organisation for Research and Treatment of Cancer) just like its US counterpart RTOG (Radiation Therapy Oncology Group) is a cooperative group unifying major medical centers throughout Europe for the purpose of conducting clinical and translational cancer research. Over 200 medical centers and universities participate in the EORTC activities. Progress in cancer care frequently requires large international trials, for which the EORTC or the RTOG can provide the necessary framework.

The mission of EORTC, being a non-profit research organization, is to do everything it can in the best interests of cancer patients. Collaboration with third parties, including private companies, may be necessary for the EORTC to develop more effective treatments.

**PHASE III TRIAL COMPARING CONVENTIONAL ADJUVANT TEMOZOLOMIDE
WITH DOSE-INTENSIVE TEMOZOLOMIDE IN PATIENTS WITH NEWLY
DIAGNOSED GLIOBLASTOMA**

EORTC Study 26052 – 22053 (RTOG 0525)

Informed Consent

- I have been properly informed about the clinical trial and have been given sufficient time to consider my participation.*
- I have received a copy of the patient information sheet.*
- All my rights have been clearly explained to me.*
- I agree to participate in above described research study.*
- I accept that any data resulting from this clinical research study can be linked with other resources for cancer research purposes.*
- My participation is completely voluntary and I have the possibility to withdraw my consent at any time without explanation. This will not affect my relationship with my treating doctor. The data collected on my behalf will be strictly confidential and treated according to the European and national applicable laws.*
- I have been informed that the data (personal, clinical and biological material) collected may be used in the future for cancer scientific research purposes while confidentiality will be ensured.*
- I consent that tumor material to the extent available from previous surgery, as well as a blood specimen and urine specimen will be stored for future molecular translational and correlative studies. I accept collection, storage and research on biological material that I provide.*
- I am aware that the EORTC will possibly need to collaborate with other academic institutions or pharmaceutical industry for further research.*
- I agree that my biological material can be used for future cancer research by another academic institution/organization*
- I agree that my biological material can be used for future cancer research by the pharmaceutical company*
- I accept that results from the biological and molecular research may be linked with the clinical outcome data.*
- I have taken notice that in case of financial return of the research conducted, this will entirely reinvested by the EORTC and its partners for future cancer research.*
- I agree that my biological material, which is sent for a central pathology and laboratory for review may also be transferred to laboratory/hospitals, which are located in different countries /continent (e.g USA) that the hospital where I will receive protocol treatment.*

All data and material collected will be treated strictly confidential. Outside the treating institution there will only be a code including date of birth recorded, thus not allowing to identifying me individually. Data will be housed at RTOG Headquarters in a password-protected database. My data will also be kept in a confidential file at EORTC. All data will be treated in compliance with the European and national applicable laws.

My consent does not discharge the organizers or treating physicians from their responsibilities and I keep all my rights guaranteed by the law.

Patients Name:

Physicians or local investigators name:

Date and Signature

Date and Signature

Name and signature of
witness (if applicable)

This document has been prepared taking the following documents into account:

- ◆ World Medical Association Declaration of Helsinki, adopted by the 18th World Medical Assembly, Helsinki, Finland June 1964. Revised 1975, 1983, 1989, 1996 and on October 6, 2000 in Edinburgh, Scotland (www.wma.net).
- ◆ ICH-GCP Guidelines; Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), Sept. 1997.
- ◆ International Ethical Guidelines for Biomedical Research involving Human Subjects, Council for International Organizations of Medical Sciences (CIOMS), Geneva 1993.
- ◆ WHO: Operating Guidelines for Ethics Committee that Review Biomedical Research, Geneva, 2000.

European Union Directive on the protection of individuals with regard to the processing of personal data (Dir/95/46/EC)