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EORTC Brain Tumor Group

Phase III trial exploring the combination of bevacizumab and lomustine in patients with first recurrence of a glioblastoma

EORTC protocol 26101

(EudraCT number 2010-023218-30)
(NCT01290939)

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Protocol 26101

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<tr><td>Methodology</td><td>This is a randomized open label multicenter phase III trial.</td></tr>
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Number planed (Statistical design)
Number analyzed</td><td>The following hypothesis will be made:
In February 2013, a first analysis of the BELOB data was carried out. The outcome is summarized in the table below:
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[95% CI]</td><td>12 mo OS in %</td></tr>
<tr><td>LOMUSTINE</td><td>46</td><td>43 [29, 57]</td><td>30 [18-44]</td></tr>
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The baseline characteristics of patients in BELOB and in the phase II of the 26101 protocol were comparable.
For this phase III, it was assumed that OS9=40% in the LOMUSTINE arm and OS9=51.7% in the BEV/LOMUSTINE 90mg/m² arm. This corresponds to a hazard ratio, HR equal to 0.72. Based on a one-sided logrank test, at an overall significance level of 2.5% and a power of 80%, a total of 327 events are needed to show this reduction in the hazard of death of 28%. The accrual assumptions for the two arms in the phase III are summarized below:
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Based on these assumptions and assuming a continuation of the 2:1 randomization scheme a total of three hundred patients must be recruited (289 in BEV/LOMUSTINE and 144 in LOMUSTINE). End of recruitment is expected to occur in December 2014. The targeted number of events should be observed in August 2015.</td></tr>
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Diagnosis and main criteria for inclusion	♦ Histologically confirmed de novo glioblastoma (primary) with unequivocal first progression after radiotherapy (RT) concurrent/adjuvant chemotherapy at least 3 months off the concomitant part of the chemoradiotherapy ♦ Availability of biological material for central review processes and translational research projects ♦ No more than one line of chemotherapy (concurrent and adjuvant temozolomide based chemotherapy including in combination with another investigational agent is considered one line of chemotherapy) Chemotherapy must have been completed at least 4 weeks prior to randomization if prior temozolomide ♦ No current or recent (within 4 weeks before randomization) treatment with another investigational drug ♦ No prior treatment with bevacizumab or other VEGF inhibitors or VEGF-Receptor signaling inhibitors ♦ No prior treatment with nitrosoureas ♦ Patient may have been operated for recurrence. If operated ♦ residual and measurable disease after surgery is not required but surgery must have confirmed the recurrence ♦ a post-surgery MRI should be available within 48 hours following surgery ♦ Surgery completed at least 2 weeks before randomization and patients should have fully recovered ♦ Craniotomy or intracranial biopsy site must be adequately healed free of drainage or cellulitis, and the underlying cranioplasty must appear intact at the time of randomization. ♦ Study treatment should be initiated > 28 days following the last surgical procedure (including biopsy, surgical resection, wound revision, or any other major surgery involving entry into a body cavity) ♦ For non operated patients recurrent disease must be at least one bi-dimensionally measurable contrast-enhancing lesion with clearly defined margins by MRI scan, with minimal diameters of 10 mm, visible on 2 or more axial slices 5 mm apart, based on MRI scan done within two weeks prior to randomization ♦ Stable or decreasing dosage of steroids for 7 days prior to the baseline MRI scan. ♦ Patients who require anti-convulsant therapy must be taking non-enzyme inducing antiepileptic drugs (non-EIAED). Patients previously on EIAED must be switched to non-EIAED at least 2 weeks prior to randomization ♦ No non tumor related surgery or other invasive procedures (major surgical procedure, open biopsy or significant traumatic injury) within 4 weeks prior to randomization, or anticipation of the need for major

	surgery during the course of the study treatment. ♦ No core biopsy or other minor surgical procedure within 7 days prior to randomization. Placement of a central vascular access device (CVAD) if performed at least 2 days prior to study treatment administration is allowed ♦ No radiotherapy within the three months prior to the diagnosis of progression. ♦ No radiotherapy with a dose over 65 Gy, stereotactic radiosurgery or brachytherapy unless the recurrence is histologically proven ♦ Before patient randomization and study related procedures (that would not have been performed as part as standard care), written informed consent must be given according to ICH/GCP, and national/local regulations. Informed consent should also be given for biological material to be stored and used for future research on brain tumors.
Treatment Test product, dose and mode of administration	Arm 1: Lomustine 90 mg/m² PO every 6 weeks (cap. 160 mg) + bevacizumab 10 mg/kg IV every 2 weeks until one of the withdrawal criteria have been met (followed by best investigators choice at further progression). In the absence of hematological toxicity > grade 1 during the first cycle the dose of lomustine can be escalated to 110 mg/m² (cap. 200 mg) in the second cycle. Arm 2 (control arm): Lomustine single agent 110 mg/m² PO every 6 weeks (cap. 200 mg) until one of the withdrawal criteria have been met (followed by best investigators choice at further progression).
Duration of treatment	♦ Patients will be treated until: ♦ disease progression ♦ patient refusal ♦ intolerable toxicity precluding further protocol therapy ♦ best patient's interest ♦ start of any other anti-cancer agent/modality (surgery at recurrence is allowed) ♦ pregnancy
Reference therapy, dose and mode of administration	Arm 2 (control arm): Lomustine single agent 110 mg/m² PO every 6 weeks (cap. 200 mg) (followed by best investigators choice at further progression).
Criteria for evaluation Efficacy	For this study, the primary endpoint is overall survival with progression free survival measures and measures of patient functioning as secondary endpoints. Response is a secondary endpoint, which will only be assessed in patients with measurable disease at the time of randomization. The radiological assessment of response and progression in trials on brain tumors treated with anti-angiogenic agents can be difficult. VEGF inhibition also normalizes abnormal vessel permeability which may result in pseudo-response. The classical Macdonald's criteria emphasize the area of contrast enhancement, which is today done with T1 weighted MR

	images. For this study, modified RANO criteria will be used to diagnose response and progression (Ref. 30). Compared to Macdonald's criteria, two major changes are present in the RANO criteria: Progressive lesions on T2 weighted images or FLAIR images will also be considered progression, regardless of the classical response as determined by T1 MR images after contrast administration. However, RANO criteria did not quantify a requirement for T2 or FLAIR changes that are considered progression. For the purpose of this protocol a 25% increase in sum of the products of perpendicular diameters of areas with abnormalities on FLAIR/T2 images compared to the nadir time point (point with the smallest FLAIR/T2 abnormalities) is considered progression, modified RANO will be then used. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if PD is confirmed at the next follow-up, the earlier date must be used as the date of progression.
Safety	CTCAE Version 4.0; NYHA criteria for heart failure
Statistical methods	All efficacy analyses will be realized in the intent-to-treat population, except response, which will only be assessed in patients with measurable disease at the time of randomization. For the primary analysis of OS, PFS, and Neurological Deterioration Free Survival (NDFS), the Cox proportional hazards model will be fitted with the treatment (BEV+LOMUSTINE compared to LOMUSTINE alone) adjusted by the stratification factors at randomization and by a variable indicating if the patient was recruited in the phase II or in the phase III. The Kaplan-Meier technique will be used to obtain estimates of OS, PFS and NDFS. Medians, OS9, OS12, OS24, PFS6, PFS12, NDFS6, NDFS12 will be presented. Logistic regression (without intercept) will be used to compare objective response and complete response between the two arms after adjustment for stratification factors at randomization and by a variable indicating if the patient was recruited in the phase II or in the phase III. PFS and response analyses will be presented both based on investigator (primary) and centrally reviewed response data (secondary). Objective and complete response according to RANO, modified RANO, and Macdonald criteria will be cross-tabulated. Kappa statistics will be computed to quantify the agreement between the two criteria. Discrepancies will be listed with detailed descriptions. The distributions of distant or diffuse progression in each arm be tabulated with frequencies, percentages rates will be presented. Fisher exact test will be used to compare the distributions between arms. All estimates will be presented with appropriate 95% confidence intervals. The safety and tolerability analyses will be presented at baseline, up to first progression. Severe grades which did not resolve after progression or

	emerged during follow-up will be identified and listed.
Translational research	The translational research program will mostly focus on the prognostic and predictive value of MGMT methylation status, IDH1 mutational status and of biomarkers of the VEGF pathway. In addition, an imaging project will be dedicated to pilot and benchmark the modified RANO criteria.
Quality of Life	The current experience with angiogenesis inhibiting agents in recurrent GBM has demonstrated considerable difficulties with assessing response and progression in bevacizumab treated patients. So, we hypothesize that measures of clinical functioning will yield information (HRQoL, need for steroids, cognitive functioning) that is critical for the patient perception of clinical benefit. HRQoL/neurocognitive assessments and their variations will be correlated with changes on contrast enhanced T1 weighted and on T2 weighted/FLAIR MR images. Combined assessments of QoL, of neurocognitive functions and of the neurological deterioration will allow a comprehensive assessment of the clinical status of the patient.

1 Background and introduction

1.1 Introduction

Gliomas are the most frequent primary brain tumors in adults, with an annual incidence between 4 and 5 per 100.000 inhabitants (Ref. 1, Ref. 2, Ref. 3, Ref. 4). According to the CBTRUS registry in the USA, each year over 20.000 patients are diagnosed with a glioma. Low-grade diffusely infiltrating glioma and anaplastic glioma constitute about 30-40% of all glial tumors in adults. Glioblastoma present most of the remaining 60-70% of glial tumors. The clinical course of glioblastoma is almost invariably fatal, with a medium survival time of 12-15 months (Ref. 5). Major prognostic factors for survival are age and performance status at the time of diagnosis (Ref. 6, Ref. 7). No curative treatment exists. Standard treatment consists of surgical resection to the extent feasible followed by radiation and concomitant and adjuvant temozolomide therapy.

Once a glioblastoma recurs, the treatment options are usually limited and no uniformly accepted standard of care exists (Ref. 5). The important prognostic factors in this setting are age, performance status and steroid dose. Other factors of relevance may include re-resection (tumor burden), promoter methylation status of O6-methyl-guanine-methyl transferase (MGMT). Many patients deteriorate rapidly at the time of recurrence, making further treatment meaningless. Some patients have recurrences that allow re-resection but most patients have lesions inaccessible for surgery (e.g., involvement of the corpus callosum, deeply seated lesions or lesions in eloquent areas). Re-irradiation is rarely an option, due to the hazards of cumulative neuro-toxicity. Chemotherapy is commonly suggested for recurrent disease. Unfortunately, results of chemotherapy in glioblastoma are poor and only few agents have demonstrated activity against recurrent glioma. Overall survival after relapse is poor. Therefore, relapsing glioblastoma continues to represent a clinically unmet need, and more effective treatments are urgently needed.

1.2 Diagnosis

Glioblastoma is considered as a grade IV tumor. According to the WHO 2007, classification of gliomas is based on the presence or absence of 4 histologic criteria: (1) nuclear atypia, (2) mitoses, (3) endothelial proliferation, and (4) necrosis. Grade I tumors have none of the criteria, grade II have at least 1, grade III have at least 2, and grade IV (glioblastoma) have at least 3 or 4 criteria present. Prominent microvascular proliferation and/or necrosis must be one of the criteria for glioblastoma. The distinction from grade IV tumors or glioblastoma is depending on the histological subtype: in tumors with an astrocytic phenotype, the presence of endothelial proliferation and necrosis automatically leads to the diagnosis of glioblastoma, where in anaplastic oligoastrocytoma (AOA) and Anaplastic Oligodendroglioma (AOD) endothelial proliferation is still considered compatible with a grade III tumor (Ref. 8). In AOD the presence of necrosis is still considered compatible with a grade III tumor, but in AOA the presence of necrosis leads to the diagnosis of glioblastoma.

1.3 Chemotherapy and outcome in recurring glioblastoma

Procarbazine and nitrosoureas are modestly effective as systemic agents, although they were evaluated much before temozolomide and rigorous trials meeting current standards are absent. Concomitant and adjuvant temozolomide to radiotherapy is now the standard of care in newly diagnosed patients; however its use at the time of recurrence is debatable and in this setting nitrosoureas are currently widely used, in particular Lomustine (CCNU). A recent randomized study on recurrent glioblastoma that used lomustine noted a 19% progression free survival probability at 6 months with lomustine, similar to what has previously been observed with temozolomide in this indication (Ref. 9). Further lomustine is used as comparator in most current trials (e.g., EORTC 26083 and REGAL). The REGAL trial aiming at proving superiority of a vascular endothelial receptor 2 antagonist (cediranib) alone or in combination with

lomustine over lomustine alone was negative as reported at a scientific meeting (T Batchelor et al.,, ESMO 2011 and Batchelor et al. J Clin Oncol in press. However, all data presented so far also speak for relevant activity of lomustine in this trial, and this drug is currently widely used as a salvage regimen for recurrent glioblastoma, despite its modest activity.

1.4 Bevacizumab and recurrent glioblastoma

In recent years studies on anti-angiogenic agents received considerable attention because of high response rates. Trials on the above mentioned tyrosine kinase inhibitor cediranib and the humanized monoclonal antibody against circulating VEGF bevacizumab have attracted the most interest. Until now phase II trials with anti-angiogenic agents have provided promising results that require confirmation in larger and, even more important, controlled trials (Ref. 18). Indeed, the randomized REGAL trial failed to provide evidence of better outcome in cediranib treated recurrent glioblastoma patients, despite high response rates in uncontrolled phase II studies. For bevacizumab, the promising activity observed in recurrent glioblastoma remains to be confirmed, despite the large number of uncontrolled phase II trials that have been conducted. In particular properly powered studies showing Overall Survival benefit from bevacizumab in recurrent glioblastoma are still lacking.

Indeed, all but one study on bevacizumab in recurrent glioma were uncontrolled phase II studies. As of today only one randomized, non-comparative phase II study has been reported, but with an irrelevant control. This randomized phase II study observed a PFS6 of 43% after bevacizumab given as single agent and of 50% if given in combination with irinotecan (Ref. 18). OS was very similar in both groups (approximately 9 months) (Ref. 18). Compared to the usually less than 10% obtained in recurrent glioblastoma, the observed response rates were exceptionally high (40-45% as judged by the local investigators, 28-38% after central review), and PFS6 (the agreed upon endpoint in trials on recurrent glioblastoma) is twice as high compared to trials on temozolomide and nitrosoureas. Based on the high response rates observed in this trial, in the US bevacizumab has been conditionally approved for use in recurrent glioblastoma. The registration application of bevacizumab for this indication in Europe has however been denied, because of lack of appropriately controlled trials (i.e., with a control arm without bevacizumab).

As part of the US conditional approval, a randomized phase III trial has been conducted in newly diagnosed glioblastoma (AVAglio, NCT00943826). In this trial, bevacizumab is added to the standard of care (combined chemo-irradiation with temozolomide). The first results were presented at the Society for Neuro-Oncology meeting 2012 (Chinot, oral communication SNO 2012). It was reported that the addition of bevacizumab increased progression free survival (HR 0.64, 95% CI 0.55–0.74), but not overall survival (HR 0.89, 95% CI 0.75–1.07, p=0.2135). Final results presented at the 2013 Annual Meeting of the American Society of Clinical Oncology (ASCO) confirm the lack of survival benefit from the addition of bevacizumab to temozolomide. However, this trial will not address the role of bevacizumab in recurrent glioblastoma, nor the best timing of administration (in newly diagnosed patients or at recurrence).

1.5 EORTC trial 26101- prior amendment #1

EORTC trial 26101 prior amendment #1 intended to document evidence for a therapeutic role of bevacizumab as well as the most favorable approach to treatment optimization for sequencing of the combination of bevacizumab and lomustine. This trial was set up as a 4-arm randomized phase II non-comparative trial, focusing on the sequencing of lomustine and bevacizumab in recurrent glioblastoma. The treatment arms are: Arm 1: Lomustine 90 mg/m² every 6 weeks (cap. 160 mg) + bevacizumab 10 mg/kg every 2 weeks; Arm 2: Lomustine 110 mg/m² every 6 weeks (cap. 200 mg) until PD, then switch to bevacizumab 10 mg/kg every 2 weeks; Arm 3: Bevacizumab 10 mg/kg every 2 weeks until PD then bevacizumab 10 mg/kg every 2 weeks + lomustine 90 mg/m² every 6 weeks (cap. 160 mg); Arm 4 (control arm): Lomustine single agent 110 mg/m² every 6 weeks (cap. 200 mg). The randomization ratio between

arms 1-4 is 2:2:2:1; the primary endpoint is OS at 12 months. The target accrual is 249 patients and the current accrual (26 June 2013) is 249 patients. We expect study closure for patient entry latest in the third quarter of 2013 based on the current accrual rate. The trial progress report generated in March 2013 did not reveal any safety issues. The trial will be one of the first to report on a properly controlled trial with bevacizumab in recurrent glioblastoma. Major assets of the trial are the central neuroradiology review on a uniform imaging protocol as a secondary analysis and the chance for tissue and plasma biomarker analyses on a large proportion of patients.

The phase II trial is expected to reach its intended number of patients in Q3 2013. Because of the described below new data coming out of the Dutch BELOB trial, a modified continuation is indicated.

1.6 The Dutch BELOB trial

Prior to activation of EORTC trial 26101 a similar trial was initiated in the Netherlands. This Dutch BELOB trial was a randomized phase II trial (principal investigator M.J. van den Bent; NTR1929) designed to identify whether in recurrent glioblastoma the activity of bevacizumab single agent or of bevacizumab in combination with lomustine warrants further investigation. As the control arm, single agent lomustine was taken. In view of all discussions on the value of progression-free survival in trials on anti-VEGF agents in glioblastoma, the primary endpoint of this study was OS at 9 months; P0 was set at 35% and P1 at 55%. Progression was defined using RANO criteria. A safety review after the first 10 patients in the combination arm was preplanned. Patients were assigned to bevacizumab 10 mg/kg iv every 2 weeks, bevacizumab 10 mg/kg iv every 2 weeks and 110 mg/m^2 lomustine every 6 weeks, or lomustine 110 mg/m^2 every 6 weeks. Because of grade 3 and 4 asymptomatic hematological toxicity in this arm in the first 8 patients, the dosage lomustine in the combination arm was lowered to 90 mg/m^2. With this dosage, treatment was well tolerated and no further undue toxicities were observed.

In February 2013, a first analysis of the BELOB data was carried out. Between December 2009 and November 2011, 153 patients were enrolled of whom 148 were considered eligible. Median age was 57 years (range, 24-77) and median WHO PS was 1. With respect to prognostic factors groups were well balanced. The outcome is summarized in the table below:

Treatment	n	9 mo OS in % [95% CI]	Median PFS (mo)	6 mo PFS in % [95% CI]
bevacizumab	50	38 [25, 51]	3	14 [6, 25]
lomustine	46	43 [29, 57]	1	11 [4, 22]
bevacizumab/lomustine 90 mg/m^2	44	59 [43, 72]	4	41 [26, 55]
bevacizumab/lomustine 110 mg/m^2	8	88 [39, 98]	11	50 [15, 78]

(n: number of patients, PFS: progression-free survival, CI: confidence interval, mo: months)

The OS at 9 months result of this trial implies that further investigation of the combination lomustine/bevacizumab in recurrent glioblastoma in a phase III study is warranted.

1.7 Rationale for the phase II to phase III amendment

The therapeutic need in recurrent glioblastoma is evident from the published OS data in that situation, usually ranging from 5 to 8 months. In the absence of phase III trials the role of bevacizumab in brain tumors is still not clear and none of the ongoing phase III trials assesses the role of bevacizumab at progression. The BELOB trial provides a strong rationale for a phase III trial on the role of bevacizumab in glioblastoma progressive after combined chemo-irradiation with temozolomide. Both the BELOB trial and the ongoing EORTC study 26101 show that the combination lomustine 90 mg/m^2 p.o. every 6 weeks and bevacizumab 10 mg/kg i.v. every 2 weeks is overall well tolerated. Therefore, a phase III evaluation comparing the combination lomustine/bevacizumab to the current standard of care, lomustine is indicated. This can be done in the most efficient way (both in terms of time and patient burden) by amending the EORTC study 26101.

The present amendment proposes to modify the ongoing EORTC 26101 trial into a phase III trial. This will be done by expanding the arm that based on the BELOB data is most likely to yield superior outcome (arm I: the combination of lomustine and bevacizumab), and compare the outcome of this arm to single agent lomustine (Arm IV) in a randomized phase III trial. This will be achieved by continuing enrollment in arm I (bevacizumab and lomustine combination) and arm IV (lomustine single agent) after completion of enrollment in arms II and III. The major advantage of this approach is that no new trial needs to be developed, and that the currently enrolled patients in these arms will not be lost for the phase III question.

This is scientifically justifiable because at present the result of the still accruing EORTC 26101 study are not known. Moreover, an interim analysis of EORTC 26101 is at present not feasible because of the presently immature follow-up. The process of transforming an ongoing phase II study (with all basic trial requirements essentially in place) into a phase III study is an attractive and very efficient way to generate phase III data, compared to initiating a fully new phase III study. It is anticipated that in Q3 2015 the first results of the phase III trial will be available. There is no way that a newly designed phase III trial can generate as quickly mature results. An amended trial would further strengthen the imaging and biomarker research projects, which may help to identify patients with the biggest benefit by tumor or plasma signatures. It is expected that by the time the amendment is activated EORTC 26101 will have met its original accrual objective, thus the phase II objectives will still be answered.

There will be no change in the treatment, follow-up or the handling of the data for the patients already randomized and treated in the phase II part of the trial.

The primary objectives of the phase II part were to document the therapeutic role of bevacizumab as well as the most favorable approach to treatment optimization for sequencing combination of bevacizumab and lomustine. These questions will be answered as the analysis of the phase II part of the trial will be performed and published independently.

1.8 Rationale for the used end point

A phase II trial with bevacizumab suggested high radiological response rates with initial response in almost every patient (Ref. 29) and possibly prolongation of overall survival, but only in a relatively small subset of patients. In some patients with extensive peritumoral edema bevacizumab produces undoubtedly a clinical benefit and will have a steroid-sparing effect; however its exact role and place in the management of glioma remains to be evaluated. Furthermore, its advantages and limitations may require careful study of relapse patterns (there is some concern that it may stimulate tumor migration and lead to a more aggressive diffuse phenotype), steroid requirements and toxicity (long term corticosteroid use is associated with substantial morbidity, bevacizumab has its inherent risks of hypertension and hemorrhage), quality of life and neurological function. Specific interest exists also to evaluate imaging, tissue or plasma markers for response/efficacy/outcome. Based on the above parameters the primary end point of the phase II part of EORTC 26101 overall survival at 12 months (OS 12) was chosen along with secondary

endpoints of response, morphological pattern of relapse, progression free survival (PFS), complete safety profile, quality of life (QoL) and steroid use. For the phase III prolongation of EORTC 26101 (taking into account the patients enrolled in the phase II part), the primary endpoint will be overall survival. Treatment at progression will be left to the discretion of the investigator, which brings the possibility of cross over to bevacizumab treatment. Therefore, efforts will be made to open new sites for the phase III part of this study, and new sites should preferentially be in countries where cross-over should not be expected.

1.9 Trial design

This will be a multicenter open label phase III study, with overall survival as the primary endpoint.

Arm 1: oral lomustine 90 mg/m^2 every 6 weeks until one of the treatment discontinuation criteria have been met and i.v. bevacizumab 10 mg/kg every two weeks in cycles of 6 weeks

Arm 2: oral lomustine 110 mg/m^2 every 6 weeks until one of the treatment discontinuation criteria have been met.

2 Objectives of the trial

2.1 General objectives

The primary objective of this study is to investigate whether the addition of bevacizumab to lomustine improves overall survival (OS) in patients with recurrent glioblastoma compared to treatment with lomustine alone.

2.2 End-points

2.2.1 Primary endpoint

The primary endpoint will be overall survival.

2.2.2 Secondary endpoints

Secondary endpoints will be:

- Progression free survival distribution according to modified RANO criteria (PFS: distribution, median PFS, PFS 6 and PFS 12)
- Response distribution, objective response rate, duration of response (according to modified RANO criteria), progression pattern based on MRI (Ref. 29).
- Overall survival: OS 9, OS 12 and OS 24
- Progression evaluated according to Ref. 29
- Complete safety profile according to CTCAE version 4.0; NYHA criteria will be used for assessing heart failure
- Patient-oriented criteria: clinical/neurological deterioration free survival, steroid use, quality of life (reported by patients and caregivers/relatives) and development of cognitive deterioration.
- Translational research: to gain insight into the molecular basis of gliomas and an emphasis on the identification of biomarkers to translate into advances in screening, diagnosis, treatment and monitoring with improved clinical outcomes.

3 Patient selection criteria

- Histologically confirmed de novo glioblastoma (primary) with unequivocal first progression after RT concurrent/adjuvant chemotherapy at least 3 months off the concomitant part of the chemoradiotherapy
- Availability of biological material (tumor) for central review processes and translational research projects (tumor and blood)
- No more than one line of chemotherapy (concurrent and adjuvant temozolomide based chemotherapy including in combination with another investigational agent is considered one line of chemotherapy). Chemotherapy must have been completed at least 4 weeks prior to randomization if prior temozolomide
- No current or recent (within 4 weeks before randomization) treatment with another investigational drug
- No prior treatment with bevacizumab or other VEGF inhibitors or VEGF-Receptor signaling inhibitors
- No prior treatment with nitrosoureas
- Patient may have been operated for recurrence. If operated:
    - residual and measurable disease after surgery is not required but surgery must have confirmed the recurrence
    - a post-surgery MRI should be available within 48 hours following surgery
    - Surgery completed at least 2 weeks before randomization and patients should have fully recovered
- Craniotomy or intracranial biopsy site must be adequately healed free of drainage or cellulitis, and the underlying cranioplasty must appear intact at the time of randomization.
- Study treatment should be initiated > 28 days following the last surgical procedure (including biopsy, surgical resection, wound revision, or any other major surgery involving entry into a body cavity)
- For non operated patients recurrent disease must be at least one bi-dimensionally measurable contrast-enhancing lesion with clearly defined margins by MRI scan, with minimal diameters of 10 mm, visible on 2 or more axial slices 5 mm apart, based on MRI scan done within two weeks prior to randomization
- Stable or decreasing dosage of steroids for 7 days prior to the baseline MRI scan.
- Patients who require anti-convulsant therapy must be taking non-enzyme inducing antiepileptic drugs (non-EIAED). Patients previously on EIAED must be switched to non-EIAED at least 2 weeks prior to randomization
- No non tumor related surgery or other invasive procedures (major surgical procedure, open biopsy or significant traumatic injury) within 4 weeks prior to randomization, or anticipation of the need for major surgery during the course of the study treatment.
- No core biopsy or other minor surgical procedure within 7 days prior to randomization. Placement of a central vascular access device (CVAD) if performed at least 2 days prior to study treatment administration is allowed
- No radiotherapy within the three months prior to the diagnosis of progression
- No radiotherapy with a dose over 65 Gy, stereotactic radiosurgery or brachytherapy unless the recurrence is histologically proven

- No previous other malignancies, except for any previous malignancy which was treated with curative intent more than 5 years prior to randomization, and except for adequately controlled limited basal cell carcinoma of the skin, squamous carcinoma of the skin or carcinoma *in situ* of the cervix
- Absence of any cardiovascular disorder, including but not limited to:
  - No history of myocardial infarction, unstable angina within 6 months prior to randomization
  - No "New York Heart Association" (NYHA) Grade II or greater congestive heart failure, or serious cardiac arrhythmia requiring medication.
  - No significant vascular disease (e.g. aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to randomization
  - No prior history of hypertensive crisis or hypertensive encephalopathy
  - No inadequately controlled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 m Hg)
- Absence of any thrombotic or hemorrhagic event, including but not limited to:
  - No evidence of recent hemorrhage on MRI of the brain. However, patients with clinically asymptomatic presence of hemosiderin depositions, resolving hemorrhagic changes related to surgery, and presence of punctate hemorrhage in the tumor are permitted entry into the study
  - No history or evidence of inherited bleeding diathesis or coagulopathy with the risk of bleeding.
  - No arterial or venous thrombosis ≤ 6 months prior to randomization
  - No history of stroke or TIAs within 6 months prior to randomization
  - No history of pulmonary haemorrhage/haemoptysis ≥ grade 2 according to the NCI-CTCAE version 4.0 criteria within 1 month prior to randomization
  - Absence of current or recent (within 10 days of first dose of bevacizumab) use of aspirin (> 325 mg/day) or other NSAID with anti-platelet activity or treatment with dipyramidole, ticlopidine, clopidogrel or cilostaz.
  - International normalized ratio (INR) > 1.5 ULN and activated partial thromboplastin time (aPTT) > 1.5 × the ULN. Use of full-dose anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard in the institution) and the patient has been on a stable dose of anticoagulants for at least two weeks before randomization. As per ASCO guidelines, LMWH should be the preferred approach.
- Absence of known hypersensitivity:
  - to any part of the bevacizumab or lomustine formulations.
  - to Chinese hamster ovary cell products or other recombinant human or humanized antibody.
- No underlying or previous conditions that could interfere with treatment, including but not limited to:
  - No history of intracranial abscess within 6 months prior to randomization
  - No clinically serious (as judged by the investigator) non-healing wounds, active skin ulcers or incompletely healed bone fracture.
  - No history of active gastroduodenal ulcer(s).
  - No history of abdominal fistula as well as non-GI fistula, gastrointestinal perforation or intra-abdominal abscess within 6 months prior to inclusion.

- No evidence of active infection requiring hospitalization or antibiotics, within 2 weeks prior to randomization.
- No other diseases, interfering with follow up.

- Normal hematological functions: neutrophils $\geq 1.5 \times 10^9$ cells/l, platelets $\geq 100 \times 10^9$ cells/l and Hb $\geq$ 6.2 mmol/l (9.9 g/dl).
- Normal liver function: bilirubin < 1.5 x upper limit of the normal range (ULN), alkaline phosphatase and transaminases (ASAT) < 2.5 x ULN.
- Normal renal function: calculated (Cockcroft-Gault) or measured creatinine clearance > 30 mL/min; Urine dipstick for proteinuria < 2+. Patients with ≥ 2+ proteinuria on dipstick urinalysis at baseline should undergo 24 hours urine collection and must demonstrate ≤ 1 g of protein/24 hr.
- Age ≥ 18 years
- WHO Performance status 0 - 2
- Absence of pregnancy. Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and 6 months beyond stop of treatment in such a manner that the risk of pregnancy is minimized. In general, the decision for appropriate methods to prevent pregnancy should be determined by discussions between the investigator and the study subject. WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Females should not be breast feeding.
  - Post menopause is defined as: amenorrhea ≥ 12 consecutive months without another cause or for women with irregular menstrual periods and on hormone replacement therapy (HRT), a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL
  - Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicide) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (e.g., vasectomy) should be considered to be of childbearing potential.
  - Women of child bearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of investigational product.
  - Female patients within one year of entering the menopause must agree to use an effective non-hormonal method of contraception during the treatment period and for at least 6 months after the last study treatment.
- Males must agree to use an effective method of contraception during the treatment period and for at least 6 months after the last study treatment.
- Absence of any psychological, familial, sociological or geographical factors potentially hampering compliance with the study protocol and follow-up schedule; such conditions should be assessed with the patient before randomization in the trial.
- Before patient randomization and study related procedures (that would not have been performed as part as standard care), written informed consent must be given according to ICH/GCP, and national/local regulations. Informed consent should also be given for biological material to be stored and used for future research on brain tumors.

- Patients with a buffer range from the normal values of +/- 5 % for hematology and +/- 10% for biochemistry are acceptable. A maximum of +/- 2 days for timelines may be acceptable (one day for post operative MRI).

Important note: All eligibility criteria must be adhered to, in case of deviation discussion with Headquarters and study coordinator is mandatory.

4 Trial Design

This is a randomized open label multicenter late phase III trial (see objectives in chapter 2).

For detailed statistical considerations see chapter 8.

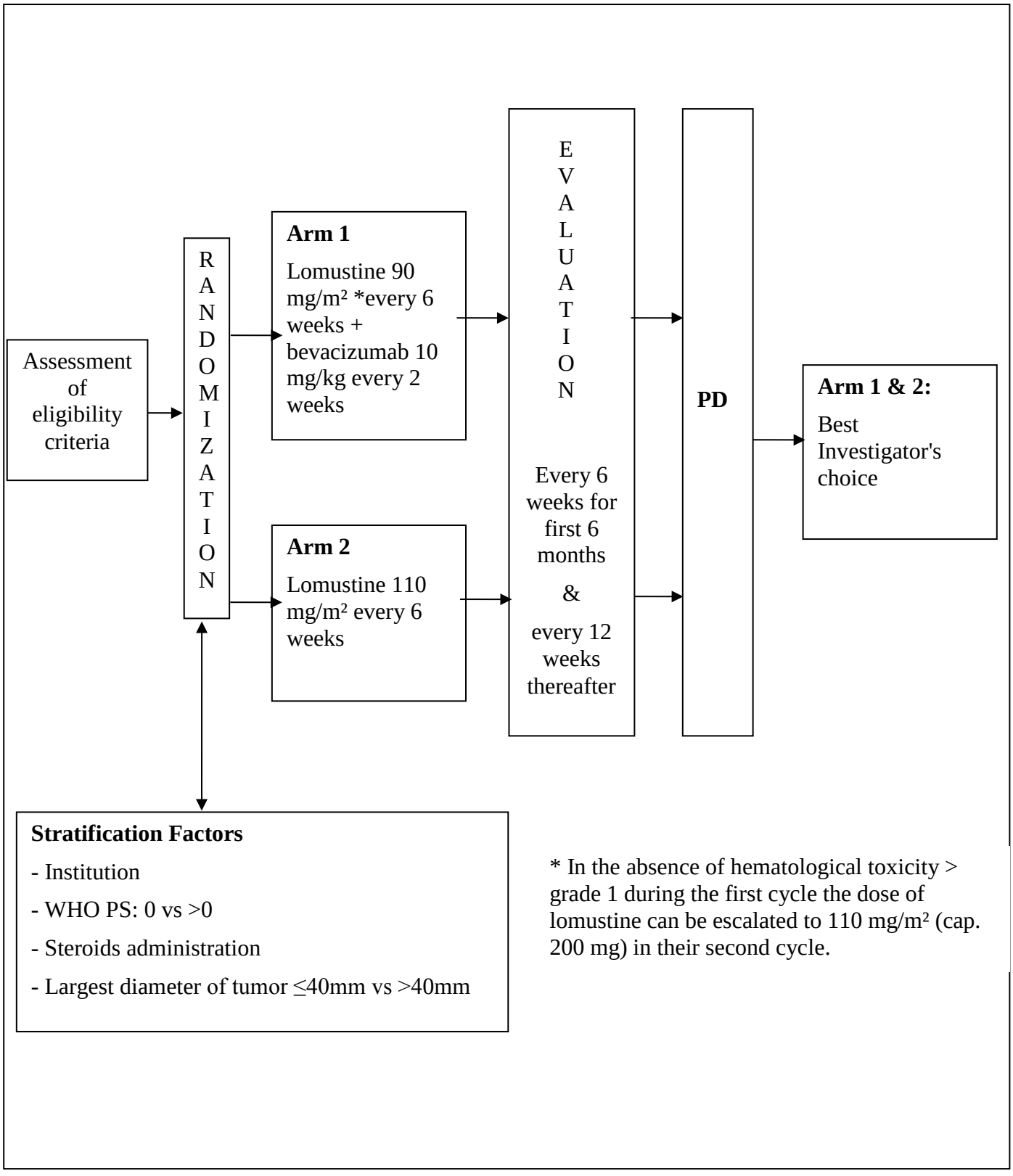
Patients will be randomized at the EORTC headquarters **after verification of the eligibility criteria (see chapter 3)** to receive one of the following:

Arm 1: Lomustine 90 mg/m² every 6 weeks (cap. 160 mg) + bevacizumab 10 mg/kg every 2 weeks (at further progression treatment will be according to investigators discretion). In the absence of hematological toxicity > grade 1 during the first cycle the dose of lomustine can be escalated to 110 mg/m² (cap 200 mg) in their second cycle.

Arm 2 (control arm): Lomustine single agent 110 mg/m² every 6 weeks (cap. 200 mg) (at further progression treatment will be according to investigators discretion).

One cycle will be defined arbitrarily (due to the lomustine sequencing) as 6 weeks for all arms. Day 1 of a cycle will be the first day when medication is taken.

Disease will be assessed by study-specific MRI according to a uniform protocol every 6 weeks for the first 6 months and every 12 weeks thereafter using both modified RANO and Macdonald's criteria (see chapter 7) until documented progression. There is an advanced MRI protocol including perfusion weighted MRI in addition for dedicated sites. Safety profile will be assessed separately for each cycle of therapy and every 12 weeks after the end of treatment until progression.


Assessment of eligibility criteria
RANDOMIZATION
Arm 1
Lomustine 90 mg/m² *every 6 weeks + bevacizumab 10 mg/kg every 2 weeks
Arm 2
Lomustine 110 mg/m² every 6 weeks
EVALUATION
Every 6 weeks for first 6 months
&
every 12 weeks thereafter
PD
Arm 1 & 2:
Best Investigator's choice
Stratification Factors
- Institution
- WHO PS: 0 vs >0
- Steroids administration
- Largest diameter of tumor ≤40mm vs >40mm
* In the absence of hematological toxicity > grade 1 during the first cycle the dose of lomustine can be escalated to 110 mg/m² (cap. 200 mg) in their second cycle.

5 Therapeutic regimens, expected toxicity, dose modifications

5.1 General information

5.1.1 Bevacizumab

5.1.1.1 Drug supplies

Drug supplies and re-supplies will be provided free of charge by Roche as long as patients are on protocol treatment (for procedures: see study manual that will be provided at the time of activation). The drug product is supplied in single-use glass vials, containing 400 mg of bevacizumab.

The investigator should ensure that the investigational product is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by Roche. If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product and contact EORTC HQ and Roche immediately. Pharmacy and clinic personnel should wear disposable chemotherapy gloves. Pregnant personnel should avoid exposure to the medication.

5.1.1.2 Packaging, dispensing and storage

Medication labels will comply with the legal requirements as applicable and will be printed in the local language. The storage conditions for study drug will be described on the medication label.

Bevacizumab vials are stable at 2−8°C (36−46°F). Bevacizumab vials should be protected from light. Do not freeze or shake. Diluted bevacizumab solutions may be stored at 2−8°C (36−46°F) for up to 8 hours. Store in the original carton until time of use.

Study drug will be prepared and dispensed by the pharmacist at the investigator’s institution. The pharmacy must maintain an individual record for the patient.

Drug supplies must be kept in an appropriate, secure area (e.g. locked cabinet) and stored in accordance with the conditions specified on the drug labels.

The clinical trial centers will keep a trial specific authorization list which determines the persons responsible for handling of the investigational drugs. The responsible person regarding the following will keep accurate records in the clinical trial centers:

- receipt of IMP supply from sponsor (clinical trial center, principal investigator, identification of IMP, Batch No, Formulation, kind and size of packaging, date of expiry, number of study drugs per participant, number of reserve study drugs, number of study drugs in total, patient identification number, date and time of receipt);
- location of storage of IMP;
- dispensing and returning of IMPs in the clinical trial center (date and time, number, batch no, patient identification number, volume of unused solution for injection when returning).

5.1.1.3 Drug reconciliation procedures

Accountability of the investigational study drug(s) is under the responsibility of the investigator and can be delegated to an appropriately qualified person.

Study drug accountability should be maintained by each site. Accountability records should include receipt date, batch numbers, expiry dates, patient SeqID, use by subject, dispensing dates, quantities (lowest unit) and stock balance.

In addition to internal accountability documentation on site, EORTC study-specific accountability and drug destruction forms will be supplied for this purpose, if site-specific forms are deemed not sufficiently detailed or do not provide enough information, according to EORTC Quality Assurance criteria.

The drug accountability and destruction forms will be verified during monitoring visits.

At the end of study, when all patients have stopped protocol treatment, complete drug reconciliation per batch should be available at the site for verification by EORTC in order to allow drug destruction or return procedure.

Both the unused and expired study medication must be destroyed, upon authorization of the sponsor, according to local regulations and procedures, and a copy of the destruction form must be returned to the EORTC Headquarters.

The medication provided for this trial is to be used only as indicated in this protocol and only for the patients entered in this study.

5.1.2 Lomustine

Lomustine is considered as a standard treatment for this indication and will not be provided nor reimbursed. Patients will receive lomustine from the pharmacist of the institution. Since temporary lomustine shortage occurred in the phase II part of the trial, close vigilance should be kept by the investigators to the availability of the compound in their respective countries.

5.2 Initial dose and administration

5.2.1 Bevacizumab

Bevacizumab at a dose of 10 mg/kg bodyweight i.v. in 90 min on day 1 is given every 2 weeks. Bevacizumab will be continued till one of the withdrawal criteria is met as defined in chapter 5.4. The subject's weight at baseline will be used to calculate the bevacizumab dose. If the weight changes by > 10% during the course of the study, the bevacizumab dose should be recalculated. The calculated dose has to be placed in a sterile, empty, i.v. bag and filled to 100 mL with 0.9% NaCl using aseptic technique.

Bevacizumab should never be dissolved in glucose 5%. Before and after administration of bevacizumab the line should be flushed with NaCl 0.9%.

If the first bevacizumab infusion is well tolerated, the infusion period may be shortened to 60 min, and if again well tolerated thereafter to 30 min.

Note: If the patient who receives bevacizumab experiences infusion-related adverse events, patient may receive pre-medication (as defined in 5.5.1.1) at the investigator's discretion prior to the next bevacizumab infusion. If pre-medication is required, the infusion time should be extended to 90 min. However, if the next infusion is well tolerated with pre-medication, the subsequent infusion time may then be decreased by 30 min per infusion to a minimum infusion time of 30 min as long as the patient continues to receive the same pre-medication

Other pre-medication schedules or other infusion times can be considered according to active guidelines in participating centers.

5.2.2 Lomustine

Arm 1: Lomustine 90 mg/m² orally on day 1 every 6 weeks (cap. 160 mg) In the absence of hematological toxicity > grade 1 during the first cycle the dose of lomustine can be escalated to 110 mg/m² (cap 200 mg) in their second cycle. Lomustine treatment will be repeated every six weeks.

Arm 2: Lomustine 110 mg/m² orally on day 1 every 6 weeks (cap at 200mg). Lomustine will be repeated every six weeks.

The doses may be rounded to the nearest 40 mg to accommodate tablet strengths. Lomustine treatment will be continued till one of the withdrawal criteria is met as defined in chapter 5.4. Dose will be rounded to the closest multiple of 40 mg.

5.3 Treatment duration

The administration of lomustine will be repeated every 6 weeks and bevacizumab every 2 weeks till one of the withdrawal criteria are met (see section 5.4 for the withdrawal criteria).

5.4 Withdrawal criteria

Whatever the disease status, study treatment will be discontinued in case of:

- disease progression:
- patient refusal
- intolerable toxicity precluding further protocol therapy
- best patient's interest
- start of any other anti-cancer agent/modality (surgery at recurrence is allowed)
- pregnancy

Patients discontinuing therapy in the absence of progression should not receive other cancer treatment before their disease progresses, unless this is clearly not in the interest of the patient.

5.5 Dose and schedule modifications

In the combination arm, dose reductions or delays should be made for the likely causative agent. If in the combination arm one of the agents should be stopped for any reason other than PD, the patient can continue on the other single agent alone. Patients who require a study treatment related delay for one of the protocol treatments for more than 4 weeks may not re-start the concerned treatment.

5.5.1 Bevacizumab

The most frequently occurring non-hematological toxicities are: arterial hypertension, allergic reactions and proteinuria. Other toxicities observed are asthenia, thrombocytopenia, neutropenia, bleeding and thromboembolic events and congestive heart failure. Wound healing may be impaired by bevacizumab. Bowel perforation has been observed during treatment with bevacizumab; however, a clear relationship has not been established. Dose reductions for bevacizumab should not be performed.

5.5.1.1 Allergy/Anaphylaxis precautions

Anaphylaxis precautions, including urgent availability of suitably trained medical and nursing staff, should be observed during bevacizumab administration.

Grade 1 Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	If a grade 1 infusion-related or allergic reaction occurs during the infusion, no treatment is needed. Supervise the patient and complete bevacizumab infusion.
Grade 2 Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <=24 hrs	When a grade 2 reaction occurs, stop the bevacizumab infusion. Administer diphenhydramine 25 mg and dexamethasone 10mg IV. After recovery, resume infusion at half the previous infusion rate for 15 minutes. If no further symptoms occur, complete the infusion as long as it can be completed within 24 hours. Pre-medication should be given with the next infusion, but the infusion time may not be reduced. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated. For example: If an infusion-related adverse event occurred after the first administration of bevacizumab, the subsequent (i.e. the 2nd) infusion must be administered over a slower infusion rate. If the infusion is then well tolerated with pre-medication, all subsequent infusions should be delivered over this extended infusion time / the subsequent infusion time may be reduced by 30 ± 10 minutes as long as pre-medication continues to be used. If grade 2 symptoms recur, bevacizumab should be permanently discontinued. When an infusion-related adverse reaction occurs during the infusion or 24 hours after the administration of the second cycle of bevacizumab treatment (i.e. the recommended 60 minutes infusion), all subsequent infusions should be administered at an infusion time of 90 ± 15 minutes with pre-medication. If this rate of infusion is well tolerated, the next infusion and all subsequent infusions may be delivered at the same infusion time. If an infusion-related reaction occurs within the 30 minutes infusion on subsequent cycles (i.e. 3rd cycle and onwards), all subsequent infusions should be administered over 60 minutes with pre-medication.

Grade 3 Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion) ; recurrence of symptoms following initial improvement ; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Or Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	The bevacizumab infusion should be stopped and not-restarted on that day. Administer diphenhydramine 25 mg and dexamethasone 10mg IV. Add epinephrine or bronchodilators as needed. At the physician's discretion, bevacizumab may be permanently discontinued or re-instituted with pre-medication and at a rate half that when the reaction occurred. However, decision to re-institute bevacizumab should be taken with great consideration If the reaction occurred during administration over 90-minutes, initially re-challenge at a slower infusion rate and gradually increase to 90 minutes. When bevacizumab is re-started, the patient should be monitored, per physician's usual practice, for a duration comparable to the duration of the initial reaction.
Grade 4 Life-threatening consequences; urgent intervention indicated	In the event of an allergic/anaphylactic reaction occurring during the infusion of bevacizumab it is suggested that the following steps are taken: Stop the bevacizumab infusion. Maintain an adequate airway. Administer antihistamines, corticosteroids, epinephrine, or other medications as required as per institution policy. Continue to observe the patient, document observations and administer further treatment according to the individual clinical case and clinical judgement Permanently discontinue bevacizumab

5.5.1.2 Grade 3 - 4 bevacizumab-related adverse events and permanent discontinuation (CTCAE v4.0)

- Specific instructions on the management of hypertension, proteinuria, thrombosis/embolism, bleeding and other events attributable to bevacizumab are specified in the following paragraphs. In general, grade 3-4 bevacizumab-related adverse-events should be managed as follows:
  - First occurrence of grade 3 Bevacizumab-related events: hold Bevacizumab until toxicity has improved to grade ≤ 1 unless otherwise specified in chapters related to specific toxicities
  - First occurrence of grade 4 non-hematological Bevacizumab-related events: patient should be withdrawn from the trial except if this is not clearly in the best interest of the patient (this will be left at the discretion of the investigator)
  - Note that in the event of grade 4 febrile neutropenia and/or grade 3-4 thrombocytopenia, the treatment with bevacizumab should be withheld until resolution or until at least improved to

CTCAE grade ≤ 1 since such conditions are predisposing factors for an increased bleeding tendency

- Second occurrence: permanently discontinue treatment

In addition, any patient who experiences the following events should permanently discontinue bevacizumab:

- reversible posterior leukoencephalopathy syndrome (RPLS)
- grade 4 hypertension (hypertensive crisis)
- grade 3-4 of new arterial thrombo-embolism
- Any grade of arterial thrombo-embolism in elderly patients (> 65 years), or if patient meets the exclusion criteria at any time for increased risk of thromboembolism
- Life-threatening (Grade 4) pulmonary embolism, patients with Grade 3 need to be closely monitored and permanently discontinue bevacizumab in case of recurrent grade 3 pulmonary embolism
- Any grade of arterial thrombo-embolism if bevacizumab is re-introduced and arterial thromboembolism recurs
- Grade 4 or recurrent grade 3 venous thrombo-embolism
- grade 3-4 non-CNS hemorrhagic events
- Grade >1 CNS hemorrhage (punctate haemorrhage or the presence of hemosiderin is not considered a Grade 1 event for the purpose of this study)
- Grade >1 pulmonary haemorrhage events
- If hemorrhagic complications occur in patients on full dose anti-coagulation therapy
- grade 3 proteinuria
- grade 3-4 left ventricular dysfunction (congestive heart failure)
- gastrointestinal perforation (including tracheo -esophagal fistula)
- grade 4 of hypersensitivity/allergic reactions related to bevacizumab.

In case of grade 2 treatment related toxicities, withhold bevacizumab until toxicity has improved to grade ≤ 1.

5.5.1.3 Hypertension

In case of hypertension this should be treated according to the guidelines of the institution. All doses of anti-hypertensive medicines should be recorded at all visits.

Specific bevacizumab-related guidelines are given hereafter:

- Grade 1 hypertension: Prehypertension (systolic BP120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)
- Grade 2 hypertension: Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent (>=24hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated. Once controlled to < 150/100 mmHg, patients may continue bevacizumab therapy.
- Grade 3 hypertension: Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated. Bevacizumab should be withheld for persistent or symptomatic hypertension until improvement to CTCAE grade ≤ 1and should be permanently discontinued if BP is not controlled.

- Grade 4 hypertension: Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated. Occurrence of grade 4 hypertension should lead to permanent discontinuation of bevacizumab.

5.5.1.4 Proteinuria

Patients with a history of hypertension may be at increased risk to develop proteinuria when treated with bevacizumab. Bevacizumab should be discontinued in patients who develop grade 3 proteinuria.

By CTCTAE version 4.0, grade 3 indicates a nephrotic syndrome with proteinuria above 3.5 g. Grade 4 no longer exists.

All patients receiving bevacizumab will have a dipstick urinalysis performed within 48 hours prior to each bevacizumab dose.

Adjustment of bevacizumab administration for proteinuria will occur according to the following guidelines.

5.5.1.4.1 First occurrence of proteinuria during treatment with bevacizumab

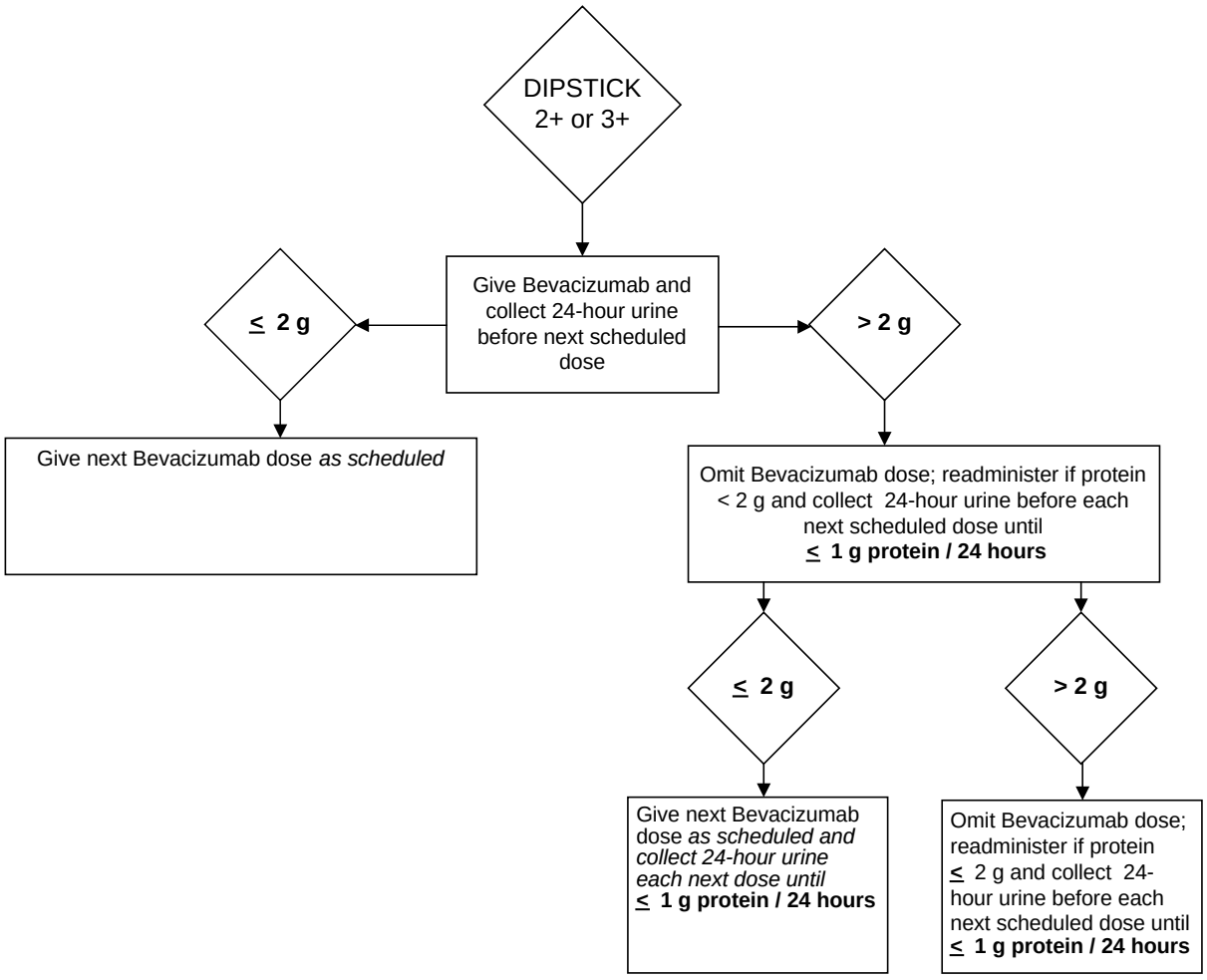
- < 2+ proteinuria (dipstick): Administer bevacizumab as scheduled, NO additional evaluation is required.
- ≥ 2+ proteinuria (dipstick): Administer bevacizumab as scheduled and collect 24-hour urine to determine the total protein within 3 days prior to the next scheduled dose:
  - 24-hour proteinuria ≤ 2 g: Administer bevacizumab as scheduled. Repeat dipstick is required before each scheduled administration of bevacizumab.
  - 24-hour proteinuria > 2 g: bevacizumab treatment should be withheld pending next 24-hour total protein.
  - Repeat 24-hour urine protein is ≤ 2 g: Administer bevacizumab as scheduled. 24-hour protein should be further monitored prior to each administration of bevacizumab until it has decreased to ≤ 1 g/24-hours. Omit bevacizumab only if protein > 2 g/24-hours.
  - Repeat 24-hour urine protein is > 2 g: bevacizumab dose should be withheld until 24-hour protein has decreased to ≤ 2 g. 24-hour protein should be further monitored prior to each administration of bevacizumab until it has decreased to ≤ 1 g/24-hour.

5.5.1.4.2 Second and subsequent occurrence of proteinuria during treatment with bevacizumab

- < 3+ (dipstick): Administer bevacizumab as scheduled
- ≥ 3+ proteinuria (dipstick): Administer bevacizumab as scheduled and collect 24-hour urine to determine the total protein within 3 days prior to the next scheduled dose:
  - 24-hour proteinuria ≤ 2 g: Administer bevacizumab as scheduled. Repeat dipstick is required before each scheduled administration of bevacizumab.
  - 24-hour proteinuria > 2 g: bevacizumab treatment should be withheld pending next 24-hour total protein.
  - Repeat 24-hour urine protein is ≤ 2 g: Administer bevacizumab as scheduled. 24-hour protein should be further monitored prior to each administration of bevacizumab until it has decreased to ≤ 1 g/24-hours. Omit bevacizumab only if protein > 2 g/24-hours.

- Repeat 24-hour urine protein is > 2 g: bevacizumab dose should be withheld until 24-hour protein has decreased to ≤ 2 g. 24-hour protein should be further monitored prior to each administration of bevacizumab until it has decreased to ≤ 1 g/24-hour.

5.5.1.4.3 Algorithm of proteinuria (dipstick) and bevacizumab dose interruption



5.5.1.4.4 Nephrotic syndrome (grade 3)

A nephrotic syndrome is clinically characterized by heavy proteinuria (>3.5g/day), hypoalbuminemia, hyperlipidemia and edema of variable degree. In case of a nephrotic syndrome permanently discontinue bevacizumab treatment.

5.5.1.5 Gastrointestinal perforation

Bevacizumab has been associated with serious cases of gastrointestinal perforation. In the E2100 pivotal registration trial in locally recurrent of metastatic breast cancer, there were two patients with gastrointestinal perforation (both died) and another patient developed grade 4 rectal/anal fistula among 362 patients that received paclitaxel plus bevacizumab (none in the paclitaxel arm) for an overall incidence of <1%. Both patients who died had risk factors for perforation (diverticulitis and tumor invasion in the bowel wall - Roche, Investigator Brochure section 6.1.2). Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation regardless of grade.

5.5.1.6 Gallbladder perforation

Patients may be at increased risk for the development of gallbladder perforation when being treated with bevacizumab. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation regardless of grade.

5.5.1.7 Surgical procedures/wound-healing complications

Bevacizumab therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed as such patients were excluded from previous clinical trials. In patients who experience wound-healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed.

Patients undergoing major surgery during bevacizumab therapy may be at increased risk for post-operative bleeding and/or wound-healing complications. Therefore, caution should be exercised in these patients. bevacizumab therapy should be withheld for a time interval of at least 4 weeks before conducting major elective surgery. Emergency surgery should be performed as appropriate without delay after a careful risk-benefit assessment.

5.5.1.8 Thromboembolic events

In case of Arterial Thrombosis/Embolism (leading to e.g. cerebrovascular ischemia of CNS or acute coronary syndrome):

- Grade 3 and 4: permanently discontinue bevacizumab treatment
- Any grade in elderly patients (> 65 years), or if patient meets the exclusion criteria at any time for increased risk of thromboembolism; permanently discontinue bevacizumab treatment
- Any grade if re-introduced and arterial thromboembolism recurs; permanently discontinue bevacizumab treatment
- Incidental findings of asymptomatic changes on MRI Diffusion Weighted Images (DWI) occurring in the post-operative or post-radiation setting will not require permanent discontinuation of bevacizumab treatment as they may reflect response to treatment (Ref. 35), non-contrast positive progression (Ref. 36) or are unspecific (Ref. 29).

In case of non-pulmonary Venous Thrombosis/Embolism:

- Grade 3 or 4 thrombosis/embolism: Delay bevacizumab treatment until resolution (full-dose anticoagulation period is over). Bevacizumab may be resumed during the period of therapeutic-dose anticoagulant therapy if the patient is on a stable level of anticoagulation for at least 2 weeks prior to restarting study drug treatment and the INR or aPTT are within therapeutic limits (according to the medical standard in the institution) and the patient has not had a Grade 3 or 4 hemorrhagic event while on anticoagulation
- Recurrent grade 3 or 4 thrombosis/embolism: discontinue the patient from bevacizumab treatment

Bevacizumab should be discontinued in patients with life-threatening (Grade 4) pulmonary embolism, patients with ≤ Grade 3 need to be closely monitored

5.5.1.9 Bleeding

In case of:

- Grade >1CNS or pulmonary haemorrhage: permanently discontinue bevacizumab treatment.
- Grade 3 or 4 bleeding of any kind: permanently discontinue bevacizumab treatment
- If hemorrhagic complications occur in patients on full dose anticoagulation therapy, permanently discontinue bevacizumab treatment and follow institutional guidelines from the 7th ACCP Conference on anti-thrombotic and thrombolytic therapy (http://health.usi.edu/summaryoftheseventhaccpconference.pdf). Standard procedures such as antagonism with protamine, vitamin K, or infusion of vitamin K dependent factors should be considered dependent on the severity of the bleeding.
- Grade ≥ 2 spontaneous INR or aPTT elevation (>1.5 x ULN): hold bevacizumab until toxicity has improved to grade ≤ 1.
- Grade ≥ 3 thrombocytopenia (platelets <50 x 10^9/L): hold bevacizumab until toxicity has improved to grade ≤ 1 (platelets ≥ 75 10^9/L).

5.5.1.10 Congestive heart failure (CHF)

Bevacizumab should be permanently discontinued in grade ≥ 3 left ventricular systolic dysfunction.

In the phase III controlled clinical trial of metastatic breast cancer (AVF2119), there were seven reports (3%) of CHF and cardiomyopathy in patients treated with bevacizumab compared with two patients (1%) seen in the control group. These events varied in severity from hospitalization and treatment. There is no information on patients with pre-existing CHF or NYHA Class II-IV at the time of initiating bevacizumab therapy, as these patients were excluded from clinical trials. All the patients treated with bevacizumab were previously treated with anthracyclines (doxorubicin cumulative dose range 240-360 mg/m^2). Several of these patients also had prior radiation therapy to the left chest wall. Most of these patients showed improved symptoms and/or left ventricular function following appropriate medical therapy.

In the other phase III trial of metastatic breci1y-1(1)-10n-4(t)-6(h)-4iJ -28. tme(I)-1(.)-10n(ol)-2(l)4(tm)-2A>

5.5.2.1 Dose levels of lomustine

Different dose levels of lomustine will be used for arms 1 and 2. The differences between arm 1 and arm 2 reflect the observations of increased hematological toxicity in the BELOB trial when lomustine at a dosage of 110 mg/m^2 was combined with bevacizumab (SNO 2010 abstract). The lomustine dose will be rounded to the closest multiple of 40 mg.

Dose	**Dose mg/m² q 6 weeks**	
	Arm 1	Arm 2
+ 1	In the absence of hematological toxicity > grade 1 during the first cycle the dose of lomustine can be escalated to 110 mg/m² (cap 200 mg) in their second cycle.	Not applicable
0	90 (cap 160 mg)	110 (cap 200 mg)
-1	75 (cap 130 mg)	90 (cap 160 mg)

5.5.2.2 Hematological toxicity

In general, the nadirs for hematological toxicity with lomustine are expeted between days 28 and 35. Hematological toxicity grade 3 or 4 (according to CTCAE v. 4.0), the dosage of the next cycle will be reduced to DL-1. If the hematological toxicity does not recover within four weeks after dose reduction or if after recovery the hematological toxicity recurs at a subsequent cycle to grade ≥ 2, the patient should be withdrawn from the study.

5.5.2.3 Non hematological toxicity

- Liver toxicity grade >2: the dose of the next cycles will be reduced to DL-1
- In case of pulmonary toxicity grade 1-2, or appearance of symptoms, DLCO will be performed.
  - If DLCO ≥ 60% of the predicted value: patient will receive the next cycle at the same dose
  - If DLCO < 60% of the predicted value: patient should be withdrawn from the study
- In case of pulmonary toxicity grade 3 or higher, patient should be withdrawn from the study
- Any grade 4 non hematological toxicity: the patient should be withdrawn from the study
- If the non hematological toxicity does not recover within two weeks or if non hematological toxicity recurs at the next cycle to a grade ≥ 2 the patient should be withdrawn from the study

5.5.2.4 Dose escalation of lomustine in arm 1 and 3

Patients in arm 1 will receive lomustine 90 mg/m² (cap 160 mg) during their first cycle. In the absence of hematological toxicity > grade 1 the dose of lomustine can be escalated to 110 mg/m² (cap 200 mg) in their second cycle. In presence of toxicity please follow sections 5.5.2.2 and 5.5.2.3.

5.6 Concomitant treatments

5.6.1 Prophylactic treatments

Anti-emetic prophylaxis as clinically indicated and is at the discretion of the treating physician. It should be recognized that a major side effect from the potent anti-emetic 5HT-3 antagonists is constipation.

Hematopoietic growth factors: The prophylactic use of growth factors is not permitted. Patients may receive red cell transfusions or erythropoietin to maintain hemoglobin >10mg/dl or 6.2 mmol/L.

5.6.2 Other concomitant medication

The administration of aspirin is allowed up to 325 mg/day. The use of NSAID's which may interfere with platelet activity, is not recommended and these drugs should be carefully considered and given if in best interest of patient.

Corticosteroids should be used in the smallest dose to control symptoms of cerebral edema and mass effect, and should be reduced and/or discontinued if possible.

No other anticancer agents or investigational drugs are allowed during the study or within 30 days of the inclusion into the trial, nor the participation into another study on investigational agents.

The use of non enzyme inducing anti epileptic and anti hypertensive agents will be collected on CRFs.

6 Clinical evaluation, laboratory tests and follow-up

Important note: Patients included in the phase II part of the trial will be followed-up according to protocol version 1 (26101 FP v1.0.pdf).

6.1 Before treatment start

Obtain informed consent prior to study-required procedures that would not have been performed as part of normal patient care. The patient must be thoroughly informed about all aspects of the study, including the study, visit and required evaluations and all regulatory requirements for informed consent.

All the pretreatment evaluations should be performed within 2 weeks before randomization.

The baseline evaluations include:

- Complete medical history
- Prior cancer therapy (including prior chemotherapy and radiation therapy)
- Physical examination including but not limited to height, weight, vital signs (blood pressure to collect possible hypertension) and neurological evaluation
- Quality of life assessment, including EORTC QLQ-C30 and EORTC-BN20 to be completed by both patients and caregivers/relatives (cf. Chapter 10)
- Neurocognitive assessment including Hopkins Verbal Learning Test-revised (HLVT-R), trail making test Part A, trail making test Part B and controlled oral word association (COWA; cf. Appendix F)
- WHO performance status
- 12 lead ECG
- Specific concomitant medications (anti-epileptic agents, anti-hypertensive agents, anticoagulants and corticosteroids - only concomitant medications actually taken by the patient at the time of study start are to be recorded in the CRFs)

- Steroid intake
- Adverse events grading according to CTCAE 4.0; NYHA criteria for congestive heart failure
- Laboratory tests, including complete blood counts (hemoglobin, hematocrit, white blood cells and differentiate - neutrophils and lymphocytes -, platelets) and serum chemistry: sodium, potassium, calcium, phosphates, chloride, creatinine, ASAT, ALAT, total bilirubin, alkaline phosphatases, total protein, albumin
- INR and aPTT
- Urine dipstick
- Serum or urine pregnancy test for premenopausal female patients within 72 hours prior to treatment start
- Gadolinium (Gd) enhanced MRI of the brain within 2 weeks prior to randomization
  - In case treatment start is delayed for more than 2 weeks after randomization it is strongly recommended to obtain a new baseline MR scan.
  - For the operated patients, the post-surgery MRI within 48 hours is mandatory and will be used as baseline. However a MRI should always be performed within 2 weeks prior randomization.
- Confirmation that biological material (at least from initial diagnosis and if further resection had been performed at recurrence) used to determine diagnosis is available for central review as well as availability of paraffin tissue block samples/slides or blood samples for translational research

6.2 From treatment start until end of study treatment

6.2.1 Every 2 weeks

- Vital signs (Blood pressure) to collect possible hypertension
- Complete blood counts; Urine dipstick
- Adverse events grading according to CTCAE 4.0; NYHA criteria for congestive heart failure

6.2.2 Every 6 weeks (day 42 of each cycle)

- Complete blood counts
- Physical examination including WHO PS and neurological evaluation
- Vital signs (Blood pressure) to collect possible hypertension
- Weight
- Gd-enhanced MRI for the first six months
- 12 lead ECG (if clinically relevant)
- Adverse events grading according to CTCAE 4.0; NYHA criteria for congestive heart failure
- Laboratory tests, including complete blood counts (hemoglobin, hematocrit, white blood cells and differentiate -neutrophils and lymphocytes-, platelets) and serum chemistry: sodium, potassium, calcium, phosphates, chloride, creatinine, ASAT, ALAT, total bilirubin, alkaline phosphatases, total protein, albumin
- Urine dipstick
- INR and aPTT

6.2.3 Every 12 weeks

- Specific concomitant medications
- Steroid intake (maximal intake (mg per day) and total duration in the observation period)
- Gd-enhanced MRI after first six months
- Quality of life assessment, including EORTC QLQ-C30 and EORTC-BN20 to be completed by both patients and caregivers/relatives (cf chapter 10)
- Neurocognitive assessment, including Hopkins Verbal Learning Test-revised (HLVT-R), trail making test Part A, trail making test Part B and controlled oral word association (COWA cf. Appendix F))

6.3 From end of study treatment until progressive disease

Every 6 weeks

- Gd-enhanced MRI (for the first six months)

Every 12 weeks

- Physical examination including neurological examination
- Vital signs if clinically relevant
- WHO-performance status
- Steroid intake (actual total dose at the day of examination)
- Specific concomitant medication collection if clinically relevant
- Adverse events grading according to CTCAE 4.0 (i.e. for events not resolved after the end of treatment and new events related to study treatment); NYHA criteria for congestive heart failure
- Gd-enhanced MRI (after the first 6 months)
- Quality of life assessment, including EORTC QLQ-C30 and EORTC-BN20 to be completed by both patients and caregivers/relatives (cf. chapter 10)
- Neurocognitive assessment, including Hopkins Verbal Learning Test-revised (HLVT-R), trail making test Part A, trail making test Part B and controlled oral word association (COWA; cf. Appendix F))

6.4 From disease progression until death

Every 12 weeks

- Gd-enhanced MRI
- Adverse events grading according to CTCAE 4.0 (i.e. for events not resolved after the end of treatment and new events related to study treatment); NYHA criteria for congestive heart failure
- Further anti-cancer treatments/modalites
- Survival follow up

6.5 Summary table

	Screen [14 days]	Protocol Treatment phase (j) until one of the withdrawal criteria is met			Follow-up: from end of study treatment until PD	Follow-up: From PD until death
		Every 2 weeks	Every 6 weeks	Every 12 weeks	Every 12 weeks	Every 12 weeks
Signed informed consent	X					
Medical history	X					
Prior cancer therapy	X					
Concomitant medication collection	X			X	X (i)	
Steroid dosage	X		X	X	X	
Complete physical examination with height(baseline) /neurological examination	X		X			
Weight	X		X			
Vital signs (a)	X	X	X		X (i)	
WHO-PS	X		X		X	
Adverse events evaluation (b)	X	X	X		X (if not resolved or newly emerging)	X (if not resolved or newly emerging)
ECG	X		X (i)			
Quality of life assessment (c)	X			X	X	
Neurocognitive assessment (d)	X			X	X	
Hematology (e)	X	X	X			
Biochemistry (e)	X		X			
INR and aPTT	X		X			
Serum/urine pregnancy test	X (f)					
Urine dipstick	X	X	X			
Gd-MRI	X (g)		X(g)	X(g)	X(g)	X(g)
Survival follow-up						X
Biological samples availability for central review and translational research	X(h)	X(h)	X(h)	X(h)		

(a) Including blood pressure to collect possible hypertension

(b) Adverse events grading according to CTCAE 4.0; NYHA criteria for congestive heart failure

(c) EORTC QLQ-C30 and EORTC-BN20 to be completed by both patients and caregivers/relatives (cf. Chapter 10).

(d) Neurocognitive assessment, including Hopkins Verbal Learning Test-revised (HLVT-R), trail making test Part A, trail making test Part B and controlled oral word association (COWA; cf. Appendix F)

(e) Including complete blood counts (hemoglobin, hematocrit, white blood cells and differentiate -neutrophils and lymphocytes-, platelets) and serum chemistry (sodium, potassium, calcium, phosphates, chloride, creatinine, ASAT, ALAT, total bilirubin, alkaline phosphatases, total protein, albumin)

(f) Serum pregnancy test for premenopausal female patients within 72 hours prior to treatment

(g) Every 6 weeks for the first 6 months (all patients without progression will be followed every 6 weeks for the first 6 months) and then every 12 weeks thereafter

(h) Refer to translational research chapter

(i) If clinically relevant

(j) As long as patient will receive protocol treatment

7 Criteria of evaluation

For this study, the primary endpoint is overall survival, with progression free survival measures and measures of patient functioning as secondary endpoints. Response is a secondary endpoint, which will only be assessed in patients with measurable disease at the time of randomization.

The radiological assessment of response and progression in trials on brain tumors treated with anti-angiogenic agents can be difficult. VEGF inhibition also normalizes abnormal vessel permeability which may result in pseudo-response. The classical Macdonald's criteria emphasize the area of contrast enhancement, which is today done with T1 weighted MR images. For this study, modified RANO and RANO criteria will be used to diagnose response and progression (Ref. 30).

Compared to Macdonald's criteria, two major changes are present in the RANO criteria:

Progressive lesions on T2 weighted images or FLAIR images will also be considered progression, regardless of the classical response as determined by T1 MR Images after contrast administration.

If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if PD is confirmed at the next follow-up, the earlier date must be used as the date of progression.

Because it is at present unclear if patients with only subtle progressive T2 and FLAIR changes may benefit from a continuous administration of bevacizumab, if in such cases there are no signs and symptoms of clinical progression treatment may continue. This also holds for cases with a gross total resection of the enhancing lesion prior to study entry, if at follow up minimal enhancement of unclear significance arises, treatment may continue until further follow-up gives unequivocal evidence of tumor progression.

Central review of the MR images will be part of the study (see chapter 16.5 central review procedure).

Considering that OS is the primary end-point of this study, patients having undergone a re-resection and who do not have clear evidence of residual disease will be eligible. The patients with resection for the first recurrence will not be studied for response. Care must be taken at the evaluation of these patients not to confuse enhancement around the surgical cavity with disease progression (see below). According to classical Macdonald's criteria, any new enhancement signifies progression (Ref. 37). For patients having undergone a complete resection of the enhancing area at the time of study entry, any new and unspecific or insignificant enhancement would therefore lead to the diagnosis of progression. In such cases, treatment may continue for another cycle, after which the response shall be re-evaluated. If further progression has occurred, the date of progression will be the date of the first demonstration of new enhancement.

7.1 Evaluation of activity

7.1.1 General method of response assessment

Response to treatment is assessed on the basis of a set of target lesion(s) chosen before the first treatment administration (the complete list of target lesions must be reported on the initial measurement form before the start of treatment). These lesions must initially be measured in their two perpendicular dimensions, and these measurements must be repeated at each evaluation of the disease by the same method. Response evaluation is based on neuro-radiological imaging (MRI) (Ref. 30). For this protocol objective response (complete, partial response) and progression will be assessed by MRI (see section 7.1.1.5). Objective response will only be assessed in patients not having undergone second surgery with complete removal of contrast enhancing lesions prior to study entry. For these patients measurable disease is required, which is defined as a clearly enhancing tumor with at two perpendicular diameters at entry equal or superior to 1 cm.

The contrast enhancing area will be considered as the basis for the tumor size assessment. Tumor size is defined as the product of the two largest perpendicular diameters. Only reductions in cross-sectional areas of 50% or more when calculating the response, the baseline scan must be used for initial comparison. In initially responding (≥ 50% reductions in cross-sectional areas) or stabilized (<50% reduction and < 25% increase in cross-sectional areas) patients, new scans must be compared to the nadir, this is the scan showing the maximum response (= minimum tumor size) during/after treatment. In assessing response, changes on T2 weighted images must be taken into consideration. For this protocol we are aiming at measuring quantitatively the FLAIR/T2 changes as well.

7.1.1.1 Definition of target lesions

Only the following lesions are eligible as target lesions:

- MRI contrast enhancing lesions with two perpendicular diameters of 10 mm or more visible on 2 or more axial slices which are 5 mm apart.
- Target lesion(s) must be measurable in two perpendicular diameters

In most patients, only one lesion will be present. In case of multifocal disease, a minimum of 2 lesions and maximum of 5 largest enlarging lesions will be chosen as target and the sum of the products of the perpendicular diameters will be determined. All other lesions than target lesions, if applicable, are assessed according to the same schedule. They are only taken into account in two situations:

- if one of them clearly progresses, the overall response to therapy will be evaluated as "progression", independent of the response of target lesions
- all lesions must have completely disappeared to report a "complete response".

Adequate investigations must be carried out at each evaluation of the disease to detect eventual new lesions. If any new lesion is found, the response will be evaluated as "progression". Regardless of the status of enhancing lesions, if progressive lesions are observed on T2 weighted images or FLAIR images, the patient will be considered radiologically progressive, but treatment may continue if this is considered to be in the best interest of the patient and there are no signs or symptoms of clinical progression.

By definition, non-target lesions are those that do not meet the criteria for target lesion.

7.1.1.2 Evaluation of patient treated after re-operation

Postoperative changes on contrast enhanced neuro-imaging may interfere with disease evaluation. Within the first three days after surgery on MR imaging a thin linear enhancement may develop around the resection cavity, thereafter this enhancement may become thick and nodular. Enhancement of dura and meninges may be more pronounced, even within the first days. The postoperative linear enhancement may persist up to 3-6 months, dural and meningeal enhancement may last much longer. If MRI made within 48 hours after surgery shows enhancing lesions with a nodular or mass like appearance in areas showing tumor on the pre-operative scans this is highly suggestive of residual tumor. The use of diffusion-weighted MR imaging in the immediate postoperative MRI may help with the identification of ischemic areas around the surgical cavity that may show enhancement with further follow-up.

7.1.1.3 Schedule of disease evaluation

The initial assessment of disease (including measurement of all target lesions) must be performed in the two weeks preceding randomization.

7.1.1.4 Response Assessment in Neurooncology (RANO) criteria

RANO criteria were developed in response to the advances in imaging technology and current treatment practices in the era of anti angiogenesis. The RANO criteria place more emphasis on the non-enhancing part of the tumor as shown on T2SE-weighted and FLAIR image sequences in contrast to the classical Macdonald criteria based on changes in area of enhancing lesions which is non-specific: the contrast area primarily reflects the passage of contrast material across the disrupted blood-tumor barrier. RANO criteria were developed by a working group for updated response assessment for high grade gliomas in this area of anti angiogenesis agents (Ref. 30).

7.1.1.5 Follow-up assessments will be performed every 12 weeks (or earlier if clinically indicated) until disease progression. Definition of response

For this trial, the primary measure of response and progression will be determined by the locally assessed response according to the modified RANO criteria. All treatment decisions should be based on the modified RANO criteria.

Follow up assessments will be done using both Macdonald (T1 plus contrast) and modified RANO (while considering T2/FLAIR). Response and progression will be assessed by both sets of criteria.

Target lesions are measured in their two largest perpendicular diameters. Their area is conventionally calculated as the product of these diameters. In case of multifocal disease with more than one target lesion, the total tumor size is calculated as the sum of the area of all target lesions.

Response is defined as follows according to the modified RANO criteria, which also consider T2 weighted and FLAIR images:

- Complete response (CR): Requires all of the following: 1) Complete disappearance of all enhancing measurable and non-measurable disease; 2) No new lesions; 3) Stable or improved non-enhancing abnormalities on FLAIR/T2 images as compared to baseline 4) Patients must be off corticosteroids (or on physiologic replacement doses only) and stable or improved clinically.
- Partial response (PR): Requires all of the following: 1) Only reductions of cross-sectional areas of 50% or more will be considered a response; when calculating the response, the baseline MRI must be used for comparison ; 2) No progression of non-measurable disease; 3) No new lesions; 4) Stable or improved non-enhancing abnormalities on FLAIR/T2 images as compared to baseline 5) Patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically.

- Progressive disease (PD):
  - Progression is defined by any of the following: 1) ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions (over baseline if no decrease) on stable or increasing doses of corticosteroids; 2) ≥ 25% increase in sum of the products of perpendicular diameters of area's with abnormalities on FLAIR/T2 images compared to the nadir time point (point with the smallest FLAIR/T2 abnormalities, even if still improved as compared to baseline, and on stable or increasing dose of steroids 3) The appearance of any new lesions; 4) Clear progression of non-measurable lesions; 5) Definite clinical deterioration not attributable to other causes apart from the tumor, or decrease in corticosteroid dose.
  - If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if PD is confirmed at the next follow-up, the earlier date must be used as the date of progression
- Stable Disease: This occurs if the patients did not qualify for complete response, partial response, or progression (see below) and requires: 1) No meaningful change in the appearance of the FLAIR/T2 images compared to baseline or to the nadir (point with the smallest FLAIR/T2 abnormalities) if a decrease occurred. 2) The patient should be stable clinically. In the event the steroid dosage has been increased for new signs and symptoms without confirmation of disease progression on imaging, and further follow-up imaging shows that with hindsight this increase in steroids was indeed unequivocally needed due to disease progression, the date of progression will be the date steroids were increased.
- For patients operated at recurrence and without measurable or non measurable disease post surgery, any new appearance of tumor will qualify for PD. In case non measurable tumor is left after surgery i.e. tumor less than 10 mm, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment. Modest increase in the size of a non-target lesion is NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used as the date of progression. This implies that in case of gross total resection of the enhancing lesion, if at follow up minimal enhancement of unclear significance arises, treatment may continue until further follow-up gives unequivocal evidence of tumor follow-up.
- In this protocol, because the primary endpoint is OS, the objective responses will not need to be systematically confirmed at 1 month by an extra MRI.
- To ensure a homogeneous radiological evaluation, all MRI images will be centrally reviewed as a secondary analysis and specific study MRI protocol will be used.

Criterion	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥ 50% ↓	<50% ↓ but <25% ↑	≥ 25% ↑
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	≥ 25% ↑
New lesion	None	None	None	Present
Corticosteroids	None	Stable or ↓	Stable or ↓	Not applicable*
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓
Requirements for response	All	All	All	Any

*increase in steroids alone does not qualify for PD

7.1.2 Overall response

The overall response is evaluated at each assessment of the disease. If progressive disease exists in any lesion, or when a new lesion appears, then the overall result will be progressive disease. Progression in non-measurable lesions leading to define deterioration of the patient due to tumor bulk should be taken to indicate progression, regardless of what happens in measurable disease.

7.1.2.1 Best overall response

Best overall response is the best response designation recorded from the date of randomization until disease progression.

7.1.2.2 Objective response

Objective response includes best overall responses CR and PR.

7.1.2.3 Clinical /neurological progression

Clinical/neurological progression is defined as the presence of the following conditions:

- decrease in WHO performance status:
  - for patients with baseline WHO performance status 0 or 1: deterioration to WHO performance status 2 or worse for which no other explanation is present
  - for patients with baseline WHO performance status 2: deterioration to WHO performance status 3 or worse for which no other explanation is present
- deterioration of neurological functions
- appearance of signs/symptoms of increased intracranial pressure (headache, nausea and vomiting without other explanations)
- and/or start of corticosteroid or increase of corticosteroid dosage by 50% for control of neurological signs and symptoms

7.1.3 Radiological assessment of progression pattern

Preclinical evidence and uncontrolled clinical studies suggest an increased risk for distant spread and development of a gliomatosis-like phenotype at progression of glioblastoma patients treated with bevacizumab. Therefore, this study will investigate the progression pattern when patients get radiological progression, to detect whether bevacizumab increases the risk of remote relapse in malignant glioma.

A distant recurrence on T1 with contrast or FLAIR sequences is defined as one of the following, compared to the tumor at study entry:

- a) Qualitative assessment of well-defined recurrence centered outside a 2 cm margin around the primary site or margin of the resection cavity,
- b) New tumor satellites,
- c) New involvement of the contralateral hemisphere,
- d) Diffuse recurrence: a recurrence with at least 50% of the tumor mass with indistinct edges located outside the borders of the original contrast-enhancing tumor on T1-weighted images plus 2 cm margin plus a shift of the center-of-mass by more than half of the diameter of the pretreatment tumor (Ref. 29).

7.1.4 Method of assessment of neurological deterioration

This study will assess neurological deterioration free survival as a secondary endpoint to correlate MRI and clinical findings. Neurological deterioration is defined as a decrease in WHO performance status:

- for patients with baseline WHO performance status 0 or 1: deterioration to WHO performance status 2 or worse for which no other explanation is present, and which is maintained for at least 3 weeks
- for patients with baseline WHO performance status 2: deterioration to WHO performance status 3 or worse for which no other explanation is present and which is maintained for at least 3 weeks

7.2 Evaluation of safety

Safety information will be collected for all randomized subjects in the phase II and in the phase III part of the trial. After the first ten patients in each arm have completed the first two cycles or have stopped treatment, an interim safety review of those patients will be conducted.

7.2.1 Adverse events and side effects

All adverse events will be recorded on the case report forms; the investigator will decide if those events are drug related (reasonable possibility, no reasonable possibility) and his decision will be recorded on the forms for all adverse events.

7.2.2 General evaluation of side-effects

This study will use the International Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, for toxicity and adverse event reporting (see Appendix D). A copy of the CTCAE can be accessed from the CTEP home page (https://webapps.ctep.nci.nih.gov). NYHA criteria will be used for reporting congestive heart failure.

Hematological toxicity will be assessed on the basis of blood counts as indicated in chapter 6. The nadir count will be computed for each cycle of therapy, and graded according to the International Common Terminology Criteria for Adverse Events version 4.0.

Non hematological acute side effects will be assessed and reported separately for each cycle of therapy, and graded according to the Common Terminology Criteria for Adverse Events version 4.0.

Any study drug toxicity will be assessed continuously. Subjects with study drug related toxicities will be followed continuously during treatment and every 12 weeks off treatment until all study drug related toxicities resolve (or ≤ CTCAE Grade 1).

7.2.3 Serious adverse events

Serious adverse events are defined by the Good Clinical Practice Guideline.

SERIOUS ADVERSE EVENTS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL (see chapter 15, Reporting of serious adverse events)

7.2.4 Toxic deaths

Toxic death is defined as death due to toxicity. The evaluation of toxic deaths is independent of the evaluation of response (patients can die from toxicity after a complete assessment of the response to therapy)

7.3 Evaluation of quality of life and neurocognitive functions

Quality of life assessment will be based on EORTC QLQ-C30 and EORTC-BN20 (see chapter 10). Neurocognitive functions will assessed by a battery of tests which will include Hopkins Verbal Learning Test-revised (HLVT-R), trail making test Part A, trail making test Part B and controlled oral word association (COWA; see Appendix F). HRQoL and neurocognitive functions assessments will be performed at baseline and every 12 weeks. HRQoL/neurocognitive assessments and their variations will be correlated with changes on contrast enhanced T1 weighted and on T2 weighted/FLAIR MR images. Combined assessments of QoL, of neurocognitive functions and of the neurological deterioration will allow a comprehensive assessment of the clinical status of the patient.

8 Statistical considerations

Important note: Data collected in the phase II part will be analyzed and published independently according to protocol version 1 (26101 FP v1.0.pdf) to answer all questions of the phase II trial. The results of the phase II part will be presented at the same time as the results of the phase III (see timing below). In the phase II, OS12 will be estimated for the four arms and the decision rule to conclude for treatment activity will be applied as planned. In the phase III, OS will be compared between arms I and IV. Compared to phase II, arm IV was renamed arm 2 (control) in the phase III.

8.1 Statistical design

8.1.1 Sample size

This is a randomized open label multicenter phase III trial. Patients recruited in the corresponding arm of the phase II trial will be included in the phase III trial. For the analysis of the phase III part overall survival is the primary endpoint and treatment arms to be compared are:

Arm 1: Lomustine 90 mg/m² every 6 weeks (cap. 160 mg) + bevacizumab 10 mg/kg every 2 weeks until one of the withdrawal criteria have been met (followed by best investigators choice at further progression). In the absence of hematological toxicity > grade 1 during the first cycle the dose of lomustine can be escalated to 110 mg/m² (cap 200 mg) in their second cycle.

Arm 2: (control arm): Lomustine single agent 110 mg/m² every 6 weeks (cap. 200mg) until one of the withdrawal criteria have been met (followed by best investigators choice at further progression).

The hypotheses are the following:

- In February 2013, a first analysis of the BELOB data was carried out. The outcome is summarized in the table below:

Treatment	n	9 mo OS in % [95% CI]	12 mo OS in %
LOMUSTINE	46	43 [29, 57]	30 [18-44]
BEV/LOMUSTINE 90 mg/m^2	44	59 [43, 72]	45[30-59]

(n: number of patients, PFS: progression free survival, CI: confidence interval, mo: months)

The baseline characteristics of patients in BELOB and in the phase II of the 26101 protocol were compared. In the BELOB trial, the median maximum diameter of the tumor was 36 mm in LOMUSTINE and 34 in LOMUSTINE+BEV. In the 26101, it was 64 and 51 respectively. Other factors had similar distribution between the two studies. In previous reports, it was shown that patients with maximum tumor

diameter larger than superior to 42 mm had a worse prognosis compared to tumor size lower or equal to 42 mm. For the phase III, it was assumed that OS9=40% in the LOMUSTINE arm and OS9=51.7% in the BEV/LOMUSTINE 90 mg/m² arm. This corresponds to a hazard ratio (HR) equal to 0.72. Based on a one-sided logrank test, at an overall significance level of 2.5% and a power of 80%, a total of 327 events are needed to show this reduction in the hazard of death of 28%. The accrual assumptions for the two arms in the phase III are summarized below:

Period	Time	Accrual (pts/mo)
#1 Pre amendment implementation	21/11/2011-09/04/2013	5.12
#2 Amendment implementation*	10/04/2013-03/10/2013	9.1
#3 Post amendment implementation	4/10/2013-December 2014	20.0

Note: * hypothesized period including the discussions about amendment #1 and its full implementation in the centers.

Based on these assumptions and assuming a 2:1 randomization scheme a total of three hundred patients must be recruited (289 in BEV/ LOMUSTINE and 144 in LOMUSTINE). The 2:1 randomization scheme was also applied in the phase II. Further to the results of the BELOB trial, it was justified to continue this scheme in order to reduce the number of patients potentially undertreated. It is expected that a majority of the patients in the Lomustine arm will not receive BEVA at first recurrence. Compared to the 1:1 randomization scheme, the number of events was increased (327 deaths instead of 291) and the time to observe all deaths was delayed by 4-5 months. End of recruitment is expected to occur in December 2014. The targeted number of events should be observed in August 2015.

8.1.2 Randomization and stratifications

All patients entered in the phase III will be centrally randomized at the EORTC Headquarters (for practical details, see chapter 13 on randomization procedure). The minimization technique (Pocock and Simon, 1975) used by the EORTC for random treatment allocation is based on the variance method with semi-random assignment dependent on a preset threshold as implemented by Freedman and White (1976). However, per suggestion of the ICH E9 statistical guidelines, the algorithm has been modified to incorporate a random allocation component in order to ensure an additional 15% of completely random assignments.

In this trial, the threshold is set to 4, the total number of stratification factors (see below).

Stratification factors are:

- Institution,
- WHO PS (0,>0)
- Steroids administration (No,Yes),
- Largest lesion diameter (<=40,>40 mm).

8.2 Statistical analysis plan

8.2.1 Primary and secondary endpoints

8.2.1.1 Primary endpoint

Overall Survival (OS) is calculated from the date of randomization up to the date of death (any cause). For patients still alive or lost to follow-up at the time of analysis, OS will be censored at last follow-up visit date.

8.2.1.2 Secondary endpoints

Progression-free Survival (PFS), PFS6, PFS12, median PFS, median OS,OS9,OS12, OS24, NDFS6, NDFS12, best overall response distribution, objective and complete response rates and median duration of objective or complete response.

PFS is calculated from the date of randomization up to the date of first progression or death (any cause) whichever comes first. In case a patient is still alive and without progression at the last follow up visit date, PFS will be censored at the date of last follow up visit date. In the phase III, the intent to treat approach is used. A patient receiving a second anti-tumoral therapy without prior documentation of disease progression, the patient will not be censored at the date of starting new anti-tumoral therapy.

Response will be assessed according to Macdonald and modified RANO criteria. Progression pattern will be locally assessed according to the criteria defined in section 7.

There will also be central review of response and progression. All response and PFS analyses will be duplicated for centrally reviewed data. Analyses based on the local investigators evaluation will be the primary analyses.

Neurological Deterioration Free Survival (NDFS) will be measured from the date of randomization until the date of neurological deterioration (see section 7) or the date of patient's death whichever occurs first. Patients without evidence of neurological deterioration will be censored at the last follow-up visit date. If a patient received a second anti-tumoral therapy in absence of neurological deterioration, the patient will not be censored at the date of starting new anti-tumoral therapy.

Percentages of worst Adverse Event (AEs) or Laboratory Event grades per AE term and category as measured by CTCAEs Version 4.0 criteria and NYHA criteria for congestive heart failure.

Quality of Life will be assessed and analyzed according to the methodology described in section 10.

Neurocognitive functions will be assessed and analyzed according to the methodology described in Appendix F.

Correlation of markers of the VEGF pathway in plasma and tissue with clinical outcome. Exploratory analyses of the prognostic and predictive value of these markers will be realized (see section 11).

8.2.2 Analysis populations

- Intention-to-treat population (ITT): All randomized patients will be analyzed in the arm they were allocated by randomization.
- Per protocol population (PP): All patients who are eligible and have started their allocated treatment (at least one dose of Bevacizumab or Lomustine).
- Safety population: All patients who have started their allocated treatment (at least one dose of Bevacizumab or Lomustine).

A patient will be considered to be eligible if the patient did not have any deviation from the patient entry criteria listed in chapter 3 of the protocol. Potential eligibility questions will be assessed by the Clinical Research Physician and the Study Coordinator at time of medical review.

8.2.3 Statistical methods

Important: PFS and OS endpoints might be re-estimated when additional follow-up data are available.

8.2.3.1 Efficacy analyses

All efficacy analyses will be realized in the intent-to-treat population.

For the primary analysis of OS, PFS, and NDFS, the Cox proportional hazards model will be fitted with the treatment (BEV+LOMUSTINE compared to LOMUSTINE alone) adjusted by the stratification factors at randomization and by a variable indicating if the patient was recruited in the phase II or in the phase III.

Note: The reason to add this new factor is that the trial will be impacted by the published results of the BELOB trial so that the distribution of patient characteristics and their prognosis might be different between the two phases.

For OS, treatment hazard ratio will be presented together with its one-sided 97.5% (two-sided 95%) confidence interval. For PFS and NDFS, treatment hazard ratios will be presented with their 95% confidence intervals.

The Kaplan-Meier technique will be used to obtain estimates of OS, PFS and NDFS. All medians will be presented with 95% confidence interval provided by the Reflected Method. OS9, OS12, PFS6, PFS12, NDFS6, NDFS12 will be presented with 95% confidence interval calculated by Greenwood formula's estimation of the standard deviation.

Logistic regression (without intercept) will be used to compare objective response and complete response between the two arms after adjustment for stratification factors at randomization and by a variable indicating if the patient was recruited in the phase II or in the phase III. Odd ratios (OR) and relative risk ratios (RR) will be presented with 95% confidence intervals.

The objective and complete response will be presented in contingency table with frequencies and percentages. The objective response and complete response rates will be reported with exact (binomial) 95% confidence interval.

The duration of objective response is the PFS measured in the subset of patients with objective response.

The duration of complete response is the PFS measured in the subset of patients with complete response.

The median duration of objective or complete response will be extracted from the PFS Kaplan-Meier curves. The Reflected Method will provide 95% confidence interval.

PFS and response analyses will be presented both based on investigator (primary analysis) and centrally reviewed (secondary analysis) response data.

Objective and complete response according to RANO and Macdonald criteria will be cross-tabulated. Kappa statistics will be computed to quantify the agreement between the two criteria. Discrepancies will be listed with detailed descriptions.

The distributions of distant or diffuse progression in each arm will be tabulated with frequencies and percentages. Rates will be presented with (exact) binomial 95% confidence intervals. Fisher exact test will be used to compare the distributions between arms.

8.2.3.2 Safety analyses

All safety and tolerability analyses will be realized in the safety population.

The safety and tolerability analyses will be presented at baseline and up to first progression. All forms up to the last safety assessment before progression will be used. Severe grades which did not resolve after first progression or emerged during follow-up will be identified and listed.

Baseline will include all information recorded up to the nearest date prior to or at randomization.

Exceptionally, assessments performed after randomization but before start of protocol treatment can be considered.

There will be no formal comparison of safety endpoints. No p-value and confidence intervals will be carried out.

Baseline laboratory and AE grades will not be included in the safety analyses performed up to first progression.

Laboratory and AE events occurring in patients who did not start their allocated treatment will be reported separately.

8.2.3.2.1 Hematological parameters

The worst value of each hematological category will be identified and graded for each patient. Frequencies and percentages of each category will be tabulated per arm. A table with grade 3/4 frequencies and percentages will be provided.

8.2.3.2.2 Biochemical parameters

The worst value of each biochemical category will be identified and graded for each patient. Frequencies and percentages of each category will be tabulated. A table with grade 3/4 frequencies and percentages will be provided.

8.2.3.2.3 All AEs

The worst grade of each AE item will be identified for each patient. Frequencies and percentages of each category will be tabulated. Tables with all grades and grade 3/4 frequencies and percentages will be provided.

8.2.3.2.4 SAEs

After reconciliation with the SAEs listing extracted from the pharmacovigilance database, the worst grade of each serious AE category will be identified for each patient. Frequencies and percentages of each category will be tabulated. Tables with all grades and grade 3/4 frequencies and percentages will be provided.

8.2.3.2.5 Related AEs

The worst grade of each likely related AE item will be identified for each patient. Frequencies and percentages of each related AE category will be tabulated. Tables with all grades and grade 3/4 frequencies and percentages will be provided.

8.2.3.2.6 Other secondary analyses

Longitudinal techniques will be used to analyze steroid use, quality of life (by patients and caregivers/relatives, see chapter 10) and development of cognitive deterioration. These analyses will be realized in collaboration with quality of life statistical methodologists.

Classical statistical methods will be used to investigate the impact of markers of the VEGF and CA9 expression on objective response rate, PFS, OS and safety parameters from both a prognostic factor and a predictive factor point of view (See chapter 11).

8.2.4 Pre-planned sensitivity or exploratory analyses

If the percentage of patients ineligible and/or who did not start allocated treatment (PP) is superior to 10%, efficacy analyses will be repeated in the per protocol population. If the percentage of patients who started any new anti-cancer therapy in absence of documented progression is superior to 10%, the primary OS analysis will be repeated by removing these patients.

Other exploratory analyses may be performed on the basis of subsets of patients, but results of these exploratory analyses may not serve as a basis for drawing conclusions concerning protocol efficacy, and the reasons for excluding patients should be clearly reported.

8.2.5 Prognostic factor analyses

Data of this trial will be added to the EORTC Recurrent GBM data warehouse for further pooled analyses of prognostic factors and other objectives.

8.2.6 Data recoding and display

Frequency tables will be tabulated (by treatment group or otherwise) for all categorical variables by the levels of the variables as they appear on the CRF (with %). Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for the patients fulfilling the condition for the specification (patient id, institution, treatment group, value of the item and text field contents).

Dates relating to events prior to entry will be presented as the delay in days (or weeks, months, or years) between the past event and the date of entry (date of randomization – date of past event + 1) and presented using the median and range. For example, on the randomization checklist, the date of last administration of prior treatment (or the date of first diagnosis of the cancer) will be presented as the time elapsed (in days, weeks, months or years, as appropriate) since the day of the last administration and the date of entry on study (date of randomization - last administration/diagnosis +1).

Other delays (e.g. re-treatment delays) are presented as continuous variables using the median and range.

Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories (for adverse events, the grading scale specified in the protocol will be used). Whenever no specific scale exists, lab data will be categorized based on the normal range: for example, below the lower normal limit (when appropriate), within the normal range, above the upper normal limit (ULN) and the degree to which it is above the ULN (for example > 2.5 x ULN, > 5 x ULN, > 10 x ULN). For laboratory data, the nadir is generally displayed. The nadir in a given cycle is the lowest laboratory value in that cycle; the overall nadir for a patient is the lowest laboratory value among all cycles.

Other continuous variables (for example age, dose …) are presented using the median and range (minimum, maximum).

If appropriate, continuous data may also be presented in categories (for example, age may also be grouped in decades).

8.3 Interim analyses

No formal interim statistical analysis will be performed.

8.4 End of study

End of study occurs when all of the following criteria have been satisfied:

1. The trial is mature for the analysis of the primary endpoint (i.e. at least when 327 deaths will be observed).

2. The database has been fully cleaned and frozen for this analysis

3. Thirty days after all patients have stopped protocol treatment

9 Data Monitoring

Safety data are reviewed within the EORTC Headquarters on a regular basis as part of the Medical Review process. Problems which are identified will be discussed with the Study Coordinators who will take appropriate measures. Safety information will also be included in trial status reports which serve as a basis of discussion during EORTC Group meetings. These reports will be made available to investigators participating in the study.

The EORTC Independent Data Monitoring Committee (IDMC) will review all safety problems identified by the EORTC Headquarters for which an advice is sought. Experts on the IDMC performing this review will be selected to have the relevant early trials/drug development expertise and will provide a review process independent of that of the Medical Review. In principle, no access to outcome data is necessary for safety reviews. However, the IDMC will also provide recommendations as an initial step in phase III trials to advise if a full review of all study data and endpoints is needed.

The EORTC IDMC is charged with the interim review (planned in the protocol or ad hoc) of randomized phase II and phase III studies. When interim analyses are carried out, the interim monitoring of efficacy and safety data is performed according to the Statistical Considerations chapter in this protocol and EORTC Policy 004 on “Independent Data Monitoring Committees and Interim Analyses”.

The results of the interim analyses are confidential and are discussed by the EORTC IDMC. The IDMC will subsequently recommend to the EORTC Group whether any changes should be made to the study.

No efficacy results will be presented at EORTC Group meetings or elsewhere before the trial is closed to recruitment and the data are mature for the analysis of the primary endpoint, unless recommended otherwise by the EORTC IDMC.

10 Quality of life assessment

Important note: Data collected in the phase II part will be analyzed and published independently according to protocol version 1 (26101 FP v1.0.pdf) to answer the initial questions.

10.1 Rationale

Health related quality of life (HRQoL) is a multidimensional construct, which can be defined as a state of general well being reflecting physical, psychological, and social well being and the impact of the disease and/or treatment related symptoms on daily-life functioning. The patient’s subjective perspective is an inherent component of HRQoL and is therefore best assessed via self-administration.
Reducing mortality and morbidity is still the most important factor in cancer clinical research. Nevertheless, issues such as reducing side effects, symptom relief and improving patients’ satisfaction have also become relevant parameters in the evaluation of medical strategies. Cancer treatments may produce adverse effects and diminish a patient’s quality of life even when survival is extended. Progress in the acceptance of new cancer therapies is sometimes critically dependent on their HRQoL consequences.

10.2 Objective

The current experience with angiogenesis inhibiting agents in recurrent GBM has demonstrated considerable difficulties with assessing response and progression in bevacizumab treated patients. So, we hypothesize that measures of clinical functioning will yield information (HRQoL, need for steroids, cognitive functioning) that is critical for the patient perception of clinical benefit.

10.3 HRQoL instrument

Quality of life will be assessed with the EORTC Quality of Life Questionnaire (QLQ-C30) version 3. This is composed of multi-item and single scales. These include five functional scales (physical, role, emotional, social, and cognitive), three symptoms (fatigue, nausea and vomiting and pain) and a global health status/HRQoL scale and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). All scales and single items meet the standards for reliability. The reliability and validity of the questionnaire is highly consistent across different language-cultural groups (Ref. 38). While this standard is used in EORTC studies, it lacks some dimensions that pertain to the QL issues in certain brain cancer. Therefore we will use the EORTC Brain Cancer module (QLQ-BN20) which is designed for use in patients undergoing protocol treatment or radiotherapy. It includes 20 items assessing: visual disorders, motor dysfunction, communication deficit, future uncertainty, as well as other specific symptoms, such as headaches, seizures or drowsiness. A retrospective validation study has been performed confirming the psychometric validity of this questionnaire (Ref. 39).

10.4 Study design

Patients are eligible for the quality of life assessment in this study if they fulfill the eligibility criteria (Chapter 3). Of course, should the HRQoL forms not be available in the required language or should the patient refuse to fill out the form, then this should not exclude the patient from further participation in the study. Patients will be informed in the patient informed consent form that they will have their quality of life assessed regularly while involved in this trial. In this phase III trial, HRQoL will be a secondary outcome and evaluated in a longitudinal design in all patients entered in this study.

10.4.1 Administration

HRQoL questionnaires must be filled out at the hospital when patients come for a scheduled visit according to the EORTC “Guidelines for administration of questionnaires” (see Appendix E). The pre-treatment questionnaires must be filled within 2 weeks before randomization. Subsequent questionnaires are administered every 3 months during protocol treatment. After discontinuation of protocol treatment, HRQoL measurements are carried out every 3 months up to disease progression. Once a patient has progressed, no further HRQoL data collection for that patient is required.

Master copies of the HRQoL questionnaires will be sent to the institutions. Additional copies or translations can be provided upon request via the EORTC contact person. The clinical report forms will include a question whether the HRQoL forms have been filled in, and if not, the reason why. The questionnaire will be handed out to the patients by the investigator or a study nurse prior to seeing the doctor for clinical evaluations. The patient should complete the questionnaires by her/himself in her/his own language during the visit to the outpatient clinic as completely and accurately as possible. It is recommended that a key person (e.g. research nurse) at each center should be responsible for questionnaire data collection in order to optimize the compliance of the patient and to ensure the completeness of the data.

During the study, compliance with completing questionnaires will be investigated at each time point. The compliance of the HRQoL assessments will also be reviewed twice a year and will be part of the descriptive report.

10.4.2 HRQoL schedule

The time windows for eligible HRQoL assessments will be as follows:

Assessment	Time window
Baseline	Can be completed before or on the day of randomization itself but no earlier than 2 weeks before.
Every 3 months during protocol treatment.	Can be completed up to 1 month before or after every 3th month after start of protocol treatment (i.e. during the 3rd and 4th month for the first assessment; during the 6th and 7th month for the second assessment etc…). A time window of 2 months length is therefore available for each assessment.
Every 3 months after end of protocol treatment; until progression.	Can be completed up to 1 month before or after every 3th month after date of protocol treatment discontinuation (ie. during the 3rd and 4th month for the first assessment; during the 6th and 7th month for the second assessment etc…). A time window of 2 months length is therefore available for each assessment.

HRQoL assessments are no longer required in case of progression, death, loss of follow-up or patient's withdrawal of consent for HRQoL assessment.

10.4.3 Quality of Life assessment in proxies

The assessment of HRQoL in brain cancer patients can represent a challenge. Whilst the EORTC has done this successfully in past studies, the accuracy of HRQoL scores in patients with brain cancer has been questioned. Brain cancer patients can suffer from cognitive limitations, which may also affect the perception of their daily quality of life. As an example, studies have shown that subjective and objective assessments of cognitive functioning in brain tumor patients are poorly correlated. Hence it is logical to see if caregivers or proxies can represent patient views and to what extent they are correlated. If caregivers or proxies have a different perspective, the next question is which gives the more accurate information.

In the phase II and III parts of the trial, we will make use of a research approach to also assess HRQoL with the patients' proxies/caregivers, who will be asked to complete the two EORTC tools at each assessment point at the same time as the patient. Once the study is completed we will then be able to directly compare the patients HRQoL scores with the patient’s representatives scores. The results will help us better understand the views of both patients and caregivers and see if these scores overlap on the various scales and understanding the relative validity and reliability of patient views versus caregiver or proxy views. They will also be correlated to performance status and imaging findings. This may then in the future help us better understand the value of using proxy assessments in this population.

10.5 Statistical considerations

The primary HRQoL endpoints that are considered relevant for this study are Global health status, cognitive functioning and pain. Other scales may be analyzed on an exploratory basis as secondary HRQoL endpoints, such as fatigue, communication deficit etc.

The Global health status scale will be used as primary outcome of interest for this study. A difference of 10 points on the 100-point QLQ-C30 scale between the four arms will be considered as clinically relevant. The standard deviation of this scale is approximately 20 points. With the 2-sided alpha set at 5% and a

power of 80% to detect a difference of 10 points (effect size of 0.5), a minimum of 128 patients (64 per treatment arm) is required. For an effect size of 0.75 (difference of 15 points), 56 patients (28 per treatment arm) are required. Therefore, this study is sufficiently powered to detect differences in HRQoL, although the emphasis is on establishing HRQoL profile estimates rather than comparative tests.

Data will be scored according to the algorithm described in the EORTC scoring manual. All scales and single items are scored on categorical scales and linearly converted to 0-100 scales.

Changes in HRQoL scores over time will be evaluated with a repeated measurement modeling using a mixed effect procedure. A linear mixed model with treatment, a time effect, a time-treatment interaction and possibly other baseline covariates as fixed effects and a patient specific random effect will be fitted. Prior to reducing the model, the most suitable covariance structure should be determined on the basis of Akaike's Information Criterion (AIC). Covariates other than the treatment and the time indicator may be dropped from the model based on a 5% significance level for the Type III fixed effect test. The main objective will be to document the HRQoL profile estimates and their respective confidence intervals in each arm. The repeated measures analysis will be supplemented by a cross-sectional analysis. Graphs will display the mean score by treatment group with their confidence intervals.

Correlation between changes in HRQoL scales, in neurological deterioration status and status of progression based on tumor enhancement and the status of progression after integration of FLAIR/T2 will be documented.

The relative validity and reliability of patient views versus caregiver/proxy views will be assessed via Cohen's kappa statistic for interrater agreement for each scale.

10.5.1 Missing data

Missing data is a potential major source of bias in HRQoL assessment.

In order to check the potential impact in the study, the compliance mechanism will be investigated prior to initiating the HRQoL analysis. Characteristics of patients with and without valid HRQoL data will be compared and trends over time per dropout pattern will be investigated. Model building will be used in order to investigate whether the compliance mechanism is linked to selected prognostic variables.

Once the main analysis is completed, sensitivity analyses will be undertaken to verify the robustness of the results vis-à-vis the missing data.

In case overall compliance is deemed too low (<50%), only an exploratory analysis will be performed in lieu of the main analysis.

11 Translational research

This trial has a strong translational research component including bio-banking to permit fundamental advances in understanding the disease. This part of the study is mandatory.

11.1 Correlative molecular analysis

11.1.1 Prospective biological samples collection

This trial provides an excellent opportunity to understand the biological mechanisms of this disease, through the conduct of research programs on biological samples prospectively collected.

Gliomas are heterogeneous tumors with complex molecular biology mechanisms and a number of interrelated pathways which dysfunction could cause tumorigenesis and tumor progression. Often therapies may only be effective for some subsets patients.

Further insight into the molecular basis of gliomas and an emphasis on the identification of biomarkers will ultimately translate into advances in screening, diagnosis, treatment and monitoring with improved clinical outcomes. This work will open the possibility to tailor different treatment options to the patients given their particular type of disease.

11.1.2 Routing and banking

The tumor material and blood samples should be sent to Heidelberg. Details on the procedure are to be found in the "Procedures and routing of tumor and blood samples".

Prior to any research performed on these samples a central neuropathology review is going to be performed to ensure homogeneity of the histopathological diagnosis as well as quality of the provided tissue samples. This will be done at the Department of Neuropathology in Heidelberg (Andreas von Deimling & Christian Hartmann), Heidelberg, Germany.

11.1.2.1 MGMT methylation status

The significance of the methylation status of the promoter gene in the various glioma subtypes and grades is less clear, reports suggest that this is an important predictor of outcome in grade IV tumors. The data on the correlation of MGMT promoter methylation on outcome of temozolomide chemotherapy in recurrent grade II-IV tumors are conflicting.

- Material: Tumor at initial diagnosis and/or recurrence if available (FFPE block or 30 unstained slides)
- Methods: Methylation status of MGMT promoter will be assessed using specific methylation-specific PCR or another technique on DNA extracted from FFPE blocks (Ref. 40).

11.1.2.2 Isocitrate Dehydrogenase 1 (IDH1)

The role of IDH1 mutations in tumorigenesis is under intense investigation. These mutations, which nearly always affect codon 132 in gliomas and which nearly always occur in a heterogeneous manner leaving one parental allele unaffected, strongly compromise the ability of the enzyme to decarboxylate isocitrate to a-ketoglutarate and to generate NADPH (Ref. 41, Ref. 42). In contrast, mutated IDH1 protein gains a novel function enabling the conversion of a-ketoglutarate to 2-hydroxyglutarate in a NADPH-consuming manner (Ref. 43, Ref. 44).

While 2-hydroxyglutarate appears to increase the levels of reactive oxygen species, its role for tumor development is not clear. The mutation causes reduced catalytic generation of a-ketoglutarate which combined with its additional consumption due to the gained function may inhibit prolyl hydroxylases thereby resulting in activation of the transcription factor, hypoxia-inducible factor (HIF) (Ref. 45). New data suggest a prominent role of IDH1 for the classification of glioma plus a determining role for the major prognosticator "age" (Ref. 46). The current sample set would provide an excellent opportunity to test the validity of these data in a recurrent glioblastoma cohort.

Since evidence emerges that relevant biological pathways alter between initial diagnosis and recurrence, it would be valuable to obtain tissue pairs from initial diagnosis (mandatory) and a re-resection potentially performed prior to inclusion of the patient into the current trial. If material is available from resection, it should be sent. The fraction of resected patients is estimated with 20%. If enough material is available, genes indicative for the neural, proneural and mesenchymal phenotypes (Ref. 47) are determined in further IHC from the retrieved tissue. Candidates include IDH1, p53, EGFR and PDGFR.

- Material: Tumor at initial diagnosis and/or recurrence if available (FFPE block or 30 unstained slides)
- Methods: IDH1 codon 132 mutation will be assessed by a newly developed and validated antibody (Ref. 48) and additional gene products may be determined by IHC .

11.1.3 Biomarkers of the VEGF Pathway

The VEGF/VEGFR signaling pathway is pivotal for new blood vessels formation or angiogenesis. This biological process is critical for tumor growth, particularly in high grade gliomas. An up-regulation of VEGF/VEGFR signaling pathway has been shown in gliomas (Ref. 49). This is in agreement with the high vascular density observed by pathologists and the contrast enhancement seen on imaging examination. Activation of VEGF/VEGFR signaling pathway is driven notably by over-expression and/or genomic amplification of VEGF and/or VEGFR (Ref. 50).

Therefore the primary aim of this part of the translational research is defined as “Evaluation of the predictive value of the molecular bevacizumab targets expressed in tumor and vascular cells of glioblastoma treated in this study”.

Based on this primary aim we will test the following study hypothesis: “An expression of molecular targets of bevacizumab in glioblastoma tissue is predictive for response to bevacizumab treatment.”

Predictive factors of response to bevacizumab are not clearly identified in recurrent grade II and grade III gliomas. Recently, it has been shown that VEGF expression is associated with response to bevacizumab in high grade astrocytomas while hypoxia-inducible carbonic anhydrase 9 (CA9) expression is associated with prognosis in the same tumor group treated with bevacizumab (Ref. 51). Therefore, investigation of these prognostic and response to treatments biomarkers sounds interesting in recurrent grades II and III gliomas.

- Material:
  - Mandatory: FFPE tissue of the initial glioblastoma - FFPE block or 9 unstained slides
  - Optional (if feasible): FFPE tissue of the first and/or second recurrence/progression of the glioblastoma
  - Optional (if feasible): FF (Fresh-Frozen) tissue
- Methods: Determining of tissue markers of tumor vascularization
  - Evaluation of the predictive value of the tumor vessel density (e.g., CD31 staining = endothelial cell marker), and microscopic appearance of vascular formations (“classic” vs. “glomeruloid”), vascular proliferation (Ki67 staining in endothelial cells) and hypoxia (HIF1-α) in endothelial and tumor cells.
  - Evaluation of the predictive value of VEGF/VEGFR targets (e.g., VEGFR1-3, FLT-3, PDGFR-β, c-KIT and RET) and other antiangionenic factors expressed in tumor and vascular cells of glioblastoma treated in this study (staining intensity and percentage of positive cells)
  - Evaluation of the predictive value of molecular markers, associated with tumor vascularization (e.g., VEGF, PDGF, Angiopoietin-2, DLL4, Axl)

A progress of tumor neovascularization during treatment with anti-angiogenic drugs is associated with an increase of several molecular markers in patients' blood (Ref. 52) Therefore we will evaluate the concentration of molecular markers associated with tumor neo angiogenesis in EDTA plasma (mandatory) during bevacizumab treatment.

Testing plasma biomarkers is an innovative strategy to monitor response to treatments (Ref. 52). For AZD2171, a pan-VEGFR inhibitor, blood analyses showed significant increases in VEGF and PlGF and decreases in sVEGFR2 plasma levels (EDTA) throughout AZD2171 treatment. In patients who experienced tumor progression while on AZD2171, increases in MRI tumor contrast enhancement volume were associated not only with decreases in levels of PlGF and increases in sVEGFR2 in plasma, but also with significant increases in plasma levels of bFGF and SDF-1.

Indeed, it has been shown in different types of cancers that response to VEGF inhibitor is associated with modulation of plasma biomarkers such as VEGF-A and VEGF-R2. Consequently, assessing plasma level of VEGF-A and VEGF-R2 appears promising.

- Material: frozen plasma (extracted from 10 ml whole blood in EDTA tubes): at baseline, 2, 6 and 12 weeks after start of treatment and at progression if feasible
- Method: ELISAs using EDTA plasma (mandatory). Plasma levels of VEGF-A and VEGF-R2 will be assessed by ELISA platforms as well as any other marker relevant to the angiogenesis pathways

Details on the procedure for samples processing are to be found in the "Procedures and routing of tumor and blood samples"

11.1.4 Biological material required for correlative molecular analysis

To achieve the above mentioned objectives the following biological material will be collected. The informed consent for trial participation will explain the need of this material of the initial resection, and eventually subsequent resections for translational research:

- Frozen tumor biopsies (optional)
- Paraffin blocks (or 40 unstained slides) from the initial operation (diagnosis) and any operation performed at recurrence
- 10 ml whole blood collected in an EDTA tube for plasma extraction (pre treatment, at 2, 6 and 12 weeks and if possible at progression)

11.1.5 Statistical analysis plan

Classical statistical methods will be used to assess the prognostic and predictive value of these biomarkers for clinical outcomes. Methods used include (but not exclusively):

Spearman Correlation Coefficient will be computed to quantify the relationship between biomarkers and between biomarkers and clinical parameters (e.g. age…). Fisher's Exact test or Wilcoxon rank sum test will be used to assess the significance of these relationships.

Objective response to treatment will be assessed in biomarkers defined subgroups of patients. Fisher's exact or Wilcoxon rank sum test will be used to assess the significance of the relationship between biomarkers and objective response. The same methods will be used for other binary outcomes. For time to event outcomes (PFS, OS, NDFS…) Kaplan Meier curves will be computed in biomarkers defined subgroups. In each subset, relevant parameters will be estimated (e.g. OS12, PFS6…). Logrank tests will be computed to assess the prognostic value of each biomarker in the whole population and in each arm. They will also be used to assess the treatment difference in the whole population and in each biomarker stratum.

Predictive value for treatment efficacy will be further assessed with interaction tests: Peto's test for quantitative interactions and Piantadosi S & Gail test for eventual qualitative interactions (Ref. 53). Cox regression models adjusted for trial stratification factors will be fit to assess prognosis and treatment hazard ratios. The predictive accuracy of any model will be assessed with the Harrel's C-index (Ref. 54). The value added by the biomarkers to the models including clinical factors only will be assessed with the parameter V of Schemper (Ref. 55).

All analyses are exploratory and will be performed without adjustment for multiplicity at 5 % significance and parameters will be presented with 95% confidence intervals.

11.2 Imaging Translational research

11.2.1 Rationale

The Macdonald's criteria were initially developed for CT scans and have subsequently been extrapolated to magnetic resonance imaging which is now the standard imaging approach. The concept of assessing tumors uni-dimensionally as promoted by the RECIST in solid tumor has not been validated in brain tumors. The current Macdonald's criteria have a number of limitations, in particular the fact they were built based on changes in area of enhancing lesions which is non-specific: the contrast area primarily reflects the passage of contrast material across the disrupted blood-tumor barrier. Because the presence of enhancement is non-specific, it may also reflect post surgical changes, ischemia, radiation effect and necrosis leading to possible wrong interpretation of real treatment effect. This issue becomes even more important with novel agents that interfere with the vascular compound of the tumor. Therefore there is a need to develop new approaches to attempt to measure the real tumor effect of anti angiogenic agents.

In the Response Assessment in Neuro Oncology (RANO) criteria, this is done by giving more emphasis on the non-enhancing part of the tumor as shown on T2SE-weighted and FLAIR image sequences. These RANO criteria (Ref. 30) have been assembled as a consensus of the neuro-oncology community but have not been subject to validation. Therefore in this protocol, though response and progression will be primarily based on the modified RANO criteria, there will be double evaluation of the cases both centrally and locally using the former Macdonald's criteria and RANO. In addition, it will correlate clinical changes to the MR changes observed using the modified RANO and the Macdonald criteria. This study will therefore pilot and attempt to validate the implementation and use of the RANO and modified RANO criteria. For this, both a local diagnosis and a central review radiological response assessment will be obtained. The central review will be done blinded for the assigned treatment and the clinical status, and may use a computer platform. For this, digitized images will be centrally stored. Guidelines will be provided before sites activation.

11.2.2 Statistical analysis plan

Methods used include but not exclusively:

Tables comparing best overall response to treatment between RANO and MacDonald's Criteria will be presented with frequencies and percentages. Kappa statistics will be computed to assess the strength of the relationship. The difference in the timing of progression with the two criteria will be analyzed by visual comparison of the PFS Kaplan-Meier curves and by tables showing the frequencies and proportions of progressions at the same date and at different schedules. Discrepancies will be documented.

11.3 Future Translational Research

The EORTC Brain Tumor Group translational research committee ("the TR committee") will decide on the use of biological material for projects not defined in the present protocol. Any future research on tissue samples would have to be scientifically valid and approved by the TR committee according to applicable legislation. Further in depth molecular analysis may include gene expression, genome copy number assessments, and proteomics using the available biological samples and appropriate molecular technologies.

Interested parties may apply for the use of biological material in TR projects that are not specified in the protocol. TR projects will be approved by a review including scientific merit but also methodological, ethical, practical, financial and other relevant feasibility factors.

- A written application for the use of biological material will be completed detailing the TR project proposal

- The study coordinator/group steering committee will prioritize the TR projects
- Prioritized projects will be reviewed by the EORTC Translational Research Advisory Committee (TRAC)
- An EORTC HQ feasibility check, including a check of all regulatory and ethical matters will take place
- Once approval from TRAC and the EORTC HQ feasibility assessment is complete the TR project can be activated and laboratory analysis of the biological material can commence.

11.4 Development of technical appendices

The translational projects will be the result of the work of collaborating institutions and EORTC HQ. Separate technical appendices will be jointly developed for each future translation research project. These appendices will be written before starting any analysis and will specify the analytical and methodological details and will precise data transfer procedures. Clinical and patient-reported outcome data will be stored in the EORTC clinical database and biological investigational data will be stored in respective collaborating laboratories. Data sharing will be performed according to existing Standard Operating Procedures.

12 Investigator authorization procedure

Investigators will be authorized to register and/or randomize patients in this trial only once they have returned the following documents to the EORTC Headquarters:

- The updated signed and dated curriculum vitae of the Principal Investigator.
- The (updated) list of normal ranges for the investigator's institution signed and dated by the head of the laboratory. Please make sure normal ranges are provided also for those tests required by the protocol but not routinely done at the investigator's institution.
- A Commitment Statement and Study Agreement between EORTC and Principal Investigator, stating that the investigator will fully comply with the protocol. This must include an estimate of yearly accrual and a statement on any conflict of interest that may arise due to trial participation.

  NB: A signed conflict of interest disclosure form will be required only if a possible conflict is declared on the Commitment Statement and Study Agreement.
- A copy of the favorable opinion of the local or national (whichever is applicable) ethics committee mentioning the documents that were reviewed (including the version numbers and version dates of all documents). A list of all members of the ethics committee is also requested.
- A copy of the translated and adapted (according to all national requirements) Patient Information / Informed Consent sheet. Version numbers and dates must be clearly stated on each page.
- The signature log-list of the staff members with a sample of each authorized signature and the indication of the level of 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 full name, address, phone numbers and e-mail address of the local pharmacist who will be responsible for the trial medication (for any trial where the drug will be provided).
- An accreditation, a certification, an established quality control / external quality assessment or another validation should be provided for the own laboratory.

- A certification for the Neurocognitive testing assessment

The center specific list of required documents will be included in the protocol activation package, with proper instructions as required by this protocol, your group 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 fulfilled.

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

13 Patient randomization procedure

Patient randomization will only be accepted from authorized investigators (see chapter on "investigator authorization procedure").

Patients should be randomized directly on the **EORTC online randomization system** (ORTA = online randomized trials access), accessible 24 hours a day, 7 days a week, through the internet. To access the interactive randomization program, the investigator needs a username and a password (which can be requested at www.eortc.be/random).

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

Through internet:	www.eortc.be/random
In case of problems randomization by phone:	*+32 2 774 16 00*

A patient can only be randomized after verification of eligibility. Both the eligibility check and randomization must be done before the start of the protocol treatment.

STANDARD INFORMATION REQUESTED:

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

PROTOCOL SPECIFIC QUESTIONS:

- all eligibility criteria will be checked one by one
- actual values for the eligibility parameters will be requested when applicable
- stratification factors
- date of written informed consent (*day/month/year*)
- date foreseen for protocol treatment start

Once eligibility has been verified, treatment will be randomly allocated to the patient, together with a **sequential patient identification number ("seqID")**. This number will allow the identification of the patients in the VISTA/Remote Data Capture system (VISTA/RDC) that will be used to complete the Case Report Forms.

14 Forms and procedures for collecting data

14.1 Case report forms and schedule for completion

Data will be reported on the forms specifically designed by the EORTC Headquarters for this study. Forms should be electronically sent to the EORTC Headquarters through the VISTA/RDC (Remote Data Capture) system, with the exception of the Quality of Life form, the neurocognitive testing form, the SAE form and the Pregnancy notification form which are paper CRFs.

These paper CRFs should be sent directly to the EORTC Headquarters:

BTG Data Manager

EORTC Headquarters
Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique

SERIOUS ADVERSE EVENTS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL (see chapter on Reporting Serious Adverse Events).

A. Before the treatment starts:

- The patient must be registered/randomized in the trial by INTERNET or in case of problems by phone.

The electronic CRFs to be completed for a patient are available on the VISTA/RDC website one day after the registration/randomization on http://rdc.eortc.be/ or on http://www.eortc.org in the section for investigators.

The paper CRF(s) will be made available to the institution at the time the institution is authorized.

B. During/after treatment

The list of forms to be completed for this study and their submission schedule are available on the VISTA/RDC website and are also described in the "guidelines for completion of case report forms" that are provided to each participating investigator.

ALL Forms must be electronically approved and sent by the responsible investigator or one of his/her authorized staff members with the exception of the paper quality of life form (no signature needed) and the paper neurocognitive testing form (signature of the accredited performer needed).

14.2 Data flow

The forms must be completed electronically, with the exception of the paper forms (the Quality of Life form, SAE form and the neurocognitive testing form), according to the schedule defined in the guidelines for completion of Case Report Forms.

The list of staff members authorized to enter data (with a sample of their signature) must be identified on the signature log and sent to the EORTC Headquarters by the responsible investigator before the start of the study. To enter the RDC system, the investigator or authorized staff member needs to use the same username and password that are used to access the interactive randomization program (ORTA).

In all cases, it remains the responsibility of the principal investigator to check that data are entered in the database as soon as possible and that the (electronic) forms are filled out completely and correctly.

The EORTC Headquarters will perform extensive consistency checks on the received data and will issue queries in case of inconsistent data. The queries for the electronic forms will appear in the VISTA/RDC system and must be answered there directly.

Only for quality of life paper form and neurocognitive form:

- If there are queries on the quality of life form, they will be raised electronically on a patient level in the VISTA/RDC system and they must be answered there directly.
- If there are queries on the neurocognitive testing form, they will be generated directly by Martin Klein and/or his staff.

The EORTC data manager, or Martin Klein and/or his staff (for neurocognitive data only), will subsequently apply the corrections into the database.

When satellite institutions are involved, all contact is made exclusively with the primary institution, for purposes of data collection and all other study related issues.

If an investigator (or an authorized staff member) needs to modify a CRF after the form has been electronically sent to the EORTC Headquarters, he/she should create a request for data correction in the VISTA/RDC system.

Only for quality of life paper form and neurocognitive testing paper form:

- If an investigator (or an authorized staff member) needs to modify the paper quality of life form after the original form has been returned to the EORTC Headquarters, he/she should create a request for data correction on a patient level in the VISTA/RDC system.
- If an investigator (or an authorized staff member) needs to modify a paper CRF after the original form has been returned to the EORTC Headquarters, he/she should directly contact Martin Klein and/or his staff.

15 Reporting of Serious Adverse Events

ICH GCP and the EU Directive 2001/20/EC require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

15.1 Definitions

These definitions reflect the minimal regulatory obligations; specific protocol requirements might apply in addition.

AE: An **Adverse Event** is defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to 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 results of 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 defined as “any noxious and unintended response to a 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 a marketed 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 (as in mild, moderate or severe, or as described in CTC grades); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as “serious,” which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

SAE: A **Serious Adverse Event** is defined as any untoward medical occurrence or effect in a patient, whether or not considered related to the protocol treatment, that at any dose:

- 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 was more severe)
- requires in-patient hospitalization or prolongation of existing patient hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is a medically important event or reaction

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

SAR: A Serious Adverse Reaction is defined as any SAE which is considered related to the protocol treatment.

SUSAR: Suspected Unexpected Serious Adverse Reaction.

SUSARs occurring in clinical investigations qualify for expedited reporting to the appropriate Regulatory Authorities within the following timeframes:

- Fatal or life-threatening SUSARs within 7 calendar days
- Non-fatal or non-life-threatening SUSARs within 15 calendar days

Inpatient hospitalization: a hospital stay equal to, or greater than, 24 hours.

15.2 Exceptions

The following situations do not need to be reported as SAEs:

- Elective hospitalization for pre-existing conditions that have not been exacerbated by trial treatment
- A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated
- A hospitalization planned for protocol related treatment or protocol related procedure as per institutional standard timelines.
- Social and/or convenience admission to a hospital
- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an (S)AE
- Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation, overdose without occurrence of an adverse event)
- 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.

By EORTC convention, clinical events related to the primary cancer progression are not to be reported as SAEs, even if they meet any of the seriousness criteria from the standard SAE definition, unless the event is more severe than expected and therefore the investigator considers that their clinical significance deserves reporting.

15.3 Severity assessment

The severity of all AEs (serious and non-serious) in this trial should be graded using CTCAE v4.0 www.eortc.org\investigators-area\ctc.

Congestive heart failure will be graded using NYHA criteria (Appendix C).

15.4 Causality assessment

The investigator is obligated to assess the relationship between protocol treatment and the occurrence of each SAE following the definitions in this table:

Relationship to the protocol treatment	**Description**
Reasonable possibility	There is a reasonable possibility that the protocol treatment caused the event
No reasonable possibility	There is no reasonable possibility that the protocol treatment caused the event

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the protocol treatment will be considered and investigated.

The decision will be recorded on the SAE form and if necessary, the reason for the decision will also be recorded.

15.5 Expectedness assessment

The expectedness assessment is the responsibility of the sponsor of the study. The expectedness assessment will be performed against the following reference documents:

- For lomustine: Summary of Product Characteristics (SmPC)
- For bevacizumab: Investigator's Brochure.

15.6 Reporting procedure for investigators

This procedure applies to all Serious Adverse Events (SAEs) occurring from the time a subject is randomized until 30 days after last protocol treatment and to any SAE that occurs outside of the SAE detection period (after the 30-days period), if it is considered to have a reasonable possibility to be related to the protocol treatment or study participation.

Randomization till 30 days after last protocol treatment:	All SAEs
From day 31 after last protocol treatment:	Only related SAEs

All reporting must be done by the principal investigator or authorized staff member (i.e. on the signature list) to confirm the accuracy of the report.

All SAE data must be collected on the study-specific SAE form.

All SAEs must be reported immediately and no later than 24 hours from the time the investigator or staff became aware of the event.

All SAE-related information needs to be provided in English.

All additional documents in local language must be accompanied by a translation in English, or the relevant information must be summarized in a follow-up SAE report form.

All SAE-related information must be faxed or e-mailed to:

EORTC Pharmacovigilance Unit:

Fax No. +32 2 772 8027

E-mail: pharmacovigilance@eortc.be

To enable the sponsor to comply with regulatory reporting requirements, all initial SAE reports should always include the following minimal information: an identifiable patient (SeqID), a suspect medicinal product if applicable, an identifiable reporting source, the description of the medical event and seriousness criteria, as well as the causality assessment by the investigator. Complete information requested on the SAE form of any reported serious adverse event must be returned within 7 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.

Queries sent out by the EORTC Pharmacovigilance Unit need to be answered within 7 calendar days.

All forms need to be dated and signed by the principal investigator or any authorized staff member (i.e. on the signature list).

15.7 Reporting responsibilities for EORTC

The EORTC Pharmacovigilance Unit will forward all SAE reports to the appropriate persons within the EORTC Headquarters and to the pharmacovigilance contact at the pharmaceutical company.

The EORTC Pharmacovigilance Unit will take in charge the expedited reporting of SUSARs to the Competent Authorities, Ethics committees, EudraVigilance Clinical Trial Module (EVCTM) and all participating investigators, whenever applicable.

The EORTC Pharmacovigilance Unit will provide a six-monthly summary which will be added in the Trial Status Report and which will be accessible to all participating investigators.

15.8 Pregnancy reporting

Pregnancy occurring during a patient's participation in this trial, although not considered an SAE, must be notified to the EORTC Pharmacovigilance Unit within the same timelines as an SAE (within 24 hours) on a Pregnancy Notification Form. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported. This also applies to pregnancies in female partners of a male patient in this trial.

- 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 protocol 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 Pharmacovigilance Unit on a Pregnancy Notification Form.
- If an SAE occurs in conjunction with the pregnancy, please also complete an SAE form as explained above.

16 Quality assurance

16.1 Control of data consistency

Data forms will be electronically sent to the EORTC Headquarters database by the VISTA/RDC (Remote Data Capture) system. Computerized and manual consistency checks will be performed on newly received forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the data manager. Inconsistent forms will be kept "pending" until resolution of inconsistencies.

16.2 On-site quality control

The EORTC Headquarters will perform on-site quality control visits.

The first visit at a site will be performed within 3 months after the first patient's randomization at the site.

Frequency of subsequent visits will depend on site's accrual and quality observed during the first visit. Overall, it is estimated that frequency will be around one visit a year per recruiting site.

The aim of these site visits will be:

- to verify that the site facilities are adequate for performing the trial and that the PI and site staff involved in the trial are working in compliance with GCP and protocol requirements
- to assess the consistency of the data reported on the case report forms with the source data on a sample of patients

- to check that Serious Adverse Events have been properly reported and that follow-up information or queries are completed
- to assist the site in resolving any outstanding queries
- to control the drug accountability process

16.3 Audits

The EORTC Quality Assurance and Control Unit (QA&C) regularly conducts audits of institutions participating in EORTC protocols. These audits are performed to provide assurance that the rights, safety and wellbeing of subjects are properly protected, to assess compliance with the protocol, processes and agreements, ICH GCP standards and applicable regulatory requirements, and to assess the quality of data.

The investigator, by accepting to participate in this protocol, agrees that EORTC, any third party (e.g. a CRO) acting on behalf of the EORTC, or any domestic or foreign regulatory agency, may come at any time to audit or inspect their site and all subsites, if applicable.

This audit consists of interviews with the principal investigator and study team, review of documentation and practices, review of facilities, equipment and source data verification.

The investigator will grant direct access to paper and/or electronic documentation pertaining to the clinical study (e.g. CRFs, source documents such as hospital patient charts and investigator study files) to these authorized individuals. All site facilities related to the study conduct could be visited during an audit (e.g. pharmacy, laboratory, archives …). The investigator agrees to co-operate and provide assistance at reasonable times and places with respect to any auditing activity.

If applicable, the company(ies) supplying the study drug(s) may have access to anonymized data but will not have access to source documents.

If a regulatory authority inspection is announced, the investigator must inform the EORTC Headquarters QA&C Unit immediately (contact at: QualityAssuranceandControlUnit@eortc.be).

In this way EORTC can provide support in preparing and/or facilitating the inspection. EORTC representatives/delegates may also attend the inspection.

16.4 External review of histology

16.4.1 Central review of histology

Samples shipments should be addressed to Andreas von Deimling & Christian Hartmann. Central pathology review will be done at the end of the study.

For the review:

- A paraffin embedded tumor sample (tumor material at initial diagnosis and/or recurrence if available) (preferably a tumor block, otherwise 30 unstained slides)
- The anonymized local pathology report

Samples must be sent to:

David Capper
Department of Neuropathology
Institute of Pathology
University Heidelberg
Im Neuenheimer Feld 224
D-69120 Heidelberg
Phone: +49 (0)6221 56 37254
Fax: +49 (0)6221 56 4566

16.4.2 Sample requirements and routing

The tumor material and blood samples should be sent to University of Heidelberg, Heidelberg, Germany. Details on the procedure are to be found in the Appendix G “Procedures and routing of tumor and blood samples”

16.5 Other central review procedures

Central review of imaging will be performed as described in the translational research chapter.

It is foreseen that a web based computerized platform will be used for additional analysis of the MR images. For this, data will be entered anonymously into a remote server, and the images will be analyzed anonymously and blinded to the central reviewers. This review process will be done blinded to the assigned treatment, the clinical data or study outcome. Both the local and the central review diagnosis of response and date of progression will be reported.

Imaging guidelines will be provided to the sites before site activation. The imaging central review should be performed based on the central review guidelines.

The objective is to assess the validity and application of the RANO and modified RANO criteria as opposed to the Macdonald's criteria.

17 Ethical considerations

17.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) 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.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf).

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

17.2 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 will be included on all case report forms. In order to avoid identification errors, the patient's code (maximum of 4 alphanumerics) and date of birth will also be reported on the case report forms.

17.3 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 a separate document dated and version controlled to this protocol.

An adapted translation of the PIS/PIC will be provided by EORTC Headquarters and it is the responsibility of the Coordinating investigators for this trial (sometimes called National Coordinators) to adapt it to national/local requirements where necessary.

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.EORTC 26101 Bevacizumab and lomustine for recurrent GBM Version 2.1 75 / 100 December 04, 2013

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.

18 Administrative responsibilities

18.1 The study coordinator

The Study Coordinator (in cooperation with the EORTC Headquarters) will be responsible for writing the protocol, contributing to the medical review, discussing the contents of the reports with the Data Manager and the Statistician, and for publishing the study results. He will assist the Clinical Research Physician for answering some clinical questions concerning eligibility, treatment, and the medical review of the patients.

Study coordinators:

Wolfgang Wick
Department of Neurooncology, Neurology Clinic and National Center for Tumor Disease
UNIVERSITAETSKLINIKUM HEIDELBERG - KOPFKLINIK
Im Neuenheimer Feld 400
69120 Heidelberg
Germany
Phone: +49 6221 567075
Fax: +49 6221 567554
E-mail: wolfgang.wick@med.uni-heidelberg.de

Martin J. van den Bent
Erasmus MC - Daniel den Hoed Cancer Center
(Postbus 5201) Groene Hilledijk, 301
3075 EA Rotterdam
Netherlands
Phone: +31 107041415
Fax: +31 107041031
E-mail: m.vandenbent@erasmusmc.nl

18.2 The EORTC Headquarters

The EORTC Headquarters will be responsible for writing the protocol and PIS/IC, reviewing the protocol, setting up the trial, collecting case report forms, controlling the quality of the reported data, organizing the medical review and generating reports and analyses in cooperation with the Study Coordinator. All methodological questions should be addressed to the EORTC Headquarters.

EORTC HEADQUARTERS

Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique
Fax: +32 2 7723545

Registration of patients:

http://www.eortc.be/random
Or
Phone (in case of problems): +32 2 774 16 00

18.3 The EORTC group

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

EORTC Brain Tumor Group

Chairman:

Wolfgang Wick
Department of Neurooncology, Neurology Clinic and National Center for Tumor Disease
UNIVERSITAETSKLINIKUM HEIDELBERG - KOPFKLINIK
Im Neuenheimer Feld 400
69120 Heidelberg
Germany
Phone: +49 6221 567075
Fax: +49 6221 567554
E-mail: wolfgang.wick@med.uni-heidelberg.de

Secretary:

Brigitta Baumert
Radiotherapeut Oncoloog
MAASTRO CLINIC - MAASTRICHT RADIATION ONCOLOGY
P.O. Box 1345 (Dr Tanslan 12)
6201 BN Maastricht
The Netherlands
Phone: +31 88 4455666
Fax: +31 88 4455667
E-mail: brigitta.baumert@maastro.nl

19 Trial sponsorship and financing

EORTC is the legal Sponsor for all EORTC participants.

The contact details of the EORTC are:

EORTC Headquarters
Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique
Phone: +32 2 7741611
Fax: +32 2 7723545
e-mail: eortc@eortc.be

20 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.

21 Publication policy

All publications must comply with the terms specified in the EORTC Policy 009 “Release of Results and Publication Policy”.

The final publication of the main trial results will be written by the EORTC Study Coordinator on the basis of the final analysis performed at the EORTC Headquarters and published in a major scientific journal.

The results of the phase II part of the trial will be analyzed and published independently.

Authors of the manuscript(s) will include the Study Coordinators, the investigators who have included more than 5% of the eligible patients in the trial (by order of inclusion), the central review pathologist, neuro-radiologists and the statistician and clinical research physician in charge of the trial at the EORTC Headquarters.

The title of all manuscripts will include “EORTC”, and all manuscripts will include an appropriate acknowledgment section, mentioning all investigators who have contributed to the trial, the EORTC Headquarters staff involved in the study as well as supporting bodies (NCI, cancer leagues, supporting company…).

Prior to submission, all publications (papers, abstracts, presentations…) including pertaining to patients data from the present trial will be submitted for review to the EORTC Headquarters, to Roche and to all co-authors prior to submission.

The above rules are applicable to publications involving any individual patient registered/randomized in the trial.

The data collected during this study are confidential. Any publications or abstracts arising from this study require approval by the EORTC prior to publication or presentation and must adhere to EORTC's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, or detailed summaries of any proposed presentations, must be submitted to the EORTC and the supporting company at the earliest practicable time for review, not less than 30 days (14 days for abstracts) before submission or presentation unless otherwise set forth in the CTA.

Appendix A: References

Ref. 1 Ohgaki H, Kleihues P. Epidemiology and etiology of gliomas. Acta Neuropathol. 2005; 109:93-108.

Ref. 2 Hess KR, Broglio KR, Bondy ML. Adult glioma incidence trends in the United States, 1977-2000. Cancer . 2004; 101:2293-2299.

Ref. 3 Schwartzbaum JA, Fisher JL, Aldape KD, Wrensch M. Epidemiology and molecular pathology of glioma. Nat Clin Pract Neurol. 2006; 2(9):494-503.

Ref. 4 Fleury A, Menegoz F, Grosclaude P, et al. Descriptive epidemiology of cerebral gliomas in France. Cancer. 1997; 79(6):1195-1202.

Ref. 5 Stupp R, Mason WP, van den Bent MJ, Weller M, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 1995; 352: 987-96.

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Appendix B: WHO performance status scale

Grade	Performance scale
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

Appendix C: New York Heart Association (NYHA) classification of heart failure

Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

(The Criteria Committee of the New York Heart Association: Diseases of the Heart and Blood Vessels; Nomenclature and Criteria for Diagnosis, 6th ed Boston, Little, Brown 1964).

Appendix D: Common Terminology Criteria for Adverse Events

In the present study, adverse events and/or adverse drug reactions will be recorded according to the

Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

However for congestive heart failure NYHA criteria should be used, see Appendix C.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address: http://ctep.cancer.gov/reporting/ctc.html.

The EORTC Headquarters web site www.eortc.org\investigators-area\ctc provides a link to the appropriate CTC web site. This link will be updated if the CTC address is changed.

Appendix E: EORTC Quality of Life evaluation: guidelines for administration of questionnaires (Revised June 2008)

EORTC Quality of Life evaluation: guidelines for administration of questionnaires (revised June 2008)

The instructions given below are intended to provide some general guidelines for collecting quality of life (QoL) data in EORTC studies. These instructions apply for all types of questionnaires.

1. Who is the responsible person (RP) for QoL data collection?

The overall-responsible person for QoL data collection is the study-co-ordinator of the trial. However, in each institution one person should be appointed as the responsible for the local organization of QoL data collection. This can be a physician, data manager, (research) nurse or a psychologist. Such a person should have the full protocol at his/her disposal as well as the questionnaire(s). This person would also be the intermediate contact point in case of any necessary clarification asked by the EORTC Headquarters.

2. Who should fill out the questionnaire?

In principle it is the patient him/herself who has to fill out QoL forms and preferably without help from others. In case a patient is too sick to fill out the questionnaire or if the patient is not able to fill out the questionnaire for reasons such as forgetting his/her glasses, another person could read the questions without making any comments and report the answers on the forms. If a patient received this type of help, please note this on the form.

3. What instructions should be given to the patient?

At entry in a study, the RP should give the patient an explanation of the objective of the study and instructions for filling out questionnaires.

The patient should be informed that participation in the QoL protocol is voluntary and that the information provided is confidential (identification is only for administrative purposes).

The following issues should be explained to the patient:

- The schedule of assessments.
- The questionnaire is a self administered questionnaire that should be filled out preferably by the patient him (her) self.
- The patient should circle the choice that best corresponds to his/her situation.
- There is no right or wrong answer to any of these questions.
- All questions should be answered.

The RP should make sure that the patient understands the instructions and that a questionnaire is available in the preferred language of the patient (questionnaires in additional languages can be obtained via the EORTC HQ).

At each subsequent assessment as defined by the protocol, the patient should receive the questionnaire from the RP or by other appropriate staff if the RP is not available.

4. Where should the patient fill out the questionnaire?

The patient should complete the questionnaire in the clinic, ideally in a quiet, private room. In general it does not take more than 5 to 10 minutes to fill out a questionnaire, but patients should be given the time they need to answer all questions.

5. When should the patient fill out the questionnaire?

When a QoL assessment is planned, the questionnaire should be given to the patient preferably before the meeting with the physician, ensuring that the patient has enough time to complete the questionnaire. If the patient receives a therapy, the questionnaire should be filled out before administration of the treatment. The questionnaire should not be taken home and/or mailed.

6. Review of the completed questionnaire.

After the patient has filled out the questionnaire, the person handling the questionnaire should:

- Check that the date of today is correctly filled in.
- Check the answers for omissions, for incorrectly completed questions and for inconsistent answers;

  If this is the case:

- Please ask the patient for the reason for omissions or incorrect answers. If the patient prefers not to answer a question this should be noted on the form;
- Additional explanation may be provided, but the questions should not be rephrased;
- Any additional comments could be added by the person handling the questionnaire (if possible in English) followed by their name and signature.

7. Missing forms

If for some reason the patient is unable or does not wish to complete a quality of life questionnaire the reason and date of visit should be documented on the questionnaire and returned to the person responsible for completing the CRFs (case report forms).

8. Mailing to the EORTC Headquarters

The questionnaire should be sent to the EORTC Headquarters with the CRFs.

As it is not possible to retrospectively collect missing QoL data, please make sure the patient completes the questionnaire at the time-point when he/she is supposed to fill it out.

Thank you very much for your cooperation. If you have any remarks on this leaflet or if you need further information, please contact:

Quality of Life Department - EORTC Headquarters:

Phone: 32 2 774 1678/1661

Fax: 32 2 779 45 68

EORTC Quality of Life evaluation: instructions for Monitors

- Check if all QoL questionnaires have been filled out on schedule
  - If not, the Monitor should inform the person in charge of data collection and explain again the schedule of the QoL questionnaires.
- Make sure the QoL questionnaires are correctly completed
  - If not, tell the responsible person to explain again to the patient how to fill out the QoL questionnaires at the next visit.

EORTC Quality of Life evaluation: instructions for Data Managers

- When a response is missing, it should be coded as “9” for missing data (cfr Scoring Manual)
- When two adjacent categories have been circled by the patient, the category which represents the worst QoL will be taken.
  For a symptom item, the highest score will be taken.
  For a functional item, the lowest score will be taken.
- When the response is not legible or ambiguous (eg. two categories which are not adjacent have been circled) then the response is not evaluable and it should be coded as “8”.

Appendix F: Certification and administration procedure for neurocognitive test battery

The healthcare professional who will be evaluating patients must complete a "practice" assessment, including completion of test forms/score sheets, and complete and sign the Certification Worksheet for test administrator (see appendix I hereunder). Fax the practice tests, score sheets, training video post test, and signed Certification Worksheet to the attention of M. Klein, FAX: +31 20 4448230.

M. Klein will be available by telephone and e-mail if questions arise about the testing procedures.
M. Klein may be contacted at phone: +31 20 4448432 or email: m.klein@vumc.nl

If there are administration or procedural errors, M. Klein will discuss the test administration and scoring issues over the phone with the healthcare professional (5-10 minutes). If the health professional meets criteria for certification, notification of certification will be sent to both the site and to EORTC, and study enrollment may commence.

Individuals previously certified for the EORTC 26053-22054-CATNON or the 26081-22086 or the 26091 trial do not need to be re-certified for this study unless M Klein considers there is a need for a re-certification. This information will be communicated to the sites by EORTC HQ.

The test forms of the first case for each certified examiner, as well as random cases during the course of the trial, will be reviewed by M. Klein for quality control purposes and to ensure ability of the sites to perform testing. Procedural deviations (if any) will be identified, and sites will be notified of the results of the review. Only if significant procedural variations are noted, re-training ('re-certification') of the test administrator will be requested. Completed test forms must be signed by the certified test administrator.

Summary of Requirements for Examiner Approval for the EORTC 26101

Prior to testing a patient, potential examiners must:

- Read "Certification & administration procedures for neurocognitive test battery"
- Obtain website and password information to get access to a password-protected website at VU University Medical Center, Amsterdam, The Netherlands, with all the necessary information, including scoring forms. For this please contact Martin Klein (m.klein@vumc.nl).
- Obtain copies of the neurocognitive tests from the password-protected website in national languages
- These copies also contain the test instructions in national languages
- Watch the training video available at MD Anderson Cancer Center:
  http://www3.mdanderson.org/depts/nco/nctbTraining
  Study ID: CTB83451
- Complete the training video post test
- Complete a "practice" assessment
- Complete the Certification Worksheet (Appendix I)

All materials (i.e., post test, complete practice assessment and scoring forms, certification worksheet) must be faxed to M. Klein, who will score it and review any procedural errors with the trainee. If the trainee demonstrates competency, he/she will be notified of the approval to administer the tests to study subjects as part of the EORTC 26101. An approval notice will be sent to EORTC for their records and to ensure that only the EORTC 26101-approved examiners are testing subjects on protocol the EORTC 26101.

1.1 General Procedures: Certification for Test Administration

The healthcare professional (e.g., nurse, psychologist) who is responsible for test administration in this study requires pre-certification by M. Klein in order to participate in this protocol.

- Test and data recording forms are available on the password-protected website provided by M. Klein. The instructions must be reviewed along with the test forms and retained for reference.
- A training video of test administration and data collection procedures are accessible through a website at MD Anderson Cancer Center for review and reference during this study:
  http://www3.mdanderson.org/depts/nco/nctbTraining
  Study ID: CTB83451
- This video must be reviewed with the "Test Instructions for the Neurocognitive Function Battery" by anyone who will administer neuropsychological assessments.
- The post test associated with this video must be completed and faxed to M. Klein.
- To obtain website and password information for the training video, contact:

Martin Klein (m.klein@vumc.nl**)**

1.2 Neurocognitive Assessment

The tests that constitute the neurocognitive function (NCF) battery were selected because they are widely used standardized psychometric instruments that have been shown to be sensitive to the neurotoxic effects of cancer treatment in other clinical trials. NCF has been demonstrated to predict tumor progression and independently predict survival for patients with CNS tumors. This battery has also been demonstrated to be practical in terms of cost and burden to the patient, with good compliance in multicenter trials. They are widely used, standardized psychometric instruments with published normative data that take into account age and, where appropriate, education, gender and handedness. The tests were also selected to minimize the effects of repeated administration. These tests are to be administered by a certified examiner and require 21 minutes or less to complete.

The test results form will be sent to the EORTC Headquarters together will the regular patient documentation. The EORTC Headquarters will then transfer the forms relating to the neurocognitive assessment to Martin Klein (VU University Medical Center, Amsterdam, The Netherlands).

Cognitive Domain	Test	Time to Administer (minutes)
Memory	Hopkins Verbal Learning Test–Revised	8
Visual-motor processing speed	Trail Making Test Part A	3
Executive Function	Trail Making Test Part B	5
Verbal fluency	Controlled Oral Word Association	5
		Total time: 21 minutes

Neurocognitive Assessment – Sequencing of Alternate Forms

Two of the tests to be administered have alternate forms or versions in order to reduce the effects of practice. See the table below for the versions to be administered at pre-entry and subsequent sessions (please refer to summary table 6.4 for time of assessments). The forms should continue to be alternated in this order for the duration of the study. The forms packet will contain alternate versions of these neuropsychological tests.

TEST	Study Registration	1st visit	3rd visit	4th visit	5th visit	6th visit	7th visit
HVLT-R	Form 1	Form 2	Form 3	Form 4	Form 5	Form 6	Form 1
COWA	'C-F-L'	'P-R-W'	'C-F-L'	'P-R-W'	'C-F-L'	'P-R-W'	'C-F-L'

Additional comments:

1. Testing should be completed in one session. Test instructions must be followed verbatim with every patient at every study visit. All tests should be completed in black pen.

2. Tests should be administered in the following order to every patient and at every study visit: HVLT-R Free Recall; Trail Making Test Part A; Trail Making Test Part B; COWA; HVLT-R Delayed Recall; and the HVLT-R Delayed Recognition.

3. You may fill the 20-minute delay interval between COWA and HVLT-R Delayed Recall with QoL questionnaires.

4. Follow the instructions on the Forms Packet Index before submission of forms to M. Klein.

5. Please keep copy of original test records. In the event of questions, contact M. Klein.

6. All test results are recorded on the test forms.

7. Patients should not be given copies of their tests to avoid learning the material between test administrations.

8. Before dismissing the patient, thank the patient for his/her cooperation. Remind the patient of his/her next appointment and that these tests will be repeated.

9. In the event that a patient cannot complete a given test, please write the reason(s) on the test form.

1.3 Test instructions for the neurocognitive function battery

Administer the tests in the following order to every patient at every visit:

HVLT-R FREE RECALL
TRAIL MAKING TEST PART A
TRAIL MAKING TEST PART B
CONTROLLED ORAL WORD ASSOCIATION
HVLT-R DELAYED RECALL
HVLT-R DELAYED RECOGNITION

1) HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)

This test has three parts and six alternate forms:

Part A - Free Recall: Complete the three learning trials first

Part B - Delayed Recall: Complete after a 20 minute delay that includes administration of Trail Making Tests and COWA

Part C - Delayed Recognition: Complete immediately after Delayed Recall

Part A – Free Recall: Trial 1

Examiner: "I am going to read a list of words to you. Listen carefully, because when I am through, I'd like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?"

- Read the words at the rate of one word every 2 seconds.

Examiner: "OK. Now tell me as many of those words as you can remember."

- Check off the words the patient recalls on the form.
- If a word is said that is not in the list (for example, "intrusion"), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- If not, move on to trial 2. Later, you can record the number of words that were correctly repeated on the test form.

Part A – Free Recall: Trial 2

Examiner: "Now we are going to try it again. I am going to read the same list of words to you. Listen carefully, and tell me as many of the words as you can remember, in any order, including the words you told me the first time."

- Read the words at the rate of one word every 2 seconds.
- Check off the words the patient recalls on the form.
- If a word is said that is not in the list (for example, "intrusion"), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- If not, move on to trial 3. Later, you can record the number of words that were correctly repeated on the test form.

Part A – Free Recall: Trial 3

Examiner: "I am going to read the list one more time. As before, I'd like you to tell me as many of the words as you can remember, in any order, including all the words you've already told me."

- Read the words at the rate of one word every 2 seconds.
- Check off the words the patient recalls on the form.
- If a word is said that is not in the list (for example, "intrusion"), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- Do not tell the respondent that recall of the words will be tested later.
- Record the time on the clock that you complete 'Part A – Free Recall' (for example, 10:00 am) on the designated space on the HVLT-R form.

2) TRAIL MAKING TEST [Timed Test]

Part A – Sample: The Sample for Part A must be completed/attempted by each patient at every assessment. Place the Sample A worksheet flat on the table, directly in front of the patient (the bottom of the worksheet should be approximately six inches from the edge of the table). Give the patient a black pen and say:

Examiner: "On this page (point) are some numbers. Begin at number 1 (point to 1) and draw a line from 1 to 2 (point to 2), 2 to 3 (point to 3), 3 to 4 (point to 4), and so on, in order, until you reach the end (point to the circle marked END). Draw the lines as fast as you can. Ready, begin."

If the patient completes Sample A correctly and in a manner demonstrating that s/he understands what to do, proceed immediately to Test A. If the patient makes a mistake on Sample A, point out the error and explain it.

The following explanations of mistakes serve as illustrations:

- "This is where you start (point to number 1)"
- "You skipped this circle (point to the circle omitted)"
- "You should go from number 1 to 2, 2 to 3, and so on, until you reach the circle marked END"

If it is clear that the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample A, take his/her hand and guide him/her through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. Then say:

Examiner: "Remember, begin at number 1 (point to 1) and draw a line from 1 to 2 (point to 2), 2 to 3 (point to 3), 3 to 4 (point to 4) and so on, in order, until you reach the circle marked END (point). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."

If the patient does not succeed, or it becomes evident that s/he cannot do the task, DISCONTINUE testing and indicate the corresponding reason on the Trail Making Data Sheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

Part A – Test: After the patient has completed Sample A, place the Part A test worksheet directly in front of the patient and say:

Examiner: "Good! Let's try the next one. On this page are numbers from 1 to 25. Do this the same way. Begin at number 1 (point) and draw a line from 1 to 2 (point to 2), 2 to 3 (point to 3), 3 to 4 (point to 4) and so on, in order, until you reach the circle marked END (point). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."

- Start timing as soon as the instruction is given to "begin"
- Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred
- The patient must complete the test in 3 minutes or less
- DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED "END"
- If the patient does not complete the test within 3 minutes terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the Trail Making Data Sheet indicating the reason the test was terminated and the last correct number reached on the test.
- If the patient successfully completes the test collect the worksheet and record the time to completion on the Trail Making Data Sheet in minutes and seconds. Then say, **"That's fine. Now we'll try another one."**

Part B – Sample: The Sample for Part B must be completed/attempted by each patient at every assessment. Place the Sample B worksheet flat on the table, directly in front of the patient (the bottom of the worksheet should be approximately six inches from the edge of the table) and say:

Examiner: "On this page (point) are some numbers and letters. Begin at number 1 (point to 1) and draw a line from 1 to A (point), A to 2 (point to 2), 2 to B (point to B), B to 3 (point to 3), 3 to C (point to C) and so on, in order, until you reach the end (point to the circle marked END). Remember, first you have a number (point to 1), then a letter (point to A), then a number (point to 2), then a letter (point to B), and so on. Draw the lines as fast as you can. Ready, begin."

If the patient completes Sample B correctly, and in a manner demonstrating that s/he understands what to do, proceed immediately to Part B. If the patient makes a mistake on Sample B, point out the error and explain it.

The following explanations of mistakes serve as illustrations:

- "You started with the wrong circle. This is where you start (point to number 1)"
- "You skipped this circle (point to the circle omitted)"
- "You should go from number 1 (point) to A (point), A to 2 (point to 2), 2 to B (point to B), B to 3 (point to 3) and so on, until you reach the circle marked END (point)"

If it is clear the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample B, take their hand and guide them through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. Then say:

Examiner: "Now you try it. Remember, begin at number 1 (point to 1) and draw a line from 1 to A (point to A), A to 2 (point to 2), 2 to B (point to B), B to 3 (point to 3) and so on, in order, until you reach the circle marked END (point). Ready, begin."

If the patient does not succeed or it becomes evident that s/he cannot do the task, DISCONTINUE testing and indicate the corresponding reason on the Trail Making Data Sheet. If the patient completes Sample B correctly and appears to understand what to do, proceed immediately to Part B.

Part B – Test: After the patient has completed Sample B, place the Part B Worksheet directly in front of the patient and say:

Examiner: "Good! Let's try the next one. On this page are both numbers and letters. Do this the same way. Begin at number 1 (point) and draw a line from 1 to A (point to A), A to 2 (point to 2), 2 to B (point to B), B to 3 (point to 3), 3 to C (point to C) and so on, in order, until you reach the circle marked END (point). Remember, first you have a number (point to 1), then a letter (point to A), then a number (point to 2), then a letter (point to B), and so on. Do not skip around, but go from one circle to the next in the proper order. Draw the lines as fast as you can. Ready, begin."

- Start timing as soon as the instruction is given to "begin"
- Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred
- The patient must complete the test in 5 minutes or less
- DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED "END"
- Collect the worksheet and record the time to completion on the Trail Making Data Sheet in minutes and seconds
- If the patient does not complete the test within 5 minutes terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the Trail Making Data Sheet indicating the reason the test was terminated and the last correct number or letter reached on the test.
- At the top of both Sample forms and Test forms please write: patient code, case number, date of evaluation, institution name, name of certified tester, and the certified tester's phone number.

3) CONTROLLED ORAL WORD ASSOCIATION TEST (COWAT) [Timed Test]

This test has three parts (letters) and two alternate forms.

Examiner: "I am going to say a letter of the alphabet, and I want you to say as quickly as you can all of the words that you can think of that begin with that letter. You may say any words at all, except proper names such as the names of people or places. So you would not say 'Rochester' or 'Robert'. Also, do not use the same word again with a different ending, such as 'Eat,' and 'Eating.'

"For example, if I say 's,' you could say 'son', 'sit,' 'shoe,' or 'slow.' Can you think of other words beginning with the letter 's'?"

Wait for the patient to give a word. If it is a correct response, say "good", and ask for another word beginning with the letter "s". If a second appropriate word is given, proceed to the test itself.

If the patient gives an inappropriate word on either occasion, correct the patient, and repeat the instructions. If the patient then succeeds, proceed to the test.

If the patient fails to respond, repeat the instructions. If it becomes clear that the patient does not understand the instructions or cannot associate, stop the procedure, and indicate the reason(s) on the scoring sheet.

If the patient has succeeded in giving two appropriate words beginning with the demonstration letter, say:

Examiner: "That is fine. Now I am going to give you another letter and again you say all of the words beginning with that letter that you can think of. Remember, no names of people or places, just ordinary words. Also, if you should draw a blank, I want you to keep on trying until the time limit is up and I say STOP."

"You will have a minute for each letter. The first letter is '___'. Begin" (Start timing immediately. See scoring sheet).

Allow exactly one minute for each letter

- If the patient discontinues before the end of the time period, encourage him/her to try to think of more words.
- If he/she is silent for 15 seconds, repeat the basic instruction and the letter (e.g., "**Tell me all the words you can think of that begin with a "c"**).
- No extension on the time limit is made in the event that instructions are repeated.
- Continue the evaluation with the remaining two letters, allowing one minute for each.

Recording and Scoring:

- The record sheet provides lines on which the patient's responses can be entered (e.g., write in the word that is said by the patient). If his/her speed of word production is too fast to permit verbatim recording, a "+" should be entered to indicate a correct response.
- Incorrect responses should be recorded and struck through with a single line followed by your initials and the date in the margin next to the error.
- If the patient provides more responses than there are lines on the record sheet, place check marks in the boxes to indicate correct responses only.
- Count all the correct responses. The number of correct words should be indicated below each column on the recording sheet that is sent to M. Klein.

Comments on scoring:

- Note: It can be helpful for the first several patients and for patients known to be fast with their word production to tape record the session for transcription at a later time.
- The instructions include a specific prohibition against giving proper names or different forms of the same word. Therefore, inflections of the same word (e.g., eat-eating; mouse-mice; loose-loosely; ran-run-runs) are not considered correct responses.
- Patients often give both a verb and a word derived from the verb or adjective (e.g., fun-funny; sad-sadness). These are not considered correct responses. On the other hand, if the word refers to a specific object (e.g., foot-footstool; hang-hanger), it would be counted as a correct answer.
- Many words have two or more meanings (e.g., foot; can; catch; hand). A repetition of the word is acceptable IF the patient definitely indicates the alternative meaning to you.
- Slang terms are OK if they are in general use.
- Foreign words (for example, pasta; passé; lasagna) can be counted as correct if they can be considered part of the lexicon of the relevant language, the criterion being their listing in a standard dictionary of that language. All incorrect and repeated responses MUST be crossed out with one single line, initialed and dated. Additionally, all duplicate entries that have been verified to have different meanings must be marked "ok", initialed and dated. Refer to the descriptions above for guidelines for acceptability. Add the total number of correct responses in each column and input the totals where indicated on the COWA worksheet.

- If the test is discontinued or omitted, please mark this on the bottom of the test form and indicate the reason.

4) HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)

Part B – Delayed Recall

- DO NOT READ THE WORD LIST AGAIN.
- Record the time on the clock that you start 'Part B – Delayed Recall' (for example, 10:20 am) on the designated space on the HVLT-R form.
- Administer 'Part B – Delayed Recall' after completing all Trail Making Tests and the COWA. There should be at least 20 minutes between 'Part A' and 'Part B' of the HVLT-R. If the time is too short, allow the patients to complete a questionnaire.

Examiner: "Do you remember that list of words you tried to learn before? Tell me as many of those words as you can remember."

- Check the box on the corresponding line of the HVLT-R worksheet for each word the patient accurately recalls.
- If a word is said that is not in the list (for example, "intrusion"), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- If not, record the number of words that were correctly recalled on the scoring form.

Part C – Delayed Recognition

Examiner: "Now I'm going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I'd like you to say "Yes" if it was on the original list or "No" if it was not. Was [word] on the list?"

- Read the words from the top of the columns down.
- Check either the "Y" (Yes) or "N" (No) box next to each word to indicate the patient's response.
- Guessing is allowed.
- If the test is discontinued or omitted, please mark this on the bottom of the test form and indicate the reason.
- The score for this portion of the HVLT-R is the number of list words (i.e., words that in CAPS) correctly identified ("yes" response) minus the number of non-list words (i.e., words in lower case) incorrectly identified ("yes" response). Therefore, the actual score can range from –12 (no list words identified and all non-list words identified) to +12 (all list words identified and no non-list words identified).

Appendix I

Certification worksheet for test administrator

EORTC 26101

Phase III trial exploring the combination of bevacizumab and lomustine in patients with first recurrence of a glioblastoma.

This worksheet must be completed and signed by the person requesting certification and submitted to M. Klein prior to the registration of any patients to the EORTC 26101 trial. Refer to “Certification procedures” for details.

___(Y) 1. Have you reviewed the Administration Procedures for the Neurocognitive Test Battery?

___(Y) 2. Have you watched the Neuropsychological Test Administration video and completed the post test?

___(Y) 3. Have you completed a "practice" Neuropsychological Assessment (see certification procedure)?

_____ _____

Signature of test administrator Date

_____ _____

Printed name of test administrator Institution number/Name

_____ _____

Telephone number of test administrator Fax number of test administrator

If you have any questions regarding the certification, please contact M. Klein. Once you have completed this form, please attach both the Neuropsychological Assessment forms from the “practice” subject and the training video post test and submit to:

M. Klein
Phone +31 20 4448432
FAX +31 20 4448230
m.klein@vumc.nl

For M. Klein’s Use Only (to fax to EORTC **Headquarters: +32 (0)2 772 35 45**)

_____(Y/N) The above individual has been certified for administering the neurocognitive assessments for this study.

Signature _____

Date _____

Appendix G: Procedures and routing of tumor and blood samples

Every effort will be made to obtain blood and tissue specimens for research. All patients will be consented for the collection and storage of blood and tumor tissue. Several molecular markers will be evaluated using appropriate research methods in either the blood or tumor tissue. Results will be correlated with the clinical data to determine associations between markers and clinical outcome to treatment.

1. Prospective biological samples collection

After the randomization of the patient into the trial the following items must be collected:

- A paraffin embedded tumor sample (tumor material at initial diagnosis (mandatory) and recurrence if available). Preferably a tumor block, otherwise 30 + 9 unstained slides.
- Fresh frozen tissue (optional).
- If feasible, it should be planned to extract representative glioblastoma tissue during open surgery of the progressed glioblastoma. The tumor sample has to be snap-frozen in liquid nitrogen within 2 minutes of harvesting.

A part of the glioblastoma tissue (appr. 1/3) has to be fixed in formalin and embedded in paraffin for histological validation of the snap frozen glioblastoma.

- 10 ml whole blood collected in an EDTA tube.

At baseline and during the indicated follow-up visits (2, 6, 12 weeks and progression) we will collect - additionally to standard laboratory analyses - EDTA plasma samples for molecular evaluations. EDTA Plasma derived from vein puncture at baseline and periodic follow-up-visits will be used for evaluation of molecular markers associated with tumor neovascularization or therapy response.

Blood samples must be prepared as described below:

All samples must be processed within an hour after the drawing of the blood sample. The sample must be centrifugated (preferably in a refrigerated centrifuge at 4° C) at 2000 rpm for 10 minutes. After separation of the plasma, the plasma is divided over 5 cryo cups (0.5 ml per cup). The plasma sample must be labelled and stored in a storage box at the local institute in upright position preferably at -80°C, if not possible at -20°C.

All samples must be labelled as follows:

- Date and time of sampling
- Patient subject number and month and year of birth
- Study name (EORTC 26101)

All blood and tissue samples must be prepared, collected and stored at each participating study site (see Table).

Sample	Purpose	Storage
FFPE	Tissue histology and molecular markers	Room temperature (15-30°C)
FF Tissue	Molecular markers	Liquid nitrogen or -80°C
EDTA (Plasma)	Plasma Molecular Markers	-80°C

2. Translational research projects: MGMT methylation status and biomarkers of VEGF pathway

To achieve these objectives the following biological samples will be collected. The informed consent for trial participation will explain the need of this material of the initial resection and eventually subsequent resections for translational research

2.1. MGMT methylation status analysis

2.1.1. Tumor material

For this translational project, the Paraffin blocks and/or slides that will be provided for the prospective tissue collection will be used.

2.2. Biomarkers of the VEGF Pathway

The following hereunder samples will be collected and sent to the central laboratory:

- FFPE block or 9 unstained slides
- Frozen blood samples (10 ml): plasma at baseline, 2, 6 and 12 weeks after start of treatment and at progression

Depending on accrual per site, sites will be contacted on a 3 or 6 monthly basis to send the samples. Samples will be shipped on dry ice to:

David Capper
Department of Neuropathology
Institute of Pathology
University Heidelberg
Im Neuenheimer Feld 224
D-69120 Heidelberg
Phone: +49 (0)6221 56 37254
Fax: +49 (0)6221 56 4566

All details regarding procedures and samples shipment will be provided in the guidelines at the time of sites activation.